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Novel MRI techniques in the assessment of dementia

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Abstract
Introduction Positive markers of Alzheimer's disease (AD) have been established in MRI that may allow early detection of AD in at-risk groups. In the near future, these markers will be of high relevance for the selection of at-risk subjects in secondary preventive trials.
Methods We describe the methodology and diagnostic value of manual volumetry of the hippocampus and entorhinal cortex, automated voxel-based morphometry, cortical thickness measurement, basal forebrain volumetry and deformation-based morphometry, implementing multivariate statistics and machine learning algorithms to improve group separation and prediction of AD in at-risk groups. We also describe the methodological basis and results obtained in AD using the recently developed technique of diffusion tensor-based morphometry (DTI). This technique gives access to the integrity of subcortical fibre systems in the human brain.
Results The best established structural biomarker of AD to date is hippocampus volume that already has been implemented as secondary endpoint in clinical trials on disease modification in AD. Automated approaches will gain an increasing role as endpoints of clinical trials in the near future given the interest in these techniques expressed by the regulatory authorities. DTI is still a developing field where analysis techniques are presently being devised to make optimal use of the multivariate data. Data on changes of fibre tract in preclinical AD are still limited, but the first results are promising in respect to a further enhancement of diagnostic accuracy by combining MRI and DTI.
Conclusion Besides their diagnostic use, MRI and DTI will broaden our understanding of the pathophysiology of AD and the structural and functional basis of normal cognition.

Keywords Alzheimer's disease · Dementia · MRI · DTI · Hippocampus · Brain atrophy · Disconnection · Diagnosis

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Introduction

The dementia syndrome is clinically defined as acquired decline of memory and other cognitive domains with significant impairment of executive functioning and of activities of daily living. The prevalence of dementia increases continuously with age and has been estimated to be about 1% in the age-group between 65 to 69 years and 29% at age 90 years and older [1]. The most frequent underlying neurobiological cause of a dementia syndrome is Alzheimer's disease (AD), accounting for at least 60% in patients older than 65. Presently, it is estimated that 7.21 million patients suffer from mild to severe AD in Europe. This number is projected to increase to 16.51 million until the year 2050 [2]. Subjects with mild cognitive impairment (MCI) have memory impairment and other cognitive decline who have not yet developed significantly altered activities of daily living but have an increased risk to develop AD [3]. Therefore, MCI has been defined as a clinical at-risk stage of AD. The prevalence of MCI is estimated to be about two to three times higher than that of AD, depending on the exact clinical criteria to define MCI. AD has grown to be among the most prevalent causes of morbidity and mortality in Europe and the US besides cancer, cardiovascular disease and stroke. With the continuous increase of the proportion of the elderly not only in the European countries but also in the USA, India and China, the devastating impact of AD on world wide health systems will dramatically increase in the next decades and pose a serious economical threat to our societies.

To date, the diagnosis of AD is primarily based on the clinical definition of the dementia syndrome and the systematic and labour-intensive exclusion of other factors that may account as causes or mechanisms for dementia. Therefore, neuroimaging, a by international guidelines such as NICE, EFNS or AAN widely recommended technical approach, particularly MRI, serves an important supportive function in the final establishment of a clinical diagnosis of AD by excluding other causes of dementia such as cerebrovascular disease, inflammation, intracranial neoplasia, subarachnoidal bleeding and normal pressure hydrocephalus.

During the last 15 years, however, monocenter studies in selected samples have defined characteristic pattern of atrophy in AD that were able to discriminate AD from healthy control subjects. Additionally, pattern of atrophy have been employed to predict the presence of AD in clinically defined at-risk groups with MCI. This is important for two reasons:

1. The development of secondary preventive treatments, i.e. treatments that delay or prevent the development of AD in clinical at-risk subjects, depends on the accurate selection of at risk samples for clinical trials. The majority of clinical trials on secondary preventive treatments in MCI so far were negative for the outcome conversion into AD [4, 5], possibly related to the fact that the study samples were very heterogeneous in respect to the risk to develop AD during clinical follow up. The use of recently developed techniques to detect the underlying neurobiological presence of AD in predementia stages in addition to clinically defined criteria will support to select true at-risk populations for future clinical trials.
2. Once preventive treatments are available, it will be particularly important to administer those compounds to early recognised patients that will benefit most from early intervention.

Therefore, non-invasive techniques to identify the individual risk of patients to develop AD will have a major impact on the ability of the health system to meet the financial burden of the prospected increasing prevalence of dementia in a worldwide aging population.

MRI, as a generally widely available non-invasive and relatively inexpensive technique, has the potential to significantly contribute to our ability to deal with the increasing impact of AD. In assessing the relevance of new MRI-based technologies, it is helpful to consider how a new imaging derived "biological marker" needs to be systematically developed [6]. In the first stage of this development process, the technical characteristics of the new biomarker are being determined, such as test–retest accuracy, patient burden and time requirements. In the second stage, the sensitivity and specificity of group discrimination is determined in selected samples. In the third stage, the biomarker is applied in samples that represent the population for which the biomarker will be applied in the future. This allows estimation of positive and negative predictive values. Finally, the use of a new biomarker is assessed in clinical routine.

In the following section, we will outline MRI-based techniques in the diagnostic assessment of a dementia syndrome in detail with special emphasis on early detection of AD. The most frequently employed labour-intensive manual volumetric techniques have been recently complemented by more convenient semi- or fully automated, hypothesis-free techniques to detect regional atrophy throughout the entire brain. Even more recently, diffusion tensor imaging (DTI), a novel technique to determine microstructural alterations of cerebral white matter has been applied to the assessment of AD. Table 1 gives an overview where these techniques are located within the four-stage development model of a new candidate biomarker.

Hippocampus volumetry

High-resolution MRI determines structural changes in the brain in vivo. Significant atrophy of the hippocampal formation can be demonstrated by MRI even in preclinical stages of AD and predict later conversion to AD with about

Table 1 MRI as a diagnostic marker

Stage I	Technical characteristics DTI, cortical thickness, substantia innominata
Stage II	Sensitivity/specificity in selected clinical samples VBM, DBM, ERC
Stage III	Predictive value in an intent to diagnose design Hippocampus, BBS
Stage IV	Efficacy in routine diagnostics –

80% accuracy [7, 8]. Manual volumetric methods are currently the gold standard to determine the hippocampal volume, but they are time intensive (Fig. 1). Hippocampal volumetry is the best-established structural biomarker for AD, particularly for early diagnosis, and appears to be suitable for risk stratification of MCI subjects in treatment trials [9]. Multicenter diagnostic studies are currently being conducted on manual hippocampal volumetry within the German Dementia Network to establish whether it would be suitable for broader clinical application [10]. However, the manual measurement is still very labor-intensive and is not yet set to become a routine diagnostic test in the foreseeable future.

Several studies have looked at the temporal pattern of hippocampal atrophy in AD patients. Atrophy rates of 3–7% per annum were demonstrated [11, 12], whereas healthy controls have a maximum atrophy rate of 0.9% in later life [13]. Thus, hippocampal volume is a potential structural marker of disease progression in AD. The hippocampus volumetry approach has already been implemented as a secondary end point in several pharmacological trials. Regulatory authorities such as European Medicines Agency and Food and Drug Administration (FDA) have expressed an increasing interest in the development and use of potential surrogate markers of disease modification in secondary preventive trials on AD and risk stages of AD [14]. MRI-based volumetry, particularly of the hippocampus, might play an important role in this respect.

The application of hippocampal volumetry might be further improved by the application of fully automated procedures. Automated methods have been developed that have a good correlation with manual measurements and reduce the measurement time from 2 to 1/2 h [15, 16]. The automated protocols of hippocampal volumetry in AD patients, however, still need to be comprehensively evaluated. An interesting extension of automated analysis of hippocampus is the determination of shape differences with aging or disease. Based on high parametric deformation algorithms, shape models of the hippocampus can automatically be determined. Data-reducing approaches, such as principal component analysis, allow extraction of characteristic parameters from these individual shape models that can be compared between diagnostic groups. In a small scale study on 18 AD patients and 26 controls, this approach yielded 67% sensitivity and 85% specificity in the discrimination between AD patients and controls [17]. Although these levels of accuracy are still not very satisfying, further refinement of these techniques may help us not only to detect early changes in hippocampal volumes but also to better understand the characteristic sites of pathological changes within the hippocampus and their dynamic evolvement over time. This may yield new insight into the selectivity of the AD pathological process and may even be used to define endophenotypical subgroups on the structural brain system level that may differ in respect to response to treatment, familial risk or genetic background.

Volumetry of the entorhinal cortex

Another very interesting structure for the early diagnosis of AD is the entorhinal cortex, which lies adjacent to the hippocampus (Fig. 2). This area is thought to be affected by the neurodegenerative process at a particularly early stage. Studies have shown that entorhinal cortex volumetry is unlikely to provide any additional benefit in patients with manifest AD [18–21]; however, at the MCI stage, it may

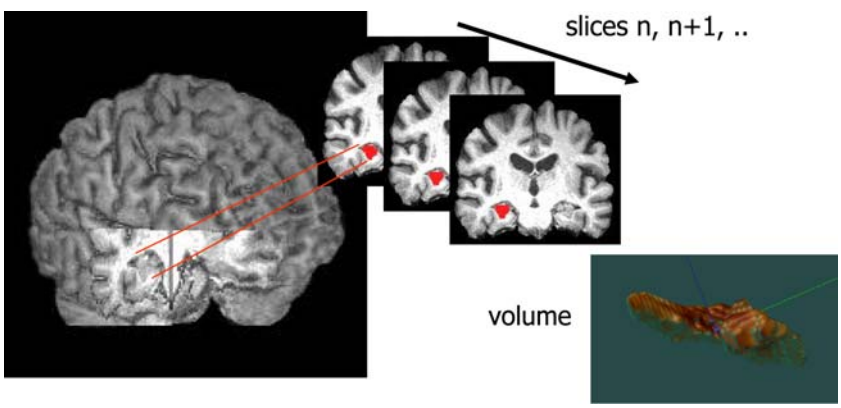

Fig. 1 Manual measurement of hippocampus volume. The ROI is manually defined in consecutive slices covering the hippocampus. The volume then is determined from summing all voxels contained in the ROI across all slices

improve prognostic efficiency by a few percent compared with hippocampal volumetry [19, 22]. It should be remembered, however, that entorhinal cortex volumetry is considerably more laborious than hippocampal volumetry and that automated procedures are not yet available for this structure. Presently, data are not sufficiently available to reliably assess whether the entorhinal cortex volume offers an additional benefit over the hippocampal volume as a surrogate end point to evaluate the efficiency of a potential disease modifying treatment.

One important aspect of the use of hippocampal and entorhinal cortex volumetry (or any other volumetric marker derived from MRI) is the question of the added value of these measures compared to more widely available and less expensive markers such as neuropsychological testing. Research into this important aspect is still very limited but will become ever more important given the increasing demands on the national health systems. Devanand et al. [23] have addressed this question in a longitudinal study of 63 controls and 139 MCI patients, 37 of which converted to AD during a mean follow-up interval of 3 years. Extended neuropsychology, together with age, yielded an overall accuracy for the prediction of AD to MCI of 80% that was increased to 87% when volumes of hippocampus and entorhinal cortex were added (Fig. 3). Conclusions from this study, however, are limited because the approach did not use cross-validation of their model such that overall levels of accuracy are very likely overestimated. If these numbers are confirmed, however, in subsequent studies, the use of hippocampus and entorhinal cortex volumetry may become particularly attractive to define study samples for secondary preventive trials, as an increase of 7% accuracy in the group selection may considerably increase the power of such trials.

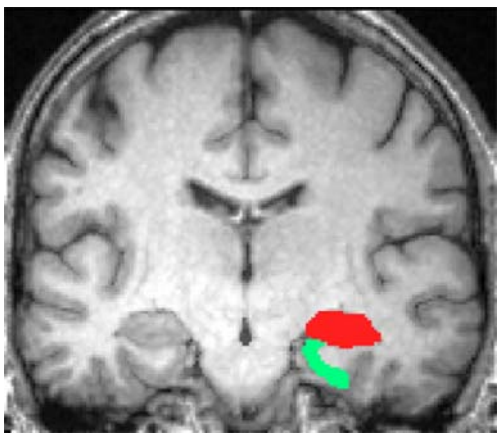

Fig. 2 Entorhinal cortex volumetry. Coronal section through the medial temporal lobe showing the location of the hippocampus (*red*) and the entorhinal cortex (*green*)

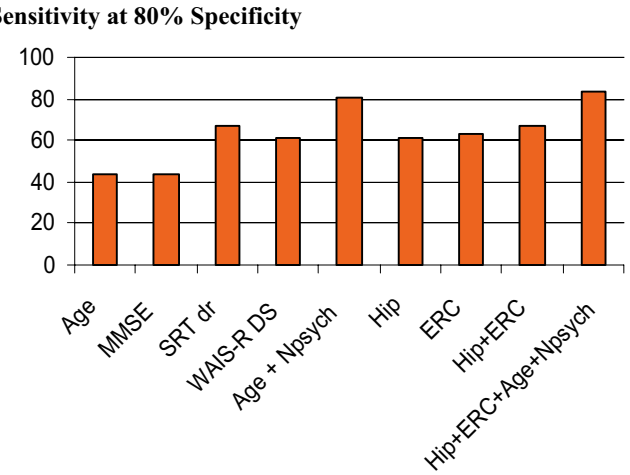

Fig. 3 Added value of hippocampus and entorhinal cortex volumetry for the prediction of AD in MCI. Sensitivity (at specificity of 80%) of prediction of conversion into AD in 139 MCI patients after 3 years of follow-up based on age, mini-mental state examination score, extended neuropsychology (*SRT dr* selective reminding test delayed recall, *WAIS-R DS* Wechsler Adult Intelligence Scale–revised digit symbol test). Data are from [23]

Automated data-driven methods

Because of the laborious nature of manual volumetric methods, automated methods have been developed to determine changes in the brain structure of AD patients using hypothesis- and rater-independent approaches. One of the best-established methods is the automated measurement of the whole-brain volume over time, which is already being used as a secondary end point in clinical treatment trials. This method demonstrated an atrophy rate of approximately 2.5% whole-brain volume reduction in AD patients over the course of 1 year, compared with only 0.4–0.9% in healthy controls [24]. However, the heuristic value of this method is limited, as only global effects can be recorded without providing information about regionally differentiated effects.

Voxel-based volumetry

The most widely published automated postprocessing method to date is voxel-based morphometry (VBM). The method is based on a low-dimensional spatial transformation of brain scans into a common reference space to get rid of global differences in brain size and shape. After segmentation, differences in grey matter volumes remaining on a local scale after accounting for global differences are the parameters of interest that drive a voxel-based univariate statistic [25] (Fig. 4). In a modified form of VBM, the normalisation process is iterated such that the final normalisation parameters are driven by brain grey matter only

[26]. This modification is supposed to increase the validity of the results by reducing the influence of non-brain tissue. When VBM began to be more widely used, it became the centre of a controversial discussion. Several authors pointed out that the distinction between global and local effects was arbitrary. They expressed the concern that the effects found in VBM studies was driven by differences in registration accuracy rather than by neurobiological differences in extent of local atrophy [27]. The controversy has still not been resolved. However, in the meantime, a large range of studies in a large variety of disease conditions, including AD, have replicated essential features of earlier quantitative neuropathological and manual volumetric studies. Thus, although theoretical assumptions underlying the application of VBM remain unvalidated, the approach itself has found a broad application and, from a pragmatic point of view, appears to yield reliable and valid results.

In AD, VBM consistently shows atrophy in the cortical grey matter in the region of the mediotemporal lobes and lateral temporal and parietal association areas [28, 29]. In MCI subjects, involvement of the mediotemporal lobe and lateral association areas of the temporal and parietal lobes was demonstrated using this method [30, 31]. Interestingly, significant atrophy of mediotemporal, laterotemporal and parietal association areas was observed in a genetic-risk model even before clinical symptoms were manifested, indicating preclinical neurodegeneration in the neocortical association areas [32, 33]. One study demonstrated a considerably different pattern of cortical atrophy between subjects with MCI who went on to develop AD in the subsequent clinical course and those whose cognitive performance remained stable [34]. The patients who converted to AD showed a pattern of atrophy that was largely consistent with that of early AD [35]. VBM, however, offers no easy and convenient way of making an individual diagnosis, as it is based on group statistics. In the last few years, approaches have been developed to apply VBM to individual subjects for the risk prediction of AD. Hirata et al. [36] determined the brain regions that showed the largest extent of atrophy in a training set of 30 AD patients and 40 controls. In an independent test set, then, the individual *z* scores for these regions were determined, i.e. the deviation of each individual region from the mean of the control group. Based on the individual *z* scores, discrimination between the AD patients and the controls in the test set reached 87% accuracy, based mainly on atrophy in the entorhinal cortex. The approach is interesting, as it requires minimal user–input and already has been cross-validated in a small sample. However, because of the a priori selection of the region of interest (ROI) in the training set, this approach loses one advantage of VBM, namely the scanning of the entire brain for significant differences between groups.

Deformation-based morphometry

Whereas VBM transforms brain images into a standard space to compensate for global differences but preserves

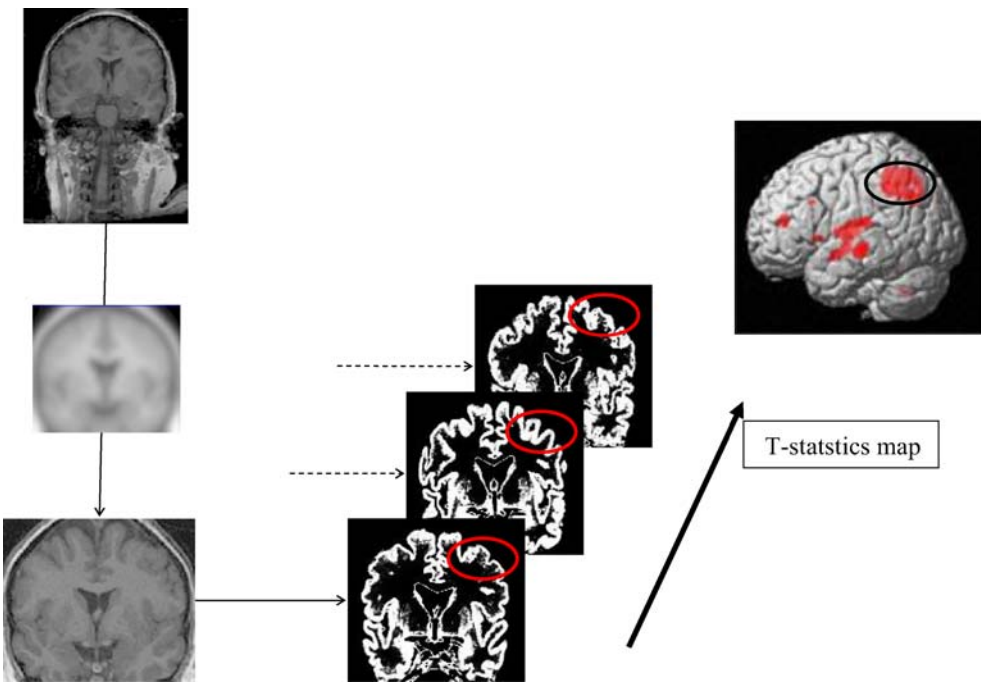

Fig. 4 The processing stream of classical VBM. In its most simple version, VBM consists of transforming the native scans into a reference space (template in MNI standard space), segmentation of normalised scans into grey and white matter and CSF spaces, smoothing of segmented grey matter maps with a Gaussian kernel and finally running a univariate linear model at each voxel across all scans in corresponding locations [25]

local differences in cortical gray matter distribution, deformation-based morphometry (DBM) transforms the brain volumes at high resolution to a standard template to completely eliminate the anatomical differences between the brains. The anatomic information then does not lay in the MRI images themselves but in the deformation fields that are required to transform the patient's brain into a standard brain. These deformation fields offer a multivariate vector field of localization information from which regional volume effects can be extrapolated (Fig. 5).

In a recent study using multivariate principal component analysis, DBM was used to calculate an individual risk for the presence of AD in MCI subjects [37]. This method yielded 80% accuracy in the discrimination between a training set of AD patients and healthy controls. Interestingly, in a cross-validation using a test set of MCI subjects, the accuracy in distinguishing between patients who developed dementia and subjects who remained cognitively stable over a period of 1 1/2 years was 80%. This method can be used for individual risk prediction and allows searching the entire brain for significant changes. It has yet to be applied more extensively to a larger number of MRI scans. An extension of this approach is based on machine learning algorithms [38, 39]. A recent study applied a machine-learning algorithm based on a support vector machine-recursive feature elimination technique to 15 MCI patients and 15 controls followed over about 6 years, where the most recent MRI scans were used to determine a distributed pattern of brain changes based on a feature selection algorithm that discriminated MCI patients from the controls [40]. Accuracy of separating MCI patients and controls was 100% using this approach but was 90% after using leave-one-out classification. However, the approach did not discriminate between MCI converters and non-converters, which is the clinically more relevant question than the discrimination between MCI patients and healthy subjects. The approach also did not use an independent test set but leave-one-out classification to estimate a priori accuracy.

Analysis of cortical thickness

Another promising fully automated method involves determining the cortical thickness of the entire cortical mantle, particularly the neocortical association areas and the entorhinal cortex [41]. Group separation showed an accuracy of more than 90% in distinguishing AD patients from healthy controls [42]. However, this method has yet to be evaluated in an independent group, and the accuracy of this method in predicting conversion to AD in MCI subjects has not yet been studied.

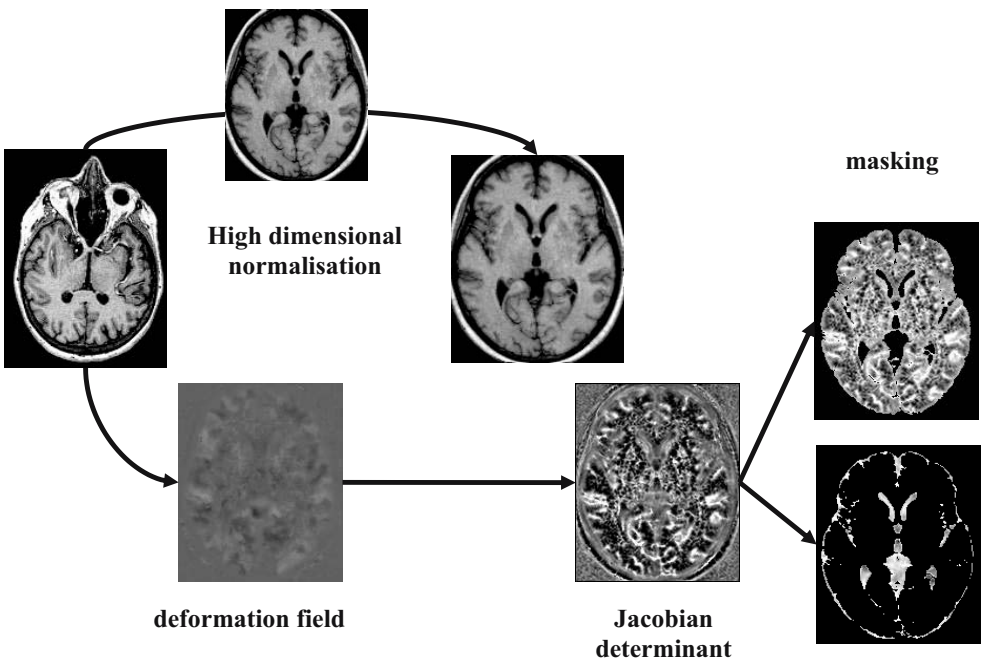

Fig. 5 An exemplary processing stream of deformation based morphometry. The brain volume in native space is spatially transformed to a standard brain in such a way that the original brain is nearly identical to the target brain. The anatomical information now is entirely contaioned within the deformation field. From the deformation field information can be derived on the extent of shrinkage or expansion that is required at each voxel to transform the native to the standard brain. This information is extracted from the multivariate deformation field using the voxel-wise Jacobian determinant maps. These maps, after adequate masking, then can be subjected to univariate or multivariate group analyses of the extent of local atrophy

Analysis of the cholinergic nuclei of the basal forebrain

AD has been associated with early changes in the cholinergic projections of the basal forebrain. The anatomy of the cholinergic nuclei is depicted in Fig. 6. The imaging of structural changes in the region of the cholinergic nuclei of the basal forebrain was recently established using a combination of automated methods with regional information, so called image regression analysis (Fig. 7). As the substantia innominata of the basal forebrain, the larger anatomical region that contains the cholinergic nuclei of the nucleus basalis Meynert (the main source of cholinergic projections into the cerebral cortex in the human brain), has no anatomically defined lateral borders, a square ROI was defined in the spatially normalised MRI scans to extract the signal within the substantia innominata. Subsequently, a linear statistics is calculated across subjects at each voxel within the ROI. Using this technique, we showed a signal reduction in the region of the lateral and medial nuclei of the basal nucleus of Meynert for the first time in vivo [43, 44]. The location of the signal changes were compared to locations of the nucleus basalis Meynert nuclei in a post mortem brain where the anatomical information was transferred into MRI space using post-mortem MRI. The results of this study agree with post-mortem evidence for early neuropathological involvement of the cholinergic projections in AD.

Summary of volumetric MRI

Hippocampus volumetry, currently, is the best-established biomarker for AD in the field of structural neuroimaging; however, because of the laborious nature of the manual procedure, it will only be used in clinical studies for the risk

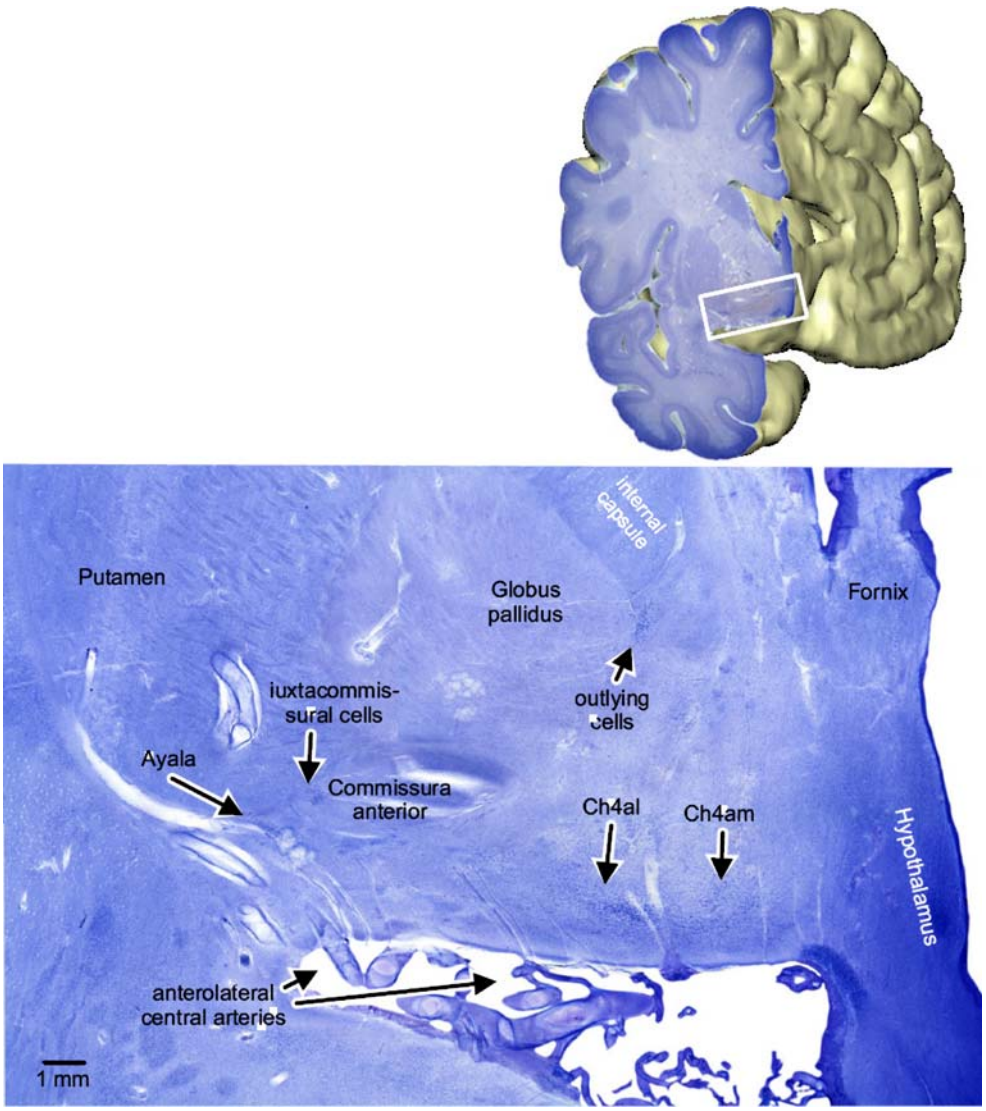

Fig. 6 Anatomy of the human basal forebrain. Histological section after Gallocyanin staining through the basal forebrain (*left hemisphere*) of a 57-year-old man (cause of death: ruptured ulcus ventriculi, no indication of cognitive impairment ante-mortem). The superior 3D reconstruction of the brain shows the localization of the histological section through the basal forebrain. The inferior section shows the localization of the medial and lateral nuclei of the nucleus basalis Meynert (Ch4 am and Ch4 al) according to Mesulam's terminology [73]. More *lateral*, one can see the localization of Ayla's nucleus or nucleus subputaminalis, a band of cholinergic cells that has exclusively been described in the human brain and has been associated with projections into cortical language areas [44]

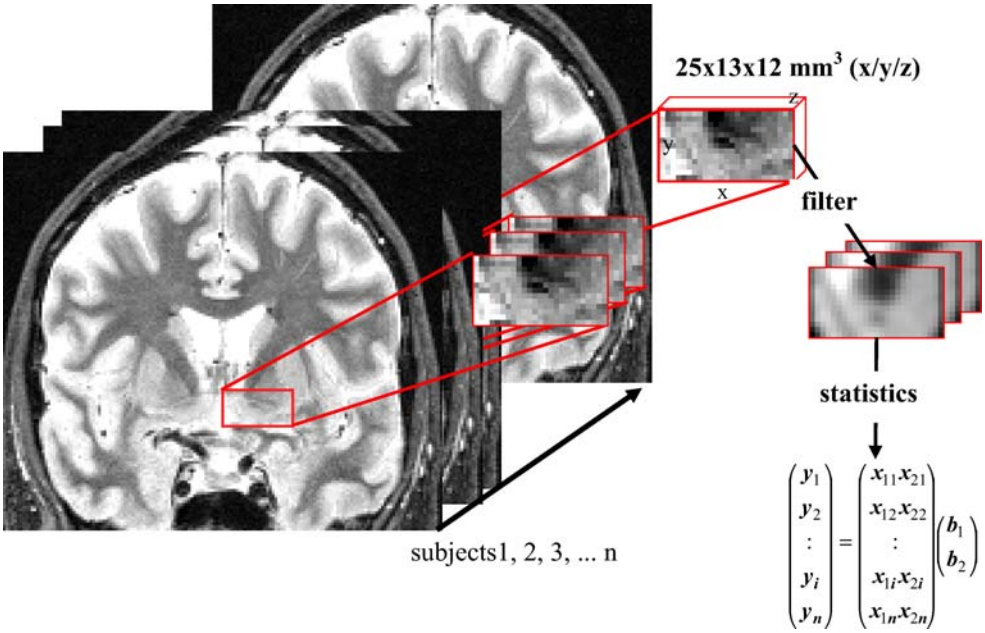

Fig. 7 Image regression analysis of basal forebrain atrophy in AD. Proton density weighted MRI scans are spatially transformed into standard space. Then a square ROI is placed on the substantia innominata (the area of the cholinergic basal forebrain) according to the middle of the anterior commissure. Signal intensity within the *square* ROI is extracted from each scan and after smoothing subjected to a univariate voxel-wise statistics

stratification of study populations and as a secondary end point for potential disease-modifying treatment effects in the foreseeable future. Automated data-driven and rater-independent methods are currently being investigated to detect regional changes, namely VBM, DBM, and the measurement of cortical thickness. In the medium term, particularly in combination with multivariate statistical analysis methods, analysis algorithms are likely to be identified that are at least as effective as hippocampal volumetry in the early detection of AD in MCI subjects and will, therefore, be used in pharmacological studies. However, if secondary preventive treatment approaches will become available in the next years, the use of these kinds of automated methods for the early detection of AD will be of socio-economic importance in routine diagnostics as well. Besides their application as biomarkers, MRI-based volumetry serves as complementary approach to post-mortem studies of neuronal degeneration in AD. The main determinants of cognitive impairment in AD are the density of synapses and neurons in distributed cortical and subcortical networks [45]. MRI-based measures of regional grey matter volume and associated multivariate analysis techniques of regional interactions of grey matter densities provide insight in the onset and temporal dynamics of cortical atrophy as close proxy of regional neuronal loss [46] and basis of functional impairment in specific neuronal networks [47]. The ability of MRI-based techniques to unravel pathological mechanisms in AD has greatly been improved through the advent of new acquisitions techniques, such as DTI and fibre tracking. This relatively new technique provides insight into the microstructural integrity of neuronal fibre tracts that are the main determinant of intracortical connectivity and are early affected by AD pathology.

Diffusion tensor imaging

In the context of diffusion-weighted MRI, diffusion describes the stochastic movement of molecules in liquids, called Brownian molecular motion. In unconstrained media, this movement is isotropic; i.e. it can be described by a Gaussian probability distribution across all spatial directions. In biological tissue, such as the cerebral white matter, however, the molecular motion of water molecules is restricted by the cellular microstructure. Diffusion barriers, such as the neuronal membrane, myelin sheets and intra-axonal transport molecules, yield a preferred spatial direction of the molecular movement. This directionality of diffusion is called anisotropy.

The measured diffusion coefficient in MRI represents the interaction of the diffusing molecules with cellular structures and is called the apparent diffusion coefficient (ADC). Since the 1980s, the measurement of the ADC has been employed using diffusion-weighted MRI DWI for the early detection of ischemic brain areas [48]. The ADC, however, does not assess the directionality of molecular movement.

In 1994, Basser et al. [49] introduced the formalism of the diffusion tensor into MRI. It considers the fact that diffusion is a three-dimensional process that is not sufficiently described by a scalar measure such as ADC. Therefore, diffusion gradients are applied in several spatial directions to determine a multidimensional diffusion tensor. From these diffusion tensor measures of movement, directionality can be derived. Fractional anisotropy (FA) and mean diffusivity (MD) are frequently employed parameters from DTI acquisitions in the cerebral white matter. FA describes the directionality of fibre tracts; MD determines the overall diffusivity. Both parameters serve as

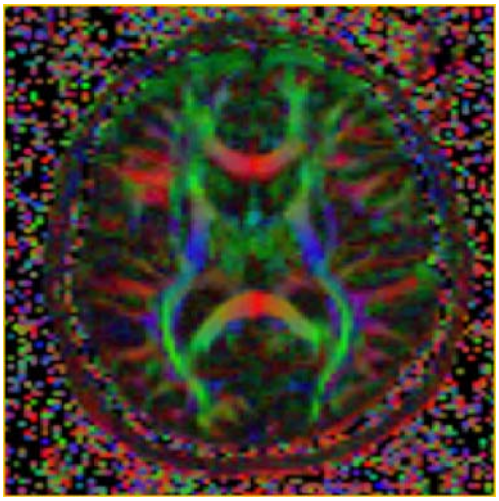

Fig. 8 Colour coding of fibre tracts in the human brain. Fractional anisotropy maps show further details by colour-coding the directionality of white matter fibres: *red* indicates left–right; *green*, anterior–posterior and *blue*, cranio-caudal orientation. Colour-coded images not only show the location of white matter tracts but also their prevalent direction using the tensor information. Note the large *left–right* connection of the corpus callosum and the head-to-feet orientated bundles of the cortico-spinal tract (pyramidal tract)

measures of fibre tract integrity (Fig. 8). Using the multivariate information of diffusion tensors, in vivo fibre tracking can be performed. This allows reconstructing the fibre tracts originating from selected white matter areas based on individual DTI scans. Figure 9 gives an example of a reconstruction from fibre tracts originating in the corpus callosum and the pyramidal tract.

The analysis of DTI data is a rapidly developing field. Fibre tracking approaches have not yet widely been employed in the assessment of dementia because only recently statistical models have become available to perform group analyses of fibre tracts. The majority of studies have employed ROI-based approaches in selected brain areas. Recently, automated voxel-based analysis of FA maps has been developed for application in AD. In the following, we will give a short overview of the findings.

FA and MD changes in AD and MCI

Consistent with a decline of cortical connectivity and impairment of axonal and dendritic integrity [50–53] early in the disease process of AD, studies using DTI found a decline of fractional anisotropy as a marker of fibre loss in posterior corpus callosum, fasciculus longitudinalis superior, temporal lobe and cingulate white matter [54–63]. One study using voxel-based analysis of low-dimensionally normalised FA maps found significant reductions of FA in posterior white matter areas [64]. However, low-dimensional normalization as employed in this study is not able to separate reductions of FA from the effects of atrophy. Employing multivariate analysis of high-dimensionally normalised FA maps, we had found significant decline of FA in intracortical projecting fibre tracts in the AD patients compared to the controls [65]. The method accounts for the effects of atrophy and, by using multivariate analysis based on principal component analysis, uncovers the entire network of fibre tract changes in AD. In mild cognitive impairment, evidence from DTI studies is more limited. However, several studies using ROI-based analysis showed significant reductions of the marker of fibre tract integrity in subcortical white matter, including the posterior cingulate [61, 66], hippocampus [67, 68] and posterior white matter [56, 69]. Similar results were obtained using automated voxel-based analysis [64, 70]. However, it is again not clear whether these findings were confounded by the effects of atrophy. Interestingly, diffusion changes in the fornix and the orbitofrontal white matter could even be detected in non-demented mutation carriers of familial AD [71].

DTI has not yet been widely employed for the early diagnosis of AD. Müller et al. [68] have compared the ability of FA and MD measures in the hippocampus with hippocampus volume to discriminate between 18 subjects with MCI and 18 controls. They found superior accuracy of group separation based on diffusion compared to volume measurements. Clearly, the data basis is not broad enough to draw any further conclusions from these data. However, these findings encourage further research in the possible application of DTI as a useful diagnostic tool in AD.

Summary of DTI

Over the last decade, DTI has arisen as one of the biggest advances in clinical imaging. We are just beginning to

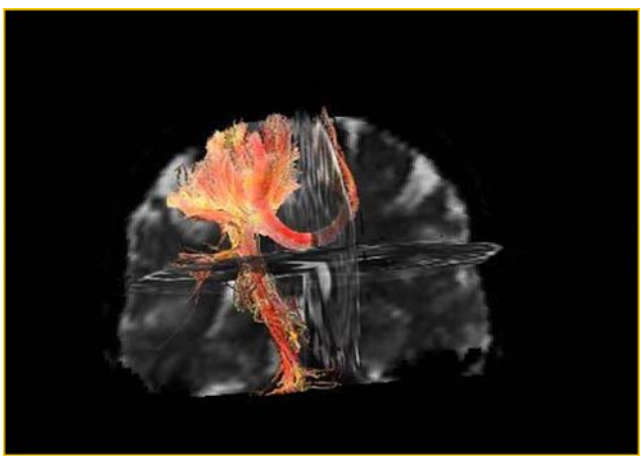

Fig. 9 DTI-based tractography. Tractographic reconstruction of a DTI dataset. By tracking principal diffusion direction (i.e. the eigenvector of the diffusion tensor) white matter tracts are visualised. The figure shows the pyramidal tract and *left–right* connection via the corpus callosum

explore the potential of this relatively new and powerful technology. Presently, there seem to lay three major lines of research ahead:

1. The methodology of analysis of DTI-based tensor maps is rapidly evolving. However, the gap between the available methodology and its application is still wide. In the next few years, however, we will be able to apply analysis algorithms that make use of the multivariate nature of the data obtained. The majority of experimentally applied approaches so far, be it ROI- or voxel-based, are based on the analysis of scalar maps that are extracted from the originally multivariate tensor fields. It will be of high relevance not only for the field of AD research but for the entire field of neuroscience to develop algorithms that make use of the entire dimensionality of these data, eventually making it available for diagnostic purposes but, perhaps, even more important, to gain further insight into the connectivity and plastic organization of the human brain.
2. DTI techniques may be evaluated for their diagnostic use involving the differential diagnoses of dementias, such as vascular dementia. From a theoretical point of view, microstructural alterations of the cerebral fibre system should be among the earliest changes in both neurodegenerative disease and cerebral ischemia. The data from studies in at-risk patients are not conclusive to date; however, the data basis is very narrow. Therefore, the application of the already available DTI acquisitions and analysis algorithms to at-risk groups of dementia will be required to decide whether DTI bears any advantage over conventional volumetric MRI for the early diagnosis of AD or the differentiation between AD and vascular dementia.
3. A particular gain in information has to be expected from the combination of DTI with other imaging modalities, such as functional MRI, structural MRI [72], or EEG. The combination approach is destined to greatly enhance our understanding not only of the pathophysiology of neurodegenerative disorder but also of the functional and structural basis of normal cognition in the human brain.

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References

1. Lobo A, Launer LJ, Fratiglioni L, Andersen K, Di Carlo A, Breteler MM, et al. Prevalence of dementia and major subtypes in Europe: a collaborative study of population-based cohorts. Neurologic Diseases in the Elderly Research Group. Neurology 2000;54:S4–9.
2. Brookmeyer R, Johnson E, Ziegler-Graham K, Arrighi HM. Forecasting the global burden of Alzheimer's disease. Baltimore, USA: The Berkeley Electronic Press; 2007.
3. Petersen RC, Doody R, Kurz A, Mohs RC, Morris JC, Rabins PV, et al. Current concepts in mild cognitive impairment. Arch Neurol. 2001;58:1985–92.
4. Birks J, Flicker L. Donepezil for mild cognitive impairment. Cochrane Database Syst Rev 2006;3:CD006104.
5. Loy C, Schneider L. Galantamine for Alzheimer's disease and mild cognitive impairment. Cochrane Database Syst Rev. 2006; CD001747.
6. Jensen K, Abel U. Methodik diagnostischer Validierungsstudien: Fehler in der Studienplanung und Auswertung. Med Klinik. 1999;94:522–9.
7. Wang PN, Lirng JF, Lin KN, Chang FC, Liu HC. Prediction of Alzheimer's disease in mild cognitive impairment: a prospective study in Taiwan. Neurobiol Aging. 2006;27:1797–806.
8. Jack CR Jr, Petersen RC, Xu YC, O'Brien PC, Smith GE, Ivnik RJ, et al. Prediction of AD with MRI-based hippocampal volume in mild cognitive impairment. Neurology. 1999;52:1397–403.
9. Chetelat G, Baron JC. Early diagnosis of Alzheimer's disease: contribution of structural neuroimaging. Neuroimage. 2003; 18:525–41.
10. Ewers M, Teipel SJ, Dietrich O, Schonberg SO, Jessen F, Heun R, et al. Multicenter assessment of reliability of cranial MRI. Neurobiol Aging. 2006;27:1051–9.
11. Jack CR, Petersen RC, Xu Y, O'Brien PC, Smith GE, Ivnik RJ, et al. Rate of medial temporal lobe atrophy in typical aging and Alzheimer's disease. Neurology. 1998;51:993–9.
12. Laakso MP, Lehtovirta M, Partanen K, Riekkinen PJ, Soininen H. Hippocampus in Alzheimer's disease: a 3-year follow-up MRI study. Biol Psychiatry. 2000;47:557–61.
13. Raz N, Rodrigue KM, Head D, Kennedy KM, Acker JD. Differential aging of the medial temporal lobe: a study of a five-year change. Neurology. 2004;62:433–8.
14. Broich K. Outcome measures in clinical trials on medicinal products for the treatment of dementia: a European regulatory perspective. Int Psychogeriatr. 2007;19:509–24.
15. Csernansky JG, Wang L, Swank J, Miller JP, Gado M, McKeel D, et al. Preclinical detection of Alzheimer's disease: hippocampal shape and volume predict dementia onset in the elderly. Neuroimage. 2005;25:783–92.
16. Hsu YY, Schuff N, Du AT, Mark K, Zhu X, Hardin D, et al. Comparison of automated and manual MRI volumetry of hippocampus in normal aging and dementia. J Magn Reson Imaging. 2002;16:305–10.
17. Wang L, Beg F, Ratnanather T, Ceritoglu C, Younes L, Morris JC, et al. Large deformation diffeomorphism and momentum based hippocampal shape discrimination in dementia of the Alzheimer type. IEEE Trans Med Imag. 2007;26:462–70.
18. Krasuski JS, Alexander GE, Horwitz B, Daly EM, Murphy DGM, Rapoport SI, et al. Volumes of medial temporal lobe structures in patients with Alzheimer's disease and mild cognitive impairment (and in healthy controls). Biol Psychiatry. 1998;43:60–8.
19. Pennanen C, Kivipelto M, Tuomainen S, Hartikainen P, Hanninen T, Laakso MP, et al. Hippocampus and entorhinal cortex in mild cognitive impairment and early AD. Neurobiol Aging. 2004; 25:303–10.

20. Teipel SJ, Pruessner JC, Faltraco F, Born C, Rocha-Unold M, Evans A, et al. Comprehensive dissection of the medial temporal lobe in AD: measurement of hippocampus, amygdala, entorhinal, perirhinal and parahippocampal cortices using MRI. J Neurol. 2006;253:794–800.
21. Xu Y, Jack CR Jr, O'Brien PC, Kokmen E, Smith GE, Ivnik RJ, et al. Usefulness of MRI measures of entorhinal cortex versus hippocampus in AD. Neurology. 2000;54:1760–7.
22. Du AT, Schuff N, Amend D, Laakso MP, Hsu YY, Jagust WJ, et al. Magnetic resonance imaging of the entorhinal cortex and hippocampus in mild cognitive impairment and Alzheimer's disease. J Neurol Neurosurg Psychiatry. 2001;71:441–7.
23. Devanand DP, Pradhaban G, Liu X, Khandji A, De Santi S, Segal S, et al. Hippocampal and entorhinal atrophy in mild cognitive impairment: prediction of Alzheimer disease. Neurology. 2007; 68:828–36.
24. Fox NC, Cousens S, Scahill R, Harvey RJ, Rossor MN. Using serial registered brain magnetic resonance imaging to measure disease progression in Alzheimer disease: power calculations and estimates of sample size to detect treatment effects. Arch Neurol. 2000;57:339–44.
25. Ashburner J, Friston KJ. Voxel-based morphometry-the methods. Neuroimage. 2000;11:805–21.
26. Good CD, Johnsrude IS, Ashburner J, Henson RN, Friston KJ, Frackowiak RS. A voxel-based morphometric study of ageing in 465 normal adult human brains. Neuroimage. 2001;14:21–36.
27. Bookstein FL. "Voxel-based morphometry" should not be used with imperfectly registered images. Neuroimage. 2001;14:1454–62.
28. Baron JC, Chetelat G, Desgranges B, Perchey G, Landeau B, de la Sayette V, et al. In vivo mapping of gray matter loss with voxel-based morphometry in mild Alzheimer's disease. Neuroimage. 2001;14:298–309.
29. Busatto GF, Garrido GE, Almeida OP, Castro CC, Camargo CH, Cid CG, et al. A voxel-based morphometry study of temporal lobe gray matter reductions in Alzheimer's disease. Neurobiol Aging. 2003;24:221–31.
30. Chetelat G, Desgranges B, De La Sayette V, Viader F, Eustache F, Baron JC. Mapping gray matter loss with voxel-based morphometry in mild cognitive impairment. Neuroreport. 2002;13:1939–43.
31. Pennanen C, Testa C, Laakso MP, Hallikainen M, Helkala EL, Hanninen T, et al. A voxel based morphometry study on mild cognitive impairment. J Neurol Neurosurg Psychiatry. 2005; 76:11–4.
32. Teipel SJ, Alexander GE, Schapiro MB, Moller HJ, Rapoport SI, Hampel H. Age-related cortical grey matter reductions in non-demented Down's syndrome adults determined by MRI with voxel-based morphometry. Brain. 2004;127:811–24.
33. Teipel SJ, Hampel H. Neuroanatomy of down syndrome in vivo: a model of preclinical Alzheimer's disease. Behav Genet. 2006; 36:405–15.
34. Chetelat G, Landeau B, Eustache F, Mezenge F, Viader F, de la Sayette V, et al. Using voxel-based morphometry to map the structural changes associated with rapid conversion in MCI: a longitudinal MRI study. Neuroimage. 2005;27:934–46.
35. Karas GB, Scheltens P, Rombouts SA, Visser PJ, van Schijndel RA, Fox NC, et al. Global and local gray matter loss in mild cognitive impairment and Alzheimer's disease. Neuroimage. 2004;23:708–16.
36. Hirata Y, Matsuda H, Nemoto K, Ohnishi T, Hirao K, Yamashita F, et al. Voxel-based morphometry to discriminate early Alzheimer's disease from controls. Neurosci Lett. 2005;382:269–74.
37. Teipel SJ, Born C, Ewers M, Bokde ALW, Reiser MF, Möller H-J, et al. Multivariate deformation-based analysis of brain atrophy to predict Alzheimer's disease in mild cognitive impairment. Neuroimage. 2007;38:13–24.
38. Fan Y, Shen D, Davatzikos C. Classification of structural images via high-dimensional image warping, robust feature extraction, and SVM. Med Image Comput. Comput Assist Interv Int Conf Med Image Comput. Comput Assist Interv 2005;8:1–8.
39. Mourao-Miranda J, Bokde AL, Born C, Hampel H, Stetter M. Classifying brain states and determining the discriminating activation patterns: support vector machine on functional MRI data. Neuroimage. 2005;28:980–95.
40. Davatzikos C, Fan Y, Wu X, Shen D, Resnick SM. Detection of prodromal Alzheimer's disease via pattern classification of MRI. Neurobiol Aging. 2007 (in press).
41. Lerch J, Pruessner JC, Evans AC, Zijdenbos A, Teipel S, Buerger K, et al. Cortical thickness in Alzheimer's disease. Neuroimage 2002;1(Suppl 1):7.
42. Lerch JP, Pruessner J, Zijdenbos AP, Collins DL, Teipel SJ, Hampel H, et al. Automated cortical thickness measurements from MRI can accurately separate Alzheimer's patients from normal elderly controls. Neurobiol Aging 2008;29(1):23–30.
43. Teipel SJ, Flatz WH, Heinsen H, Bokde AL, Schoenberg SO, Stockel S, et al. Measurement of basal forebrain atrophy in Alzheimer's disease using MRI. Brain. 2005;128:2626–44.
44. Heinsen H, Hampel H, Teipel SJ. Computer-assisted 3D reconstruction of the Nucleus basalis complex, including the Nucleus subputaminalis. Brain. 2006;129:E43.
45. Giannakopoulos P, Herrmann FR, Bussiere T, Bouras C, Kovari E, Perl DP, et al. Tangle and neuron numbers, but not amyloid load, predict cognitive status in Alzheimer's disease. Neurology. 2003; 60:1495–500.
46. Smith AD. Commentary: imaging the progression of Alzheimer pathology through the brain. PNAS. 2002;99:4135–7.
47. Teipel SJ, Bokde ALW, Born C, Meindl T, Reiser MF, Möller H-J, et al. The morphological substrate of face matching in healthy aging and mild cognitive impairment: a combined MRI-fMRI study. Brain 2007;130(7):1745–58.
48. Moseley ME, Kucharczyk J, Mintorovitch J, Cohen Y, Kurhanewicz J, Derugin N, et al. Diffusion-weighted MR imaging of acute stroke: correlation with T2-weighted and magnetic susceptibility-enhanced MR imaging in cats. Am J Neuroradiol. 1990;11:423–9.
49. Basser PJ, Mattiello J, LeBihan D. MR diffusion tensor spectroscopy and imaging. Biophys J. 1994;66:259–67.
50. Su JH, Cummings BJ, Cotman CW. Identification and distribution of axonal dystrophic neurites in Alzheimer's disease. Brain Res. 1993;625:228–37.
51. Kowall NW, Kosik KS. Axonal disruption and aberrant localization of tau protein characterize the neuropil pathology of Alzheimer's disease. Ann Neurol. 1987;22:639–43.
52. Brun A, Englund E. A white matter disorder in dementia of the Alzheimer type: a pathoanatomical study. Ann Neurol. 1986; 19:253–62.
53. Leys D, Pruvo JP, Parent M, Vermersch P, Soetaert G, Steinling M, et al. Could Wallerian degeneration contribute to "leukoaraiosis" in subjects free of any vascular disorder. J Neurol Neurosurg Psychiatry. 1991;54:46–50.
54. Stahl R, Dietrich O, Teipel SJ, Hampel H, Reiser MF, Schoenberg SO. White matter damage in Alzheimer's disease and in mild cognitive impairment: assessment with diffusion tensor MRI using parallel imaging techniques. Radiology. 2007;243:483–92.
55. Bozzali M, Falini A, Franceschi M, Cercignani M, Zuffi M, Scotti G, et al. White matter damage in Alzheimer's disease assessed in vivo using diffusion tensor magnetic resonance imaging. J Neurol Neurosurg Psychiatry. 2002;72:742–6.
56. Fellgiebel A, Wille P, Muller MJ, Winterer G, Scheurich A, Vucurevic G, et al. Ultrastructural hippocampal and white matter alterations in mild cognitive impairment: a diffusion tensor imaging study. Dement Geriatr Cogn Disord. 2004;18:101–8.
57. Head D, Buckner RL, Shimony JS, Williams LE, Akbudak E, Conturo TE, et al. Differential vulnerability of anterior white matter in nondemented aging with minimal acceleration in

dementia of the Alzheimer type: evidence from diffusion tensor imaging. Cereb Cortex. 2004;14:410–23.
58. Rose SE, Chen F, Chalk JB, Zelaya FO, Strugnell WE, Benson M, et al. Loss of connectivity in Alzheimer's disease: an evaluation of white matter tract integrity with colour coded MR diffusion tensor imaging. J Neurol Neurosurg Psychiatry. 2000;69:528–30.
59. Takahashi S, Yonezawa H, Takahashi J, Kudo M, Inoue T, Tohgi H. Selective reduction of diffusion anisotropy in white matter of Alzheimer disease brains measured by 3.0 tesla magnetic resonance imaging. Neurosci Lett. 2002;332:45–8.
60. Yoshiura T, Mihara F, Ogomori K, Tanaka A, Kaneko K, Masuda K. Diffusion tensor in posterior cingulate gyrus: correlation with cognitive decline in Alzheimer's disease. Neuroreport. 2002;13:2299–302.
61. Fellgiebel A, Muller MJ, Wille P, Dellani PR, Scheurich A, Schmidt LG, et al. Color-coded diffusion-tensor-imaging of posterior cingulate fiber tracts in mild cognitive impairment. Neurobiol Aging. 2005;26:1193–8.
62. Müller MJ, Greverus D, Dellani PR, Weibrich C, Wille PR, Scheurich A, et al. Functional implications of hippocampal volume and diffusivity in mild cognitive impairment. Neuroimage. 2005;28:1033–42.
63. Naggara O, Oppenheim C, Rieu D, Raoux N, Rodrigo S, Dalla Barba G, et al. Diffusion tensor imaging in early Alzheimer's disease. Psychiatry Res. 2006;146:243–9.
64. Medina D, Detoledo-Morrell L, Urresta F, Gabrieli JD, Moseley M, Fleischman D, et al. White matter changes in mild cognitive impairment and AD: a diffusion tensor imaging study. Neurobiol Aging. 2006;27:663–72.
65. Teipel SJ, Stahl R, Dietrich O, Schoenberg SO, Perneczky R, Bokde AL, et al. Multivariate network analysis of fiber tract integrity in Alzheimer's disease. Neuroimage. 2007;34:985–95.
66. Zhang Y, Schuff N, Jahng GH, Bayne W, Mori S, Schad L, et al. Diffusion tensor imaging of cingulum fibers in mild cognitive impairment and Alzheimer disease. Neurology. 2007;68:13–9.
67. Fellgiebel A, Dellani PR, Greverus D, Scheurich A, Stoeter P, Muller MJ. Predicting conversion to dementia in mild cognitive impairment by volumetric and diffusivity measurements of the hippocampus. Psychiatry Res. 2006;146:283–7.
68. Muller MJ, Greverus D, Weibrich C, Dellani PR, Scheurich A, Stoeter P, et al. Diagnostic utility of hippocampal size and mean diffusivity in amnestic MCI. Neurobiol Aging. 2007;28:398–403.
69. Huang J, Auchus AP. Diffusion tensor imaging of normal appearing white matter and its correlation with cognitive functioning in mild cognitive impairment and Alzheimer's disease. Ann NY Acad Sci. 2007;1097:259–64.
70. Rose SE, McMahon KL, Janke AL, O'Dowd B, de Zubicaray G, Strudwick MW, et al. Diffusion indices on magnetic resonance imaging and neuropsychological performance in amnestic mild cognitive impairment. J Neurol Neurosurg Psychiatry. 2006; 77:1122–8.
71. Ringman JM, O'Neill J, Geschwind D, Medina L, Apostolova LG, Rodriguez Y, et al. Diffusion tensor imaging in preclinical and presymptomatic carriers of familial Alzheimer's disease mutations. Brain. 2007;130:1767–76.
72. Sydykova D, Stahl R, Dietrich O, Ewers M, Reiser MF, Schoenberg SO, et al. Fiber connections between the cerebral cortex and the corpus callosum in Alzheimer's disease: a diffusion tensor imaging and voxel-based morphometry study. Cereb Cortex 2007;17:2276–82.
73. Mesulam MM, Geula C. Nucleus basalis (Ch4) and cortical cholinergic innervation in the human brain: observations based on the distribution of acetylcholinesterase and choline acetyltransferase. J Comp Neurol. 1988;275:216–40.