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Journal
Alzheimer's & Dementia, 15(12)

ISSN
1552-5260

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Publication Date
2019-12-01

DOI
10.1016/j.jalz.2019.07.012

Peer reviewed

Published in final edited form as:

Alzheimers Dement. 2019 December ; 15(12): 1568–1575. doi:10.1016/j.jalz.2019.07.012.

Undetectable gadolinium brain retention in individuals with an age-dependent blood-brain barrier breakdown in the hippocampus and mild cognitive impairment

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Structured Abstract

INTRODUCTION—Blood-brain barrier (BBB) breakdown is an early independent biomarker of human cognitive dysfunction, as found using gadolinium (Gd) as a contrast agent. Whether Gd accumulates in brains of individuals with an age-dependent BBB breakdown and/or mild cognitive impairment remains unclear.

METHODS—We analyzed T1-weighted MRI scans from fifty-two older participants with BBB breakdown in the hippocampus 19-28 months after either cyclic or linear Gd agent.

RESULTS—There was no change in T1-weighted signal intensity between the baseline contrast MRI and unenhanced MRI on re-examination in any of the studied ten brain regions with either Gd agent suggesting undetectable Gd brain retention.

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DISCUSSION—Gd does not accumulate in brains of older individuals with a BBB breakdown in the hippocampus. Thus, Gd agents can be used without risk of brain retention within a ~2-year follow-up to study BBB in the aging human brain in relation to cognition and/or other pathologies.

Keywords

magnetic resonance imaging; gadolinium; blood-brain barrier; normal aging; mild cognitive dysfunction

1. Introduction

Gadolinium (Gd) chelates are widely used as contrast agents for magnetic resonance imaging (MRI) of blood-brain barrier (BBB) in neurological disorders[1,2]. Using dynamic contrast-enhancement (DCE)-MRI with Gd, we found an age-dependent, progressive BBB breakdown in the hippocampus in the living human brain, but not in any other central nervous system (CNS) regions including cortex, deep brain regions, or the white matter[3]. Moreover, there was an accelerated BBB breakdown in the hippocampus in individuals with mild cognitive impairment (MCI), who also had an intact BBB in other CNS regions[3]. The BBB breakdown on DCE-MRI positively correlated with elevated cerebrospinal fluid (CSF) levels of soluble platelet-derived growth factor receptor-β (sPDGFRβ)[3], a biomarker of brain capillary vessel wall injury, particularly of its specialized cell - pericyte[4,5]. More recently, we found that BBB breakdown in the hippocampus and the parahippocampal gyrus is an early biomarker of human cognitive dysfunction independent of Alzheimer's disease (AD) classical biomarkers amyloid-β (Aβ) and/or tau[5].

Recently, it has been reported that patients with multiple sclerosis (MS) or brain tumors, both with a pronounced and widespread BBB breakdown in the white matter or within the tumor and/or peri-tumoral tissue, respectively, develop Gd brain retention after multiple and frequent Gd administrations[6-8]. This has been shown by increased signal intensity (SI) on unenhanced T1-weighted (T1w) MR scans, particularly in deep brain regions such as globus pallidus and dentate nucleus[6-8]. In most studies, Gd brain retention resulted from Gd administrations as frequent as 4-6 months apart[9]. Some studies suggested that the risk of retention is higher with the linear compared to cyclic Gd chelates[10-12]. Post-mortem electron microscopy and mass spectrometry studies also found Gd brain deposition in patients with glioblastoma multiforme and stroke who received frequent Gd injections[13-15].

Since no neurotoxic effects have been shown so far, Gd DCE-MRI remains as a gold standard for clinical diagnosis and/or evaluation of lesion progression in MS, brain tumors, cancer metastases, and other neurological disorders. It still has not been used routinely in neurodegenerative disorders associated with cognitive dysfunction such as AD or Parkinson's disease (PD), although a few recent studies have found BBB breakdown in the hippocampus, cortex and deep gray matter and normal appearing white matter regions in AD[16-18], as well as in the basal ganglia in PD[19] and in the caudate nucleus in Huntington's disease (HD)[20], as recently reviewed[2]. It remains unknown, however, whether Gd can accumulate in brains of individuals with neurodegenerative disorders, and/or a moderate, but pathophysiologically important BBB breakdown, as found in the aging human hippocampus

and/or MCI[3,5]. Because of the relatively slow disease process compared to brain tumors, cancer metastases, MS, or stroke, these individuals do not need a frequent assessment of their BBB status, but a 1-3-year follow-up would still provide important information for the role of BBB in disease pathogenesis and progression in relation to other pathologies and cognition.

Therefore, the goal of the present study was to find out whether individuals with an age-dependent, moderate BBB breakdown in the hippocampus, but not other CNS regions[3], and/or with MCI retain Gd in the brain ~2 years after administration of either linear or cyclic Gd agent. To address this question, we re-examined 52 participants from our previous study that had BBB breakdown in the hippocampus[3], and analyzed their Gd brain retention using conventional MRI.

2. Methods

2.1 Study Cohort

Participants were recruited through the University of Southern California (USC) Alzheimer's Disease Research Center (ADRC), Los Angeles, CA, and the Huntington Medical Research Institute (HMRI), Pasadena, CA. The study was approved by the USC Institutional Review Board (IRB). All participants were included after written informed consent was obtained. All participants underwent neurological exams and received a clinical diagnosis of either normal cognition or mild cognitive dysfunction. Fifty-two participants underwent DCE-MRI to assess BBB integrity[3] and were re-examined months later with an unenhanced MRI to measure potential Gd brain retention (see demographic data, Table 1). Thirty participants received one injection of cyclic chelates (Gadoterate meglumine, Dotarem®, Guerbet) and twenty-two participants received one injection of linear Gd chelates (Gadobenate dimeglumine, Multihance®, Bracco Diagnostics) at 0.05 mmol/kg. All quantitative MRI analyses were conducted by investigators blinded to the clinical status of the participant and/or chemical structure of the Gd compound.

Clinical diagnosis and Clinical Dementia Rating (CDR) assessments of older individuals with no cognitive impairment (NCI) or MCI followed the standardized Uniform Data Set (UDS) procedures[21,22]. Participants underwent clinical interview, including health history and a physical exam. Participant CDR scores were obtained through standardized interview and assessment with the participant and a knowledgeable informant. In addition, the following neuropsychological tests were given: California Verbal Learning Test, block design, letter-number sequencing, letter fluency, and token test. Cognitively intact NCI participants were defined by CDR=0 and neuropsychological test scores within normal limits; MCI participants were defined by CDR=0.5 and impairment in neuropsychological test scores in one or more cognitive domains.

2.2 MRI Acquisition and Processing

The MR datasets were obtained using a GE 3T HDXT MR scanner with a standard eight-channel array head coil at Keck Medical Center of USC ADRC. All participants underwent a blood draw to ensure appropriate kidney function for Gd administration prior to imaging.

The imaging protocol performed was originally developed to detect subtle BBB changes in patients with cognitive impairment and is detailed in Montagne et al.[3]. Anatomical coronal spin echo T2-weighted scans were first obtained through the hippocampi (TR/TE 1550/97.15 ms, NEX = 1, slice thickness 5 mm with no gap, FOV = 188 × 180 mm, matrix size = 384 × 384). Baseline coronal T1-weighted maps were then acquired using a T1w 3D fast spoiled gradient echo (FSPGR) pulse sequence. Briefly, BrainSuite software was used to pre-process T1w images, *i.e.*, automated skull stripping and brain segmentation, in order to get T1w SI and volumes for 10 pre-selected brain areas (*i.e.*, hippocampus, globus pallidus, parahippocampus, caudate nucleus, precuneus, thalamus, putamen, amygdala, cingulate, and cerebellum).

2.3 Statistical Analysis

One-way ANOVA followed by Bonferroni's multiple comparisons test was used to compare BBB K_{trans} values within the entire hippocampus and globus pallidus in young cognitively normal controls, older NCI and MCI individuals at first visit. Unpaired two-tailed Student *t*-tests were used to compare T1w SI and volumetric data between first visit (Pre) and re-examination (Post) and also within groups receiving linear or cyclic chelates separately. Pearson's correlations were used to evaluate relationships between BBB breakdown and T1w SI within the entire hippocampus and globus pallidus. GraphPad Prism 8 was used for all statistical analyses. An alpha of 0.05 is used as the cutoff for significance.

3. Results

We followed 52 participants, 30 who received one injection of cyclic Gadoterate meglumine (Cyclic Gd; 16 men and 14 women; mean [SD] interval between first Gd injection and non-contrast re-examination: 19 months [8]; age range: 64-88 y) and 22 who received one injection of linear Gadobenate dimeglumine (Linear Gd; 7 men and 15 women; mean [SD] interval between first Gd injection and non-contrast re-examination: 28 months [9]; age range: 59-94 y) (Table 1). Importantly, these older NCI and MCI participants exhibited statistically significant and progressive 53% and 92% increase in the BBB permeability K_{trans} values in the hippocampus, respectively (Figure 1A-C), but not in other CNS regions including globus pallidus (Figure 1A,B,D), compared to cognitively normal younger individuals (3 men and 3 women; age range: 23-47 y), consistent with a previous report[3].

No increase in T1w SI was noticed across ten different brain regions including hippocampus, globus pallidus, parahippocampus, caudate nucleus, precuneus, thalamus, putamen, amygdala, cingulate, and cerebellum between the baseline pre-contrast MRI scan and re-examination on unenhanced MRI scan (Figure 1E-J). Furthermore, no increase in T1w SI was observed in participants who received either cyclic or linear Gd agent (Supplementary Figure 1A-J). No correlation was found between BBB K_{trans} permeability values at baseline and averaged T1w SI values in the hippocampus and globus pallidus re-examination (Figure 1K,L) further indicating that Gd chelates do not accumulate in brains of individuals with a moderate BBB leakage. No volumetric changes were found at re-examination (Figure 2A-C) in either contrast group across the studied ten regions-of-interest (Supplementary Figure 2A-J). Moreover, no correlation was seen between the BBB K_{trans}

permeability values at baseline and volumetric values in the hippocampus and globus pallidus on re-examination (Figure 2D,E).

4. Discussion

Our findings show that a single administration of either cyclic or linear Gd chelate did not result in T1w MRI SI increase or volumetric changes in the studied ten brain regions as shown 19 to 28 months after Gd administration, suggesting that Gd does not accumulate in the brain in older individuals with age-related BBB breakdown in the hippocampus and/or MCI compared to younger, neurologically normal controls[3]. In contrast, studies in patients with MS and/or brain tumors with a pronounced BBB breakdown who received multiple injections of a linear Gd 4-6-month apart have shown increased SI on subsequent unenhanced T1w MRI images, suggestive of Gd brain retention[8,23,24]. The difference between these previous studies[8,23,24] and the current study might likely be attributed to more Gd entering the brain in patients with MS and tumors *i*) due to a greater degree of BBB breakdown compared to the present study, *i.e.*, one order of magnitude or more[25,26]; and *ii*) much higher frequency of Gd administration. These two factors working synergistically could potentially lead to Gd brain accumulation in MS and tumor patients exceeding the capacity of brain clearance systems to eliminate Gd efficiently.

Several studies have demonstrated lower effects on T1w MRI SI with cyclic compared to linear Gd chelates[11,27,28]. In agreement with our findings, cyclic Gd did not cause a significant increase in T1w SI even in adult MS patients who received more than 20 administrations[29,30]. Interestingly, multiple doses of linear Gd followed by cyclic Gd led to dentate nucleus-pons SI ratio smaller than 0, suggesting a washout effect after 6-7 injections within a 3-month period[31]. In contrast, increases in SI were found in pediatric patients (mean age 8 years) after 10 administration of cyclic Gd with a frequency of DCE-MRI scans every 3 months[32]. Of note, the patient population in this study mainly consisted of brain tumor patients[32] that were compared to age-matched controls with diagnoses such as headache, epilepsy, and/or mental retardation.

Overall, our present findings suggest that DCE-MRI does not lead to Gd brain retention of either cyclic or linear Gd agent in individuals with an age-dependent BBB breakdown in the hippocampus and/or accelerated BBB breakdown as in MCI, as examined by a conventional MRI after a ~2-year follow-up. As the BBB breakdown has been recently shown to be an early independent biomarker of human cognitive dysfunction[5,33], the need for advanced and accurate neuroimaging techniques capable of detecting and quantifying low-to-moderate grade focal and/or regional BBB breakdowns in neurodegenerative disorders with vascular, cognitive and/or motor dysfunction, such as AD and related dementias, and PD, HD and others, respectively[34,35], is increasing. The present DCE-MRI technique also allows for early detection of BBB changes in asymptomatic people at genetic risk for AD, such as for example carriers of the apolipoprotein E type 4 allele (*APOE4*), who we know from pathological studies develop an accelerated BBB breakdown compared to *APOE4* non-carriers[36-40], and will also be applicable to evaluate BBB in individuals exposed to other AD risk factors, such as environmental toxins[41] and/or vascular risk factors[35].

One limitation of the present study is the relatively small sample size. We expect that the future studies following longitudinally participants from our initial cohort stratified by *APOE* genotype will provide within next couple of years a sufficient number of participants to reproduce the present findings on a much larger sample size. The present results suggesting undetectable Gd brain retention should also be validated in a more general population in individuals with neurological disorders and BBB disruption in different CNS regions, such as patients with PD[42,43], HD[20,44], human immunodeficiency virus (HIV-dementia[45-47] and/or post-traumatic brain syndrome that all have BBB breakdown on post-mortem pathological analysis, as recently reviewed[2]. With new and more sensitive MRI scanners, this DCE-MRI test should find in the future a more generalizable use to evaluate health of the cerebrovascular system on a more global level. This will be useful, not only in individuals with neurological, psychiatric and/or neurosurgical disorders, but also in those who suffer from other organ functions that may affect vascular brain health in systemic diseases of liver, kidney, and cardiovascular and/or respiratory system. Thus, the present findings provide important preliminary data for a hypothesis to be tested and validated by future studies using a larger sample size, and in a more general population of individuals with neurological and systemic disorders leading to cerebrovascular dysfunction and BBB breakdown.

AD is increasingly recognized as multifactorial and heterogeneous disorder, and vascular dysfunction is a notable contributor to AD pathophysiology[33]. Neuropathological studies reveal that approximately 80% of individuals that develop MCI and are followed to autopsy have brain vascular pathology (*e.g.*, atherosclerosis, arteriolosclerosis, gross infracts, microinfarcts, and/or cerebral amyloid angiopathy) as a major contributor to their cognitive dysfunction, whereas only 7% of individuals develop MCI attributable to only Aβ and tau pathology[48]. Moreover, neuropathological studies suggest that < 5% of individuals with probable AD diagnosis have only pure Aβ and tau pathology[48], whereas the presence of vascular pathology in addition to classical AD Aβ and tau biomarkers[49] increases by 3-fold the odds ratio for probable AD. The present study suggests that Gd does not accumulate in brains of older individuals with BBB breakdown in the hippocampus supporting use of Gd agents within a ~2- year follow-up to evaluate BBB function in the aging human brain in relation to cognition and/or other pathologies. As DCE-MRI use in clinical research studies and clinical trials increases, lack of Gd brain toxicity should be additionally confirmed in AD and in other cohorts of patients with neurological disorders and BBB breakdown. Routine clinical use of DCE-MRI has the potential to inform early detection of individuals at risk for cognitive impairment and AD, and will also aid in research and discovery efforts for prevention of MCI, dementia, AD and related neurological conditions.

Aducanumab, a promising monoclonal antibody against Aβ, was recently terminated in Phase 3 clinical trials due to lack of efficacy despite its potent amyloid-clearing effect[50]. Unfortunately, the majority of clinical trials targeting only Aβ pathology, including aducanumab, have relatively limited information about vascular pathology in the brain, and whether vascular dysfunction can potentially contribute to lack of efficacy of Aβ lowering treatments on cognitive function. The field has just begun recognizing that in addition to Aβ and tau pathology, the cerebrovascular dysfunction should also be evaluated and recognized as a potential therapeutic target for MCI and AD[33]. Therefore, efforts to develop

combinatorial target interventions may prove to be more efficacious to arrest, prevent and/or reverse AD pathophysiology and cognitive impairment than treatments focusing only on classical AD biomarkers such as Aβ and tau[49]. Evaluating the efficacy of such treatments would require routine and simultaneous use of vascular biomarkers of BBB breakdown and blood flow, in addition to Aβ and tau biomarkers.

Since vascular contributions are increasingly recognized in AD, we suggest that vascular imaging measures should be incorporated in AD research studies, large epidemiological studies, and interventional clinical trials[33]. Widespread utilization of various imaging sequences could be easily implemented to evaluate different types of vascular dysfunction in AD pathophysiology. Examples of a few established vascular MR sequences include DCE for BBB permeability, T2*- and susceptibility-weighted for microbleeds, pseudo-continuous arterial spin labelling (pCASL) for cerebral blood flow (CBF), time-of-flight (TOF) for angioarchitecture, among others[33]. Integrating these imaging modalities of cerebrovascular function into the diagnostic process with standard structural diffusion imaging and functional MRI connectivity measures in relation to cognition will allow us to further establish the role of neurovascular and BBB dysfunctions in cognitive impairment in AD, vascular dementia, mixed dementia, and related disorders. Evaluating cerebrovascular disorder, and supporting the neurovascular and BBB functions during different treatment procedures, as for example with Aβ- or tau-antibody therapy, with agents that seal and/or stabilize the BBB, such as for instance the vasculoprotective 3K3A-activated protein C[51], could significantly contribute to prevention and treatment efforts for AD, dementia, and related disorders.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

A.M. and B.V.Z. designed the research study and analyzed and interpreted the data. A.M., G.R., and F.S. performed the experiments and analyzed the data. L.M.D., M.G.H., H.C.C., M.L., and A.W.T. recruited the participants and performed and provided the imaging scans. M.T.H., M.D.S., D.A.N., M.G.H., H.C.C., M.L., and A.W.T. provided critical reading of the manuscript. A.M. contributed to manuscript writing and B.V.Z. wrote the manuscript.

This study was funded by the National Institutes of Health grants 5P01AG052350 (Zlokovic/Toga), and 5P50AG005142 (Chui), in addition to the Alzheimer's Association strategic 509279 grant (Zlokovic/Toga) and the Foundation Leducq Transatlantic Network of Excellence for the Study of Perivascular Spaces in Small Vessel Disease reference no. 16 CVD 05.

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Research in Context

1.Systematic review: Retrospective MRI studies suggest regional brain retention of Gd in patients with MS, brain tumors, cancer metastases, or stroke who received multiple and frequent Gd injections for evaluation of BBB integrity and who develop a pronounced BBB breakdown. Whether Gd can accumulate in brains of individuals with a moderate and more focal BBB breakdown, as found in the aging human hippocampus and/or MCI, is unclear.

2.Interpretation: Our findings show that Gd agents do not accumulate in brains of individuals with age-dependent BBB breakdown in the hippocampus and MCI as shown at ~2 years after administration. Therefore, Gd agents can be used without risk of brain retention within a ~2-year follow-up to study the role of BBB in disease pathogenesis in relation to other brain pathologies, cognition, and neurodegenerative process.

3.Future directions: Future studies need to *i*) confirm the present findings in a larger sample size, *ii*) validate the present findings in different neurodegenerative diseases, and *iii*) incorporate vascular imaging sequences for early detection and prevention efforts for AD and dementias.

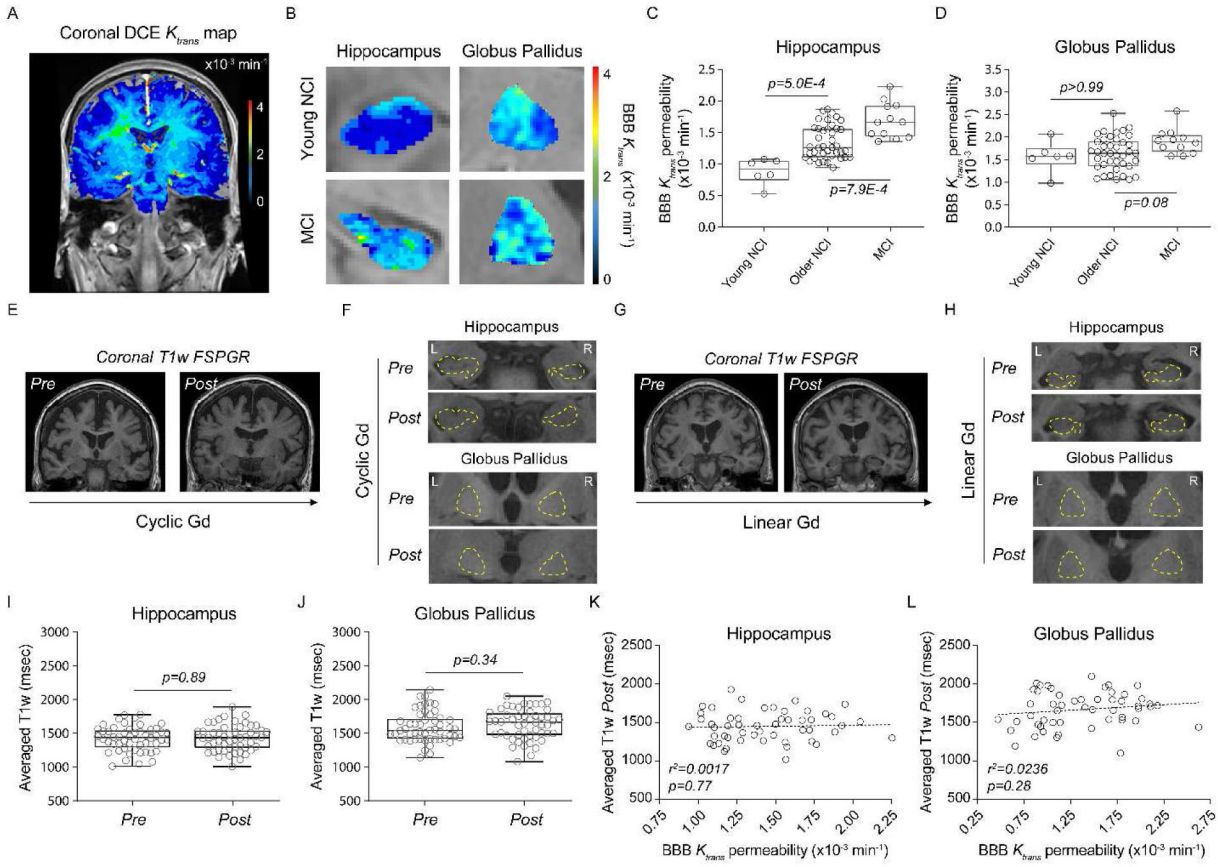

Figure 1. Longitudinal T1-weighted signal intensity follow-up after one injection of Gd chelates in hippocampus and globus pallidus in the living human brains.

(**A**) Representative blood-brain barrier (BBB) K_{trans} maps of the whole brain in an older participant with no cognitive impairment (NCI). (**B**) Representative BBB K_{trans} maps in the hippocampus and globus pallidus in a young NCI (*upper row*) and a participant with mild cognitive impairment (MCI; *lower row*). (**C, D**) Overlaid scatterplots and box-and-whisker plots showing quantification of BBB K_{trans} values in hippocampus (**C**) and globus pallidus (**D**) in young NCI (n=6, ages 23-47, both genders), older NCI (n=40, ages 59-94, both genders) and age-matched MCI (n=12, ages 60-86, both genders). Boxplots indicate median values, boxes indicate interquartile range and whiskers indicate minimum and maximum values; *p*, significance by one-way ANOVA followed by Bonferroni's multiple comparisons test. (**E-H**) Representative unenhanced coronal T1-weighted (T1w) fast spoiled gradient echo (FSPGR) MR images acquired before (*Pre*) a single administration of cyclic Gadoterate meglumine (Cyclic Gd; **E**) or linear Gadobenate dimeglumine (Linear Gd; **G**) in elderly individuals with mild cognitive dysfunction and after (*Post*) the unenhanced MRI followup 19 ± 8 and 28 ± 9 months later, respectively. Zoomed representative coronal T1w FSPGR MR images of the hippocampus (*top*) and globus pallidus (*bottom*) before (*Pre*) one administration of cyclic (**F**) or linear Gd (**H**) and after (*Post*) the unenhanced MRI follow-up in individuals with MCI. Yellow dotted lines delineate hippocampus and globus pallidus before and after Gd chelate injections. (**I, J**) Overlaid box-and-whisker plots and scatterplots showing the averaged T1w values in hippocampus (**I**) and globus pallidus (**J**) before (Pre)

one administration of Gd compound and after (Post) the unenhanced MRI followup in individuals with no or mild cognitive dysfunction. Boxplots indicate median values, boxes indicate interquartile range and whiskers indicate minimum and maximum values; 30 Cyclic Gd and 22 Linear Gd subjects combined at *Pre* and *Post*; unpaired two-tailed Student's *t*-tests were used. (**K, L**) Pearson correlation scatter plots of BBB K_{trans} permeability measures after dynamic contrast-enhanced (DCE)-MRI at first visit and averaged T1w values at re-examination (*Post*) for hippocampus (**K**) and globus pallidus (**L**); r^2, Pearson's correlation coefficient.

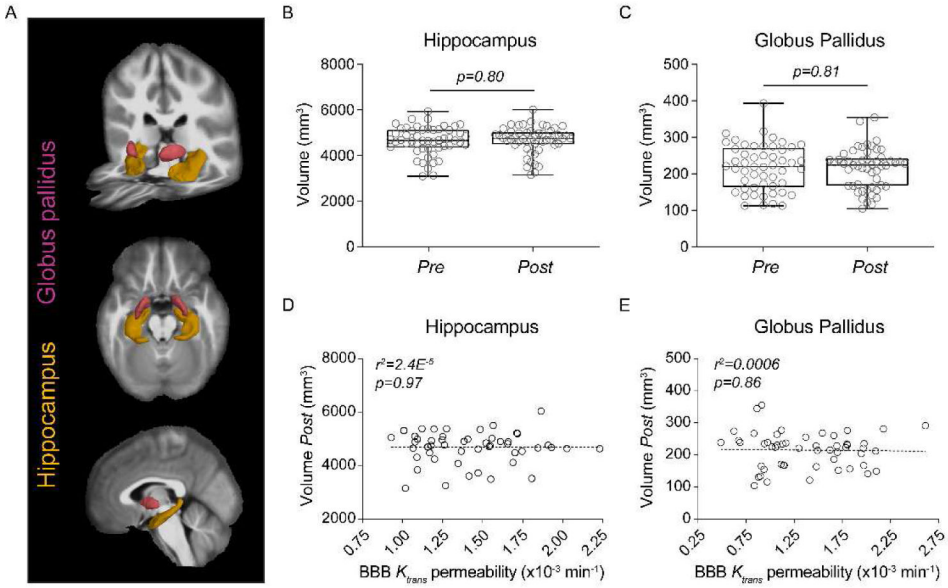

Figure 2. Longitudinal volumetric analysis follow-up after one injection of Gd chelates in hippocampus and globus pallidus in the living human brains.

(**A**) 3D-segmented brain rendering of the anatomical ROIs, hippocampus and globus pallidus, overlaid on an MRI template in 3 orientations: coronal, axial, and sagittal. (**B, C**) Overlaid box-and-whisker plots and scatterplots showing volumetric data in hippocampus (**A**) and globus pallidus (**B**) before (*Pre*) one administration of Gd compound and after (*Post*) the unenhanced MRI follow-up in elderly individuals with no or mild cognitive dysfunction 19 ± 8 and 28 ± 9 months later, respectively. Box-and-whisker plot lines indicate median values, boxes indicate interquartile range and whiskers indicate minimum and maximum values; 30 Cyclic Gd and 22 Linear Gd subjects combined at *Pre* and *Post*; unpaired two-tailed Student's *t*-tests were used. (**D, E**) Pearson correlation scatter plots of blood-brain barrier (BBB) K_{trans} permeability measures after dynamic contrast-enhanced (DCE)-MRI at first visit and volumetric data at re-examination (*Post*) for hippocampus (**D**) and globus pallidus (**E**); r^2, Pearson's correlation coefficient.

Table 1.

Demographic information.

	Cyclic Gd	Linear Gd
Total # of participants having MRI re-examination	30	22
Interval between first Gd injection (*Pre*) and noncontrast re-examination (*Post*) (m ± SD)	19 ± 8	28 ± 9
Age at re-examination (y ± SD)	74 ± 6	75 ± 8
% Female	47%	68%

Gd, gadolinium; m, months; MRI, magnetic resonance imaging; SD, standard deviation; y, years.