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Brain imaging of mild cognitive impairment and Alzheimer's disease☆

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Abstract
The rapidly increasing prevalence of cognitive impairment and Alzheimer's disease has the potential to create a major worldwide healthcare crisis. Structural MRI studies in patients with Alzheimer's disease and mild cognitive impairment are currently attracting considerable interest. It is extremely important to study early structural and metabolic changes, such as those in the hippocampus, entorhinal cortex, and gray matter structures in the medial temporal lobe, to allow the early detection of mild cognitive impairment and Alzheimer's disease. The microstructural integrity of white matter can be studied with diffusion tensor imaging. Increased mean diffusivity and decreased fractional anisotropy are found in subjects with white matter damage. Functional imaging studies with positron emission tomography tracer compounds enable detection of amyloid plaques in the living brain in patients with Alzheimer's disease. In this review, we will focus on key findings from brain imaging studies in mild cognitive impairment and Alzheimer's disease, including structural brain changes studied with MRI and white matter changes seen with diffusion tensor imaging, and other specific imaging methodologies will also be discussed.

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Key Words
neural regeneration; neuroimaging; mild cognitive impairment; Alzheimer's disease; diffusion tensor imaging; fractional anisotropy; entorhinal cortex; hippocampus; magnetic resonance imaging; photographs-containing paper; neuorregeneration

Research Highlights
(1) Recent advances in MRI scanning techniques have allowed the examination of structural changes of the hippocampus, entorhinal cortex, and gray matter structures in the medial temporal lobe.
(2) Functional imaging techniques, such as positron emission tomography, greatly assist in early diagnosis of mild cognitive impairment and Alzheimer's disease.

INTRODUCTION

Memory impairment is one of the most common cognitive complaints during the course of aging[1]. Memory loss during normal aging differs from that associated with Alzheimer's disease. Mild cognitive impairment is a condition in which people experience memory problems more often than expected for their age[2].

However, the symptoms do not prevent them from daily activities and are not as severe as those of Alzheimer's disease. Mild cognitive impairment occurs in 10–20% of people aged 65 and over[3]. Symptoms of memory decline or mild cognitive impairment usually represent a transitional state between healthy aging and Alzheimer's disease.

Although individuals with memory complaints do not meet criteria for dementia, they may perform poorly on episodic memory tests. In some older people, mild cognitive impairment may ultimately develop into a degenerative dementia. Alzheimer's disease and neurodegenerative dementias are growing health problems that affect all ethnic groups worldwide[3]. Alzheimer's disease is characterized by widespread cortical changes, loss of neurons, and presence of senile plaques and neurofibrillary tangles. Although definitive diagnosis is based on pathological examination, recent advances in imaging techniques may contribute to early diagnosis of mild cognitive impairment and Alzheimer's disease. Increasing evidence from structural and functional MRI studies suggests that Alzheimer's disease and mild cognitive impairment may target specific brain networks[4]. Proton magnetic resonance spectroscopy appears to be a valuable means of tracking brain metabolic changes due to cognitive impairment[5]. Structural imaging can detect the time course of brain atrophy in patients with Alzheimer's disease and may serve as a surrogate marker for pathological changes in people with suspected Alzheimer's disease. Emerging magnetic resonance techniques such as diffusion tensor imaging and proton density weighted imaging, and advances in image analysis software, provide us with an efficient tool for early detection of subtle microstructural, perfusion and metabolic changes in the brain.

In this review, we highlight the body of literature on brain abnormalities detected by imaging in mild cognitive impairment and Alzheimer's disease. In particular, we address the viability of MRI techniques to discriminate between dementias and to measure disease progression.

STRUCTURAL IMAGING OF MILD COGNITIVE IMPAIRMENT AND ALZHEIMER'S DISEASE

Volumetric MRI is becoming an increasingly important tool in the early detection and monitoring of people suspected to have mild cognitive impairment or Alzheimer's disease[6]. Previously, the detection of atrophy depended on the measurement of regional brain volumes, using volumetric imaging techniques. Patients with Alzheimer's disease may have typical pathologic changes in cortical gray matter, characterized by the accumulation of amyloid beta plaques, formation of neurofibrillary tangles, and neuronal and synaptic loss[7]. All these changes lead to cerebral atrophy in specific brain regions. The vast majority of structural brain imaging studies have been based on histopathological evidence that the entorhinal cortex and hippocampus are among the first sites affected by mild cognitive impairment. Similarly, in patients with Alzheimer's disease, atrophy has been found to occur in the hippocampal formation and entorhinal cortex, as demonstrated by several volumetric MRI studies[8-12].

To date, many imaging methods have been developed to monitor disease progression and understand the pathogenesis of dementia. MRI is extensively used for the diagnosis of mild cognitive impairment and Alzheimer's disease. T1-weighted MRI are useful for the assessment of the topographic distribution of cortical and subcortical atrophy. Recently, three-dimensional gradient-echo sequences that allow calculation of volumes and coregistration of images during follow-up examinations have been used in clinical practice[13]. Unlike T1-weighted imaging, T2 relaxometry allows the quantitative measurement of signal changes on T2-weighted images. However, the ability of T2-weighted imaging to differentiate between patients with mild cognitive impairment or Alzheimer's disease and healthy subjects is very limited because various confounding pathologies such as brain edema, demyelination and axonal loss may also result in changes similar to those seen in Alzheimer's disease. The hippocampal T2 prolongation may serve as a specific marker for Alzheimer's disease. Elevated T2 values are found in the hippocampus, and these values correlate strongly with the severity of functional and cognitive impairment in patients with Alzheimer's disease[14]. Early reports used serial manual delineating of the anatomical boundaries of the hippocampus and entorhinal cortex[15]. Patients with mild cognitive impairment have a smaller entorhinal cortex and hippocampus than healthy age-matched subjects. However, patients with Alzheimer's disease may have a prominent reduction in the entorhinal cortex and hippocampus. Volume reductions in patients with mild cognitive impairment appear to be intermediate, between those of healthy subjects and patients with Alzheimer's disease[16]. A larger hippocampal volume is also associated with better memory and overall clinical ratings[17]. MRI volumetry of the entorhinal cortex, the superior temporal sulcus and the anterior cingulate cortex may also differentiate normal subjects from patients with mild cognitive impairment. Although mild cognitive impairment can present with a variety of symptoms, when memory loss is the predominant symptom it is termed "amnestic mild cognitive impairment" and is frequently

seen as a prodromal stage of Alzheimer's disease. In previous studies, patients with amnestic mild cognitive impairment were examined using high-resolution functional MRI during a continuous recognition task. The authors found that structural and functional changes in the CA3/dentate region of the hippocampus contributed to the deficits in episodic memory that were observed in patients with amnestic mild cognitive impairment[18]. Another study suggested that patients with amnestic mild cognitive impairment were selectively impaired on a functional MRI task that emphasized pattern separation; the response distribution was strikingly similar for lures and repetitions[19]. MRI studies using morphometric techniques have demonstrated that the CA1 region of the hippocampus is structurally compromised early in the course of amnestic mild cognitive impairment[20].

WHITE MATTER DAMAGE IN ALZHEIMER'S DISEASE AND MILD COGNITIVE IMPAIRMENT

In addition to the examination of the hippocampi and entorhinal cortices, there is a growing interest in white matter changes in mild cognitive impairment and Alzheimer's disease[12-21]. Vascular risk factors such as hypertension, hypercholesterolemia, and the apolipoprotein E4 allele may occur in patients with Alzheimer's disease. Although it is sometimes difficult to differentiate between vascular dementia and vascular lesions in Alzheimer's disease, vascular lesions are generally less severe in patients with Alzheimer's disease than those with vascular dementias.

White matter damage may result in increased brain water content. There are a variety of MRI techniques by which to measure changes in water content. The MRI T2 signal decay is sensitive to water content and has been used to measure white matter damage in patients with mild cognitive impairment and Alzheimer's disease. However, conventional MRI techniques yield insufficient contrast to provide information on the microstructural integrity of white matter. Diffusion tensor imaging is a promising technique that allows documentation of hydrogen-based alterations in MRI signal at the microstructural level. This makes it possible to measure the restricted diffusion of water in tissue and thus produce neural tract images, instead of using the data solely for the purpose of assigning contrast or colors to pixels in a cross-sectional image. By applying diffusion weighted gradients in at least six non-collinear gradients, the technique sensitizes the MRI signal to the movement of hydrogen in the micron range. Using diffusion tensor imaging, it is also possible to measure the direction and magnitude of hydrogen movement and discriminate fiber tracts in the white matter. Thus, it is sensitive to fiber integrity as well as orientation.

The application of diffusion tensor imaging allows examination of diffusion characteristics, irrespective of head position. Cortical neuronal loss in patients with Alzheimer's disease is associated with axonal degeneration in specific white matter pathways. In patients with mild cognitive impairment, diffusion tensor imaging abnormalities are seen in various brain areas such as the hippocampus, thalamus and posterior white matter[21-23]. White matter diffusivity abnormalities may also be present in patients with Alzheimer's disease[24]. Region of interest measurement has been used extensively in the imaging of cognitive impairment. However, variability in region of interest placement may hinder the consensus identification of white matter in Alzheimer's disease. The fiber tractography can easily parcellate the white matter tracts with the use of high-field-strength MRI scanners and modern gradient coils. Reduced fractional anisotropy values were detected in white matter regions using region of interest analysis in diffusion tensor imaging studies[25-26]. The white matter abnormalities were observed in the frontal, temporal and parietal lobes. Sometimes, the splenium of the corpus callosum might also be involved, as demonstrated by diffusion tensor imaging fractional anisotropy reductions[27].

FUNCTIONAL IMAGING AND SPECIFIC IMAGING TECHNIQUES IN MILD COGNITIVE IMPAIRMENT AND ALZHEIMER'S DISEASE

Specific imaging techniques

During the past few years, the widespread application of advanced MRI techniques such as diffusion tensor imaging and functional MRI has detected a rapid increase in neurodegenerative disorders[28]. Disease-specific alterations in brain function can be assessed by advanced MRI studies. A great variety of innovative methods of extracting diffusion tensor imaging data have been employed in the study of white matter changes in Alzheimer's disease and mild cognitive impairment[29-30]. For most studies employing diffusion tensor imaging technology, comparisons are made from memory impaired individuals and healthy control participants. Most studies are all multiple-subject group comparison studies, usually one group of experimental subjects compared with a matched group of control subjects. Region of interest and whole brain voxelwise

analyses are the most commonly used approaches to analyzing MRI data[31]. Region of interest approaches were based on a process called normalization. The process includes either hand-drawn region of interests from negative images of individual scans, or template-based region of interests applied to scans that have been warped into a common coordinate system. Each of these approaches has different strengths and weaknesses. It is highly operator-dependent, and a skilled operator may provide superior delineation of cerebral structures. Because the operator has great control over which voxels to include, the drawing of multiple region of interests for many subjects can be laborious. More importantly, if more than one operator is constructing the region of interests, inter-operator reliability must be established. Template-based region of interests have been applied to normalized scans to improve efficiency[32-33]. Because of individual differences in brain morphology, the accuracy of this approach is dependent upon the normalization process and relies on the alignment of different brain regions across individuals. Partial voluming (in which a voxel represents more than one tissue type), in either native space or normalized space, is relatively common in both region of interest approaches. The partial voluming effect means that the values extracted from the region of interests are, to some extent, averaged for the entire region of interest.

Whole-brain voxelwise approaches are widely used in diffusion tensor imaging studies[34-39]. Compared with the region of interest approach, the whole-brain voxelwise approach has the advantage of being extremely time efficient. Large numbers of scans can be processed quickly, thereby potentially increasing the power of statistical analyses. Because most diffusion tensor imaging studies with statistical testing were performed in one or more of the aforementioned ways, a fast measuring approach such as whole-brain voxelwise analysis would be a great advantage. However, whole-brain voxelwise analysis also has potential weaknesses, such as mismatching between the native and normalized image due to imperfect warping algorithms, alteration of the diffusion tensor imaging values due to the effects of normalization, and possible alteration of the diffusion tensor imaging values caused by smoothing[40-42].

In clinical practice, the structural properties of white matter are being increasingly investigated by diffusion tensor imaging and voxel-based approaches. Diffusion tensor imaging is a relatively sensitive technique that reveals group differences between patients with Alzheimer's disease and those with mild cognitive impairment. Although diffusion tensor imaging meets the requirements of many basic and clinical research purposes, the technique has several limitations. For example, water diffusion is an indicator of the underlying neuroanatomy, and there are numerous microscopic structures that may affect the diffusion. Therefore, different histopathological conditions may result in similar alterations of diffusion tensor imaging-derived parameters[43-44].

Structural and functional MRI may allow the prediction of future conversion from mild cognitive impairment to Alzheimer's disease[45]. People with mild cognitive impairment may not yet notice any impairment in daily function. Previous studies have suggested that Alzheimer's disease is associated with reduced anisotropy and increased diffusivity compared with healthy controls. It is prominent in widespread brain regions, most notably in the frontal and temporal lobes, corpus callosum, and posterior cingulum[46]. Recent studies have suggested that hippocampal volume predicts conversion from mild cognitive impairment to Alzheimer's disease with high accuracy. A recent study compared volumetric MRI with clinical measures predicting progression from mild cognitive impairment to Alzheimer's disease. The authors measured the whole brain, and ventricular, hippocampal, and entorhinal cortex volumes, and participants were followed up with clinical and cognitive evaluations until formal criteria for Alzheimer's disease were met. Of the four MRI measures evaluated, only changes in ventricular or hippocampal volumes were associated with progression to Alzheimer's disease. Maximal predictive accuracy using only MRI measures was obtained by hippocampal volumes[47]. In a recent study using deformation-based morphometry and principal component analysis, patterns of regional brain atrophy including the medial temporal lobes, neocortical association areas, thalamus, and basal ganglia, as well as concurrent ventricle widening, were detected[48]. These findings may provide a clue by which to discriminate mild cognitive impairment converters from nonconverters.

The vast majority of studies that employ diffusion tensor imaging to investigate white matter integrity in Alzheimer's disease and mild cognitive impairment have greatly increased during the past decade. A large number of these studies have used mean diffusivity and fractional anisotropy as markers of cerebral integrity[49-54]. Mean diffusivity, which is a scalar measure of the total diffusion within a voxel, is commonly used in the clinic to localize white matter lesions. Although the mean diffusivity does not provide information about the directionality of diffusion, it gives essential information

regarding measure of translational diffusion. Therefore, mean diffusivity may increase in the presence of tissue damage. Previous results have suggested that mean diffusivity increases may have a significant negative correlation with cognitive performance measures. Increased mean diffusivity has been observed in many parts of the brain in patients with Alzheimer's disease, including frontal lobes, temporal lobes, parietal lobes and occipital lobes[55-56]. The regional distribution of increased mean diffusivity has been documented in fiber tracts that were involved in intercerebral communications. These areas include the superior longitudinal fasciculus, corpus callosum, hippocampus, parahippocampus, and cingulum[57-59]. These changes seem to follow the pathological progression of Alzheimer's disease.

Fractional anisotropy is a scalar value that describes the degree of anisotropy of a diffusion process that could provide an *in vivo* marker of cerebral integrity. It is commonly used in diffusion imaging and it is thought to reflect fiber density, axonal diameter, and myelination in the white matter. Fractional anisotropy is an extension of the concept of eccentricity of conic sections in three dimensions and provides a measure of the directionality of diffusion. High fractional anisotropy is seen in highly organized tissue with parallel structure in white matter. Therefore, any damage to the white matter may break down the organization of the anatomical structure, leading to a decrease in fractional anisotropy. Fractional anisotropy changes have been reported in multiple regions including the frontal and parietal lobes in patients with mild cognitive impairment and Alzheimer's disease. However, no differences in fractional anisotropy were observed in the occipital lobes between subjects with Alzheimer's disease or mild cognitive impairment, or healthy controls[60]. Despite some conflicting findings of fractional anisotropy in Alzheimer's disease and mild cognitive impairment, there have been frequent reports of decreased fractional anisotropy in the medial temporal lobe including the hippocampus, entorhinal cortex, parahippocampal white matter, and posterior cingulum[55-60]. Although the substrates of mean diffusivity and fractional anisotropy may differ, alterations of these two indices can be secondary to changes in diffusion, either parallel or perpendicular to the principal direction of the tensor. Tract-based spatial statistics are also useful in diffusion tensor imaging of Alzheimer's disease and mild cognitive impairment. In a recent study, significant decreases were observed in fractional anisotropy values in patients Alzheimer's disease, compared with that of controls, whereas patients with mild cognitive impairment had fractional anisotropy values between those of controls and Alzheimer's disease patients[61]. Therefore, voxel-based analysis with tract-based spatial statistics is a promising method for examining the degeneration of neurofiber tracts in Alzheimer's disease and mild cognitive impairment patients.

Diffusion tensor imaging is also an important tool in differentiating Alzheimer's disease from other neurological disorders. Diffusion tensor imaging can be used to estimate white matter lesions in dementia patients. In a recent study, the value of diffusion tensor imaging in the diagnosis and differential diagnosis of patients with subcortical ischemic vascular dementia and Alzheimer's disease were studied. Compared with normal controls and patients with Alzheimer's disease, patients with subcortical ischemic vascular dementia had lower fractional anisotropy values and higher diffusion coefficients in the genu and splenium of the corpus callosum, and in the superior longitudinal fasciculus. Patients with Alzheimer's disease had lower fractional anisotropy values in the anterior frontal lobe, temporal lobe, and hippocampus, and higher diffusion coefficients in the temporal lobe and hippocampus compared with controls and patients with subcortical ischemic vascular dementia[62]. The potential of using diffusion tensor imaging in conjunction with machine learning algorithms to automate the classification of healthy older subjects and those with mild cognitive impairment has also recently been examined. When diffusion tensor imaging measures were then used together with support vector machines, greater than 90% sensitivity and specificity was achieved using this method[63]. In patients with mild cognitive impairment and Alzheimer's disease, a reduction in size of the hippocampal formation could be seen in region of interest and voxel-based volumetric structural studies[64-66]. It is well established that the temporal lobe has higher atrophy rates in patients with mild cognitive impairment than in healthy people. A recent study suggested that diffusion tensor imaging changes in temporal lobe white matter correlate well with episodic memory, frontal changes with executive function, and parietal changes with general cognition[67]. Furthermore, patients with mild cognitive impairment may mark diffusion tensor imaging abnormalities in multiple locations along the cingulum fiber bundle, including the posterior cingulate and parahippocampal regions[67].

Recently, magnetization transfer imaging has also been used for imaging of patients with cognitive impairment. Magnetization transfer is a new technique for improving image contrast in MRI[68]. It is based on the exchange of magnetization between immobile and free protons, and

is an innovative imaging method that provides essential information regarding the underlying histopathologic changes in brain tissue. Furthermore, magnetization transfer imaging allows the assessment of ongoing global and regional brain damage, independent of atrophy, in patients with Alzheimer's disease[68].

The magnetization transfer ratio is a parameter that quantifies the degree of magnetization transfer. It is dependent on the concentration, surface chemistry, and biophysical characteristics of macromolecules. During the past 20 years, magnetization transfer imaging has been used regularly in the evaluation of subjects with multiple sclerosis[69]. A decrease in the white matter magnetization transfer ratio indicates tissue demyelination. A reduction in magnetization transfer ratio has also been reported in the hippocampus of early dementia patients, compared with control subjects[70]. Such studies suggest that measurements of magnetization transfer ratio may be valuable in the detection of structural damage in the hippocampus of Alzheimer's disease patients. Interestingly, magnetization transfer is particularly sensitive to gray matter abnormalities[70] and provides complementary information to conventional MRI in the characterization of Alzheimer's disease by quantifying gray matter atrophy[71]. The characteristic histopathological findings in the hippocampus of Alzheimer's disease patients include a loss of pyramidal cells accompanied by an increase in the number of astrocytes, microglia, and oligodendrocytes. The most specific pathological change is the accumulation of senile plaques and neurofibrillary tangles. Although the exact mechanism for the reduction in magnetization transfer in the hippocampus of patients with Alzheimer's disease is not yet clear, such pathologic changes may decrease magnetization transfer ratio because of a decrease in the bound-proton fraction. Results of studies in patients with clinically diagnosed Alzheimer's disease suggest that quantitative measurement of certain parameters using magnetization transfer imaging may serve as a potential biomarker of the disease[70-71].

Functional imaging

With the growing prevalence of cognitive impairments, functional imaging for neurodegenerative diseases is increasingly important in clinical and research settings. Proton magnetic resonance spectroscopy is a viable imaging method for tracking brain metabolic changes due to neurodegenerative diseases[72]. In addition, proton magnetic resonance spectroscopy may also play a role in discriminating between dementias, and measuring disease progression. The amyloid plaques and neurofibrillary tangles in Alzheimer's disease present in a characteristic pattern, with early involvement of the medial temporal lobes and hippocampus. Mild cognitive impairment is a transitional phase between normal cognitive aging and Alzheimer's disease. Patients with mild cognitive impairment may have subjective complaints of memory loss and objective impairment on memory testing compared with normal age-matched individuals, while their activities of daily living may be generally preserved. A recent study suggested that mild cognitive impairment may be associated with widespread reduction in brain volume and changes in regional function[73]. Previous proton magnetic resonance spectroscopy studies have investigated patients with mild cognitive impairment. The technique allows monitoring of metabolic ratios such as myoinositol/creatine-phosphocreatine, choline/creatine-phosphocreatine, and N-acetyl aspartate/creatine-phosphocreatine. In patients with mild cognitive impairment or Alzheimer's disease, such metabolic ratio changes are most apparent in the left temporal lobe, the posterior cingulate cortex, and the medial occipital lobe[72-73]. However, significantly lower ratios of myoinositol/creatine-phosphocreatine were seen in patients with mild cognitive impairment than in those with Alzheimer's disease. These findings suggest that increased myoinositol may indicate early pathological changes preceding neuronal dysfunction. Patients with mild cognitive impairment may also have a significant increase in choline/creatine-phosphocreatine ratio in the right frontal cortex and posterior cingulate, as demonstrated by proton magnetic resonance spectroscopy studies[72-74]. Another prominent feature of mild cognitive impairment is reduced N-acetyl aspartate/creatine-phosphocreatine ratio in the left medial temporal lobe and the right hippocampus. Cross-sectional magnetic resonance spectroscopy further confirmed that metabolic abnormalities in mild cognitive impairment are transitional between normal older adults and patients with Alzheimer's disease. The observed progression of metabolic changes generally corresponds to the known early neuropathology of Alzheimer's disease[75].

Proton magnetic resonance spectroscopy studies indicate that patients with Alzheimer's disease have a reduced N-acetyl aspartate/creatine-phosphocreatine ratio[70-76], most prominently in the hippocampus and medial temporal lobe, but also in the temporal-parietal area, frontal and occipital lobes[72-78]. Furthermore, whole brain magnetic resonance spectroscopy has demonstrated reductions in N-acetyl aspartate in Alzheimer's disease, primarily observed in posterior gray

matter. These findings of widespread reductions in N-acetyl aspartate are consistent with the progression of neurofibrillary tangles in Alzheimer's disease. In general, proton magnetic resonance spectroscopy can reproducibly distinguish between early Alzheimer's disease patients and normal subjects as well as patients with mild cognitive impairment. Further studies will be needed to confirm whether changes in precuneus/posterior cingulate metabolite ratios reliably correlate with measures of function, and whether they may yet prove useful as longitudinal biomarkers in clinical trials of disease-modifying therapies[79-82].

The cerebral metabolic rate of glucose consumption is a parameter that measures glucose metabolism within the brain. [18F]-fluorodeoxyglucose-position emission tomography can assist with the diagnosis of Alzheimer's disease at an early stage. The utility of [18F]-fluorodeoxyglucose-position emission tomography in Alzheimer's disease has greatly improved early diagnosis and may also be used in monitoring drug effects in the future[83-84]. It is well established that by the time a patient presents with clinical symptoms of Alzheimer's disease, the cerebral metabolic rate of glucose consumption is severely reduced in some cortical regions[83-84]. In patients with mild cognitive impairment, [18F]-fluorodeoxyglucose-position emission tomography findings are inconsistent. Interestingly, while position emission tomography measures were not sensitive for people with early stage mild cognitive impairment[85], reports using [18F]-fluorodeoxyglucose-position emission tomography have suggested that the cerebral metabolic rate of glucose consumption was reduced in patients with more advanced mild cognitive impairment, particularly in the limbic structures, including the hippocampus, medial thalamus and posterior cingulate[85-86]. A recent study suggested that combining [18F]-flutemetamol position emission tomography with structural MRI may provide additional information for categorizing disease and potentially predicting time to progression from mild cognitive impairment to Alzheimer's disease[87].

SUMMARY

Interest is growing in the early investigation of mild cognitive impairment and Alzheimer's disease. Early identification of mild cognitive impairment is extremely important for the counseling of patients, making therapeutic decisions, and planning clinical trials. Recent advances in MRI scanning techniques have allowed the examination of structural changes of the hippocampus, entorhinal cortex, and gray matter structures in the medial temporal lobe. Diffusion tensor imaging allows accurate depiction of white matter microstructural integrity based on the directionality of diffusion in the brain. Magnetization transfer is also used for imaging patients with cognitive impairment. Measurements of magnetization transfer ratio may be valuable for the detection of structural damage in the hippocampus of Alzheimer's disease patients. Proton magnetic resonance spectroscopy has emerged as an increasingly important tool in discriminating between dementias and measuring disease progression. Cross-sectional magnetic resonance spectroscopy confirmed that metabolic abnormalities in mild cognitive impairment are transitional between normal healthy older adults and patients with Alzheimer's disease. The cerebral metabolic rate of glucose consumption can be measured by position emission tomography. The utility of such functional imaging techniques has greatly improved the early diagnosis of mild cognitive impairment and Alzheimer's disease. Technical advances in multiple imaging modalities allow us to assess both anatomical and functional changes in Alzheimer's disease and mild cognitive impairment, thereby advancing our understanding of the pathophysiological evolution of these diseases.

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