Seven-Tesla MRI and neuroimaging biomarkers for Alzheimer's disease

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The goal of this paper was to review the effectiveness of using 7-T MRI to study neuroimaging biomarkers for Alzheimer's disease (AD). The authors reviewed the literature for articles published to date on the use of 7-T MRI to study AD. Thus far, there are 3 neuroimaging biomarkers for AD that have been studied using 7-T MRI in AD tissue: 1) neuroanatomical atrophy; 2) molecular characterization of hypointensities; and 3) microinfarcts.

Seven-Tesla MRI has had mixed results when used to study the 3 aforementioned neuroimaging biomarkers for AD. First, in the detection of neuroanatomical atrophy, 7-T MRI has exciting potential. Historically, noninvasive imaging of neuroanatomical atrophy during AD has been limited by suboptimal resolution. However, now there is compelling evidence that the high resolution of 7-T MRI may help overcome this hurdle. Second, in detecting the characterization of hypointensities, 7-T MRI has had varied success. PET scans will most likely continue to lead in the noninvasive imaging of amyloid plaques; however, there is emerging evidence that 7-T MRI can accurately detect iron deposits within activated microglia, which may help shed light on the role of the immune system in AD pathogenesis. Finally, in the detection of microinfarcts, 7-T MRI may also play a promising role, which may help further elucidate the relationship between cerebrovascular health and AD progression.

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KEY WORDS 7-T MRI; Alzheimer's; amyloid plaques; biomarkers; hippocampal atrophy

MORE than 100 years after the German psychiatrist Dr. Alois Alzheimer discovered the illness named after him, the gold standard for a confirmatory Alzheimer's disease (AD) diagnosis remains postmortem neuropathology. Clinical assessments have been shown to be unreliable in diagnosing AD—even in its late stages—and so at best clinical judgment can render a “highly probable” diagnosis of AD.^{6,80} Only postmortem findings, under the microscope, of an abnormal accumulation of amyloid plaques and neurofibrillary tangles in the brain can definitively confirm a diagnosis of AD.^{12,61,68} Given such a constraint, there has been a push to develop a noninvasive technique to reliably diagnose and study AD onset and progression in vivo.

High-field MRI is one technique by which AD has been increasingly studied noninvasively and in vivo. Most MRI units used in clinical practice today operate at a magnetic field of 1.5 or 3.0 T. However, starting a little less than a decade ago, 7-T MRI scanners began to emerge as powerful tools for studying various biomarkers for AD in vivo. The studies published so far have mainly focused on the

ability of 7-T MRI to detect 1) neuroanatomical atrophy; 2) the molecular characterization of hypointensities; and 3) microinfarcts. This review will discuss the results of these studies, as well as comment on the future utility of 7-T MRI in detecting biomarkers for AD.

Neuroanatomical Atrophy

Atrophy of the brain has been a known finding of AD ever since the disease was first discovered.¹ Currently, there is a widely recognized pattern of neuroanatomical atrophy in AD. It starts in the medial temporal lobe, beginning specifically in the entorhinal cortex and advancing to the hippocampus before finally encompassing the rest of the neocortex.⁴² This pattern of atrophy is associated with the presence of neurofibrillary tangles.^{94,95} As mentioned previously, the presence of neurofibrillary tangles is a requirement for the pathological diagnosis of AD, and pathologists have long used these neurofibrillary tangles as guideposts in determining during which stage of AD a person died.¹³ Unfortunately, because of the small size

ABBREVIATIONS AD = Alzheimer's disease; CA1 = Cornu Ammonis 1; PiB = Pittsburgh compound B.

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of these neurofibrillary tangles, they are not detectable on in vivo imaging studies. Since neuroanatomical atrophy is associated with the presence of neurofibrillary tangles, the imaging of such atrophy—particularly in the hippocampus—offers a compelling biomarker for AD.²⁷

Indeed, whole hippocampus volumetry has been assessed in the literature as an important marker for neurodegeneration and atrophy in many neurological disorders, such as epilepsy, stress, and schizophrenia.^{9,15,38,65} More recently, imaging studies have focused on hippocampal subfield volumetry as more specific markers of dementia.¹⁰¹ Subfield segmentation protocols have been derived from imaging studies performed on scanners from a spectrum of higher-than-clinical field strengths: 4 T, 4.7 T, 7 T, and even an ex vivo 9.4 T, as well as histology-derived labeling.^{2,57,63,97,100} Due to the plethora of labeling protocols and guidelines in the literature, there have been attempts to compare different protocols and standardize across guidelines to produce a unified segmentation protocol.⁹⁹

For AD, hippocampal subfields have been examined with 3 T since the 2000s, showing potential findings regarding thinning of the entorhinal cortex in early AD.^{19,49,92,98} The advent of MRI scanners with increased magnetic field strengths has allowed for higher-resolution scans, and thus more detailed investigation of anatomical abnormalities (Fig. 1). Beginning in 2010, a series of studies was published that used 7-T MRI to examine neuroanatomical atrophy occurring in patients with AD (Table 1). The first of these, built on the work of postmortem studies, found that a layer of hippocampal subfield Cornu Ammonis 1 (CA1), the stratum lacunosum-moleculare, is one of the first sites of atrophy during AD. By comparing patients with mild AD to age-matched controls, the authors were able to demonstrate atrophy in the CA1 hippocampal subfield, showing for the first time the ability of 7-T MRI to identify in vivo focal atrophy in AD.⁴⁴ The same group 2 years later was able to demonstrate that CA1 atrophy is linked to diminished recall performance.⁴³ Two subsequent studies in 2013 and 2014 further built on the knowledge base. The 2013 study was able to convincingly show a temporal connection between atrophy of the entorhinal cortex and CA1, two structures thought to be involved in the early stages of AD.⁴² Finally, the 2014 study further widened the field by demonstrating atrophy in all but 1 hippocampal subfield in AD patients compared with mildly cognitively impaired patients and also age-matched controls.⁹⁶

Molecular Characterization of Hypointensities

Traditionally, the accumulation of amyloid plaques was the primary focus of attempts to molecularly characterize hypointensities found on 7-T MRI images applied to AD. We will review the literature on this below. However, there is emerging evidence that the immune system plays a potentially critical role in AD pathogenesis; to that end, we will also review an interesting new study that has shown microglia appearing as hypointensities in postmortem AD specimens imaged with 7-T MRI.

First, amyloid plaques have garnered special attention in the AD world ever since the disease was first discovered.

FIG. 1. T2*-weighted (a and b), T2-weighted (c and d), and FLAIR (e and f) images of the medial temporal lobe obtained at 1.5 T (a, c, and e) and 7 T (b, d, and f), illustrating the strikingly improved resolution that high-field MRI offers. Reprinted from Theysohn et al.: *The human hippocampus at 7 T—in vivo MRI*, *Hippocampus* 19:1–7, 2009, copyright 2008, Wiley-Liss, Inc.

Indeed, in his 1907 neuropathology report, Dr. Alois Alzheimer remarked finding “minute miliary foci caused by the deposition of a special substance.”^{1,56} However, it was not until 1984 in a landmark paper that Glenner and Wong sequenced the composition of these “minute miliary foci” and discovered them to be composed of a peptide called amyloid-beta.³⁰ Through a combination of subsequent genetic, animal, cell culture, and pathological studies, it was eventually reasoned that the abnormal accumulation of the soluble form of the amyloid-beta peptide could be the primary cause of AD.⁴⁰ These soluble accumulating amyloid-beta peptides are implicated in inappropriate inflammatory responses, the creation of neurofibrillary tangles, the disruption of neural synapses, and the death of neurons.⁵³ Amyloid plaque formation is, indeed, another facet of the so-called “amyloid cascade hypothesis” for AD pathogenesis (Fig. 2). Thus, the amyloid plaques themselves have been researched as potentially useful biomarkers for the illness.⁴⁰

To noninvasively study amyloid plaques, researchers in the recent past have used 1 of 2 imaging modalities: PET or high-field MRI. The most widely used PET tracer for amyloid imaging is Pittsburgh compound B (PiB). With PiB-PET, several groups have been able to successfully demonstrate imaging of amyloid plaque accumulation.^{5,35,39,46,47,52,73} However, a number of issues exist with PiB-PET, such as a relatively low spatial resolution, the use of the radioactive PiB tracer, nonspecific white mat-

TABLE 1. 7-T MRI and imaging of AD-related neuroanatomical atrophy: published studies*

Authors & Year	Type	MR Sequence	Image Resolution	Scan Time	No. of Patients/Specimens	Major Finding(s)
Kerchner et al., 2010	In vivo	T2*-weighted gradient-recalled	0.195 x 0.26 x 2 mm ³	9.6 mins	14 AD patients; 16 age-matched controls	The CA1 hippocampal subfield is an early site of atrophy during AD
Kerchner et al., 2012	In vivo	T2-weighted FSE	0.22 x 0.22 x 1.5 mm ³	<10 mins	9 mild AD patients	Correlation btwn the size of the CA1 hippocampal subfield & recall performance
Kerchner et al., 2013	In vivo	T2-weighted FSE	0.22 x 0.22 x 1.5 mm ³	<10 mins	11 AD patients; 15 mild cognitive impairment patients; 18 healthy older controls; 9 healthy younger controls	Atrophy of the entorhinal cortex & CA1 are temporally connected in AD
Wisse et al., 2014	In vivo	3D T2-weighted turbo spin echo	0.70 mm isotropic	10–15 mins	9 AD patients; 16 mild cognitive impairment patients; 29 controls	All but 1 hippocampal subfields have relatively increased atrophy in AD patients
Apostolova et al., 2015	Postmortem	Not reported	0.125 x 0.125 x 0.195 mm ³	20 hrs	9 AD autopsy specimens; 7 controls	Subfield atrophy is significantly associated w/ the presence of tau protein, amyloid-beta peptides, neuronal count, & Braak & Braak staging

FSE = fast spin echo.

* The effectiveness of 7-T MRI in assessing neuroanatomical atrophy during AD has been studied so far in 5 publications. Notably, the in vivo studies illustrate the ability of 7-T MRI to perform scans in a tolerable period of time.

ter binding in fluorinated versions of the tracer, positive findings in amyloid angiopathy (which co-occurs but is not diagnostic of AD⁵), and the inability to simultaneously perform functional and anatomical imaging on the vast majority of PET scanners.^{74,89}

High-field MRI has been proposed as an alternative to PiB-PET. Indeed, research studying amyloid plaques on ex vivo tissues with 7-T MRI has been published since 1999.⁸ That year, Benveniste and colleagues studied postmortem hippocampal specimens that were pathologically confirmed to have AD; their findings were the first to demonstrate the ability of 7-T MRI to detect amyloid plaques.⁸ While some challenges were present in replicating the result,²⁴ subsequent research on postmortem samples from humans and ex vivo specimens from mice has supported the concept that plaques can be seen with MRI.^{21,26,36,51,60,71,104} These early studies demonstrated a number of important concepts. First, histopathological staining could be used to confirm 7-T MRI-based detection of amyloid plaques. Second, these studies suggested that perhaps amyloid plaques contain iron deposits, which may allow them to appear more conspicuous on high-field T2-weighted MRI.²⁵ More recent work has shown that image acquisition time can be reduced (early studies often spent more than 10 hours imaging a single specimen) while still preserving the sensitivity of amyloid plaque detection.^{11,14,21,26,41,84}

There are currently 2 studies in the literature about the use of 7-T MRI in detecting amyloid plaques in living patients with AD. The first study, published in 2008, examined 10 AD patients and 10 age-matched controls.⁶⁴ The authors showed multifocal hypointensities in the entire parietal cortex in all AD patients, and also found such hypointensities in 2 of the age-matched controls. However, this study was not histologically validated and has not been replicated, so it is unclear what the hypointensities represent. The second study, published in 2014, investigated the putative relationship between amyloid plaques and iron content by applying a novel imaging technique known as “phase shift.”⁸⁹ Utilizing high-field T2-weighted MRI, the researchers discovered increased phase shift in regions of the brain of AD patients that were known to be involved in AD pathogenesis, and they were able to successfully correlate their findings on phase shift to the results of a mini-mental examination.

A limitation in studying amyloid plaques is that their presence is not enough in itself to cause the cognitive dysfunction present in AD.^{66,67} Indeed, postmortem analyses in elderly individuals have found increased levels of amyloid plaques, but without a diagnosis of AD.^{48,72,76} Rather, it is the soluble amyloid peptides that are implicated in AD progression, and these cannot be picked up by either PiB-PET or high-field MRI. (However, there is emerging evidence of the ability to detect increased levels of soluble amyloid peptides in CSF via lumbar puncture several years before AD onset.¹⁸) Indeed, if anything, perhaps the presence of amyloid plaques is a positive sign, because it may indicate that fewer amyloid-beta peptides are floating around in their more neurotoxic soluble form. Nevertheless, given the success of PiB-PET in discerning amyloid plaques, 7-T MRI is less likely to shed specific light on amyloid.

FIG. 2. In a 2010 *Lancet Neurology* article, Jack and colleagues proposed this model to represent the changing levels of biomarkers during AD progression. Amyloid-beta proteins accumulate first, consistent with the “amyloid cascade hypothesis” for AD onset. By the mild cognitive impairment (MCI) stage of the disease, levels of tau-mediated neuronal injury and dysfunction, as well as the amounts of brain structure atrophy, have significantly risen. This chart also illustrates that by the time clinical symptoms present, biomarkers for AD have already been present for a long time. Reprinted from *The Lancet Neurology*, vol 9, Jack CR Jr, Knopman DS, Jagust WJ, “Hypothetical model of dynamic biomarkers of the Alzheimer’s pathological cascade,” pp 119–128, 2010, with permission from Elsevier.

More recent developments, however, suggest that 7-T MRI may potentially offer useful insight into iron and microglia in AD. Microglia are immune cells of the nervous system, and a compelling series of studies has implicated them in the pathogenesis of AD.^{22,23,28,29,33,34,59,79,103} In a recent study by Zeineh et al., conspicuous focal hypointensities were found in the hippocampus, and specifically in the subiculum (a peripheral subregion of the hippocampus), in 4 out of 5 advanced AD specimens, but not in any of the controls¹⁰² (Fig. 3). A sophisticated histological evaluation that was coregistered with the MRI demonstrated that these hypointensities were iron deposits, and these iron deposits were largely within activated microglia. This opens a tantalizing new avenue of exploring the inflammatory nature of AD with MRI if this visualization can be translated from ex vivo to in vivo, similar to noninvasive visualization that has been shown in the disease amyotrophic lateral sclerosis.⁵⁰

Microinfarcts

Microinfarcts are so-called “mini-strokes” that occur on a scale of less than 1 mm³. Several studies have implicated their role in the progression of dementia, suggesting a 2-hit hypothesis: amyloid, neurofibrillary, and inflammatory pathology explain the principal neurodegenerative process, while microvascular ischemic disease results in a loss of neurocognitive reserve and can itself even result in production of amyloid.¹⁶ Indeed, the broader fields of cerebrovascular blood flow and hypoperfusion have been getting attention as a cause behind neurodegeneration ever since a series of papers demonstrated head injuries could increase one’s risk of developing AD.³² Microinfarcts are found pathologically in the brains of about 33% of the deceased, but they are found at even higher rates in patients with AD.^{17,81,82} The relationship of microinfarcts to AD

is unclear; nevertheless, they serve as another potential biomarker or risk factor for AD. Due to their small size, however, the study of microinfarcts has been waiting for a noninvasive imaging modality with high enough resolution to study them. To that end, a study published in 2013 made use of 7-T MRI in successfully detecting microinfarcts in the brains of 22 elderly individuals.⁹⁰

So far there has been 1 study published that used 7-T MRI to study microinfarcts in patients with AD (Fig. 4).⁸⁸ The study found with high interobserver reliability that patients with AD have significantly increased amounts of microinfarcts as compared with healthy controls. Moreover, the study found that these microinfarcts were mainly related to AD when compared with patients with cerebral amyloid angiopathy, a degenerative disease that is similar but distinct from AD. Given this promising early study, there is potential to further study the role of cerebrovascular health more broadly, and microinfarcts more specifically, in the progression of AD.

7-T MRI Limitations and Challenges

Despite the gains in sensitivity, signal-to-noise ratio, and increase in MR contrast of 7 T, the transition to high-magnetic-field scanners presents several notable challenges and drawbacks. First, B1 inhomogeneity is more than 2-fold that of 3-T systems, and radiofrequency power consumption is significantly higher; hence, specific absorption rate limits/restrictions are reached much earlier than with lower-field scanners.^{49,92} In addition, MRI susceptibility effects increase linearly with field strengths, specifically in iron-rich areas in the brain, which causes increased susceptibility artifacts and signal dropouts due to off-resonance frequencies.^{50,98} The much higher cost of the scanners, as compared with clinical 1.5- and 3-T systems, has proved to be another hurdle for transitioning

FIG. 3. Five AD hippocampal specimens (A1–A5) and one normal control (N4) are shown. Note the signal voids in AD specimens along the hippocampus compared with the lack of such signal voids in the normal control. The border between field CA1 and the subiculum is indicated by the white line derived from coregistered acetylcholine, myelin, and Nissl staining. The variability in their locations relative to the medial aspect of the hippocampal body illustrates the challenges inherent in *in vivo* imaging studies of hippocampal subregions. Reprinted from *Neurobiology of Aging*, vol 36, Zeineh M, Chen Y, Kitzler HH, Hammond R, Vogel H, Rutt BK, “Activated iron-containing microglia in the human hippocampus identified by magnetic resonance imaging in Alzheimer’s disease,” pp 2483–2500, 2015, with permission from Elsevier.

high-field MRI into the clinic. In studies comparing discomfort at 3 T versus 7 T, a quarter of the patients reported induced vertigo when the table was moving at 7 T; about 20% experienced peripheral nerve stimulation (tingling) in their arms during a head scan, and lengthy examination durations were regarded as more uncomfortable at higher fields.⁸⁷ Efforts are under way to deal with these challenges, including parallel transmission combined with mathematical modeling for improved B1 homogeneity and specific absorption rate monitoring,^{45,75} slower table speeds to avoid vertigo upon magnet entry, and advanced sequences to accelerate sequences and reduce imaging times.^{20,58,77,105} However, these studies suggest that subject tolerability and subjective acceptance will be lower at 7 T and more subjects may decline examinations.

In addition to the general limitations, there are several

challenges pertaining specifically to performing imaging in patients who are elderly or have AD or mild cognitive impairment that need to be addressed by the field to improve the appeal of 7 T for AD clinical investigation. For instance, due to the potential of higher signal-to-noise ratio at 7 T, higher resolution is often pursued (most commonly to assess the hippocampal morphometry of patients with dementia), which leads to longer scan times for a patient population that can only tolerate short examinations. Many hardware technologies and software techniques are being developed to deal with the increasing scan times, including coil-based acceleration schemes,^{7,54,58,78} compressed sensing,⁹¹ multiband and multislice excitation,^{62,77} and improved coil design.³ High-field systems tend to have smaller bores as well as higher acoustic noise, which, when combined with longer scan times and decreased

FIG. 4. 7-T FLAIR MRI in the (left to right) transverse (**left**), sagittal (**center**), and coronal (**right**) views. The arrow is pointing to a microinfarct. Reprinted with permission from van Rooden S, Goos JD, van Opstal AM, Versluis MJ, Webb AG, Blauw GJ, et al: Increased number of microinfarcts in Alzheimer disease at 7-T MR imaging. *Radiology* 270:205–211, 2014.

comfort, present higher probability of motion during the scan,¹⁶ especially for elderly patients. Adaptive motion correction techniques^{55,69,83} and real-time navigators⁹³ have the potential to mitigate patient motion artifacts. MRI susceptibility effects increase linearly with field strength, specifically in iron-rich areas in the brain, which causes increased susceptibility artifacts and signal loss that could affect the medial temporal lobe in particular.^{50,98} Nevertheless, this presents a more complex problem for functional and diffusion MRI as compared with the structural imaging we discuss here. Finally, in addition to imaging improvements, image analysis techniques (such as automated hippocampal segmentation¹⁰¹) need to be developed to capture relatively smaller subfields or pathways,⁷⁰ such as the endfolial pathway, in atrophied hippocampi of elderly, mildly cognitively impaired, and AD patients.

Future of 7-T Imaging in AD

The future of utilizing 7-T MRI to study AD patients is promising. Indeed, an AD study published in 2015 correlated in vivo 7-T MRI of atrophy of hippocampal subfields with postmortem analysis of amyloid plaques, neurofibrillary tangles, and neuronal count and found a significant correlation between atrophy and all of them.⁹⁶ A challenge of examining hippocampal subfields is that imaging-based segmentation schemes are quite variable without a ground truth.⁹⁹ The demarcation between the hippocampal CA fields and the subiculum, for instance, can be quite variable in a way that is difficult to capture with in vivo imaging (Fig. 3).¹⁰² Standardization of anatomy should facilitate greater ease of communication for further research into atrophy during AD, especially during the early stages of AD when only very specific regions of the hippocampus are involved. With the continuous advancement in imaging hardware and reconstruction software, as well as the use of simultaneous multislice techniques, it is now possible to achieve high in vivo resolutions comparable to the current ex vivo resolutions, in clinically feasible times. These submillimeter resolutions will aid in the visualization and study of hippocampal substructures and micropathways in neurodegeneration.⁷⁰ In addition to T1- and T2-weighted

imaging, high-resolution quantitative techniques such as R2*, susceptibility-weighted imaging, and quantitative susceptibility maps have shown promise in detecting microbleeds in vascular dementia, quantifying iron content in normal aging, and as a tool for assessing hippocampal subfield differences.^{10,31,85} Hence, these techniques may play a role in detecting neuroanatomical atrophy and visualizing microinfarcts in AD, as well as providing insights to better understand the role of iron and inflammation in the progression of the disease.

Conclusions

Significant advancements in our understandings of AD have been made through pathological study. Now is an era in which noninvasive tools can further enhance our understanding of this disease process, particularly in its early stages. In this paper we reviewed the role of high-field 7-T MRI as a means to study 3 biomarkers for AD. The results of these studies are edifying and point to a future in which 7-T MRI will continue to be used in AD research and perhaps even clinical care.

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