Review

Clinical Use of Brain Volumetry

CME

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Upon completion of this educational activity, participants will be better able to assess the application of MRI-based brain volumetry for a wide range of neurologic conditions.

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Magnetic resonance imaging (MRI)-based brain volumetry is increasingly being used in the clinical setting to assess brain volume changes from structural MR images in a range of neurologic conditions. Measures of brain volumes have been shown to be valid biomarkers of the clinical state and progression by offering high reliability and robust inferences on the underlying disease-related mechanisms. This review critically examines the different scenarios of the application of MRI-based brain volumetry in neurology: 1) supporting disease diagnosis, 2) understanding mechanisms and tracking clinical progression of disease, and 3) monitoring treatment effect. These aspects will be discussed in a wide range of neurologic conditions, with particular emphasis on Alzheimer's disease and multiple sclerosis.

Key Words: volumetric MRI; brain atrophy; Alzheimer's disease; multiple sclerosis; parkinsonisms; epilepsy
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MAGNETIC RESONANCE IMAGING (MRI), because of the exclusive capacity of providing excellent anatomical detail in a safe setting, is currently the imaging modality of choice for assessing neurologic disorders. Decisions in the setting of clinical neurology mostly rely on qualitative (ie, visual) interpretation of structural brain images. On visual assessment, for example, global brain atrophy is recognized by an increase of cerebrospinal fluid (CSF) spaces and shrinkage of parenchymal structures. However, such an assessment can detect only macroscopic changes with a rather low level of interobserver agreement.

Quantitative assessment of brain volumes, obtained through volumetric MRI, has been increasingly applied in recent years to a wide range of neurologic conditions due to advances in computational technology. Its role should be complementary to that of visual assessment of brain structural images, with the specific aim of improving the detection of focal and subtle brain pathology. Volumetric methods, which have shown to be reliably performed at any MR center, are mainly based on brain segmentation, ie, the separation of the intracranial content into parenchymal and nonparenchymal tissue classes.

After a brief overview of the different volumetric MRI techniques, the review will assess the application of MRI-based brain volumetry for a wide range of neurologic conditions. The clinical use of MRI-derived brain volumetry will be framed in different contexts (Table 1): 1) supporting disease diagnosis, 2) understanding mechanisms and tracking clinical progression of disease, and 3) monitoring treatment effects.

OVERVIEW OF THE VOLUMETRIC MRI TECHNIQUES

The relatively large number of methods used in MRI clinical studies to assess brain volumes is summarized in Table 2. They could be simply divided into manual, semiautomated, and fully automated, depending on the amount of user intervention.

The prototype of *manual* methods has been the manual segmentation of limbic structures, such as hippocampus and amygdala. Past manual techniques have used 2D measures such as linear measures (eg, diameter) whereas, more recently, manual segmentation in the three planes of the space, through the outlining of regions of interest (ROIs), has been performed.

In order to provide a more objective assessment of brain volumes, advanced MRI techniques have developed several methods, which make use of computational algorithms. These may require some level of user intervention (*semiautomated*) or may be *fully automated*. Both have demonstrated accuracy and reproducibility and have been extensively used in a number of clinical studies, especially for the volumetric assessment of the whole brain and cerebral tissue types (eg, white matter [WM], gray matter [GM]). Fully automated computational methods are particularly attractive because they speed up analyses and allow the assessment of large datasets.

SUPPORTING DISEASE DIAGNOSIS

The diagnosis of neurologic disorders is often a very complex task. Patient history and neurologic examination remain the foundation for a correct diagnosis, with conventional MRI often having a crucial, supportive role in this process. In this context, volumetric MRI has now become an important tool, which can be useful on a number of occasions. We report here on its application in the diagnostic process of Alzheimer's disease (AD), frontotemporal dementia (FTD), focal epilepsy, and parkinsonisms.

Alzheimer's Disease

Sporadic AD is the leading cause of dementia in people older than 65 years and one of the most frequent causes of mortality and morbidity in Western countries. MRI has been recently proposed, together with other markers able to bring in vivo evidence of AD pathology, in revised criteria for a diagnosis of AD, even at the stage of earliest clinical manifestations (prodromal or predementia phase) (1,2), in the absence of a clinical picture of dementia.

The latest criteria do not use the traditional clinically based term of "probable" to indicate a diagnosis of AD (3). In fact, for a diagnosis of AD the presence of an episodic memory deficit of hippocampal type not sufficiently severe to affect activities of daily living is

Table 1
Use of MRI-Based Brain Volumetry in Different Clinical Scenarios

Supporting disease diagnosis	Understanding mechanisms and tracking clinical progression of disease	Monitoring treatment effect
Alzheimer's disease	Alzheimer's disease	Alzheimer's disease
Frontotemporal dementia	Multiple sclerosis	Multiple sclerosis
Focal epilepsy	Focal epilepsy	
Parkinsonisms	Headache/migraine	
	Amyotrophic lateral sclerosis	
	CADASIL	

Table 2
MRI-Based Methods for Measuring Brain Volumes

	Features
Manual methods	
Bicaudate ratio	The minimum intercaudate distance divided by brain width along same line
Brain width	Distance between two points on the cortical surface, measured at the same level as lateral ventricle width on axial slices
Corpus callosum area	Measured on midsagittal T1-weighted image
Tracing of the hippocampus, amygdala, entorhinal cortex, parahippocampus, cholinergic nuclei of the basal forebrain	Several anatomical protocols available for delineation of these structures
M/P	Ratio of midbrain-to-pons areas measured on midsagital T1-weighted image
MCP width	Distance between the superior and inferior borders of the MCP, as delimited by the peripeduncular CSF spaces of the pontocerebellar cisterns
MRPI	Value obtained by multiplying the pons to midbrain areas by the MCP-to-SCP widths
Third and lateral ventricle width	Determined along a plane corresponding to the anteroposterior midpoint of the ventricle on axial slices
Semiautomated methods	
Anatomatic	Segmentation algorithm for ventricles
Cavalieri method	Stereological method where brain volumes are obtained by the sum of the points counted on all the sections of the structure of interest multiplied by the sectioning intervals
Fuzzy connectedness	An operator identifies points of GM, WM and CSF, each of which is then automatically detected as a fuzzy connected object
ILAB4	Segmentation of thin-slice T1-weighted images based on a modified watershed transform and an automatic histogram analysis
Losseff method	A large central volume of the brain is defined based on anatomical criteria
MIDAS	Thresholding technique for measurement of ventricle volumes
SABRE	Use of individualized Talairach brain maps for brain regions in each hemisphere
Seed growing technique	Intensity threshold-based algorithm propagating from a seed positioned in any part of the brain parenchyma
Automated methods	
Alfano method	Multispectral method based on the relaxometric features of brain tissues
BBSI	Measurement of total volume difference between serial scans
BICCR	Digital morphometry for intracranial cavity classification and Bayesian tissue classification into GM, WM, lesions and CSF
BPF	Ratio of the volume of parenchymal brain tissue to the total volume within the outer surface of the brain
BICVR	Ratio of brain volume to intracranial volume
Central cerebral volume	Volume of four to seven (depending on the thickness) axial slices from the central portion of the brain
Chupin method	Use of simultaneous region deformation driven by probabilistic and anatomical priors for hippocampus and amygdala segmentation
CIVET algorithm	Series of algorithms for corticometric analysis of MRI images including tissue classification and segmentation
Cortical pattern matching	Surface-based cortical modeling and 3D GM mapping
DBM	Variant of VBM in which brain volumes are compared on the basis of the deformation fields required to register them onto a common template
FIRST	Subcortical brain segmentation using Bayesian shape and appearance models
Freesurfer	Calculation of the cortical thickness after inflation of the folded cortical surface
HAMMER	High-dimensional warping of brain images producing gyral and subcortical brain structures and tissue density maps
Histogram segmentation	Brain extraction and segmentation technique optimized for 2D T1-weighted images
IBA	Percent ratio of the supratentorial brain parenchyma to supratentorial parenchyma and CSF
LocalInfo	Entropy-based segmentation algorithm for subcortical brain structures
Segmentation propagation	Deformation field applied to the segmentation of the baseline brain and then automatically propagated through serial images to provide an estimate of volume change
SIENAx	Global and tissue-type volumes normalized for subject head size
SIENA, SIENAr	Percent brain volume change (PBVC) assessed by estimating the local shift in brain edges across the brain and its voxelwise extension for regional assessment
SPM-based segmentation	Prior spatial information are used to classify voxels according to their location and signal intensity features as GM, WM and CSF
STAND score	Score based on the voxelwise degree and pattern of atrophy of a scan in comparison to the scans of a large database of well characterized AD and cognitively normal subjects
Support vector machines	Multidimensional classification of cerebral region (e.g., hippocampus) shape features

(Continued)

TABLE 1. (Continued)

	Features
TDS	Brain tissues are identified by projecting anatomically labelled images of a template brain onto images of the patient 's brain
3DVIEWNIX	A data-, machine-, and application-independent software system for the visualization and analysis of multidimensional images
VBM	Characterizing regional volume and tissue "concentration" differences throughout global brain
WBR	Ratio of the difference between intradural and CSF volumes to intradural volume

M/P, midbrain/pons; MCP, middle cerebellar peduncle; CSF, cerebrospinal fluid; MRPI, magnetic resonance parkinsonism index; SCP, superior cerebellar peduncle; SABRE, semiautomatic brain region extraction; GM, gray matter; WM, white matter; MIDAS, medical image display and analysis software; BPF, brain parenchymal fraction; BBSI, brain boundary shift integral; BICCR, brain to intracranial capacity ratio; BICVR, brain to intracranial cavity volume ratio; CIVET, corticometric iterative vertex-based estimation of thickness; DBM, deformation-based morphometry; FIRST, FMRIB's integrated registration and segmentation tool; HAMMER, hierarchical attribute matching mechanism for elastic registration; IBA, index of brain atrophy; SABRE, semiautomatic brain region extraction; SIENA, structural image evaluation of normalized atrophy; SPM, statistical parametric mapping; VBM, voxel-based morphometry; STAND, structural abnormality index; TDS, template-driven segmentation; WBR, whole brain ratio.

now required alongside at least one among atrophy of the medial temporal lobe (ie, hippocampus, parahippocampus, amygdala, entorhinal cortex), hypometabolism in temporoparietal cortices on positron emission tomography (PET), and abnormal CSF marker (tau, β-amyloid) (Fig. 1). Subjects with these features were previously categorized under the term of mild cognitive impairment (MCI) (4), ie, carrying a high risk of developing AD. However, according to the new criteria these patients already have AD at a prodromal stage. Thus, the term MCI is applied now to those subjects who do not fulfill criteria for prodromal AD, ie, with a memory deficit without significant effect on activities of daily living or without biomarker evidence of AD pathology.

In such a context, the inclusion of medial temporal lobe atrophy as a supportive biomarker for early diagnosis of AD has shown to yield good specificity when applied to memory clinic populations (5,6). In particular, hippocampal atrophy, estimated through manual segmentation, is currently the best-established structural biomarker for early diagnosis of AD and it has been studied in both cross-sectional and longitudinal studies.

Hippocampal volume is normally reduced in old subjects, especially after 70 years of age, with differences in the range of 5%–10% (7). This means that a certain degree of overlap between demented patients and older normal subjects might be found and stresses the need of using age-matched cohorts when making these kinds of comparisons in clinical studies.

Finally, it should be stressed that atrophy of the entorhinal cortex can be even more marked than that of the hippocampus, suggesting that the first measure may be better than the latter in differentiating MCI from normal controls (8). However, because of the high variability in the measurement of the entorhinal

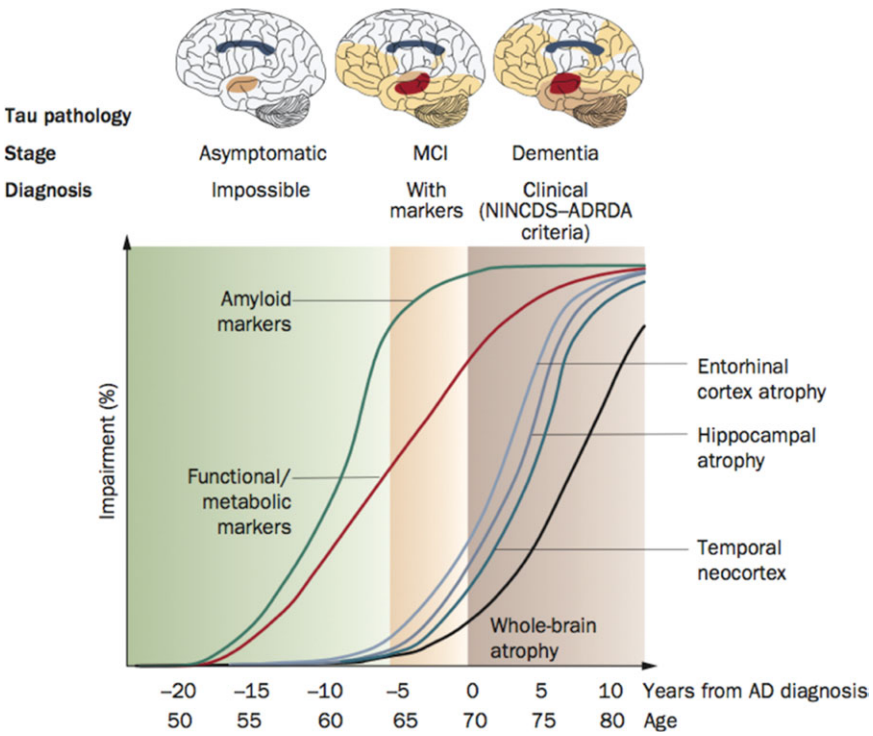

Figure 1. Natural progression of biological markers in AD. Markers of brain atrophy are relevant for supporting diagnosis of incipient AD. See text for details. Adapted with permission from Macmillan Publishers: Nat Rev Neurol 2010;6:67–77 ©2010.

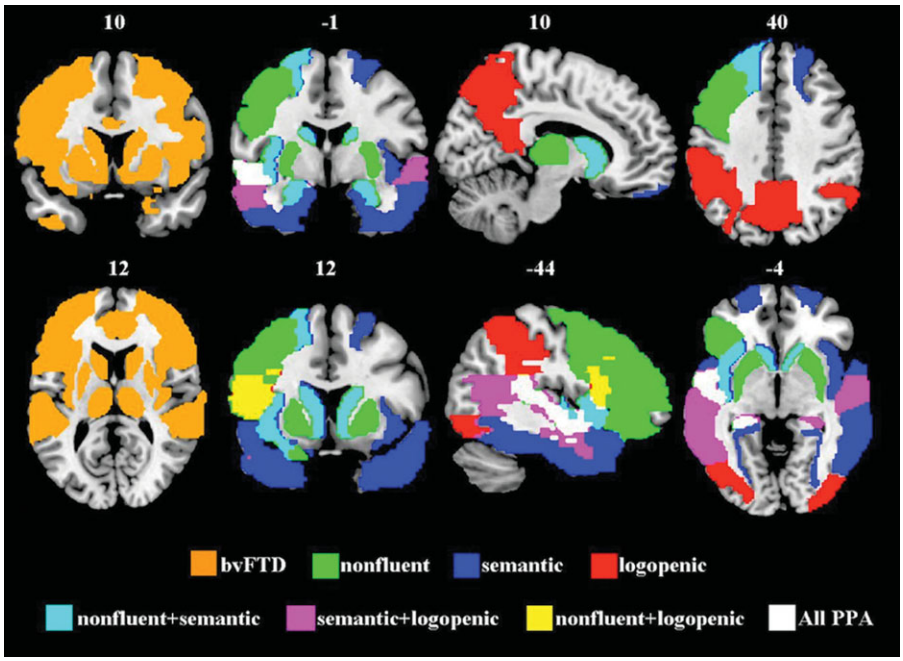

Figure 2. Regional patterns of brain atrophy in the different forms of FTD. See text for details. Figure courtesy of Federica Agosta and Massimo Filippi, Milan (Italy).

cortex volume (considerably more challenging than that of the hippocampus), its diagnostic role is currently under debate.

Frontotemporal Dementia

FTD is a clinical condition characterized by focal degeneration of anterior parts of frontotemporal lobes and insula. MRI-based volumetry has revealed unique patterns of brain atrophy and has been included as a supportive feature to diagnose FTD and as marker to differentiate FTD from AD (9). By contrast, since tissue loss can be moderate at the early stages of disease, a normal brain MRI on visual inspection does not rule out a diagnosis of FTD.

In patients with the behavioral variant of FTD (bvFTD), volumes of the frontal lobe regions underlying cerebral emotional processing such as ventromedial prefrontal cortex, posterior orbitofrontal cortex, insula, and anterior cingulate cortex are usually markedly reduced (Fig. 2), whereas they are less involved in AD patients until the late stages (10–12). A recent study identified four different patterns of brain atrophy in this disease, two in frontal and the other two in temporal lobe, which differed in terms of clinical measures of executive function and episodic memory but not in behavioral severity (13), suggesting that they cannot be used to identify different behavioral (ie, apathetic and disinhibited) subtypes of disease (14). Cerebral atrophy in bvFTD is also present in different structures of the deep GM (Fig. 2).

A left-sided atrophy in the anterior hippocampus and temporal lobe, particularly in the entorhinal cortex, amygdala, middle and inferior temporal gyri, fusiform gyrus, and a relative sparing of frontal lobe volumes was demonstrated in the "semantic" subtype of the primary progressive aphasia (PPA), which is the language variant of FTD (Fig. 2) (12,15,16). By contrast, no evidence of asymmetry or anteroposterior gradient was ever shown in AD, consistent with neuropathology studies (17). The other two subtypes of PPA are usually associated with different patterns of atrophy in the left frontoinsular, perysilvian, and deep GM regions ("nonfluent" subtype) and in the temporoparietal regions ("logopenic" subtype) (Fig. 2).

Finally, the clinical utility of brain atrophy patterns has been highlighted in a study where volumes of different regions of frontal lobe correctly distinguished FTD from AD on an individual patient basis using high-dimensional pattern classification of MRI scans obtained in a typical clinical setting (18).

Focal Epilepsy: Temporal Lobe Epilepsy and Focal Cortical Dysplasia

Volumetric MRI has been fundamental in the diagnosis and management of drug-resistant epilepsy, allowing the detection of subtle abnormalities of brain tissue that are difficult or impossible to reveal on visual inspection (19).

Temporal lobe epilepsy (TLE) is the most common type of focal epilepsy in adults and the model of surgically remediable focal epilepsy. TLE can present with or without mesial temporal sclerosis or hippocampal sclerosis. In the first case, there exist in the majority of cases both atrophy and increased T2 signal intensity in ipsilateral hippocampal subfields such as cornu ammonis sector 1 (CA1) and CA3/dentate gyrus.

Antiepileptic drugs may poorly control seizures in patients with TLE. In these cases, the standard treatment is anterior temporal lobectomy, which includes the removal of hippocampus and amygdala and leads to improvement in up to 85% of the cases (20). Volumetric MRI is useful in the presurgical evaluation of the epileptogenic site in TLE, showing asymmetry of the hippocampal volume ipsilateral to the seizure focus with a sensitivity up to 95% (21), and in the

prediction of the postsurgical cognitive outcome, given the strong relationship between larger hippocampus and postsurgical cognitive decline (22). The presence of bilateral hippocampal atrophy in TLE does not preclude the surgical intervention, although it is related to poor postsurgical prognosis (ie, nonseizure-free outcome) (23).

Volumetry can also be used to detect and measure volumetric abnormalities in the brains of single patients with focal cortical dysplasia (FCD), a type of malformation of cortical development, which represents the most frequent cause of refractory extratemporal epilepsy in children (24).

Although originally developed for group studies, voxel-based morphometry (VBM) has been adapted to assess volumetric differences in single patients compared to normal controls (25). Such studies showed increased GM volume, which colocalized with the histologically proven epileptogenic lesion in most of the cases. However, the sensitivity of VBM in individual patients can be reduced in some patients with FCD, especially in the presence of highly hyperintense lesions on T1-weighted images determining tissue misclassification (26).

Because of the relatively low specificity of VBM toward morphological features of FCD, alternative volumetric approaches have been used more recently. Indeed, methods of sulcal morphometry have revealed the presence of small FCD lesions at the base of deep and abnormally oriented cortical sulci (27), whereas computational models found cortical thickening and blurring of the GM–WM boundary in the majority of FCD cases (28).

Parkinsonisms

Although clinical consensus criteria exist, the differentiation of the various forms of parkinsonism is sometimes difficult, especially at the early stage, due to the presence of overlapping symptoms. Quantitative MRI, particularly volumetry, may potentially aid clinicians in their diagnostic work-up.

Different volumetric measures have indeed been proposed. In Parkinson's disease (PD), the most frequent form of parkinsonism, atrophy of the frontal cortex and hippocampus usually occur at the late stages, consistent with the timing of deposition of α-synuclein-positive Lewy bodies.

The simplest volumetric measure applied to differential diagnosis of parkinsonisms was the diameter and area of brain structures. An anteroposterior midbrain diameter less than 14 mm was originally considered peculiar of progressive supranuclear palsy (PSP), whereas in more recent work overlapping values with other forms of parkinsonism were reported (29). Also, the use of the ratio of pontine-to-midbrain areas to separate patients with different forms of parkinsonism has been controversial (29,30). More recently, a new index has been proposed, termed the MR Parkinsonism Index (MRPI), which is obtained by multiplying the ratios of pontine-to-midbrain areas by that of the middle cerebellar peduncle to superior cerebellar peduncle width (Fig. 3). MRPI was useful on an individual basis in diagnosing patients with PSP (29) and in differentiating patients with PSP from those with the Parkinson variant of multiple system atrophy (29) and from those with probable and possible PD (31).

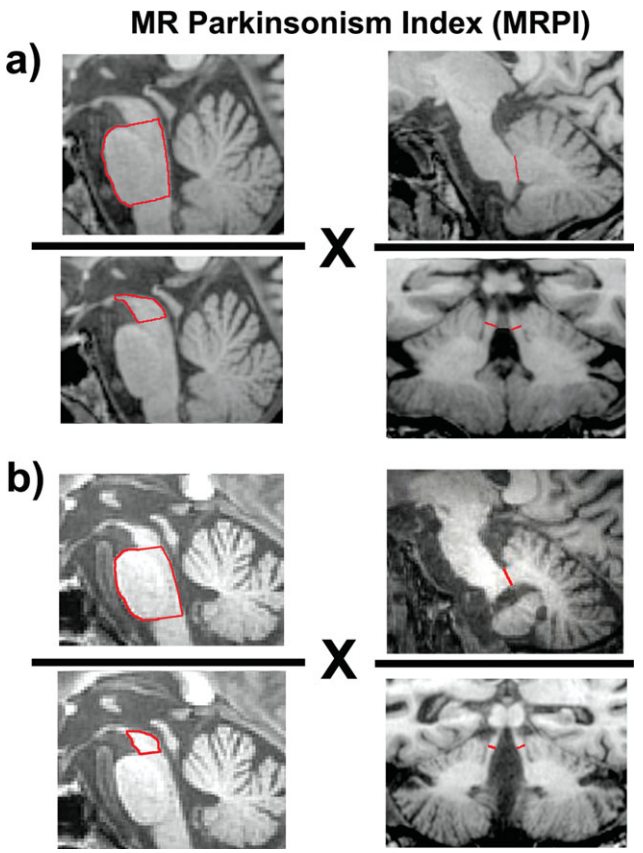

Figure 3. MRPI formula using anatomical landmarks. **a:** MRPI measurement on a patient with Parkinson Disease (PD). **b:** MRPI measurement on a patient with PSP. MRPI was calculated with the formula [(P/M) × (MCP/SCP)] where P/M is the pons area–midbrain area ratio and MCP/SCP is the middle cerebellar peduncle width–superior cerebellar peduncle width ratio. For further details see Ref. 29. Figure courtesy of Antonio Cerasa and Aldo Quattrone, Catanzaro (Italy). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Semiautomated segmentation techniques based on ROIs were also used in patients with parkinsonisms. Volumes of striatum, cerebellum, and brainstem are low in patients with multiple system atrophy, whereas volume reduction of brain, striatum, midbrain, and cortical regions of frontal lobe is usually found in patients with PSP. In corticobasal degeneration, frontal lobe atrophy predominates (32).

UNDERSTANDING MECHANISMS AND TRACKING CLINICAL PROGRESSION OF DISEASE

Measures of brain volumetry cannot define tissue features (ie, the cellular components) but can help to quantify the extent and magnitude of disease effects. On this basis, volumetric measures of brain structures have provided valuable insight into the understanding of pathologic mechanisms of several disease conditions. Moreover, the study of brain volume changes over time is particularly relevant in the

setting of chronic and progressive neurologic conditions such as AD and MS, where rates of brain atrophy have been shown to correlate with and to predict clinical decline.

Alzheimer's Disease

The familial form of AD (FAD) can represent a good model for studying the anatomic changes occurring preclinically in the brains of AD patients (33–35). The onset of FAD is in early/middle adulthood and some studies have investigated hippocampal volumetry. In these presymptomatic subjects, volumes of hippocampus and entorhinal cortex were lower and global brain atrophy rate was higher than in normal subjects (34). The timing of the volume loss in all these structures was estimated to lie between 3.5 and 5.5 years before the clinical onset of AD (34).

The annual rate of conversion to AD is significantly higher in subjects with the traditional amnestic MCI than in normal controls (4). In particular, a very high risk of progression to AD is present in those MCI subjects with abnormalities in both CSF and medial temporal lobe (36), where the hippocampal atrophy rate is in the order of 3.5% per year compared to about 1% per year of MCI subjects not converting to AD (37). However, likelihood of progression to AD in MCI subjects is predicted not only by structures of the medial temporal lobe but also by volumes of cortical regions in parietal and lateral temporal lobes (38). Moreover, an MRI score reflecting the degree of AD-like brain atrophy features showed slightly higher predictive value for future cognitive impairment than CSF measures (39). Predicting short-term conversion to AD on an individual basis was recently assessed through an atrophy pattern classifier, which demonstrated lower volumes in a number of GM and WM regions in those MCI subjects converting to AD within an average period of 15 months (40).

In sporadic AD, the relationship between hippocampal atrophy and neuropathology findings is close, as demonstrated by significant associations between MRI-based hippocampal volume and the Braak stage of intraneuronal neurofibrillary tangle deposition (41). Temporal dynamics of tau deposition and neuroaxonal loss and thus MRI-based volume changes usually follow a characteristic sequence. In fact, the earliest sites of damage are those areas located along the so-called "hippocampal pathway," including not only hippocampus but also entorhinal and posterior cingulate cortices and this explains the early memory complaints in patients with AD. Later in the course of disease, atrophy in the GM, particularly of frontotemporoparietal cortices, in keeping with the diffuse nature of AD, reveals itself with deficits in language, praxias, behavior, and visuospatial skills (17).

In general, atrophy rates in different brain structures of AD patients are related to deterioration of cognitive performance (17) and seem more sensitive to disease-related changes than markers of β-amyloid deposition assessed through PET imaging (42) or CSF (43). Certainly, tracking disease progression in AD patients would benefit from longitudinal follow-up of hippocampal volume over short periods of time, because this timeframe does not seem to significantly increase variance of volumetric measurements (44). This could also be beneficial in clinical trials for an earlier assessment of the efficacy of a given treatment.

Multiple Sclerosis

One of the most impressive features of MS is the heterogeneity of clinical expression and course, which is mirrored by the heterogeneity of neuropathology findings. The underlying mechanisms of brain atrophy in MS are complex. In the brain of a patient with MS, demyelination and inflammation add to neurodegeneration and, consequently, loss of myelin, glial cells, and water space changes contribute with loss of neuronal cells (body and axons) to the reduction of tissue volume. Consistent with this, brain atrophy in MS is a global process related to both GM and WM pathology.

Global brain atrophy occurs at a faster rate in MS patients (0.5%–1% per year) (45) than in age-matched healthy controls (0.1%–0.3% per year) (46), appears to proceed relentlessly throughout the MS course (Fig. 4), and to occur from the earliest stages (45), even after the first clinical presentation of disease (47,48). In fact, patients with clinically isolated syndrome (CIS) suggestive of MS who later convert to MS usually show more brain atrophy than those who do not (47,49).

Compared to normal controls, global brain atrophy has been demonstrated in relapsing-remitting (RR), secondary progressive (SP), and primary progressive (PP) MS (50–52), with a rate that is quite heterogeneous across studies. However, in general the loss of brain volume over time seems to be largely independent from the MS subtype (53), as also recently demonstrated in

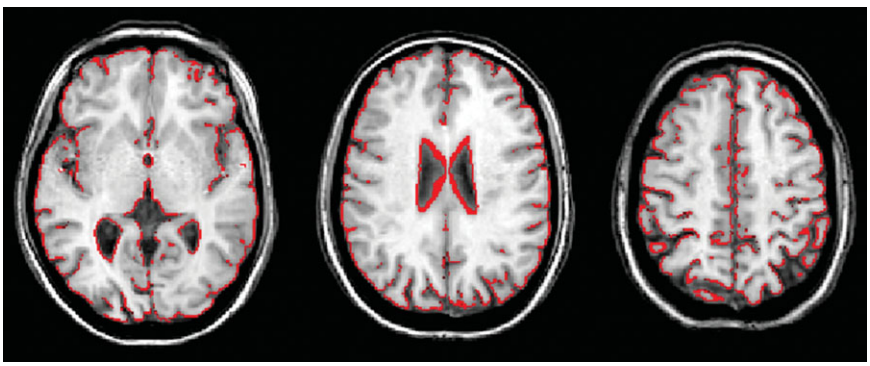

Figure 4. Illustrative example of percent brain volume change (PBVC), computed with the SIENA software, over 10 years in a patient with RR MS (PBVC = −8.2%). Atrophy is shown in red. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary. com.]

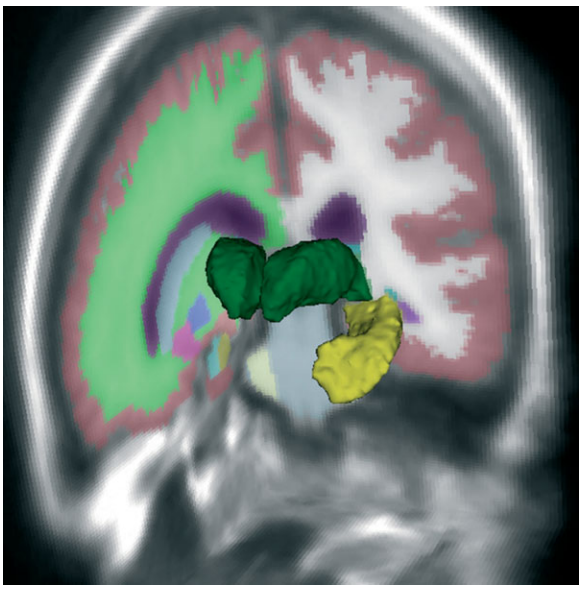

Figure 5. Subcortical brain regions mainly involved in the neurodegenerative processes of patients with mild TLE. Recent VBM studies demonstrated that mild TLE patients with mesial temporal sclerosis are characterized by abnormal gray matter losses involving bilateral thalami (colored in green) and left hippocampus (colored in yellow) with respect to normal controls. Figure courtesy of Antonio Cerasa and Aldo Quattrone, Catanzaro (Italy). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

a large MS population of untreated patients, when controlling for baseline brain volume (54).

Although MS is classically viewed as a demyelinating disorder, a plethora of histologic and MRI studies have demonstrated that cortical GM pathology is present in this disease. Indeed, cortical GM loss has been shown in CIS patients who converted to clinically definite MS 3 years later (55) and in early RR MS patients (56,57), and is able to evolve over periods as short as 1 year (58). It is intriguing that GM regions are differently vulnerable to pathology in MS. A consistent finding is that frontal, temporal, and parietal lobes of the brain are the most involved in MS patients (59–63). In terms of temporal evolution, atrophy seems to start in frontal and superior temporal gyri and then to extend to other clinically eloquent brain areas (eg, motor cortices) in more advanced stages of MS (64).

Atrophy of important deep GM structures, especially caudate and thalamus (up to 25% in RR and 35% in SP MS) is also significant in MS patients (65–68). Interestingly, the only GM regions reported to be atrophic in pediatric MS are thalamus and globus pallidus (69,70). GM atrophy seems comparable between RR and SP MS by combining MRI and neuropathology studies (66,68).

Atrophy of WM has been reported in some cross-sectional studies on RR and progressive forms of MS (56,71,72), whereas no WM volume loss was found in CIS patients who later (3 years) converted to clinically definite MS (55) and in early RR MS over 2-year follow-up (73). In a 4-year longitudinal study, the rate of WM atrophy was lower than that of GM and constant across all disease stages (74). It is possible that, at least in the active stages of MS, the increased volume of WM lesions, due to inflammation and edema, leads to an "artificial" increase of WM volume and thus to a masking of the atrophy process.

In general, compared to WM lesion load, global brain atrophy is a better predictor of long-term clinical disability in all MS stages. For example, a higher atrophy rate over the first 2 years was the best predictor of disability 8 years later after correcting for lesion load measures (75). Further, patients with the largest amount of atrophy at 8 years carried a risk 4 times higher to need walking assistance. Several studies have also linked cognitive functioning to brain volumes in MS. Different cognitive domains can be impaired in patients with MS such as those supported by subcortical (eg, attention, processing speed) and cortico-subcortical (eg, visuospatial memory) networks. The magnitude of correlations between cognitive tests and specific atrophy measures has been moderately close. Thus, global atrophy measures as well as measures of the third ventricle width, corpus callosum, deep brain GM structures, and neocortex have all been reported as good predictors of cognitive impairment (67,76–83). Taken together, MRI-based volumetric data lead to the conclusion that brain atrophy, especially in the GM, is a clinically relevant measure to track progression of physical and cognitive disability in MS (57,62,74,84,85).

Focal Epilepsy

A number of volumetric studies found that several brain regions were atrophic in TLE patients compared with normal subjects (86). Atrophy was found in structures of the medial temporal lobe (hippocampus, parahippocampal gyrus, and entorhinal cortex), but also bilaterally in extratemporal lobe structures, especially thalamus and parietal lobe (86,87) (Fig. 5). These findings were in line with those from neuropathology studies (86).

For the temporal lobe, the site of atrophy is generally ipsilateral to the seizure onset (88). Atrophy in TLE is generally viewed as a consequence of seizure frequency, although edema resolution rather than true structural damage may actually be responsible for apparent volume decrease in the hippocampus of these patients (89).

In longitudinal MRI studies of patients with TLE and hippocampal sclerosis, the progression of brain atrophy in the GM seems to be associated with poorer seizure control and a longer duration of epilepsy. By contrast, an increase of GM volume can be related to the presence of developmental malformations causing reduced contrast between GM and WM on MR images (90).

Headache/Migraine

In headache/migraine, changes in GM volume are not haphazard across the brain but tend to involve specific and highly organized cerebral areas. Although some studies (91,92) did not find differences in cerebellar, global, and regional (ie, GM and WM) cerebral volumes between patients with migraine and normal subjects, other studies have questioned this finding.

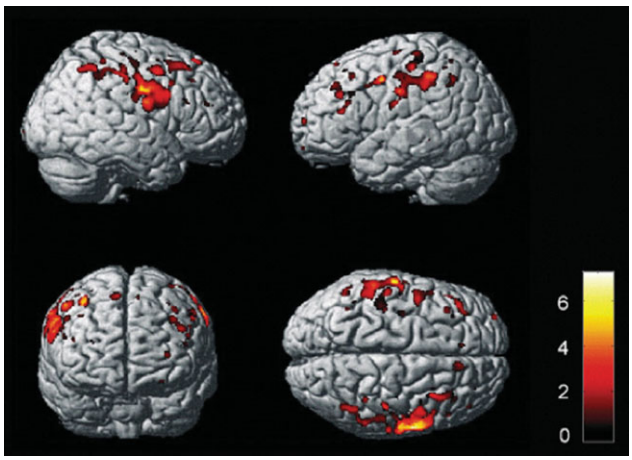

Figure 6. GM atrophy (in red-yellow on a standard T1-weighted brain) in patients with ALS compared with healthy subjects is evident bilaterally not only in the primary motor cortex but also in the premotor, parietal and frontal regions. Reprinted with permission of BioMed Central: BMC Neurol 2006;6:17.

In fact, migraineurs showed atrophy in regions involved in central pain processing (anterior and posterior cingulate cortices, insula, orbitofrontal cortex, prefrontal cortex, posterior parietal cortex) (93–95), but not in those specific for migraine (eg, brainstem). Progression of GM atrophy in these areas seems to be related to increasing duration of migraine (95). On the other hand, patients with migraine, especially those with aura and T2-weighted visible lesions, seem to have increased volume of the periaqueductal gray and dorsolateral pons (93), probably caused by adaptive remodeling of neural circuits, gliosis reactive to functional changes, or osmotic phenomena secondary to vascular changes during migraine attacks. A thickening in the caudal part of the somatosensory cortex, containing trigeminal areas of head and face, has also been observed in migraineurs compared to normal controls (96). This finding demonstrates that somatosensory pathways do play a role in mechanisms of migraine and probably explains the coexistence of migraine with other chronic pain disturbances (eg, fibromyalgia, low back pain) and sensory changes (eg, allodynia).

Patients with cluster headache showed an increased GM volume in the hypothalamus, supporting the notion of the presence of a hypothalamic dysfunction in this condition (97).

Compared to normal subjects, patients with chronic tension-type headache show atrophy in some pain-transmitting areas (anterior cingulate cortex, insula, orbitofrontal cortex, parahippocampal gyrus), whereas patients with medication overuse headache show non-significant volume decrease in the left orbitofrontal cortex and right midbrain (98). This is an important finding because the two conditions are clinically similar in determining pain at the level of the first division of the trigeminal nerve.

Because of the association with the number of migraine attacks and pain duration, all these volumetric changes in patients with headache/migraine might be considered the result of central sensitization caused by prolonged pain stimuli from the pericranial tissues. In other words, chronic pain might be regarded as a manifestation of neuronal plasticity (99,100). It is unknown, however, whether these changes are structural and irreversible or are rather the endproduct of a functional and reversible process. Given that the frequency and severity of migraine attacks might be different during the lifetime of a patient, longitudinal studies could potentially clarify this issue.

Amyotrophic Lateral Sclerosis

In amyotrophic lateral sclerosis (ALS) the diagnosis relies on clinical features, whereas laboratory tests are only used to exclude other neurodegenerative conditions. No agreement exists across volumetric MRI studies on the presence of atrophy in the motor cortex of ALS patients, despite such damage being clearly demonstrated by neuropathology studies. Atrophy of the corticospinal tract has been shown, especially in those patients with a bulbar onset. However, atrophy extends beyond the motor cortex, also affecting cortical regions of frontotemporoparietal lobes, as demonstrated at the group level by VBM (Fig. 6). This finding is consistent with neuropathology studies, where neuronal loss and deposition of ubiquitin-positive neuronal inclusions have been demonstrated in the above areas (101). Volumetric MRI has been proposed as part of the MRI protocol for the study of ALS in combination with other MRI techniques to improve knowledge of different aspects (diagnosis, progression, pathophysiology) of disease (102,103). A recent study has indeed demonstrated that the combination of VBM and indices of diffusion tensor imaging improved the classification of ALS cases with very high sensitivity, specificity, and accuracy (104).

CADASIL

CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) is a model of small-vessel disease that predominantly affects WM and deep GM. However, global brain atrophy and morphological changes of the cortex have been demonstrated to be reliable markers of motor disability and cognitive status (105–107). These changes occur early, as shown in presymptomatic subjects with genetically proven disease, where lower values of cortical volumes, especially in the frontal lobes, were found (108). Indeed, widespread neuronal apoptosis in the cerebral cortex of CADASIL patients seems to be associated with a higher load of subcortical ischemic lesions and higher brain atrophy (109). In general, brain atrophy seems associated with the remote effects of lacunar lesions (lesions of CSF intensity on T1-weighted images consistent with lacunar infarcts) and with changes in multiple clinical aspects of CADASIL, including cognition (107). In such a context, hippocampal volume seems to predict cognitive scores better than vascular lesions and global brain atrophy (110), stressing again the clinical importance of this brain structure not only in neurodegenerative diseases but also in small-vessel diseases.

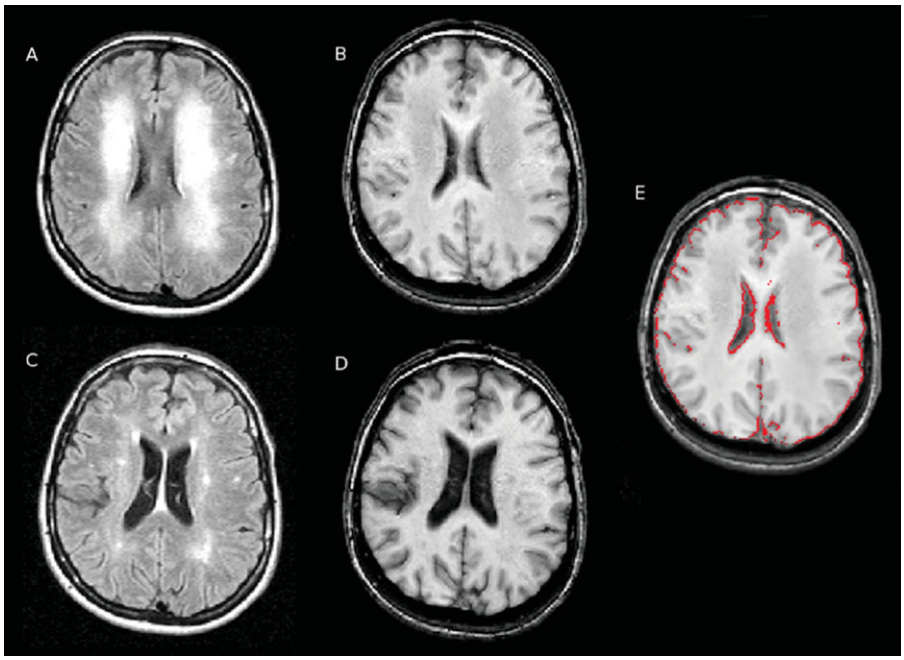

Figure 7. FLAIR and T1-weighted images at baseline (**a**,**b**) and after 9 months (**c**,**d**) in a patient with an acute demyelinating disorder. The SIENA output (**e**) shows the decrease in brain volume (in red) due to the resolution of the edema in the acute demyelinating lesions ("pseudoatrophy"). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

MONITORING TREATMENT EFFECT

Another area of interest for brain volumetry is monitoring response to treatment. Thus far, this has happened especially for AD and MS in the context of pharmacological trials but not in single patients. Because of the robustness and reliability of most of the volumetric MRI methods as well as their increased sensitivity in comparison to clinical endpoints, brain volumetry can contribute to the approval of novel drugs, by reducing sample size and shortening trial duration.

Clinical Trials in AD

The rate of hippocampal atrophy was implemented as a secondary endpoint in a number of pharmacological trials in AD. This measure was shown to be a reliable biomarker across MR centers and to have a greater effect size than clinical measures in the 52-week, randomized, placebo-controlled trial of milameline, a partial agonist of muscarinic receptors, which was suspended because of lack of efficacy (111). In a more recent AD trial on the disease-modifying drug tramiprosate (homotaurine) (112), a decrease in atrophy rate over serial MR scans was shown, although no clinical benefits ensued. The effect of donepezil in slowing hippocampal atrophy was assessed in a 24-week pilot study (113) and then replicated in a more recent prospective cohort study, with a 24% difference compared to the placebo group (114). Finally, only one therapeutic trial on MCI has been conducted thus far (115). This showed no treatment effect (atrophy reduction) with either donepezil or vitamin E, although a trend was found with donepezil in carriers of the apoE ϵ4 allele.

Because of the concern about biomarkers, power estimates for pharmaceutical trials are still based on the traditional cognitive performances. Measures of volumetric MRI have indeed shown much better longitudinal power to track disease-related changes than any clinical measures in both MCI and AD (116,117). When including MCI subjects with a specific AD-like atrophy pattern, there was a 57% reduction of sample size ("neuroimaging enrichment strategy") using the Clinical Dementia Rating scale as the primary outcome (118). In this context, the use of the new proposed criteria (1,2) for early diagnosis of AD would select only "true" AD patients, thus leading probably to a significant increase of the study power.

Pharmacological Treatments in MS

Brain atrophy has been used as a secondary outcome measure in several MS clinical trials. In the trial of once-weekly intramuscular (i.m.) interferon (IFN) β-1a (50), there was a 55% reduction of brain atrophy in treated RR MS patients compared to the placebo group in the second but not first year of treatment. In a second larger trial with the same medication, a slowing of brain atrophy was demonstrated over the 3-year study (119).

In a post-hoc analysis of a trial in patients with mono- and polysymptomatic CIS, a therapeutic effect on brain atrophy rate, measured through percent brain volume change, of once-weekly subcutaneous (s.c.) IFN β-1a was shown after 2-year treatment compared to the placebo group (120). These findings differ from those of the post-hoc analysis of a trial in RR MS patients, where three-times-a-week s.c. IFN β-1a did not affect brain atrophy loss over 2 years. Two small analyses on subsets of RR and SP MS trial patients showed a reduction in brain atrophy rate over 18 months (121). Another trial studied the effect of i.m. IFN β-1a (30 and 60 μg) in patients with PP MS (122). In those patients treated with the high dose of the drug there was a higher rate of ventricular enlargement over 2 years, possibly due to the effect of treatment on the resolution of cerebral edema and inflammation leading to a decrease in water content and a nontissue-related (ie, without loss of cell structures) brain volume loss ("pseudoatrophy") (123) (Fig. 7).

In line with this, a study on SP MS patients treated with IFN β-1b showed a trend toward greater reduction of cerebral volume in the presence of enhancing lesions at baseline (124).

Glatiramer acetate (GA) has also been demonstrated to slow brain atrophy in MS. A small study showed that reduction of brain volume loss over 3 years was a third lower in GA-treated patients compared to the placebo group (125). Another larger study of shorter duration (18 months) showed reduction in the loss of brain volume in the group treated with GA for the whole study period compared to the group on placebo for the first 9 months and then switched to active treatment when analyzed with a sensitive automated approach (126).

The effects of intravenous (i.v.) methylprednisolone (MP) on brain atrophy have also been investigated in a clinical trial of MS (127). The study found that patients treated with pulsed i.v. MP every 4 months for the first 3 years and then every 6 months for the remaining 2 years had significantly lower brain atrophy and disability progression compared to patients treated only with i.v. MP for relapses. However, it should be noted that the results of this study have not been replicated and pulsed i.v. MP is not currently advocated as first-line treatment in MS.

Treatment with natalizumab, a humanized monoclonal antibody, slowed the loss of bran volume, computed with the brain parenchymal fraction, during the second year of a study compared to placebo (128).

Finally, among the oral treatments recently available for patients with MS, a beneficial effect on brain atrophy was found with fingolimod, which showed, for both doses (0.5 and 1.5 mg), a significant reduction in the percent brain volume change over 24 months, detected as early as 6 months from study onset, compared to placebo (129). This beneficial response of fingolimod on brain atrophy was confirmed in two other studies (original and extension) comparing fingolimod with i.m. IFN β-1a (130,131).

Overall, the results emerging from pharmaceutical trials in MS suggest that treatments may have an effect on brain atrophy and that this effect is often delayed in time. However, the time course of brain atrophy in MS is not yet completely understood, and thus atrophy measures may result suboptimal in tracking the underlying pathologic process. Moreover, atrophy measurements, which are sensitive to demyelination and neuroaxonal loss, can be complicated by other pathologic factors such as glial proliferation, remyelination, and, most important, the aforementioned "pseudoatrophy" (132). Both of these effects would mask the neuroprotective effects of treatment, and thus there is need for longer trial duration to establish stable baselines.

LIMITATIONS AND FUTURE DIRECTIONS

In spite of the development of MR scanners and the role demonstrated by a plethora of research studies, brain volumetric MRI has yet to be widely translated into clinical practice. Indeed, several hurdles exist. Manual methods of volumetry rely upon manual segmentation, which is time-consuming, requires a great deal of expertise in anatomy, introduces intra- and interobserver variations in labeling procedure, and often makes use of empirical guidelines for establishing anatomic boundaries. For semiautomated and automated methods, issues may arise from the anatomic variability of brain structures across subjects, the segmentation of small-sized structures (eg, hippocampus), signal inhomogeneities, and the presence of blurred boundaries between different tissue types (partial volume effect). Further, it should be kept in mind that, even when using fully automated methods, anatomical knowledge has to be the foundation of quality control (ie, visual inspection of the results), as would happen for any type of quantitative analysis.

Other issues limiting the clinic application of brain volumetry are related to 1) variation in imaging protocols (MRI parameters, spatial distortions, motion artifacts) across MR centers; 2) lack of normative data that would allow the physician to interpret biomarker values in patient care; and 3) poor integration of image formats typically used in research with clinical imaging workflow.

Notwithstanding the above limitations, advances in computational technology are paving the way for a more convincing clinical use of MRI-based brain volumetry in a range of neurologic conditions. Different brain atrophy markers, derived from several automated data-driven approaches, have been proposed for the early diagnosis of AD and for discrimination of AD and MCI from normal aging, although their clinical role has yet to be proven in larger studies. These markers include application of VBM to individual subjects for the risk prediction of AD, volumetric measurement of the region of the nucleus of Meynert in the basal forebrain, automated classification of global atrophy in MR scans through the use of support vector machines, atrophy pattern classification, the AD-specific structural abnormality index, tensor- or deformation-based morphometry, multidimensional classification of hippocampal shape features, and volume measurement of hippocampal subregions. Finally, the structural definition of specific brain regions will definitely improve with the clinical use of high-field MR scanners because of the gain in signal, resolution, and sensitivity (assuming an adequate control for parallel increased inhomogeneities and artifacts). Furthermore, new and better methods for image segmentation have been developing (133–136) and will certainly help push the field of brain volumetry forward for prompt clinical use.

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