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A critical discussion of the role of neuroimaging in mild cognitive impairment*

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Objective – In this paper, the current neuroimaging literature is reviewed with regard to characteristic findings in mild cognitive impairment (MCI). Particular attention is drawn to the possible value of neuroimaging modalities in the prediction and early diagnosis of Alzheimer's disease (AD). *Methods* – First, the potential contribution of neuroimaging to an early, preclinical diagnosis of degenerative disorders is discussed at the background of our knowledge about the pathogenesis of AD. Second, relevant neuroimaging studies focusing on MCI are explored and summarized. Neuroimaging studies were found through Medline search and by systematically checking through the bibliographies of relevant articles. *Results* – Structural volumetric magnetic resonance imaging (MRI) and positron emission tomography (PET)/single photon emission tomography (SPECT) are currently the most commonly used neuroimaging modalities in studies focusing on MCI. There were considerable variations in demographical and clinical characteristics across studies. However, significant hippocampal and entorhinal cortex volume reductions were consistently found in subjects with MCI as compared with cognitively unimpaired controls. While hippocampal and entorhinal cortex atrophy in subjects with MCI are also well-established risk factors for the development of AD, these measures cannot be regarded as being of high predictive value in an individual case. Evidence for other typical neuroimaging changes in MCI is still scarce. In PET and SPECT studies, reduced blood flow and/or glucose metabolism in temporoparietal association areas, posterior cingulate and hippocampus were associated with a higher risk of progressive cognitive decline in MCI. In quantitative electroencephalogram (QEEG), low beta, high theta, low alpha and slowed mean frequency were associated with development of dementia. *Conclusions* – Existing studies suggest that neuroimaging measures have the potential to become valuable tools in the early diagnosis of AD. To establish their value in routine use, larger studies, preferably with long prospective follow-up are needed.

Henrike Wolf[1], Vesna Jelic[1], Hermann-Josef Gertz[2], Agneta Nordberg[1], Per Julin[1], Lars-Olof Wahlund[1]

[1]Karolinska Institutet, Neurotec, Division of Geriatric Medicine, Huddinge University Hospital, Sweden; [2]Department of Psychiatry, University of Leipzig, Germany

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Henrike Wolf, Karolinska Institutet, Neurotec, Division of Geriatric Medicine, Huddinge Sjukhus, B84, S-14186 Huddinge, Sweden
e-mail: wolfh@medizin.uni-leipzig.de

The general idea of a border zone of impairment between age-related cognitive decline and clinically diagnosed dementia is not new, beginning with concepts such as 'vorzeitige Versagenzustände' ('premature failure conditions') (1) in the German psychiatric literature or Krals 'benign senescent forgetfulness' (2). Such ideas

*Throughout this paper, the designation mild cognitive impairment (MCI) is used as a generic term for all cognitive changes observed in ageing that are insufficient to meet dementia criteria. When reference is made to one of the specific concepts named MCI (such as MCI according to Zaudig, MCI according to Petersen), this is made clear in the text.

were first crystallized conceptually in 1982 as the mildly impaired stages of the Global Deterioration Scale (3), the Clinical Dementia Rating scale (4) and the category 'minimal dementia', derived from CAMDEX in 1986 (5).

The potential value of neuroimaging in the 'grey zone' between normal aging and dementia concerns two essential aspects. First, neuroimaging modalities provide the unique facility to detect age- and disease-related changes in the human brain and to monitor their progression *in vivo*. This is possible for both morphological (structural) and functional changes, and it may improve our understanding of the physiology of aging and the pathogenesis of dementia diseases. Second, neuroimaging mild cognitive in impairment (MCI) may facilitate early diagnoses of dementia disorders. Early diagnosis of dementia disorders with respect to neuroimaging techniques refers to the ability to diagnose the disease at a very early stage, preferably before symptoms are so clear that a diagnosis can be made, i.e. before a dementia syndrome is apparent. As Alzheimer's disease (AD) is the most common cause of progressive cognitive deficits in old age, and new treatment strategies are being developed for AD [for review, see Jelic & Winblad (6)], current research on MCI has particularly aimed toward the detection of preclinical AD. In contrast, subjects in preclinical stages of other dementia disorders have not yet been studied systematically.

Despite a growing interest of neuroimaging researchers in the field of aging and AD research, and despite fascinating methodological advances in recent years, clinical diagnostic criteria and investigation guidelines for dementia disorders do not usually include neuroimaging measures. A recent evidence-based consensus report recommended only the use of structural neuroimaging with either noncontrast computer tomography (CT) or magnetic resonance imaging (MRI) scan in the routine initial evaluation of patients with suspected dementia. Linear or volumetric MR or CT measurement strategies for the diagnosis of AD, as well as single photon emission tomography (SPECT) and/or positron emission tomography (PET) were not recommended for routine use because of insufficient data on validity (7).

In this paper, the current neuroimaging literature is reviewed with regard to characteristic findings in MCI. Particular attention is drawn to the possible value of neuroimaging modalities in the prediction and early diagnosis of AD.

Theoretical considerations. Is it possible to diagnose a degenerative disorder before the appearance of clinical symptoms?

In contrast to physiological age-related changes, AD is believed to be the most common cause of pathological and progressive cognitive impairment in old age. Therefore, it may be worthwhile to discuss the theoretical possibilities to diagnose AD in its early stages, i.e. before the onset of clear clinical symptoms.

Preconditions for an early detection of a degenerative disorder

The potential of a procedure to detect a dementia disorder is based on the following:

- the ability to detect a specific pathological feature of the disease; and/or
- the ability to detect a feature that is closely related to early symptoms of the disease.

The ability to detect a specific pathological feature of the disease – AD is defined by its histopathology. Pathological diagnostic criteria for AD are usually based on the findings of senile plaques (SP) and neurofibrillary tangles (NFT) in predefined age-adjusted quantities. Routine neuroimaging procedures to date are not able to visualize directly histopathological changes. However, the pathological features – in particular, the regional NFT count in the hippocampus – have been shown to correlate with atrophy measured by CT (8) and MRI (9), as well as with the regional metabolic rate of glucose (rMRG) as measured by PET (10). It can be theoretically assumed that metabolic and blood flow changes in the association areas, as seen in PET and SPECT, are associated with plaque pathology, although this hypothesis could not be proved by the one study looking at it (10). SP and NFT seem to accumulate years to decades before symptoms become apparent (11), which is another important precondition for our ability to detect the disease when still nonsymptomatic. Furthermore, the accumulation of NFT in particular seems to follow a predictable hierarchical pattern (11). Based on large autopsy series, Braak and Braak proposed a six-stage model of AD (11). According to this model, NFT first appear in the transentorhinal and entorhinal cortices and occasionally in the hippocampus (transentorhinal stages), followed by more severe NFT pathology in the transentorhinal cortex and hippocampus and occasional NFT in the neocortex in stages 3 and 4 (limbic stages). In stages 5 and 6, numerous tangles appear in all

neocortical association areas and also in the primary sensory areas (isocortical stages). Dementia is present with high certainty when NFT appear in the neocortical association cortices. SP show a less regular distribution but a certain preponderance in neocortical association areas has been noted (11). Based on this model, and on the aforementioned correlations between regional NFT count and atrophy in limbic structures, it can be expected that early changes in brain structure and function, in particular in limbic structures, can be detected by neuroimaging procedures in preclinical stages of AD.

The ability to detect a feature that is closely related to early symptoms of the disease – What causes the cognitive symptoms in AD? Despite being controversially discussed, it has been shown that NFT and possibly SP correlate with cognitive function (12). Figure 1 was derived from recently published findings of the Nun study (13). It shows the association between Braak stages, i.e. NFT severity (post-mortem) and cognitive state assessed only a few months before death. Despite a moderate overall correlation ($r = 0.59$), there is a notable variation of cognitive states beyond the Braak stages, particularly in entorhinal and limbic stages, which has also been found in other studies (14). A possible explanation is that clinical symptoms in AD are not directly caused by the deposition of amyloid or formation of tangles. It has been suggested that the loss of neurons (particularly synapses) is more directly related to cognitive decline than plaques and tangles (15). Atrophy of brain tissue can be caused by shrinkage or death of neurons, loss of axons and dendrites or shrinkage of fibre tracts. All these have been implicated in the atrophy of medial temporal lobe structures that occurs in AD. Neuron loss in AD predilection areas was reported to be as high as 87% in subregions of the hippocampus (16) and up to 60% in the entorhinal cortex (17), even in early disease stages. However, atrophy of the hippocampus may also occur in a number of other conditions, such as hippocampal sclerosis caused by ischaemic vascular damage. It is likely that the (nonspecific) functional and structural changes detected by neuroimaging are more closely correlated with cognitive symptoms than theoretically defined 'specific' disease markers. Furthermore, regional metabolic rates of glucose metabolism in PET have been shown to be particularly sensitive to loss of neuronal and synaptic function (18), which is likely to occur in the presence of AD, but which may also be caused by other conditions (Table 1).

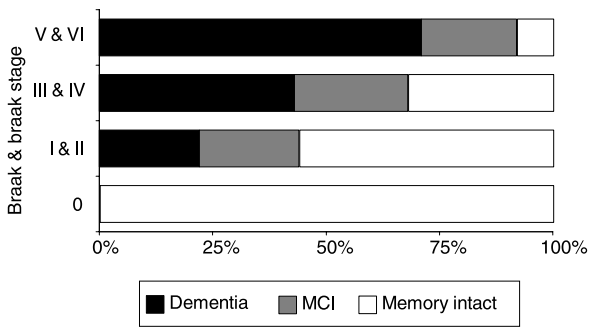

Figure 1. Correlations between neuropathological changes and cognitive state. Braak and Braak stages (NFT severity) and cognitive state in 130 cases from the Nun Study. Modified/ recalculated from (13). MCI in this figure is defined as evidence of isolated memory impairment or memory impairment plus one or more other cognitive domains in the absence of dementia. The correlation between Braak stage and six cognitive states in this study was $r = 0.59$. Only subjects that were free from cerebral infarcts and from other neuropathological conditions that could have caused cognitive decline were included in this sample.

Theoretical limitations for an early detection of neurodegenerative disorders

Strategies to detect 'specific' pathological features of AD *in vivo*, such as plaques and tangles, are currently under development and may become available as clinical methods in the near future (19).

However, some obvious limitations of this approach have to be discussed. Despite the definition of AD via histopathological changes, the specificity of plaques and tangles can be questioned. Plaques and tangles are not refined to AD, but may also occur in other degenerative disorders. Furthermore, plaques and tangles show a strong age-related increase in frequency (11). The delineation between age-related and disease-specific changes remains an unresolved problem in AD research. While often cited as the 'gold standard' of diagnosis, it has to be noted that pathological criteria themselves are rather quantitative than qualitative (12) (Table 2).

Figure 1 shows the overall validity, but also the limits of clinicopathological correlations in cases that were selected to represent 'pure' AD cases.

Table 1 Synopsis 1

Preconditions for an early detection of a degenerative disorder (example, AD)
• The disease has a long preclinical phase (11) and is distinct from physiological aging [?]
• The morphological and functional changes follow a characteristic pattern with a predictable chronological sequence (12)
• Neuroimaging findings adequately reflect pathologic morphological changes (9)

Table 2 Synopsis 2

Limitations for an early detection of a degenerative disorder (example, AD)
• Plaques and tangles are not specific for AD (152)
• Histopathological `markers' by which the disease is defined are quantitative rather than qualitative (11)
• Brain reserve mechanisms (20)
• Atypical cases/order violations from the supposed stageing models (14)
• Clinicopathological correlations become weaker with advancing age (152)

Why do some individuals with relatively little AD pathology succumb to clinical dementia, while others with advanced AD pathology avoid the clinical manifestation of dementia? Answers have to be sought in individual variations of reserve capacity against AD pathology. In addition to constitutional reserve markers, such as genetic factors, age and brain volume (20), co-occurrant pathological conditions, primarily cerebrovascular lesions (21), may alter the individual reserve capacity. Such factors have to be considered by neuroimaging studies in order to improve the accuracy of diagnostic and prognostic models. Furthermore, atypical forms of AD and order violations to the proposed staging model have been described on both a clinical and neuropathological level (14). These findings raise the further question of just how commonly patients with AD might have atypical presentations with prominent early deficits other than episodic memory (22). Awareness of such atypical presentations in AD is certainly needed to identify the complete spectrum of potentially treatable cases.

Review of the literature

Methods

This section is a review of neuroimaging studies in MCI that were found through a Medline search and by systematically checking through the bibliographies of relevant articles published in English. The major criterion for the inclusion was that the main focus of the study was on MCI. All concepts that are discussed by Palmer et al. in this Supplement (23) were considered as MCI. In addition, studies that defined MCI as subjective memory complaints without evidence for dementia in clinic-based settings were also considered. Studies that included 'at risk' subjects merely on the ground of theoretical considerations (such as background of a positive family history for AD, ApoE E4 carriers, etc.) were not considered. All neuroimaging techniques were included, but the focus is on the most widely available imaging techniques, i.e. structural MRI and CT, SPECT, PET and electroencephalogram (EEG). In addition, significant publications concerning the theoretical background of neuroimaging findings in MCI, primarily studies focusing on early changes in Alzheimer's disease and other dementia disorders, have also been used in this review.

Results

A total of 52 neuroimaging studies comprising a total of 1504 subjects with MCI were identified as the core studies (published until October 2002). They assessed cross-sectional characteristics of MCI in comparison with normal controls (33 studies) and/or studied progression of cognitive symptoms in nondemented subjects, largely defined as MCI, longitudinally (25 studies). Eight studies were considered as both cross-sectional and longitudinal study. In two instances, study populations and methods from two studies originating from the same centre overlapped completely. In these cases, only one study was considered. Considerable overlap ($>50\%$) was present between study populations in five publications from two different centres (24–28). Partial overlap between study populations was known for further five publications and may be suspected for a number of publications originating from the same research groups. Hence, the total number of studied subjects with MCI in neuroimaging studies rather overestimates the true figures.

Cross-sectional studies focusing on MCI in comparison with normal controls are summarized in Tables 3 and 4. Longitudinal studies in MCI subjects and their main results are listed in Table 5.

Study samples, designs and research focus

Study samples – The diagnostic criteria used for MCI in the core studies are listed in Tables 3–5. The majority of studies was based on memory clinic settings and used clinical staging procedures such as the Global Deterioration Scale (GDS) (3) or Clinical Dementia Rating (CDR) scale (4). Eight studies used the related concept of (amnestic) MCI (29). Very few studies defined their subjects primarily via statistical approaches, based on recommended cut-offs on neuropsychological tests, as for age-associated memory impairment (AAMI) or age-associated cognitive decline (AACD). In many of the studies, subjects were highly selected with regard to fulfilling criteria for 'primary degenerative MCI' (30).

There was a striking inhomogeneity with regard to demographic characteristics, in particular age, both within studies (not shown) and

Table 3 Structural volumetric studies

Study	N MCI	MCI criteria	Setting	Mean MMSE	Mean age	EC/PHG	Am	Hc	TL	VV	ECSF	BV	Other	Correct classification
Very mild AD														
Krasuski et al. (57)	21 NC, 13 AD	MMSE >20, AD	Research/ memory clinic	23.7	71	(ant PHG) −13% −23%	−39% −26%	−22% −15%	N/A	N/A	N/A	N/A		95% controls, 85% of VMAD
Jack et al. (133)	126 NC, 36 AD	CDR 0.5 (early AD)	Memory clinic	21.6	78	–	–	−1.75SD	N/A	N/A	N/A	N/A		Sens 77.8%/ at fixed Spec of 80%
Laakso et al. (50)	16 NC, 32 AD	'Early AD'	Memory clinic	22.8	69	N/A	-18^{NS} -14^{NS}	−38%	N/A	N/A	N/A	N/A	Right frontal lobe $-13\%^{NS}$	
Mizuno et al. (58)	27 NC, 15 AD	CDR 0.5 (early AD)	Memory clinic	23.2	68	(ant PHG) 11% (ns)	−20%	−14%	N/A	N/A	N/A	N/A		(§)
MCI														
Structural imaging														
Convit et al. (46, 143)	27 NC, 22 MCI	GDS 3	Memory clinic	28.3	74	(PHG) $-5\%^{NS}$	N/A	−14%	–	N/A	N/A	–		73.4% 81.5 NC, 63.6% MCI
De Santi et al. (37)	11 NC, 15 MCI	GDS 3	Memory clinic	29.1	75	(ant PHG) $-4.7\%^{NS}$	N/A	−15%	–	N/A	N/A	N/A	Combined study/see PET studies	73% (Hc)
Visser et al. (31)	18 NC, 20 MCI	CAMDEX, minimal dementia	Population based	22.6	79	(PHG) $-4.6\%^{NS}$	N/A	$-1\%^{NS}$	-2.0^{NS}	N/A	N/A	N/A		
Wolf et al. (54)	17 NC, 12 MCI	CDR 0.5, no dementia (ICD-10/DSM IV)	Population based	25.7	78	N/A	N/A	−14L/ −11%R	–	–	N/A	–		79.3% (Hc) 82.4 NC, 75.0 MCI
Hensel et al. (78)	33 NC, 27 MCI	CDR 0.5, no dementia (ICD-10, DSM IV)	Population/ memory clinic	26	79	N/A	N/A	N/A	N/A	N/A	N/A	N/A	CC $(-5\%^{NS})$	Sign. 10% callosal reduction in CDR 1, low classification accuracy based on CC (42%)
Dickerson et al. (47)	31 NC, 28 MCI	Cognitive complaints, no dementia	Memory clinic	27.0	69	−22L/ −17%R	N/A	−7%L −9%R	N/A	N/A	N/A	N/A		69% (EC) (§)
Bottino et al. (45)	20 NC, 21 MCI	Cognitive complaints for at least 6 months, no psychiatric diagnosis, no functional impairment	Memory clinic	26.5	67	−14L/ $-9.1\%^{NS}$R	-15L/ $-12\%^{NS}$R	−10.5L/ $-8\%^{NS}$R	N/A	N/A	N/A	N/A		
Xu et al. (55)	30 NC, 30 MCI	MCI acc. to Petersen	Memory clinic	25.7	78	−21%	N/A	−12%	N/A	N/A	N/A	N/A		Sens 63% (Hc), 57% (EC) with fixed Spec of 80%
Killiany et al. (24)	24 NC, 60 MCI	CDR 0.5 (stable over 3 years)	Conven	29.1	72	−32%	N/A	N/A	−10%	–	–	N/A	Post cingulate	85% correct based on EC

Killiany et al. (25)	28 NC, 73 MCI	CDR 0.5 (stable over 3 years)	Conven	29.2	72	−30%	N/A	+7%^{NS}	N/A	N/A	N/A	N/A		83% correct based on EC
Du et al. (48)	36 NC, 36 MCI	Objective CI, not demented (DSM IV)	Research/ memory clinic	25.8	75	−13%	N/A	−11%		N/A	N/A	N/A	Cortical grey matter	83% EC 86% Hc
Parnetti et al. (38)	6 NC, 6 MCI	AAMI	Memory clinic	>26	69–84		N/A	−29%	N/A	N/A	N/A	N/A		See also H MRS and SPECT studies
Soininen et al. (52)	16 NC, 16 AAMI	AAMI	Population based	28	68	N/A	–	–	N/A	N/A	N/A	N/A		Decreased Hc asymmetry in AAMI
Förstl et al. (53)	53 NC, 32 AAMI	AAMI modified (−1SD compared with age-matched controls)	Memory clinic/ conven	27.3	67	N	N/A	–	N/A	–	NA	–		
Laakso et al. (144)	43 NC, 43 AAMI	AAMI	Population based	28	70	N/A	N/A	–	N/A	N/A	N/A	N/A		
De Carli et al. (81)	369 NC 37 MCI	Lower 10th percentile (=1.4SD or below) on CVLT	Cohort study of male twins (NHLBI twin study)	–	73.5	N/A	N/A	N/A	N/A	N/A	N/A	N/A	White matter hyperintensity volume (WMHV)	2.2-fold increase as compared with subjects without MCI in the same cohort, ApoE and WMHV were associated with significantly increased risk for MCI
Scheltens et al. (118)	19 NC, 22 MCI	'Minimally demented' acc. to CAMDEX HMPAO-SPECT	Population based (AMSTEL)	CAMCOG 70	78.5			MTA					Combined study/ see SPECT studies	
PET (comparison study)														
De Santi et al. (37)	11 NC, 15 MCI	GDS 3 FDG PET	Memory clinic	29.1	75	−17% (ant PHG); −8.2% (post PHG)	N/A	−11%	–	N/A	N/A	N/A		85% (anterior PHG rMRG)

Key to Table 3: Review of neuroimaging studies that assessed cross-sectional differences between subjects with mild cognitive impairment and cognitively normal controls. Four studies using patients with very mild AD are shown for comparison. Some studies included dementia groups in addition to MCI and normal controls, but these groups have been omitted from this table. Classification rates are based on the percentage of subjects correctly assigned to normal controls and MCI. (§) Calculated from results reported in the manuscript.

Abbreviations: NC, normal controls; AD, patients with Alzheimer's disease; MCI, mild cognitive impairment; N/A, not assessed; EC, entorhinal cortex; PHG, parahippocampal gyrus; Am, amygdala; Hc, hippocampus; TL, (nonmedial) temporal lobe and substructures; VV, ventricular volume; ECSF, external CSF spaces; BV, brain volume; CBF, cerebral blood flow; HMRS, proton magnetic resonance spectroscopy; NAA, N-acetyl aspartate; MTA, medial temporal lobe atrophy; visual severitiy rating; CDR, clinical dementia rating; GDS, global deterioration scale; AAMI, age-associated memory impairment; ARCD, age-related cognitive decline. Conven, Convenience; Sens, Sensitivity; Spec, Specificity; percentage differences refer to normal control subjects in the same study; all differences were significant unless otherwise stated. ^{NS} nonsignificant.

Table 4 Functional (SPECT, PET, EEG) and new imaging techniques

Study	Method	Subjects	Definition of MCI	Setting	Mean MMSE	Mean age	Main result
*PET/*SPECT							
De Santi et al. (37)	FDG PET/volumetric MRI, see structural imaging	11 NC, 15 MCI	GDS 3	Memory clinic	29.1	75	Significant rCMRG reduction in anterior and posterior PHG, and hippocampus, most marked in hippocampus
Celsis et al. (117)	CBF based on Xenon 133	18 NC, 24 MCI	ARCD (DSM IV)	Neurology clinic	27.5	62	Mean CBF (−9%), parietotemporal CBF (−2%)
Scheltens et al. (118)	HMPAO SPECT, ROI to cerebellum ratios (frontal, temporoparietal, parietal to cerebellum)	19 NC, 22 MCI	'Minimally demented' acc. to CAMDEX	Population based (AMSTEL)	CAMCOG 70	78.5	Three SPECT ratios did not differ between NC and MCI, but visual assessment of medial temporal lobe atrophy did differ
Nordberg et al. (119)	FDG PET	20 NC, 27 MCI	Objective cognitive impairment in one or more areas, no dementia/AD (DSM IV/NINCDS)	Memory clinic	27	62	RCMRG: temporoparietal association cortex ($-6\%^{NS}$), asymmetry index ($-22\%^{NS}$)
Parnetti et al. (38)	HMPAO SPECT	6 NC, 6 MCI	AAMI	Memory clinic	>26	69–84	Perfusional pattern in three ROIs (frontal, temporoparietal, occipital) in AAMI was intermediate between 6 NC and 6 AD cases, but not significantly so
Kogure et al. (32)	(99 m)Tc-ethyl cysteinate dimer SPECT, SPM	45 NC, 32 MCI	Initially CDR 0.5, MMSE >24, fulfilled 'probable AD' criteria at follow-up	Memory clinic	26.2	72	Adjusted CBF at baseline was significantly decreased bilaterally in posterior cingulate and precunei in MCI as compared with NC
EEG							
Jelic et al. (107)	QEEG, power and coherence	16 NC, 19 MCI	Objective memory impairment	Memory clinic	27.4	62	No significant differences in alpha, theta power and coherence
Huang et al. (110)	QEEG, amplitude and source localization	24 NC, 31 MCI	Objective cognitive impairment in one or more areas, no dementia/AD (DSM IV/NINCDS)	Memory clinic/ research	26.7	63	No significant baseline differences between MCI and NC, but high predictive value of anterior shift of alpha activity (see longitudinal studies)
Grunwald et al. (112)	QEEG power	20 NC, 16 MCI	CDR 0.5 (two fulfilled criteria for NINCDS 'possible AD')	Population based	26.8	79	No significant differences in theta power under rest conditions, decrease in theta power under haptic tasks in MCI (and dementia), but not in controls, over postfrontal regions, significant differences between NC and MCI under haptic tasks over occipital regions
Zappoli et al. (108)	QEEG power	10 NC, 12 MCI	Clinical presumption of an early stage of a degenerative disorder but DSM-III-R criteria were not fulfilled	Memory clinic	N/A	59	Significantly lower alpha/theta ratios over parietal leads in MCI, signifcantly lower peak frequency over central leads, no significant differnes between NC and controls in alpha, beta, and theta power
Frodl et al. (111)	Event-related P300 potentials	26 NC, 26 MCI	MCI acc. to Petersen	Memory clinic/ research	27.5	66	No significant differences between MCI and NC

Olichney et al. (113)	ERP, word repetition paradigm	14 NC, 14 MCI	CDR 0.5, no dementia (mild impairment on neuropsychological tests, predominantly memory deficits, no functional impairment)	Memory clinic / research	27	75	Slower latency of N400, reduced repetition effect
Other techniques							
Parnetti et al. (38)	Proton magnetic spectrosopy (H MRS), HMPAO SPECT, structural MRI	6 NC, 6 MCI	AAMI	Memory clinic	>26	69–84	Increase in Inositol in 6 MCI (similar to AD) but MCI did not differ significantly from controls. MCI in this study was defined as the rather mild AAMI but subjects had significant hippocampal atrophy (comparable with mild–moderate AD in this and other studies)
Kantarci et al. (145)	H MRS	63 NC, 21 MCI	MCI acc. to Petersen	Memory clinic / research	26.6	83	Myo-inisitol / Creatine (Mi / Cr) ratio in posterior cingulate differed significantly between 19 MCI subjects and 57 NC. Mi / Cr ratio changes may be the first detectable change on MRS in AD
Catani et al. (146)	H MRS	11 NC, 11 MCI	CDR 0.5, no functional decline	Research	27	78	Significant decrease in left N-acetylaspartat (NAA) / Cr ratio in MCI in paratrigonal white matter. This suggests an altered white matter biochemical pattern in MCI (similar to AD)
Kabani et al. (68)	MTI	15 NC, 12 MCI	AACD	Memory clinic / research	N / A	77	Significantly decreased MT ratios in temporal lobe in MCI, nonsignificant decrease in temporal lobe volume, nonsignificantly lower MT ratios in frontal, parietal and occipital lobe
Van der Flier et al. (66, 67)	MTI	28 NC, 13 MCI	MCI acc. to Petersen	Memory clinic / research	26	74	Peak heights of MTI histogramms were significantly reduced in MCI (and did not differ from AD) (66). MTI measures of the whole brain, as well as of frontal and temporal lobes, correlated with the degree of global cognitive impairment (67)
Kantarci et al. (147)	Regional diffusivity of water based on MRI	55 NC, 18 MCI	MCI acc. to Petersen	Memory clinic / research	26.8	81	Hippocampal apparant diffusion coefficient (ADC) was significantly different between control subjects and MCI patients. Elevation in hippocampal ADC suggests ultrastructural changes in MCI (similar to AD)
Chételat et al. (59)	Unbiased VBM	22 NC, 22 MCI	Objective verbal and / or visual memory impairment (<1.5SD of norm)	Neurological clinic	27.3	71	Most pronounced grey matter loss occured bilaterally in medial temporal lobe (Hc, PHG, Am, periamygdaloid cortex), extending into the middle temporal gyrus and anterior cingulate, less pronounced grey matter loss was observed in the posterior cingulate, hypothalamic and thalamic regions, right temporoparietal, lingual-fusiform areas, and in the caudate nucleus

Key to Table 4: Review of neuroimaging studies that assessed cross-sectional differences between subjects with mild cognitive impairment and cognitively normal controls. Four studies using patients with very mild AD are shown for comparison. Some studies included dementia groups in addition to MCI and normal controls, but these groups have been omitted from this table. Classification rates are based on the percentage of subjects correctly assigned to normal controls and MCI.

Abbreviations: NC, normal controls; AD, patients with Alzheimer's disease; MCI, mild cognitive impairment; MTI, magnetic transfer imaging; N / A, not assessed; EC, entorhinal cortex; PHG, parahippocampal gyrus; Am, amygdala; Hc, hippocampus; TL, (nonmedial) temporal lobe and substructures; VV, ventricular volume; ECSF, external CSF spaces; BV, brain volume; CBF, cerebral blood flow; HMRS, proton magnetic resonance spectroscopy; NAA, N-acetyl aspartate; MTA, medial temporal lobe atrophy; visual severitiy rating; CDR, clinical dementia rating; GDS, global deterioration scale; AAMI, age-associated memory impairment; ARCD, age-related cognitive decline; VBM, Voxel-based morphometry. Conven, Convenience; Sens, Sensitivity; Spec, Specificity; percentage differences refer to normal control subjects in the same study; all differences were significant unless otherwise stated; ^{NS} nonsignificant.

Table 5 Review of longitudinal neuroimaging studies of MCI (broadly defined as CIND)

Source	MCI definition	Setting	*N*	*N* (%) with P MCI	FU	Age	Baseline MMSE	Possible predictors of PMCI	Classific. rate	Value in addition to NP	Additional findings/remarks
MRI/CT											
1. Kaye et al. (35)	Initially nondemented/ no cognitive deficits Initially nondemented	OBAS	30	12 (40)	3.5	90	26.9	Age, Hc, temporal volume, time-dependent temporal volume loss, but not PHG, predicted decline	N/A	N/A	No further HcA occurred during follow-up
2. Marquis et al. (34)	Initially nondemented Initially MCI ('optimally aged')	OBAS	108	38 (35) [c]	7	83	28.1	'Persistent cognitive impairment' was independently predicted by logical memory test performance, hippocampal volume, and time to walk 30 ft	N/A		ApoE status and depression did not enter the model significantly. Brain volumes differed significantly at basline between decliners and nondecliners
3. De Leon et al. (44)	GDS 2 and 3	Memory clinic/ research	86	25 (29)	4			Presence of perihippocampal cerebrospinal fluid predicted dementia	91% Sens/ 89% Spec		
4. Visser et al. (31)	CAMDEX, minimal dementia	Population based (AMSTEL)	20	9 (45)	3	79	22.6	Memory score, PHG, and MTA [Hc] predicted dementia	96%	+	
5. Visser et al. (125)	GDS 2 and 3	Memory clinic	31	10 (32)	1.9	65	27.7	Age, delayed recall, Hc [MTA, PHG] predicted dementia	100%	+	MTA score (75% Sens, 87% Spec) was a better predictor of outcome than PHG (56% Sens, 87% Spec)
6. Jack et al. (148)	MCI acc. to Petersen	Memory clinic/ research	80	27 (34)	2.8	78/80	S 26.7/ P 25.3	Hippocampal atrophy and neuropsychological measures were independent risk factors	N/A		RR 0.69/hippocampal w score. Carriers of the ApoE 4 allele were more likely to be demented at follow-up
7. Convit et al. (126)	GDS 3	Memory clinic/ research	20	12 (60) +2 NC	3.2	75	27.6	Hc, fusiform gyrus, middle inferior temporal gyrus, but not PHG, predicted dementia	92.8%	N/A	Hc alone was a weak predictor (57% correctly classified)
8. Dickerson et al. (47)	Memory complaint, nondemented	Memory clinic	23	12 (52)	3.3 (1–6.5)	69	27.0	EC, but not Hc, predicted dementia	74% [b]	N/A	
9. Killiany et al. (24)	CDR 0.5, no AD acc. to NINCDS	Research/ conven.	79	19 (24)	3	72	29.1	Superior temporal sulcus banks, anterior cingulate, but not EC [suprasellar cisterns, third ventricle] differed between SMCI and PMCI	75%	N/A	ApoE status did not improve the discrimination. Tests of memory and executive functions discriminated 80% of PMCI from SMCI in a similar sample from the same setting (149)
10. Killiany et al. (25)	CDR 0.5, no AD acc. to NINCDS	Research/ conven.	94	21 (22)	3	72	S 29.1/ P 28.7	Neither Hc nor EC discriminated SMCI from PMCI. Both HcA and ECA increased the risk for PMCI	–	N/A	Subjects with the greatest atrophy of the EC were 1.6 times, subjects with the greatest HcA 1.5 times more likely to progress to AD

11. Fischl et al. (26)	CDR 0.5, no AD acc. to NINCDS	Research/ conven.	92	21 (23)	3	72	S 29.1/ P 28.7	Ventricles, right Hc, bilateral amygdala, left thalamus (BLD) differed between SMCI and PMCI	N/A	N/A	EC not assessed
12. Wolf et al. (28)	MCI according to Zaudig (150) (quantitative, SIDAM)	Memory clinic/ research	27	8 (30)	2.6	72	26	WML score, medial temporal lobe thickness (neuropsychology) differed between NC and MCI	92% [a)]	+[a)]	WML score and medial temporal lobe thickness were independent predictors of dementia
PET/SPECT											
1. De Leon et al. (36)	Initially nonimpaired GDS 1 and 2 outcome: progression to GDS 3	Population/ conven.	25	13/48 (27)	3	69	29.3	Metabolic reductions in the entorhinal cortex at baseline predicted conversion from NC to MCI in 12 subjects with decline compared with 13 age- and education matched controls without decline	84% (83% decliners, 84% nondecliners)		Among those who declined, ApoE E4 carriers showed marked longitudinal temporal neocortex reductions, but ApoE carrier status did not influence longitudinal neuropsychological chances
SMCI/PMCI											
2. Celsis et al. (117)	ARCD (DSM IV)	Memory clinic	18	5 (28)	2	62	27.5	Temporoparietal CBF reduction differed between SMCI and PMCI			
3. Wolf et al. (27)	MCI acc. to Zaudig (quantitative, SIDAM)	Memory clinic/ research	41	8 (20)	2.6	65	26	Left medial temporal lobe thickness (CT) but not semiquantitative SPECT differed between SMCI and PMCI	N/A	+ (CT)	
4. Johnson et al. (94)	CDR 0.5, no dementia (NINCDS)	Memory clinic/ research	45	18 (40)	2	72	Not reported	Hippocampal amygdaloid complex, posterior cingulate, anterior thalamus, anterior cingulate	77.8% of P / 81.5% of S[b)]	N/A	HMPAO SPECT, singular value composition. ApoE status did not improve the predictive model
5. Arnaiz et al. (102)	Objective cognitive impairment in one or more areas, no dementia/ AD (DSM IV/NINCDS)	Memory clinic/ research	20	9 (45)	3	60/ 65	S 27.2/ P 26.7	Block design and left temporoparietal rCMRG predicted decline to dementia	90%	+	
6. Huang et al. (96)	As in (102)	Memory clinic	54	17 (32)	2.4	60/ 64	S 27.0/ P 26.2/	Posterior cingulate predicted decline to dementia	76% (area under ROC curve)	N/A	
7. McKelvey et al. (120)	AACD (151)/ CDR 0.5 not demented (NINCDS)	Memory clinic	36	18 (50)	2.9	71	26.9 (3)	No difference between SMCI and PMCI in baseline SPECT patterns	–		No correlation of SPECT measures with cognitive decline
8. Okamura et al. (95)	MCI acc. to Petersen	Memory clinic	24	17 (74)	3.1	72	S 26.6/ P 25.6	Ratio of CSF tau/CBF in posterior cingulate predicted decline to dementia	Sens 88.5%/ Spec 90%	N/A	
PMC1/NC											
9. Minoshima et al. (33)	CDR 0.5, MMSE >24, later progressed to 'probable AD'/average 23 months compared with 23 NC	Memory clinic/ research	8	–	1.9	69	25	Marked reduction (21–22%) in rCMRG posterior cingulate cortex and cinguloparietal transition area as compared with NC			
10. Kogure et al. (32)	Initially CDR 0.5, MMSE >24, fulfilled 'probable AD' criteria at follow-up	Memory clinic, 45 NC/32 MCI	32	–	1.3	72	26.2	Adjusted CBF at baseline was significantly decreased bilaterally in posterior cingulate and precunei in MCI as compared with NC			

Table 5 (*Continued*)

Source	MCI definition	Setting	*N*	*N* (%) with P MCI	FU	Age	Baseline MMSE	Possible predictors of PMCI	Classific. rate	Value in addition to NP	Additional findings/remarks
EEG											
11. Jelic et al. (115)	Objective cognitive impairment in one or more areas, no dementia/AD(DSM IV/NINCDS)	Memory clinic/research	27	14 (51)	1.7	58/58	S 28.3/P 26.9	Increased theta/decreased alpha power, not MMSE, predicted decline to dementia	85%	+ (MMSE)	
12. Huang et al. (110)	As in (102)	Memory clinic/research	31	14 (45)	2.1	61	26.7	Anterior shift of alpha activity predicted decline to dementia	77%	N/A	
13. Elmståhl et al. (114)	Healthy, cognitively elderly women without objective cognitive decline based on neuropsychological test results	Population/conven.	31	6 (19%)	5	82		Low beta power on EEG, and higher orthostatic blood pressure reaction at baseline were associated with cognitive impairment during follow-up			Decliners ('cases') were defined as MMSE <27 at follow-up, and objective signs of impairment in memory and at least one of the following: abstract thinking, aphasia, apraxia, agnosia, personality changes, behaviour
14. Olichney et al. (113)	CDR 0.5, no dementia (mild impairment on neuropsychological tests, predominantly memory deficits, no functional impairment)	Memory clinic	14	7/14 (50%)	2	75	27	Significantly reduced LPC repetition effect distinguished PMCI from SMCI in a word repitition ERP paradigm	85%	+ (MMSE)	

Key to Table 5: Classification rates refer to the percentage of correctly identified subjects with either progressive (PMCI) or stable (SMCI) MCI at follow-up. If SMCI were classified as normal controls and PMCI were classified as AD by a discriminant function, they were regarded to be correctly classified. The value in addition to neuropsychology is regarded as positive when neuroimaging measures alone or in combination with neuropsychological tests achieved a higher overall accuracy of prediction than neuropsychological tests alone. Many of these studies comprised also control subjects and patient groups with AD, however, only the number of subjects with MCI is stated.
[a)] Calculated from the original data set. [b)] Calculated from results reported in the manuscript. [c)] Persistent cognitive impairment' defined as development of permanent CDR 0.5 during follow-up interval of 7 years. ,
Oregon Brain Aging Study; Conven., Convenience; PMCI, progressive MCI; Hc, hippocampal volume; MTA, visually assessed medial temporal lobe atrophy; PHG, parahippocampal gyrus; EC, entorhinal cortex; Sens, Sensitivity; Spec, Specificity; NP, neuropsychology; BLD, baseline difference.

between studies. The mean Mini-Mental State Examination (MMSE) score in MCI groups averaged 26–27, and ranged between 22.6 in an elderly population-based sample with minimal dementia (31) and 29.2 in a population-based convenience sample.

Beyond the gross distinction of longitudinal and cross-sectional study designs, a number of differences were found.

Cross-sectional designs, comparison between MCI and normal controls – (1) The majority of cross-sectional studies compared MCI and normal controls, and based the MCI 'diagnosis' on a single examination. (2) Two studies defined MCI longitudinally as subjects remaining stable MCI over time (24, 25). (3) Two studies defined MCI retrospectively as patients who presented initially with mild cognitive deficits which later progressed to dementia, i.e. MCI was confirmed to be 'preclinical AD' (32, 33).

Longitudinal study designs – (1) The majority of studies enrolled MCI subjects at baseline and then compared MCI subjects with progressive cognitive deficits (PMCI) (defined as progression to dementia/AD/other disorder) to MCI subjects remaining stable (SMCI). (2) Some studies used only PMCI subjects from their baseline group and compared them with normal controls (32, 33). (3) Three studies used originally nondemented, and/or cognitively normal subjects and followed them longitudinally until cognitive decline occurred (defined as GDS 3 or higher, or CDR 0.5 or higher) (34–36). Design (1) should be considered to be clinically most useful design. Design (3) is interesting with regard to the early pathogenesis of cognitive decline.

Study aims – Subjects with MCI in most studies were selected to represent cases in which cognitive deficits are most likely to be caused by AD.

Consequently, the studies have been largely focused on the detection of the functional and morphological epiphenomena of the degenerative process in subjects that were highly selected with regard to fulfilling criteria for 'primary degenerative MCI' (30). Such an approach does not fully reflect the everyday clinical situation. However, with regard to the contribution of neuroimaging to an early diagnosis of AD, such clinical studies allow estimations of the sensitivity and specificity of neuroimaging methods as well as comparison with other diagnostic tools, for example clinical assessments and screening tests, neuropsychology, biological markers, and other neuroimaging methods.

Neuroimaging strategies used in MCI

The majority of studies used structural neuroimaging, mainly based on quantitative volumetric MRI with region-of-interest (ROI) analyses (17 cross-sectional, 12 longitudinal studies). Sixteen studies used PET or SPECT (10 longitudinal studies). Four of the 16 studies combined structural and functional facilities (27, 37–39). Nine EEG (including ERP) studies were identified (four longitudinal). Seven studies used new methods, such as proton magnetic resonance spectrocopy (^{1}H MRS) (three studies), magnetization transfer imaging (MTI) (two studies), unbiased voxel-based morphometry, and assessment of regional diffusivity of water on MRI based on MRI. We did not find published articles that used functional MRI explicitly in MCI patients, but promising work seems to be under way (40, 41).

Synopses 3 and 4 (Tables 6 and 7) give a brief overview of the methods used in MCI neuroimaging studies and refer to further texts regarding the techniques.

Neuroimaging findings in MCI

The core studies focusing on MCI that were identified are listed and their designs and results briefly summarized in Tables 3–5.

Discussion

Structural neuroimaging findings in early AD and MCI

Theoretically, any neuroimaging parameter that has been shown to differ between demented and normal control subjects is of potential value for the characterization of MCI. On the basis of Braak-and-Braak staging, structural and functional changes in preclinical AD can be expected in the entorhinal cortex, the hippocampus, and other limbic structures, followed by changes in neocortical association areas. Since the first pathological changes concern the projection neurons in the parahippocampal gyrus (11), early functional and possibly structural changes may also occur in the association areas to which these neurons project (42).

Medial temporal lobe – The broad, initial recognition of the superior value of hippocampal formation atrophy to detect AD (43) and to predict dementia in nondemented subjects (44) was based on studies using relatively simple assessments from CT studies. At the background of the selective vulnerability of the limbic system in AD and the

Table 6 Synopsis 3

Modality	Characterization, advantages, disadvantages
Structural MRI (153)	Routine clinical tool (exclusionary approach), good availability, highest spatial resolution of all imaging facilities <1 mm, high potential as research tool, numerous other MR modifications, including structural sequences to focus on tissue characteristics, functional MRI, MR spectroscopy, relatively high costs, noninvasive
CT (153)	Routine clinical tool (exclusionary approach), widely available, spatial resolution 1–5 mm, low costs, limited grey–white matter contrast, noninvasive
SPECT (154)	Promising research tool with a wide spectrum of possible applications, widely available, spatial resolution about 1 cm, low temporal resolution, requires i.v. application of radioactive tracer substance
PET (119)	As SPECT, even wider spectrum of applications, higher spatial and temporal resolution than SPECT, expensive, requires radioactive tracer
EEG (106)	Routine clinical and research tool, high temporal, low spatial resolution, widely available, cheap, noninvasive

Table 7 Synopsis 4

Commonly used assessment techniques in structural neuroimaging
• volumetric/planimetric (quantitative): manual outlining, automated segmentation of brain structures
• simple linear measurements
• qualitative/semiquantative visual assessments (rating scales for medial temporal lobe atrophy and white matter lesions)

Comment: The diagnostic value of simple linear measurements/rating scales may be comparable with more accurate, but extremely time-consuming manual segmentation strategies [for review, see (153)].

early disturbance of memory functions in AD, structural neuroimaging studies in MCI have been largely focused on limbic structures, primarily the hippocampus, the entorhinal cortex, and amygdala.

Hippocampal and entorhinal cortex atrophy are the most consistent cross-sectional findings in MCI (Tables 3 and 4). Although the study samples differed with regard to image protocols, demographic measures, MCI definitions and type of setting, studies based on hippocampal volumetry reported strikingly homogeneous findings: the hippocampal volume reduction in MCI subjects ranged between 9% and 15% relative to normal controls (37, 45–48) in the majority of studies (Tables 3 and 4). Only two neuroimaging studies (Tables 3 and 4) failed to find significant cross-sectional group differences between MCI and normal controls (25, 31). In comparison, in questionably and mildly demented subjects, who were presumed to have early AD, hippocampal volume reductions ranged between 18% (49) and 38% (50), with one exception of a study comprising a very small sample (38). In contrast, subjects with AAMI, which has been defined as a mild and supposedly benign memory impairment, did not demonstrate a significant hippocampal volume reduction when compared with normal controls (51–53). Two population-based studies, which involved rather unselected community dwelling subjects with a cognitive continuum, concluded that hippocampal volumetry may be useful in detecting elderly subjects with MCI (54) and in predicting the development of dementia (31).

Regarding the entorhinal cortex, there is a greater variation of findings. Studies measuring the anterior parahippocampal gyrus including white matter usually did not find significant differences between controls and MCI. Studies measuring the entorhinal cortex directly reported significant reductions of between 13% and 32% (25, 47, 48, 55) (Tables 3 and 4). Despite the theoretical rationale for the superiority of entorhinal measurements to distinguish MCI from normal controls, this could not be confirmed by two studies out of four studies which combined entorhinal and hippocampal measurements (48, 55). The visualization of entorhinal cortex on MRI is difficult and often obscured by anatomic ambiguity and imaging artefact due to magnetic susceptibility effects at the interface between petrous bone and the base of the brain (55). It has been suggested that because of these methodological difficulties, hippocampal volumetry might be preferable (55, 56).

While results in patients with mild AD (57, 58) and neuropathological findings (12) indicate an early involvement of the amygdala in AD, this structure has rarely been examined as a separate structure in subjects with MCI. One recent report suggested a possible prognostic value of the amygdala in MCI (26). In two studies using subjects with AAMI, no significant amygdaloid volume reduction compared with normal controls were found. In contrast, two out of four studies in patients with very mild AD revealed significant reductions, which ranged between 20 and 39% (57, 58). Of the two negative studies, one reported a (nonsignificant) mean reduction by −14% to −18% for left and right amygdala, respectively. Similar to the situation regarding the entorhinal cortex, considerable methodological difficulties might contribute to this situation.

Early changes in AD beyond the medial temporal lobe – Despite being known as a part of the limbic system and essentially involved in memory, the cingulate cortex has only recently become a focus of structural neuroimaging studies in Alzheimer's disease and MCI. Two of the reviewed neuroimaging

studies in MCI, one using conventional ROI analyses, the other based on VBM, reported atrophy in the posterior cingulate in MCI (24, 59). The remaining studies basically did not look for it. This finding has support from recent studies in AD. Mainly based on unbiased voxel-based analyses, a number of very recent studies reported early structural changes in the *posterior cingulate* as well as in the adjacent *precuneus* in early AD (60, 61). Two studies found cingulate atrophy in presymptomatic mutation carriers with familial AD (62, 63). One MCI study found pronounced grey matter loss in temporoparietal areas in MCI (59). In mild AD, the parietal lobe (64) and the insular cortex (65) have been reported to be atrophied.

Some of the reviewed studies in MCI reported a rather unexpected global volume loss or global brain damage in MCI (48, 59, 66–68). These findings suggest more widespread brain tissue changes and atrophy in MCI than previously believed. However, the evidence is controversial (24, 34, 46, 48, 53, 54). Despite occasional reports of reduced grey matter or global brain volume (34, 48), the magnitude of these studies imply that global brain volume, white or grey matter atrophy is not usually pronounced in MCI (24, 46, 53, 54). However, studies suggesting more widespread brain atrophy are supported by recent findings in early AD (62, 65, 69). The controversy may be caused by a high variability of global brain atrophy in MCI. However, differences in global brain volumes between MCI and demented patients (24, 46, 48, 53, 54) have been reported quite consistently. Such findings suggest that the transition of MCI to dementia involves global brain atrophy. Some longitudinal studies (26, 34, 70) have supported this view and suggested a possible predictive value of global brain volume with regard to the further course of MCI. These findings would be in keeping with the notion that subjects with more widespread degenerative changes are more likely to progress to AD. However, they may also point towards nonspecific volume reserve effects. The latter has been implied by the finding of smaller intracranial and total brain volumes in subjects with AD and MCI as compared with controls (71), as well as by an association between total brain volume and subsequent cognitive decline in initially unimpaired elderly (34). However, the evidence for cerebral reserve effects in neuroimaging studies is still scarce. The additional predictive value of MRI measures representing more global atrophy and possibly volume reserve awaits further study in prospective studies.

As early as in Braak stage III, mild neurofibrillary changes of magnocellular forebrain nuclei, anterodorsal and reuniens nuclei of the thalamus, and the hypothalamic tuberomamillary nucleus may occur, while the basal portions of claustrum, putamen and accumbens nucleus begin to be affected in stage IV (13). The study of the histological substructures of the thalamus, basal ganglia and the nucleus basalis Meynert is not possible with currently used MRI protocols. However, volumetric differences between normal controls and early/mild AD have been demonstrated for the substantia innominata (72, 73), and the thalamus (26, 74), caudate nucleus (60, 65, 75) and putamen (62). Two of the reviewed MCI studies reported pronounced atrophy in thalamus and caudate nucleus (26, 59).

A very recent publication deserves special attention, because it introduced a new automated method of anatomical labelling of brain structures (26). Based on probabilistic information automatically estimated from a manually labelled training set, one of 37 different labels is assigned to each voxel. When the method was applied to the initial MR scans from 71 subjects with stable MCI (here defined as subjects with initial CDR 0.5 who remained in this category during 1–3-year follow-ups) and 21 subjects with progressive MCI (initial CDR 0.5, who converted to NINCDS probable AD), all ventricular substructures (third, fourth, lateral and inferior lateral ventricle), the right hippocampus, left and right amygdala, and the left thalamus differed between those two groups. Thus, this study is the first to provide direct evidence for a possible predictive value of the amygdala, the thalamus, and enlargement of the cerebral ventricles subjects with MCI.

Corpus callosum – The corpus callosum (CC) is the main intracerebral fiber connection. Age-related (76) and white matter lesion- (WML-) related (77) volume reductions of the CC have been reported, as well as significant CC atrophy in moderately to severely demented patients with AD. In AD, callosal atrophy has been discussed as a mechanism to cause a cortico–cortical disconnection syndrome that contributes to the severity of dementia. Little is known about how early such changes occur in the course of AD, and cases with MCI have not often been studied. In a cross-sectional study from our own centre (78), a nonsignificant 5% reduction in total callosal area was observed in 27 subjects with questionable dementia compared with normal subjects, and a significant reduction of 10% in 23 patients with mild dementia. The groups were matched with regard to age and the severity of

WMLs. All callosal measurements in questionable dementia were intermediate between controls and mild dementia, and no regionally pronounced atrophy was noticed in either questionable or mild dementia. The discrimination of normal controls, questionable cases and dementia based on CC measurements was poor. These findings are supported by a longitudinal study in which the CC size did not differ between incident AD cases (here defined as nondemented cases at baseline who developed cognitive decline or AD during follow-up) and normal controls (79). These findings suggest that, although a certain degree of CC atrophy seems to occur at the transition between normal aging and dementia, this does not seem to be an early event in AD. While it has been suggested that the CC may significantly contribute to the rate of cognitive decline in cases with established dementia, its predictive value in MCI subjects remains to be investigated.

WMLs – Cerebrovascular disease – first of all lacunar infarcts and ischaemic white matter lesions – and Alzheimer pathology are likely to co-occur in old age. There is evidence from postmortem studies that cerebrovascular disease can enhance the capacity of AD pathology, particularly in its earliest stages, to promote dementia (21). Furthermore, vascular risk factors in mid-life have been shown to be associated with a higher risk of late-life cognitive impairment and AD (80).

Two recent publications have suggested that WMLs on brain imaging are associated with an increased risk of MCI (81) and conversion to dementia in subjects with MCI (28). Further support for an association between WMLs and cognitive decline has been provided by large-scale longitudinal studies focusing on cardiovascular risk factors (82) and studies on old-age depression (83).

Functional neuroimaging findings in early AD and MCI

Three main sites have been described in PET and SPECT studies which seem to be affected early in AD: the temporoparietal association cortex (84–91), the posterior cingulate (32, 33, 92–96) and the hippocampal-amygdaloid complex (32, 37, 94, 97–99).

Temporoparietal association cortex – Through numerous studies, it has been well established that patients with AD show typical regional deficits in cortical metabolism and blood flow in posterior parietal and temporal cortices (100). Early PET studies (84, 85) reported increased hemispheric asymmetries in the association cortices in a longitudinal study of 11 mildly impaired patients with AD. These metabolic abnormalities usually preceded impairment of neocortically mediated functions, such as attention, abstract reasoning and visuospatial functions by 8–37 months. It was concluded that the reduction in blood flow and rCMRG in the association cortices seems to be already pronounced in early disease stages when the association cortices may be largely unaffected by neurofibrillary pathology. This is consistent with the functional disconnection hypothesis due to pathological changes in projection neurones of the entorhinal cortex (42).

Temporoparietal metabolic alterations have also been reported in young cognitively normal subjects who carry the ApoE4 epsilon4 allele, a well-established genetic susceptibility factor for AD (101), as well as years to decades before the expected disease onset in asymptomatic mutation carriers from pedigrees with familial forms of AD (FAD) (86–91). While the latter studies may add very valuable information to our knowledge about preclinical AD, the data regarding the influence of ApoE4 genotype leave open the possibility that some changes detected by SPECT and PET reflect features that are associated with inheritance of the ApoE4 genotype rather than being predictive of AD.

One recent study examined the predictive value of temporoparietal rCMRG in patients with MCI. This study suggests a predictive value of temporoparietal rCMRG in patients with MCI (102).

Posterior cingulate – For many years, the metabolic abnormality in AD in the posterior cingulate has rarely been studied and was only reported occasionally (92). Recent topographical analysis of PET images suggested that functional alterations in the posterior cingulate cortex may occur in patients with Alzheimer's disease. The reduction in rCMRG in the cingulate has been shown to precede the changes in temporoparietal areas (103) and to be already present in the preclinical phase of AD (33). These findings have been corroborated by a number of subsequent studies with SPECT (32, 93–96). The human cingulate seems to be essentially involved in memory processing (92) and visual–spatial functions (104).

Little can be said about the extent to which the atrophic changes of the cingulate that have been shown in MCI and early AD could contribute to metabolic and blood flow changes. A recent longitudinal study with serial neuroimaging comprising 15 patients with mild AD suggests a discordance between functional and structural

changes in the course of AD. While the medial temporal lobe showed the most pronounced grey matter loss within 1 year, the largest reduction in rCBF was seen in the posterior cingulate. The reduction in rCBF in the association cortices was in a more posterior part than the reduction in grey matter in this area (93).

Hippocampus and entorhinal cortex – While it was long believed that metabolic changes occurred primarily in association areas, methodological advances revealed early metabolic and blood flow changes in AD in the hippocampal-amygdaloid complex (32, 94, 97–99) and the entorhinal cortex (32, 37).

Johnson et al. reported that the initial SPECT findings in the hippocampal-amygdaloid complex, the posterior cingulate, the anterior thalamus and the caudal portion of the anterior cingulate predicted progression to dementia in 78% of 18 subjects with MCI at baseline (CDR 0.5) who progressed to AD during the 2-year follow-up (94).

However, some findings suggest that, despite the hippocampal formation being the site of the earliest structural alterations, hypoperfusion in these structures may not be the earliest change in the progression of AD. Kitayama et al. studied 21 patients with mild AD (mean MMSE 23.3) and 16 controls and measured both the hippocampal grey matter volume and hippocampal blood flow in the same individuals. The hippocampal grey matter volume was significantly smaller in mild AD, while the hippocampal blood flow did not differ between AD and controls (105). Kogure et al. performed a serial SPECT study applying SPM and evaluated the progression of rCBF abnormalities in 32 patients with initial MCI who declined to AD during a mean follow-up interval of 15 months (referred to as 'early AD'). At baseline, the early AD patients showed significantly decreased rCBF in the posterior cingulate and precuneus. In the follow-up SPECT study only, a selective reduction was observed in the left hippocampus and parahippocampal gyrus (32).

QEEG findings in subjects with MCI – Most studies of quantitative EEG (qEEG) changes in AD have used fast Fourier transformation (FFT) spectral analysis. There is a general agreement that the earliest changes in AD are an increase in theta activity, accompanied by a decrease in beta activity, which are followed by a decrease in alpha activity. Delta activity increases in the late disease stages [for review, see (106)].

EEG studies in MCI subjects usually found that theta power (107–109) as well as other EEG parameters (107, 110) and event-related potentials (111) differed only significantly between controls and mildly demented subjects (107–109). In MCI subjects, these EEG parameters were mostly found to be intermediate between normal controls and dementia, but with considerable overlap. A recent study confirmed this situation under rest conditions, but found significant theta power differences during haptic tasks between normal controls and subjects with MCI (112). This implies that activation paradigms in EEG studies may increase the sensitivity for cases at risk of developing AD. The results of an event-related potential (ERP) study using a word repetition paradigm point in the same direction (113).

Furthermore, there is evidence from prospective studies that low beta activity, high theta, low alpha, slowed mean frequency and spatial aspects of alpha frequency may be predictors of dementia in subjects with MCI (110, 114, 115).

Cross-sectional classification rates

Based on cross-sectional differences in limbic structures, mainly the hippocampus and entorhinal cortex or parahippocampal gyrus, respectively, the rate of correct cross-sectional classification of MCI and normal controls was reported to be around 75% in several of these studies (Tables 3 and 4). This probably reflects the transitional character of MCI, in which an overlap with normal variants is to be expected in cross-sectional studies. These figures actually exceed the reported radiological detection rates of the early pathological stages in AD (entorhinal) stages, which were reported to be just above 50% (116).

With regard to the ability of neuroimaging 'markers' to detect the early AD stages, the study by Nagy et al. (116) deserves special attention. In this prospective study of 86 cases with premortem CT and autopsy-confirmed diagnosis, a minimum width of the medial temporal lobe falling below the 5th percentile was 95% sensitive but only 40% specific for AD (116). While this CT measure was positive in most of the cases in pathologically advanced (isocortical) disease stages, it was only positive in 12/21 patients in early (entorhinal) disease stages, and also identified cases with non AD-type destruction of the medial temporal lobe. Furthermore, a negative radiological diagnosis in entorhinal stages was more likely in cases with pure AD-related pathology. This suggests that hippocampal atrophy may be caused and/or aggravated by other pathological processes than AD.

It may be argued that more accurate measurements of hippocampal or entorhinal volume may

improve the diagnostic value of radiological markers. However correlations between MR derived hippocampal volumes and Braak stages are comparable with those found with linear measures (9, 116). Jack reported $r^2 = 15\%$ in 67 autopsy cases with premortem MR, Nagy $r^2 = 21\%$. In pure AD cases these figures were 36% (9) and 33% (116).

Unlike the situation in structural neuroimaging (Tables 3 and 4), cross-sectional findings that compare MCI subjects with normal controls have rarely been reported in SPECT and PET studies (37, 117–119). This may be because of the difficulties and legal restrictions in enrolling healthy controls in such studies.

We found only three studies reporting significant cross-sectional differences between MCI and controls (32, 37, 117). A fourth study found intermediate values in rCMG in MCI subjects, but the differences were not significant (119). The classification rates reported by one of these studies compare with findings based on structural neuroimaging (37) (Tables 3 and 4). However, there are some studies with negative findings that also have to be mentioned. In particular, studies that used semiquantitative assessments and conventional SPECT with cerebellum-to-region of interest ratios, i.e. widely used clinical routine techniques, do not support the use of this method in the early diagnosis of AD (27, 118, 120) and found that CT or MRI were superior to SPECT in discriminating normal controls from MCI and dementia (118) and progressive from stable MCI (27, 120). In contrast, two recent large prospective studies that assessed the diagnostic value of PET concluded from their results that PET ratios and typical PET patterns may be useful in detecting subjects with early neurodegeneration and predicting the progression of clinical symptoms in AD, even in cases with questionable and/or mild dementia (121, 122). The study by Herholtz et al., comprising 186 patients with possible or probable AD, included 24 patients with MCI defined by an MMSE score >24. The risk of deterioration in these MCI patients was reported to be 4.7 times higher if the neocortical metabolism was low at baseline (122). Silverman et al. analysed a subset of 55 patients who had questionable and/or mild dementia at the time of PET and received an ultimate pathological diagnosis. For this group, 41 (75%) of whom had AD, the overall accuracy of PET was found to be 89%. This was as high as for the whole group ($n = 138$) (121).

Combining structural and functional imaging

Because structural neuroimaging studies have revealed atrophy in the same areas that are affected in functional modalities, the question may be raised as to which are the first changes to occur.

The most convincing evidence for the notion that the earliest alterations in AD can be detected with functional modalities derives from prospective studies of asymptomatic mutation carriers of encoded APP and presenilin mutations causing FAD (not shown in Tables 3–5) (87, 89, 90). In these studies, reduced temporal lobe glucose metabolism preceded the development of subjective and objective cognitive dysfunction (87), as well as the first detectable structural changes in the medial temporal lobe (90). The clearest change related to the development of clinical AD was a reduction of rCBF in the basal and lateral temporal lobe (89).

Another interesting question is whether the combination of functional and structural modalities may enhance the diagnostic gain of neuroimaging procedures as has been suggested by a few studies (89, 105, 123).

Interestingly, this does not necessarily seem to be the case. Two well-designed studies suggested that the diagnostic accuracy of combined measures might even be lower, particularly in very mild AD or dubious cases (116, 118).

Scheltens et al. (118) examined 51 randomly selected elderly subjects from participants of an epidemiological study in Amsterdam. The sample included 22 subjects with MCI ('minimal dementia'). The temporoparietal/cerebellar SPECT ratios did not differ over cognitive stages and had a sensitivity of 30% and specificity of 71%. The MRI ratings of the medial temporal lobe differed significantly over the groups and yielded a sensitivity for AD of 70% and a specificity of 71%. The combined sensitivity when both tests were positive was lower than the individual sensitivity values of MRI or of the SPECT values. The gain in diagnostic certainty over the pretest probability of AD was maximal when the combination of SPECT and MRI was used. The gain in diagnostic certainty over the pretest probability that AD was absent was higher when only MRI findings were considered. The authors concluded that the combination of SPECT and MRI is only useful when a diagnosis of AD is suspected clinically. When serious doubt exists (high negative prior probability), MRI suffices (118). Likewise, the analysis of the first 86 longitudinally followed-up cases from the OPTIMA neuroimaging study that came to autopsy revealed that the combination of SPECT and CT findings slightly reduced the number of early AD cases identified as fulfilling the requirements of the diagnostic criteria (116).

Prognostic value of neuroimaging findings

A prognostic value of a neuroimaging measurement may generally be presumed if a measurement distinguishes subjects who remained stable (stable MCI) from those who progressed to dementia and/or AD (progressive MCI) over a variable follow-up interval (in most studies, between 2 and 4 years). Such a distinction may be defined by a baseline difference in one or more measurements, by classification rates given from discriminant function or regression analysis, or by an increased hazard ratio. Different statistical approaches may yield differing results. Furthermore, being 'stable MCI' does not necessarily rule out the presence of AD, neither does the progression of MCI to mild dementia fully validate that AD was the underlying reason. This might introduce error and variations in the findings from different studies. From the point of view of an individual patient and his or her relatives, the crucial point is whether the condition will progress or remain stable. Therefore, at least in part, the specificity of a neuroimaging finding can be neglected as long as it only predicts the further course of cognitive impairment with high certainty.

A number of longitudinal studies have found a prognostic value of hippocampal (27, 31, 34, 35, 44, 124, 125) and entorhinal cortex atrophy (31, 47) in MCI with regard to subsequent dementia and/or cognitive decline. Taking the findings in structural imaging studies together, the existing prediction studies clearly point in the direction that, although the presence of hippocampal and entorhinal cortex atrophy increases the risk of subsequent dementia, such measures alone would not yield the required prognostic accuracy. In particular neocortical areas in the temporal and parietal lobe (24, 126) as well as the cingulate cortex (24), and possibly global brain atrophy (34, 70) were found to be predictors with additional value.

Some PET and SPECT studies suggested that metabolic abnormalities and blood flow reductions that typically occur in temporoparietal areas (102, 117), the posterior cingulate (94–96) and the hippocampal formation (94) may predict dementia in subjects with MCI with similar predictive accuracy to that of structural measures. Longitudinal EEG studies suggest a prognostic value of several aspects of quantitative EEG that is comparable with the results from structural and functional neuroimaging (110, 114, 115).

Based on neuroimaging alone, accurate prediction rates between 74% (47) and 93% (126) have been reported. However, to be useful in clinical practice, neuroimaging studies should prove their value against more simple clinical and less expensive neuropsychological assessments. In population-based settings, even such simple measures as the MMSE score have been shown to have considerable power as predictors of dementia (Palmer et al., in press; Riedel-Heller, personal communication). Only a minority of the neuroimaging studies (which are listed in Table 5) reported the value of neuroimaging findings in direct comparison with simple screening tests and neuropsychological data (31, 34, 102, 115, 124, 125). In the studies by Visser et al. (31, 125), measurements of hippocampus and temporal lobe atrophy provided valuable information in addition to memory performance. In the latter study, the delayed memory score predicted cognitive decline with 73% sensitivity and 67% specificity in a model that included age. The inclusion of the hippocampus increased the accuracy of the predictive model to 100%. Similar findings were reported by Arnaiz et al. (102). In their study, 20 patients with MCI were followed over 3 years. The nine patients with progressive MCI who were diagnosed with AD at follow-up had a significantly lower rCMRG in the left parietotemporal cortex and lower scores on three neuropsychological tests than those who remained stable. Regional (left temporoparietal) CMRG and block design were the most effective predictors of progression to AD and correctly classified 90% of the subjects when combined, whereas rCMRG and neuropsychology alone correctly classified only 75% and 65% respectively (102). The MMSE was found to lack significance against EEG as a predictor in the study by Jelic et al. (115). A subsequent analysis of our own data – which is not part of the original publication (28) – revealed that, while the subscores of a cognitive screening test (SIDAM) were significant predictors of dementia, the addition of CT data increased the predictive accuracy.

It remains to be shown how far additional pathological features, such as WMLs and infarcts, may alter the prognosis of MCI. The recent evolvement of automated techniques to detect and quantify WMLs (81, 127, 128) will help to tackle this important question in dementia research. So far, only one of the reviewed studies with a clear focus on MCI included WML severity together with atrophy measures in the analyses (28). Another longitudinal study included 29 patients with MCI of the vascular type (MCI-V), based on modified criteria for subcortical vascular dementia, and 14 with degenerative MCI, based on Petersen's criteria. During a mean follow-up interval of 32 months, patients with MCI-V were

considerably more likely to be dead, in nursing home placement and to have undergone cognitive or functional decline (129).

Serial studies: pathogenetic models *in vivo*. Is it possible to monitor disease progression?

Few serial studies monitoring the time sequence of brain changes have been conducted in AD and MCI. They may be particularly helpful to answer the question of how the structural changes in AD evolve. Furthermore, they may help to compare the capacity of different imaging facilities.

The evolution of structural changes – Earlier studies focused on changes in medial temporal lobe structures. In presymptomatic mutation carriers with familial AD, an asymmetric annual hippocampal volume loss of up to 8% has been reported (130). Taking together the results from studies on mutation carriers in the presymptomatic phase (90, 130), longitudinal studies on MCI (35) and AD (63, 131), one may presume that a more pronounced hippocampal atrophy occurs in the years preceding the onset of dementia, whereas the volume loss is less pronounced and may even reach a plateau in the later stages of the disease. The results underline the usefulness of hippocampal measurements in an early, preclinical diagnosis of AD. Initial optimism that serial hippocampal measurements could also provide a useful tool for monitoring disease progression – for example, during the treatment with a disease-modifying drug – has been opposed by the obvious difficulties in measuring the relatively small hippocampal volume changes reliably over time. However, recent studies have demonstrated the usefulness of whole-brain segmentation techniques, such as fluid registration and related techniques, which allow a more accurate and reliable measurement of disease progression (62, 63, 132).

The evolution of functional changes – The time sequence of functional changes has been rarely examined. The findings by Wahlund et al. (90) and Kogure et al. (32) have been discussed earlier in this review article.

Aspects of specificity

Most studies that assessed the brain changes associated with 'normal aging' reported some degree of time-dependent brain atrophy, even in the absence of cognitive impairment that might involve the same brain regions as AD-related brain changes, i.e. the hippocampus, as well as more global brain atrophy (133–136). Beyond the obviously problematic distinction between normal age-related changes and AD, the question of the specificity of typical neuroimaging findings in MCI with regard to AD and other dementia disorders has not yet been addressed. Clinical criteria for prodromal frontotemporal dementia, dementia with Lewy bodies, vascular dementia and other dementia diseases are lacking. It is doubtful whether it will be possible and necessary to develop such criteria, because, even in cases which meet current consensus criteria for frontotemporal dementia or dementia with Lewy bodies, the correlation with the pathologically verified diagnosis has been low (8) and no pharmaceutical treatments other than those used for AD can be offered to date [for discussion, see also Jelic & Winblad (6)]. Neuroimaging studies that included cases with fully developed AD and other dementia disorders revealed that, despite a large overlap between the disease groups (for example, with regard to the quantitative degree of hippocampal atrophy) (137), there might be topographically specific patterns of change that may help to distinguish FTD from AD (138–141). With regard to vascular dementia and AD, it has become clearer that the two pathologies may overlap and exert additive effects to cause dementia and possibly hippocampal atrophy in subjects with mild Alzheimer pathology (116, 142). Such findings support the usefulness of a broad concept of MCI rather than subdefinitions for specific underlying diseases. Even if the topographic-morphological hallmarks of MCI, such as atrophy of the hippocampal formation, are considered to be nonspecific with regard to the underlying aetiology and pathology, they may all result in a similar clinical syndrome and may be classified as a group of 'hippocampal dementias'.

Future perspectives

New neuroimaging facilities, such as unbiased voxel-based analyses, the visualization of plaques and tangles, functional MRI paradigms and a number of different MR applications, such as MR spectroscopy and other MR applications may substantially support the progress in the field of MCI research in the near future.

Future research may, in particular, focus on useful measures that distinguish early neurodegenerative disorders from each other. More studies are needed that compare different neuroimaging facilities with each other, as well as with alternative diagnostic strategies such as clinical, neuropsychological and biochemical assessments.

Summarizing remarks and conclusions

Structural MRI and CT, SPECT, PET and QEEG are the most commonly studied imaging procedures in patients with MCI.

In a number of neuroimaging studies comprising mainly clinic-based but demographically heterogeneous samples, it has been shown that structural and functional changes are already present in the phase that precedes the onset of overt dementia. Structural changes in MCI and early AD seem to be pronounced in medial temporal lobe structures, particularly in the entorhinal cortex and hippocampus. The earliest functional changes seem to involve the posterior cingulate cortex, the hippocampal formation and temporoparietal association areas. The most important EEG change seems to be an increase in theta frequency.

No single neuroimaging 'marker' for AD has been identified to date. As the pathological hallmarks of the disease process, disease-related neuroimaging findings are quantitative rather than qualitative in nature. A certain overlap between cognitively normal and diseased subjects as well as between different dementia disorders will always be present. With regard to the early diagnosis of a dementia disorder, a higher sensitivity will thus result in a lower specificity and vice versa.

While the presence of hippocampal and entorhinal cortex atrophy in subjects with MCI is a well-established risk factor for the development of AD, the data are inconclusive with regard to their value as predictors in an individual case. The volumes of other brain regions that are typically affected in more advanced cases with AD, as well as more widespread atrophic changes, may add to the predictive value of medial temporal lobe atrophy.

The existing studies suggest that neuroimaging facilities have the potential to become valuable tools in the early diagnosis of AD beyond the exclusionary approach. However, to establish their value in clinical routine, studies involving larger, preferably population-based samples with longitudinal follow-up are needed. Therefore, not only the accuracy, but also the practicability and cost-effectiveness will be important aspects for the choice of a diagnostic procedure. In particular, the value of neuroimaging against clinical, neuropsychological and biochemical assessments in large representative (i.e. clinically heterogeneous) samples, and the complementary value of the various facilities remains to be demonstrated.

Appendix: Commonly used terms and abbreviations

18F-fludeoxyglucose	FDG
Cerebrospinal fluid	CSF
Computed tomography	CT
Electroencephalography	EEG
Event-related potentials	ERP
Hexamethylpropylene amine oxime	HMPAO
Magentization transfer imaging	MTI
Neurofibrillary tangles	NFT
Nuclear magnetic resonance imagingMRI	
Positron emission tomography	PET
Proton magnetic resonance spectroscopy	^{1}H MRS
Regional cerebral blood flow	rCBF
Regional cortical metabolic rate of glucose	rCMRG
Senile plaques	SP
Single-photon emission computed tomography	SPECT

Analysis methods

Co-registration with MRI (154)	
Singular value decomposition	SVD (94)
Statistical parametric mapping	SPM
Three-dimensional stereotactic surface projection	3D SSP (155)
Voxel-based morphometry	VBM

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