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Cortical phase changes in Alzheimer's disease at 7T MRI: A novel imaging marker

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Abstract

Background: Postmortem studies have indicated the potential of high-field magnetic resonance imaging (MRI) to visualize amyloid depositions in the cerebral cortex. The aim of this study is to test this hypothesis in patients with Alzheimer's disease (AD).

Methods: T2*-weighted MRI was performed in 16 AD patients and 15 control subjects. All magnetic resonance images were scored qualitatively by visual assessment, and quantitatively by measuring phase shifts in the cortical gray matter and hippocampus. Statistical analysis was performed to assess differences between groups.

Results: Patients with AD demonstrated an increased phase shift in the cortex in the temporoparietal, frontal, and parietal regions ($P < .005$), and this was associated with individual Mini-Mental State Examination scores ($r = -0.54$, $P < .05$).

Conclusion: Increased cortical phase shift in AD patients demonstrated on 7-tesla T2*-weighted MRI is a potential new biomarker for AD, which may reflect amyloid pathology in the early stages.

Keywords: Alzheimer's disease; Brain imaging; Human 7T MRI; AD pathology; Phase changes; Biomarker

1. Introduction

Alzheimer's disease (AD) can only be diagnosed with certainty at autopsy, based on the histological detection of senile plaques containing fibrillary amyloid beta (Aβ) and neurofibrillary tangles. Currently, because of the absence of validated sensitive and specific tests, the clinical diagnosis of AD can only be made at a late stage of disease progression and with a considerable degree of uncertainty—probable AD, at best—and is based on criteria from the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, and the National Institute of Neurological, Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association. Nevertheless, the histological hallmarks of AD pathology, comprising amyloid plaques and neurofibrillary tangles, are known to occur up to 10 to 20 years before the objective detection of cognitive decline [1]. Recently, positron emission tomography (PET) using Pittsburgh compound B (PiB) has been introduced as a diagnostic tool to detect cerebral amyloid in vivo [2–8]. The major disadvantages of PiB-PET are the need to use a radioactive tracer, the relative scarcity of institutions that can perform such scans because of the requirement for an onsite cyclotron, the inability to acquire anatomic and functional information in the brain during the same examination, and the greater chance of false positives, making interpretation of PiB-PET scans more difficult, especially in the elderly, which hampers the use of this method as a diagnostic tool in the elderly [9].

Earlier research demonstrated the potential of high-field (7T) magnetic resonance imaging (MRI) in the diagnosis of AD by showing distinct intensity changes in the cortex on T2*-weighted images of postmortem brain specimens of AD patients. These features included hypointense foci and diffuse granular patterns of less distinct hypointense foci in the cerebral cortex [10]. Similar patterns have been

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described in studies of AD transgenic mice and postmortem human AD cases, and were attributed to the presence of amyloid plaques using histological confirmation [11–19]. It has been proposed that the visualization on MRI of plaques in humans and mice is based on the fact that these deposits colocalize with iron, which gives rise to magnetic susceptibility effects on T2*-weighted images over volumes that are much larger than the actual size of amyloid plaques [17,19–24]. An alternative method to measure these susceptibility changes in the brain is to measure the relative phase in regions of interest (ROIs), because it has been shown that this is a reliable indicator of the iron content in the brain [25–28]. Although previous studies have demonstrated the potential of this approach in high-field MRI [29,30], no clinical studies have been performed yet on AD patients in vivo for the detection of AD pathology.

The overall aim of the current study is to confirm previous postmortem findings by detecting AD pathology in the cerebral cortex and hippocampus using a novel, in vivo, 7T high-field magnetic resonance (MR) approach.

2. Materials and methods

2.1. Participants

This study was approved by the local institutional review board. In all cases, informed consent was obtained according to the declaration of Helsinki [31]. In total, 16 AD patients with a mean age of 76.9 years (range, 68–86 years; 10 male/6 female) and 15 control subjects with a mean age of 75.1 years (range, 69–80 years; 10 male/5 female) were included.

The AD patients were recruited from the memory clinic of the Leiden University Medical Center. Memory clinic patients were referred to the hospital by their general practitioner or a medical specialist. Prior to the 7T study, these patients all underwent a routine clinical protocol comprising a whole-brain MRI (3T), a battery of neuropsychological tests, and a general medical and neurological examination performed by a neurologist, psychiatrist, or internist–geriatrician. The diagnosis was made in a multidisciplinary consensus meeting using the National Institute of Neurological, Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria for diagnosing probable AD [32]. Participants with the diagnosis of probable AD who were capable of giving informed consent (Mini-Mental State Examination (MMSE) score $\geq$19 points) with late-onset dementia (age $>$67 years) were selected for inclusion in the 7T study either retrospectively within 1 year after attending the memory clinic, or prospectively. Only patients with a "pure" form of AD were selected. Patients categorized as having a mixed form of dementia, or cerebral amyloid angiopathy (CAA), were not included in the study. Patients showing hemorrhagic lesions on T2*-weighted 3T MRI and/or diagnosed as possible or probable CAA according to the Boston criteria [33] were excluded.

Healthy control subjects were recruited by focused advertisement. Subjects with an age between 69 years and 80 years who were living independently, had an MMSE score $\geq$25 points, and had a Geriatric Depression Scale score $\leq$4 points were selected for inclusion. Subjects were screened by an internist–geriatrician (including for any cognitive deficits), and subjects with the following diseases were excluded: hemorrhagic and ischemic stroke, Morbus Parkinson, dementia, mild cognitive impairment, diabetes mellitus, rheumatoid arthritis, polymyalgia rheumatica, cancer, heart failure, and chronic obstructive pulmonary disease.

2.2. MRI

2.2.1. Image acquisition

MRI was performed on a whole-body human 7T MR system (Philips Healthcare, Best, The Netherlands) using a quadrature transmit and 16-channel receive head coil (Nova Medical, Wilmington, MA). Participants were scanned using a two-dimensional (2D), flow-compensated, transverse T2*-weighted gradient echo scan that included the frontal and parietal regions for amyloid detection with a total imaging duration of 10 minutes. Positioning of this stack was done on the sagittal plane of the survey within the frontal and parietal region above the occipital lobe. The middle of the stack was positioned through the corpus callosum, just above the thalamus. Fig. 1 shows a typical positioning of these 20 slices. Imaging parameters were repetition time/echo time, 794/25 ms; flip angle, 45°; slice thickness, 1.0 mm with a 0.1-mm interslice gap; number of slices, 20; field of view, 240 $\times$ 180 $\times$ 22 mm; and matrix size, 1000 $\times$ 1024; resulting in an in-plane nominal spatial resolution of 0.24 $\times$ 0.24 mm^2. The bandwidth per pixel was 46 Hz, corresponding to a readout length of approximately 22 ms. The frequency and phase-encoding directions were

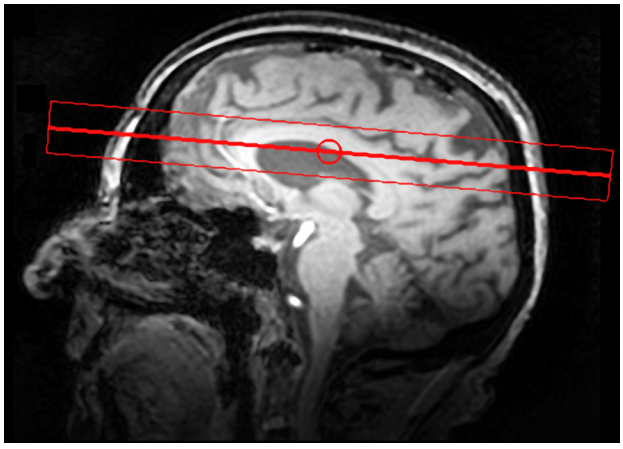

Fig. 1. Survey image on which the stack position of the two-dimensional T2*-weighted gradient echo scan, including the frontal and parietal cortex for amyloid detection, is shown. Image shows sagittal plane.