MRI in Dementia

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KEYWORDS

• MRI • Cognitive disorder • Alzheimer's disease • Imaging • Dementia

The incidence of both cognitive disorders and dementing illnesses is rising in our ageing population. As a consequence, imaging modalities are becoming increasingly important for differential diagnosis and monitoring of disease progression in daily clinical practice and for use as surrogate markers in treatment trials. Such technologies as conventional CT, MRI, proton magnetic resonance spectroscopy (MRS), positron emission tomography (PET), and single photon emission CT are currently being applied for this purpose.

Additionally, diffusion-weighted imaging, diffusion tensor imaging (DTI), perfusion-weighted MRI, magnetic transfer imaging, and a combined visualization of different modalities (eg, MRI/PET) have been proposed for in vivo tracing of biomarkers. We provide a review of original papers as well as published review articles on the role of MRI in various cognitive disorders.

In general, every measurement method runs through different stages of development and validation before it can be used as a routine tool (**Fig. 1**). Along these lines, we will assess the usefulness of MRI for early diagnosis, for monitoring of disease progression, and for use as a surrogate marker for documenting drug efficacy in therapeutic clinical studies.

ALZHEIMER'S DISEASE

Conceptually, treatment of Alzheimer's disease should start early in the disease, ideally in a clinically presymptomatic stage, before widespread synaptic and neuronal loss has occurred. This approach would require tools that already pick up with high sensitivity subtle Alzheimer's disease–related brain changes.

Structural MRI

Methods to assess brain volume changes in Alzheimer's disease patients include voxel-based morphometry or the voxel-based specific regional analysis system for Alzheimer's disease involving transformation to a normalized brain,[1–5] cortical pattern matching,[6–8] and brain boundary shift integral measurements.[9] These techniques make it possible for clinicians to discriminate between the magnitude of progression of brain atrophy in normal ageing and the higher rates of volume loss observed in Alzheimer's disease. Brain boundary shift integral measurements might additionally be useful for assessing subtle regional volume changes. Such assessments have been helpful for demonstrating significant drug effects even in relatively small patient groups.[9]

Structural MRI has also been used in several studies to predict progression from mild cognitive impairment to Alzheimer's disease. Other MRI measurement techniques employed in the assessment of Alzheimer's disease are manual and semiautomated measurements of regional atrophy in specific regions of interest (**Fig. 2**). Studies using this approach have focused primarily on the hippocampus and the medial temporal lobes, yet the corpus callosum has also been shown to be vulnerable to Alzheimer's disease–related brain atrophy.[10] In this context, it is of note that hippocampal atrophy in MRI is strongly related to the histologic finding of neuronal loss[11] and to the

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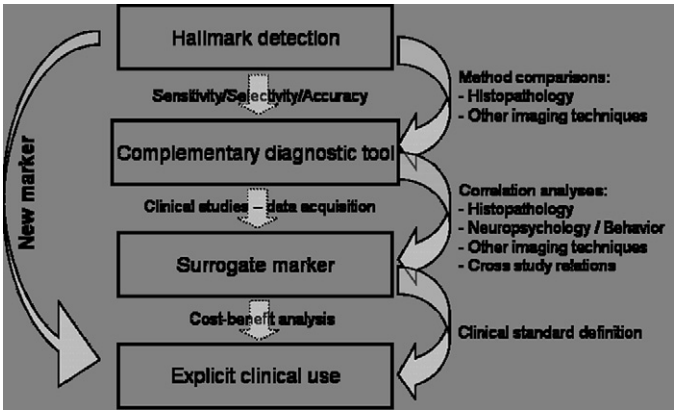

Fig. 1. Stages of a measurement method from detection of a disease hallmark to the explicit clinical use of the technique for diagnosis.

severity of Alzheimer's disease pathology,[12,13] and that hippocampal atrophy correlates with cognitive impairment.[14–16]

In even earlier disease stages, tracking shrinkage of the entorhinal cortex may also be useful for predicting Alzheimer's disease.[17–19] Atrophy rates have been reported to be larger in entorhinal cortex than in the hippocampus (~7% per year versus ~6% per year),[20] but difficulties in unambiguously defining this brain structure on the basis of landmarks make entorhinal cortex measurements highly variable.[21] In general, manual regions-of-interest measurements are both operator-dependent and labor-intensive.

Both regions-of-interest measurements and automated measurement approaches assessing hippocampal volume changes have already proven meaningful and feasible in clinical trials. However, a recent study suggested that whole brain atrophy measures might even be more closely related to clinical and cognitive scores (Mini-Mental State Examination, Dementia Rating Scale, Clinical Dementia Rating) than to the annual change in hippocampal and entorhinal cortex volume.[22]

MRI indices enable assessments of processes linked to disease progression with sensitivity far beyond what would be detectable on the basis of cognitive and clinical scores. Consequently, trials incorporating such MRI markers require fewer subjects, which in turn makes it easier to conduct proof-of-concept studies[9,22–24] (for a more detailed review on quantitative MRI of different brain regions see Ramani and colleagues[25]). As for potential applications of MRI in related clinical trials, a consensus report of the Alzheimer's Association[2] identified two main areas: (1) for supplementary exclusion and for more stringent stratification criteria to define a homogeneous study population, and (2) for strong correlation with clinical symptoms and neuropathology at earlier stages of the disease and the possibility to trace the progression of the disease.

Nonetheless, because of its lack in specificity, structural MRI cannot currently be considered an

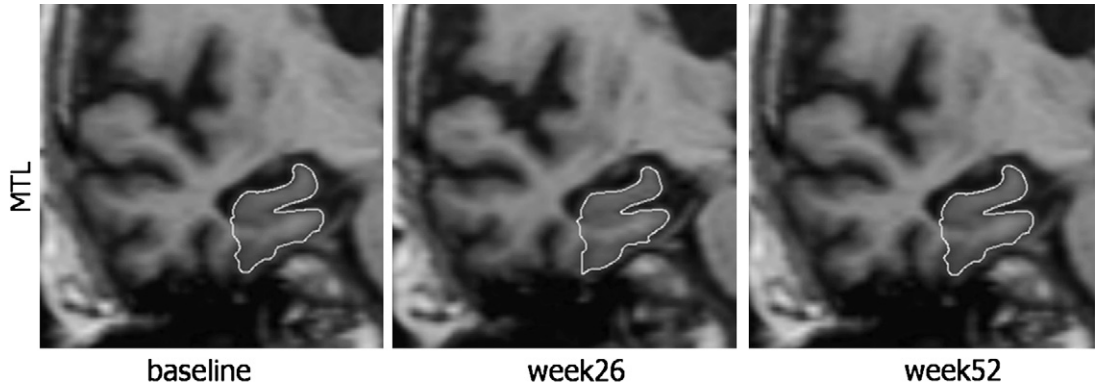

Fig. 2. Measurement of medial temporal lobe (MTL) atrophy using manual segmentation on coronal T1-weighted scans.