Dementia: Radiologic Perspective

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INTRODUCTION

Recent years have witnessed impressive advances in the use of magnetic resonance imaging (MRI) with varying success either to contribute to patient clinical work up aimed at establishing a diagnosis of degenerative dementia, as well as to monitor disease progression. Conventional MRI of the brain has an important role in differentiating Alzheimer Disease (AD) from other pathologies, including non-AD neurodegenerative dementias (1). MRI-based measures of atrophy are regarded as valid markers of disease state and progression, and the quantification of volumetric changes from serial MRI scans has the potential for monitoring the efficacy of disease-modifying agents (2). In addition, several other promising non-conventional MR approaches have emerged or are under development/refinement to provide a new complete picture of AD pathology in vivo . These new techniques are likely able to fill voids and improve our ability to diagnose and monitor or understand the pathophysiology of the disease.

STRUCTURAL VOLUMETRIC MRI

In typical late onset sporadic AD, the medial temporal lobes (MTL), especially the hippocampus and entorhinal cortex (ERC), are among the earliest sites of pathologic involvement (3). Accordingly, studies of hippocampal and ERC volumes have repeatedly shown decreased hippocampal and ERC volumes in AD patients compared with agematched controls (4). MTL atrophy can reliably separate AD patients from normal controls with sensitivities and specificities greater than 85% (1,2,5).
Voxel-based studies of grey matter (GM) loss in AD patients demonstrated that cerebral atrophy begins in the MTL, but gradually involves other parts of the cerebral cortex at later stages (4, 6-8), resembling the Braak stages of NFT deposition (6). Among areas outside the MTL, the parietal and posterior superior temporal regions on the lateral cerebral surfaces (9-11), and the posterior portion of the cingulated gyrus on the medial surface (12,13) are the most severely affected. Early onset (EO) AD patients (i.e., subjects showing onset of symptoms before the age of 65 years) showed greater GM and white matter (WM) atrophy in the parietal and dorsal temporal regions compared to LOAD patients (14-16).

In Patients with Amnestic MCI several studies have shown that structural MRI estimates of tissue loss in characteristically vulnerable brain regions, such as the hippocampus and ERC, are predictive for conversion from amnestic MCI to AD (17-24). A recent meta-analysis estimated that MTL atrophy has 73% sensitivity and 81% specificity for predicting whether patients with amnestic MCI will convert to dementia (25).

The availability of in vivo biomarkers that correlate with the regional distribution of AD pathology and predict the development of AD in MCI cohorts formed the basis of the recent new research criteria for AD (26, 27). The diagnosis of AD now relies on a dual clinicobiological entity that requires the evidence of both specific memory deficits and in vivo markers of AD pathology. MTL atrophy on MRI is one of the

supportive biomarkers proposed by Dubois and colleagues, i.e., volume loss of hippocampi, ERC, and amygdala. This can be detected by qualitative ratings based on visual scoring, or by quantitative volumetry of regions of interest (referenced to a well characterized population with age norms).

Structural Volumetric MRI Helps in the Differential Diagnosis of AD

Structural volumetric imaging is recognized as having an important role in differentiating various causes of neurodegenerative dementia from each other. A pattern of relatively focused atrophy of the midbrain, hypothalamus and substantia innominata, with a relative sparing of the MTL and temporoparietal cortex was found to be associated with dementia with Lewy bodies (DLB) (28,29).

Consensus criteria for frontotemporal dementia (FTD) include frontal and/or temporal atrophy as supportive features (30). Despite variation and overlap of atrophy patterns, visual inspection of regional atrophy on MRI may aid in discriminating AD from frontotemporal lobar degeneration (FTLD). Combining bilateral symmetrical hippocampal atrophy and a posterior greater than anterior gradient of atrophy ensured a higher specificity for discriminating AD from FTLD than that achieved by hippocampal atrophy alone (31).

Serial Structural MRI Assessments Correlate with Concurrent Change of Cognition in AD. Rates of whole brain atrophy in AD have been estimated at 1.4-2.2% per year, whereas rates of atrophy during normal aging (for a mean age of 70 years) do not usually exceed 0.7% per year (2). A recent meta-analysis showed that mean annualized hippocampal atrophy rates are 4.7% for AD subjects and 1.4% for controls, with a difference of 3.3% (32).

THE ROLE OF NON CONVENTIONAL MRI IN THE DIAGNOSIS AND PROGNOSIS OF AD AND MCI

DT MRI

DT MRI studies in AD have consistently found increased MD and decreased FA compared with controls in several brain regions, most notably in temporal and frontal lobes, posterior cingulum, corpus callosum, superior longitudinal fasciculus (SLF), and uncinate fasciculus (33). WM changes in AD generally follow the anatomical pattern of GM atrophy (33,34), supporting a Wallerian degeneration theory of WM involvement in this condition.

A recent metaanalysis showed that differences between MCI and controls parallel those between AD and controls, but fewer regions reached statistical significance (33), possibly because MCI consists of an heterogeneous group of patients and there are no universally recognized criteria to define this condition.

Hippocampal diffusivity measurements were found to be more sensitive than hippocampal volume in predicting conversion to AD in patients with amnestic MCI (35,36). The severity of microstructural damage beyond the MTL were associated with an increased short-term risk to develop AD in amnestic MCI patients (37). An individual classification of MCI cases using support vector machine analysis of DT MRI data allowed for an individual classification with an accuracy up to 91.4% (healthy controls vs. MCI) and 98.4% (stable vs. progressive MCI at one year).

Furthermore, support vector machine analysis of DT MRI data provided highly accurate individual classification of stable vs. progressive MCI at one year, regardless of the MCI subtype, indicating that this method may become a tool for early detection of MCI subjects evolving to overt dementia (38).

DT MRI is also increasingly being used to examine differences across dementia subtypes. Diffusivity changes in the cortex of patients with AD were more widespread and severe than in those with DLB (39, 40). Patients with AD had an increased diffusivity and a reduced GM volume in the MTL, posterior cingulate cortex, precuneus, and temporoparietal association cortex compared to both healthy controls and patients with DLB. The addition of diffusivity values of the hippocampus and parahippocampal gyrus to those of GM volumes improved further the ability to distinguish AD patients from those with DLB (39). Furthermore, while patients with AD were characterized by decreased FA in the fornix, cingulum, and inferior longitudinal fasciculus (ILF), those with DLB experienced a decreased FA in the ILF, only. In a recent study comparing AD and behavioural variant FTD (bvFTD), it was shown that bvFTD is associated with a greater reduction of FA in frontal brain regions, whereas no brain areas in AD showed greater FA reductions than in bvFTD (41). These results suggest that WM integrity loss measured with DT MRI may improve the diagnostic differentiation between AD and other neurodegenerative dementia.

Functional MRI

The main problem in the interpretation of fMRI studies in cognitively diseased people is that the observed changes might be biased by disease-driven differences in task performance between patients and controls. FMRI studies have shown that spontaneous fluctuations of the BOLD signal occur continuously in the resting state (RS, i.e., in the absence of external stimuli) in the human brain (42). Therefore, RS fMRI is a promising new tool for the investigation of the intrinsic connectivity of brain networks in patient populations. Although task-related and RS fMRI techniques do investigate two completely different states of the brain, RS fMRI makes no demand on subject other than holding still, as a consequence, can be acquired in patients that can not perform a task. The default mode network (DMN), which includes the posterior cingulate, inferior parietal, inferolateral temporal, ventral anterior cingulate, and hippocampal regions, has received the greatest attention, and has been shown to be less active in AD (43) and MCI (44) patients than in healthy elderly controls. Disconnection of the DMN seems to precede GM atrophy in the posterior cingulate cortex in patients with MCI (45). Sensitivity of RS fMRI measures in differentiating AD patients from healthy elderly controls ranges from 72 to 85% and specificity from 77 to 80% (43, 46, 47).

Enhanced RS functional connectivity in frontal regions has also been reported in AD patients when compared with healthy controls (47). Zhou et al. (48) suggested that regions of enhanced connectivity in AD could be part of the RS network for salience processing. On the contrary, relative to healthy controls, bvFTD patients experienced a decreased salience network connectivity in the frontal and anterior insula, mid-cingulate and numerous subcortical, limbic and brainstem nodes, as well as an increased left parietal DMN connectivity. This study suggests that AD and bvFTD target distinct, anticorrelated RS networks and lead to divergent network connectivity

patterns. A combination of salience network and DMN connectivity scores was found to be able to classify healthy subjects, AD patients, and bvFTD patients with 92% accuracy, and to separate AD and bvFTD patients with a 100% accuracy (48).

CONCLUSIONS

With the prospect of disease-modifying therapies, early detection of AD and accurate monitoring of its progression are important research goals. Metrics derived from structural volumetric MRI, including atrophy within and beyond the MTL, have improved our diagnostic ability, and should be used to assess the efficacy of experimental AD therapies in clinical trials. The utility of structural imaging will certainly be increased further by a standardization of acquisition and analysis methods, and by the development of robust algorithms for automated segmentation, which will guarantee that measures of hippocampal, ERC, and amygdalar volumes are stable across laboratories worldwide.

Since new disease-modifying therapies in AD will likely be most beneficial before substantial neuronal loss and clinical impairment have occurred, advanced MR techniques hold promise as valuable tools for selecting candidates for clinical trials and as predictive markers of dementia progression in defined risk groups of patients.

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