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In vivo detection of microstructural correlates of brain pathology in preclinical and early Alzheimer Disease with magnetic resonance imaging

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ABSTRACT

Background: Alzheimer disease (AD) affects at least 5 million individuals in the USA alone stimulating an intense search for disease prevention and treatment therapies as well as for diagnostic techniques allowing early identification of AD during a long pre-symptomatic period that can be used for the initiation of prevention trials of disease-modifying therapies in asymptomatic individuals.

Methods: Our approach to developing such techniques is based on the Gradient Echo Plural Contrast Imaging (GEPCI) technique that provides quantitative *in vivo* measurements of several brain-tissue-specific characteristics of the gradient echo MRI signal (GEPCI metrics) that depend on the integrity of brain tissue cellular structure.

Preliminary data were obtained from 34 participants selected from the studies of aging and dementia at the Knight Alzheimer's Disease Research Center at Washington University in St. Louis. Cognitive status was operationalized with the Clinical Dementia Rating (CDR) scale. The participants, assessed as cognitively normal (CDR=0; n=23) or with mild AD dementia (CDR=0.5 or 1; n=11) underwent GEPCI MRI, a collection of cognitive performance tests and CSF amyloid (Aβ) biomarker $A\beta_{42}$. A subset of 19 participants also underwent PET PiB studies to assess their brain Aβ burden. According to the Aβ status, cognitively normal participants were divided into normal (Aβ negative; n=13) and preclinical (Aβ positive; n=10) groups.

Results: GEPCI quantitative measurements demonstrated significant differences between all the groups: normal and preclinical, normal and mild AD, and preclinical and mild AD. GEPCI quantitative metrics characterizing tissue cellular integrity in the hippocampus demonstrated much stronger correlations with psychometric tests than the hippocampal atrophy. Importantly, GEPCI-determined changes in the hippocampal tissue cellular integrity were detected even in the hippocampal areas not affected by the atrophy.

Our studies also uncovered strong correlations between GEPCI brain tissue metrics and beta-amyloid (Aβ) burden defined by positron emission tomography (PET) – the current *in vivo* gold standard for detection of cortical Aβ, thus supporting GEPCI as a potential surrogate marker for Aβ imaging – a known biomarker of early AD. Remarkably, the data show significant correlations not only in the areas of high Aβ accumulation (e.g. precuneus) but also in some areas of medial temporal lobe (e.g. parahippocampal cortex), where Aβ accumulation is relatively low.

Conclusion: We have demonstrated that GEPCI provides a new approach for the *in vivo* evaluation of AD-related tissue pathology in the preclinical and early symptomatic stages of AD. Since MRI is a widely available technology, the GEPCI surrogate markers of AD pathology have a potential for improving the quality of AD diagnostic, and the evaluation of new disease-modifying therapies.

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1. Introduction

Alzheimer disease (AD) is a neurodegenerative disorder that is characterized by intraneuronal aggregates of tau called neurofibrillary tangles and extracellular aggregates of amyloid-beta (Aβ) protein called plaques. Clinically, AD is characterized by memory deficits and progressive cognitive impairment leading to dementia. To date all disease-modifying experimental therapies for AD have failed to demonstrate clinical benefit in individuals with symptomatic AD (Albert et al., 2011; McKhann et al., 2011), possibly because the drugs were administered too late in the course of the disease which begins 15–20 years prior to the onset of clinical symptoms (Selkoe, 1991; Hardy and Allsop, 1991; Hardy and Higgins, 1992; Hardy and Selkoe, 2002; Jack et al., 2010; Bateman et al., 2012; Benzinger et al., 2013; Sperling et al., 2011). This preclinical stage of AD provides a large window for therapeutic intervention (Morris et al., 2012). Hence, one of the important directions in AD therapy is developing widely accessible neuroimaging techniques that can detect AD brain pathology in the preclinical stages (Fagan et al., 2005; Reiman et al., 2016).

One of the prevailing hypotheses of AD is the amyloid cascade hypothesis (Selkoe, 1991; Hardy and Higgins, 1992; Hardy and Selkoe, 2002; Jack et al., 2010) that suggests that abnormal accumulation of (Aβ) in the neocortex is one of the earliest pathological markers of AD. Paradoxically, it is also known that the medial temporal lobe (MTL), a region that mediates short-term memory, is affected early in the disease but is not the most affected region by Aβ deposition compared with neocortical regions (e.g. prefrontal cortex and precuneus (Ikonomovic et al., 2008; Klunk et al., 2004; Price et al., 2005)). At the same time, histological studies show that the MTL is particularly vulnerable to neurofibrillary pathology in the early stages of aging and AD (Braak and Braak, 1991; Mitchell et al., 2002; Hyman et al., 1984; Arnold et al., 1991; Price and Morris, 1999; Thangavel et al., 2008). The reduction of volume and the loss of cells in the entorhinal cortex and hippocampus have been extensively reported in participants with mild cognitive impairment (MCI) and AD (Schuff et al., 2009; Jack et al., 2000; Price et al., 2001; Gomez-Isla et al., 1996; Juottonen et al., 1998). Importantly, neuropathology studies have established that symptomatic AD begins only when cell loss occurs in the hippocampal area (Price et al., 2001).

MRI is a potentially powerful tool to identify changes in the Alzheimer brain. Most MRI studies so far have focused on AD-related volumetric measurements of brain atrophy (Dickerson et al., 2011). A few studies attempted to identify plaques via MRI in postmortem specimens or mice models (Benveniste et al., 1999; Meadowcroft et al., 2009; Wengenack et al., 2011; Chamberlain et al., 2009; Lee et al., 2004; Maier et al., 2015), though the latter methods require long imaging time and have not been translated to human studies.

In this paper we use an MRI-based method allowing *in vivo* simultaneous detection of Aβ accumulation and cellular damage in humans with Alzheimer disease. Our approach is based on the Gradient Echo Plural Contrast Imaging (GEPCI) technique (Sati et al., 2010; Luo et al., 2012; Ulrich and Yablonskiy, 2015) previously used in normal aging studies (Zhao et al., 2016) and to identify brain tissue damage in multiple sclerosis (Sati et al., 2010; Luo et al., 2012; Luo et al., 2014; Wen et al., 2014; Wen et al., 2015; Patel et al., 2015) and psychiatric diseases (Mamah et al., 2015). The GEPCI technique provides quantitative *in vivo* high resolution 3D measurements of several brain-tissue-specific parameters of the gradient recalled echo MRI signal (GEPCI metrics – see specific definitions in the next section). The GEPCI metrics depending on the molecular constituents of cell-building materials present in the brain (Zhao et al., 2016) can serve as surrogate markers reflecting disease-related tissue damage.

The goal of this study was to establish the relationship between GEPCI metrics and AD-related tissue damage at preclinical and very early symptomatic stages of AD. To this end, we enrolled participants from the Washington University Knight Alzheimer's Disease Research Center (Knight ADRC) with well-characterized clinical status ranging from cognitively normal to very mild and mild AD, and with a battery of psychometric, CSF and neuroimaging data. We demonstrated a significant correlation between GEPCI metrics of brain tissue cellular damage in the hippocampus and cognitive performance. Importantly, this correlation is stronger than the correlation between cognitive performance and hippocampal atrophy, thus suggesting that the integrity of the remaining tissue is a more important parameter for brain functioning than the loss of tissue volume alone. We also uncovered a remarkable correlation between GEPCI metrics and β-amyloid load measured by positron emission tomography (PET) (the current *in vivo* gold standard), thus supporting GEPCI as a potential surrogate marker for Aβ imaging in preclinical and early Alzheimer disease.

Our results demonstrate that GEPCI is sensitive to early AD-related pathological changes in brain tissue. Since our approach is based on MRI that is widely available worldwide, is non-invasive, and does not require radiation exposure, it can open opportunities for obtaining new information on the pathogenesis of AD, one of the most devastating diseases of older adults. The new method can also open the door for screening cohorts for clinical drug trials that are enrolling individuals with preclinical or early symptomatic AD.

2. Methods

2.1. Participants

This study was approved by the Institutional Review Board of Washington University School of Medicine (WUSM). 34 participants were selected from the studies of aging and dementia at the Knight Alzheimer's Disease Research Center (ADRC) at WUSM. All participants provided informed consent. Cognitive status was operationalized with the Clinical Dementia Rating (CDR) (Morris, 1993), as determined by Knight ADRC clinicians according to standard protocols; diagnoses were in accordance with standard criteria (McKhann et al., 2011). The participants were assessed to be cognitively normal (CDR=0) or to have mild (CDR=0.5 or 1) AD dementia. All participants in this study underwent a collection of cognitive performance tests (Johnson et al., 2008), including Free and Cued Selective Reminding Test (Srtfree), Animal Naming (ANIMALS), and Trail making Test Part A (Tma). CSF biomarker $A\beta_{42}$ (INNOTEST, Fujirebio, Gent, Belgium) was available for 31 participants. 19 participants underwent PiB PET imaging to estimate amyloid deposition in their brains. According to the Aβ status (see below), cognitively normal participants (CDR=0) were divided into normal (CDR=0; Aβ negative) and preclinical (CDR=0; Aβ positive) groups. Demographic information for all groups is presented in Table 1. For participants that underwent PET amyloid imaging, amyloid positivity was defined by a cutoff of mean cortical binding potential (MCBP)=0.18 (Mintun et al., 2006) which corresponds to a mean cortical standardized uptake value ratio (MC-SUVR) of 1.3 referenced to cerebellar grey matter. MC-SUVR for Aβ imaging is calculated as the average of regions within the prefrontal cortex, gyrus rectus, lateral temporal, and precuneus regions. For participants that did not have PET Aβ measurements, Aβ positivity was determined by

Table 1
Distribution of participants between groups and their demographic information. Note that nine participants in Mild AD group were Aβ positive and two were Aβ negative.

	Normal	Preclinical AD	Mild AD
	CDR=0, Aβ negative	CDR=0, Aβ positive	CDR=0.5 or 1
N	13	10	11 (7/4)
Age	69.6 ± 8.7	72.3 ± 8.4	76.0 ± 8.4
Female/Male	7/6	4/6	3/8