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REVIEW ARTICLE

Hippocampal Atrophy on Magnetic Resonance Imaging as a Surrogate Marker for Clinical Benefit and Neurodegeneration in Early Symptomatic Alzheimer's Disease: Synthesis of Evidence from Observational and Interventional Trials

Susan Abushakra[1] · P. Murali Doraiswamy[2] · John A. Hey[1] · Duygu Tosun[3] · Frederik Barkhof[4,5] · Jerome Barakos[6] · Jeffrey Petrella[7] · J. Patrick Kesslak[1] · Aidan Power[1] · Marwan Sabbagh[8] · Anton Porsteinsson[9] · Sharon Cohen[10] · Serge Gauthier[11] · Craig Ritchie[12] · David Watson[13] · Emer McSweeney[14] · Merce Boada[15,16] · Earvin Liang[1] · Luc Bracoud[17] · Rosalind McLaine[1] · Susan Flint[1] · Jean F. Schaefer[1] · Jeremy Yu[1] · Margaret Bray[1] · Suzanne Hendrix[18] · Sam Dickson[18] · Abe Durrant[18] · Adem Albayrak[1] · Martin Tolar[1]

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Abstract

Amyloid-plaque reduction is currently the only recognized surrogate outcome for Alzheimer's disease (AD) trials, allowing accelerated approval of plaque-clearing amyloid antibodies. However, plaque reduction does not facilitate the development of new non-plaque-clearing treatments. The hippocampus is among the first brain regions affected by AD pathology, exhibiting synaptic dysfunction and neurodegeneration that manifests as hippocampal atrophy and memory decline. We evaluated hippocampal volume (HV) as a potential surrogate outcome that can predict clinical benefit in disease-modification trials. Using published data from observational and interventional studies that examined both cognition and HV on volumetric magnetic resonance imaging (vMRI), we evaluated the cross-sectional correlations of HV to cognitive performance, the longitudinal correlations of HV atrophy to cognitive decline, HV sensitivity to drug effects, and the correlations between drug effects on HV atrophy and cognitive decline. We also examined the magnitude of HV protection that corresponds to meaningful clinical benefit. Analyses from 30 observational studies encompassing 13,187 individuals (2633 cognitively normal; 10,554 early AD) showed significant cross-sectional correlations between baseline HV and cognition, and longitudinal correlations between HV atrophy and cognitive decline over ≥ 1 year. The relationship of HV–cognitive drug effects was examined at the group level in nine placebo-controlled trials of five antiamyloid agents that evaluated HV in early AD trials of at least 18 months' duration. These trials included four amyloid antibodies (aducanumab, lecanemab, donanemab, and gantenerumab) and one oral anti-oligomer agent (valiltramiprosate). Individual-level HV–cognition relationships were examined in two valiltramiprosate studies, one of which included diffusion tensor imaging (DTI) providing microstructural correlates of HV drug effects and helping distinguish neuroprotection from brain edema. Across these anti-amyloid drug trials (total N ~10,000), there was a linear relationship between drug effects on slowing of cognitive decline and slowing of HV atrophy. Two anti-oligomer trials (valiltramiprosate) reported significant subject-level correlations between drug effects on HV and cognition over 18–24 months ($r = -0.40$ to -0.44, $p < 0.005$, $N = 50/69$), with significant correlations of drug effects on brain microstructure (decreased mean diffusivity) with both HV and cognitive benefits, supporting reduced neurodegeneration. The minimal HV preservation at the mild cognitive impairment (MCI) stage that is associated with clinical benefit is estimated to be ≥ 40 mm^3 or ≥ 10% of atrophy in the placebo arm over 18 months. Our findings demonstrate that hippocampal atrophy is an early indicator of cognitive decline in AD, linked to amyloid and tau-related neurodegeneration. HV on standardized vMRI is sensitive to anti-amyloid treatments, demonstrating strong correlations between slowed hippocampal atrophy and slowed cognitive decline. Data from over 23,000 subjects over three decades support HV as a surrogate marker for predicting clinical benefit in early symptomatic AD.

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Key Points

Amyloid plaque clearance has been accepted as a surrogate outcome that is likely to predict clinical benefit in early Alzheimer's disease (AD) but is not useful in developing non-plaque-clearing AD treatments. Hippocampal volume (HV), which is affected early in AD, may be a suitable surrogate outcome in early symptomatic AD.

Published data from 30 observational studies in early AD showed consistent and significant cross-sectional correlations and longitudinal correlations between HV atrophy and cognitive decline.

Nine placebo-controlled trials with five anti-amyloid agents showed a linear relationship between slowing of HV atrophy and cognitive benefit over ≥18 months, with two studies reporting significant subject-level correlations between slowing HV atrophy and slowing cognitive decline.

HV preservation of ≥ 40 mm^3 or ≥ 10% of the placebo decline over 18 months at the mild cognitive impairment stage is likely clinically meaningful. These data support HV on volumetric MRI as a surrogate outcome likely to predict clinical benefit in early AD.

1 Introduction

Alzheimer's disease (AD) is a leading cause of morbidity and disability among older adults and poses a significant impact on healthcare systems globally [1, 2]. Although anti-amyloid antibody treatments are available, current options do not fully address efficacy, safety, or accessibility concerns of these treatments [3]. The development of new types of anti-amyloid or other disease-modifying therapies is identified as a priority for global health.

Recent developments in brain imaging and fluid biomarker technologies have advanced understanding of the underlying mechanisms and progression of AD. These advancements support a biological definition of AD, focusing on two main pathologies: amyloid (Aβ) and tau proteins (Fig. 1). Aβ misfolding and aggregation represent the earliest pathology along the AD continuum, followed by tau aggregation and neurodegeneration, as outlined in the A/T/N framework [4–7]. The updated AD diagnostic and staging model requires positive fluid biomarkers that identify soluble amyloid and tau species, or positron emission tomography (PET) imaging to detect aggregated Aβ and tau (amyloid plaques and tau tangles) [8]. These biomarkers are also used to monitor disease progression and evaluate treatment effects. Volumetric magnetic resonance imaging (vMRI) is a sensitive, accurate, and noninvasive method for quantifying regional atrophy in areas such as the medial temporal lobe and hippocampus, aiding in the assessment of early neurodegeneration and the impact of disease-modifying therapies [9–11].

Despite significant advances in our understanding of AD pathophysiology and the wealth of data from imaging and biomarker studies, the development of biomarkers as surrogate endpoints to accelerate novel treatments has been limited to amyloid-plaque reduction for plaque-clearing antibodies [12, 13]. In clinical trials investigating early symptomatic AD, current regulatory guidance [14] recommends using psychometric cognitive scales or functional measures as primary outcomes. However, these approaches present several challenges. Traditional cognitive scales are influenced by participant motivation and effort, resulting in substantial variability both between and within subjects. Furthermore, tools such as the Clinical Dementia Rating Sum of Boxes (CDR-SB) are highly dependent on the clinical skill and judgment of the evaluator, whereas imaging measures tend to demonstrate considerably less variability (Fig. 2). Findings from the long-running Alzheimer's Disease Neuroimaging Initiative (ADNI) reveal substantial variability in observed clinical trajectories [15]. In addition, these psychometric assessment tools may not accurately reflect the true extent of underlying neurodegeneration in the early stages of disease owing to factors such as cognitive reserve or educational background [16, 17], which further contribute to subject heterogeneity and necessitate large sample sizes in clinical trials.

The hippocampus is among the earliest brain regions affected by AD pathology, with synaptic dysfunction, tau pathology, structural degeneration, and neuronal loss manifesting clinically as memory and learning deficits characteristic of the early symptomatic stage of AD [18–25]. Hippocampal volume (HV) was one of the initial structural imaging markers assessed in ADNI studies through vMRI and has been proposed as a pharmacodynamic outcome measure for AD clinical trials [26, 27]. Early MRI studies in patients with AD utilized manual tracings or visual assessments, consistently revealing atrophy in the medial temporal lobe, including the hippocampus [18, 28, 29]. Later research employed automated vMRI methods to examine correlations between HV atrophy and cognitive decline, as well as its utility in predicting disease progression from presymptomatic phases to mild cognitive impairment (MCI) and mild AD dementia [30–32]. Comprehensive analyses of these datasets led the US Food and Drug Administration (FDA) Critical Path Institute to propose HV as a predictive marker for disease progression, contributing to its adoption as an

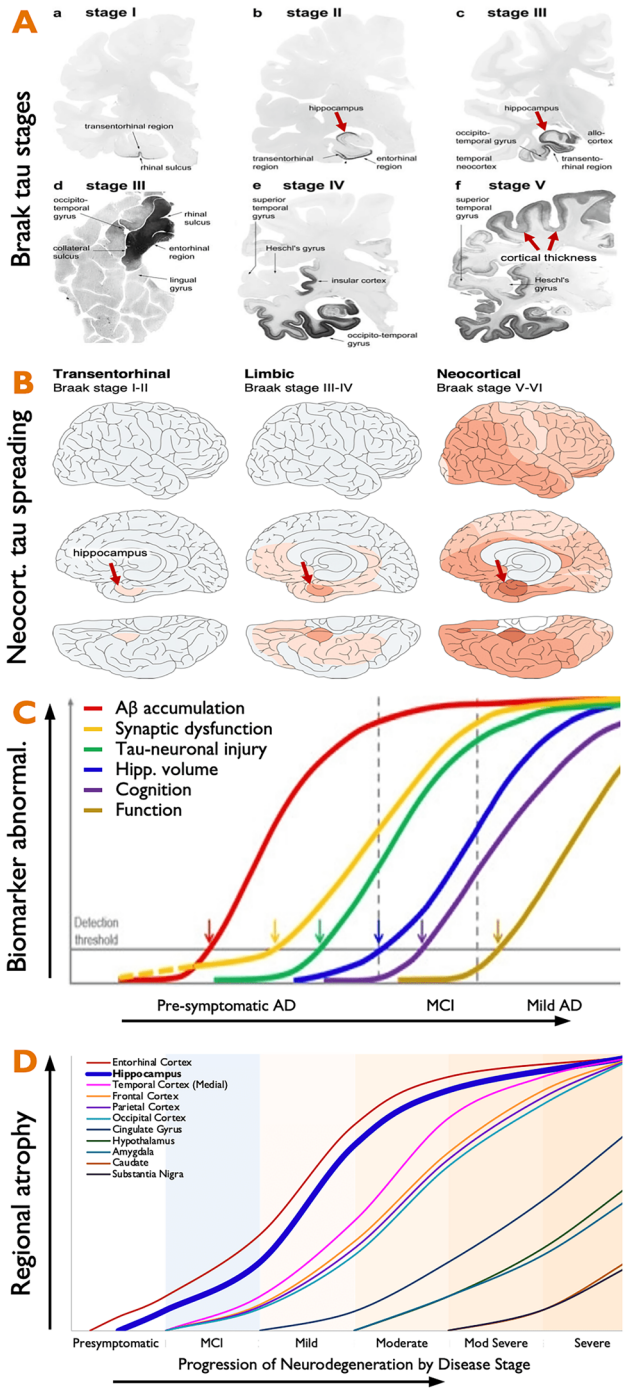

Fig. 1 Stereotypical progression of amyloid and tau, neurodegeneration, and regional brain atrophy (highlighting early hippocampal atrophy). **A** Braak and Braak stages I–V: Progression of tau/neurofibrillary tangles using tau silver staining (MCI = stages III–IV). **B** Illustration of the spread of tau from entorhinal cortex and hippocampus to medial temporal areas, then the rest of the neocortex [4, 6]. **C** Progression of pathologies from presymptomatic stage to dementia detected by fluid biomarkers (soluble Aβ42/Aβ40, p-tau), positron emission tomography (aggregated Aβ/tau), functional MRI (synaptic dysfunction), and volumetric MRI (hippocampal atrophy); amyloid (Aβ) plaque accumulation indicates the various Thal stages. **D** Hippocampus: one of the earliest regions showing atrophy from the presymptomatic to the moderate AD stages [5, 7]. *Aβ* amyloid, *MCI* mild cognitive impairment

enrichment tool for early AD drug trials [33, 34]. Regulatory guidelines have since recommended the inclusion of vMRI-based imaging outcomes in clinical trials assessing disease modification [35].

Selecting a surrogate outcome for AD disease modification trials should match the drug's mechanism and the stage of disease. For drugs that target neurodegeneration without clearing plaques, HV may be a suitable surrogate in early AD trials. HV must: (1) be involved in disease pathophysiology; (2) correlate with cognitive measures over time; (3) respond to drug effects; (4) demonstrate that HV preservation indicates preserved microstructure; and (5) show drug effects on HV aligning with clinical benefit per recent FDA guidance [36].

Several studies have documented HV atrophy rates in AD, with annual decline ranging from 1% to 1.5% in normal aging and approximately 3%–5% in MCI and mild AD dementia [10, 11, 26]. Recent research has incorporated participants who are positive for core AD biomarkers, further substantiating HV's role as a predictive marker of cognitive decline and disease progression [11, 37, 38]. Building on these findings, we analyzed observational studies reporting associations between HV and cognition and extended this examination to amyloid-targeted drug trials that were evaluated in MCI or early AD (MCI and mild AD).

2 Identification and Presentation of Data from Relevant Studies

2.1 Observational Studies Reporting Correlations Between Hippocampal Volume (HV) and Cognition

By searching the literature, we identified and reviewed cross-sectional and longitudinal studies on HV atrophy and cognition, focusing on subject-level correlations at baseline between HV and cognitive performance, and the longitudinal correlations between HV atrophy rates and cognitive decline, respectively. We also included studies that examined baseline HV in relation to disease progression or conversion to AD dementia over time. Subjects spanned the AD continuum, including those with subjective cognitive decline (SCD), MCI, mild AD dementia, or cognitively normal (CN) individuals of similar ages.

We searched PubMed and Google Scholar using keywords related to MRI, imaging, AD, MCI, hippocampus, hippocampal volume, and atrophy, up to 30 September 2025. Only English titles and abstracts relevant to our objectives were reviewed, and additional papers were found via references and recent HV reviews [10, 11]. Observational studies were included if they had more than ten participants, addressed sporadic AD, provided sufficient methodology and statistical details, and had at

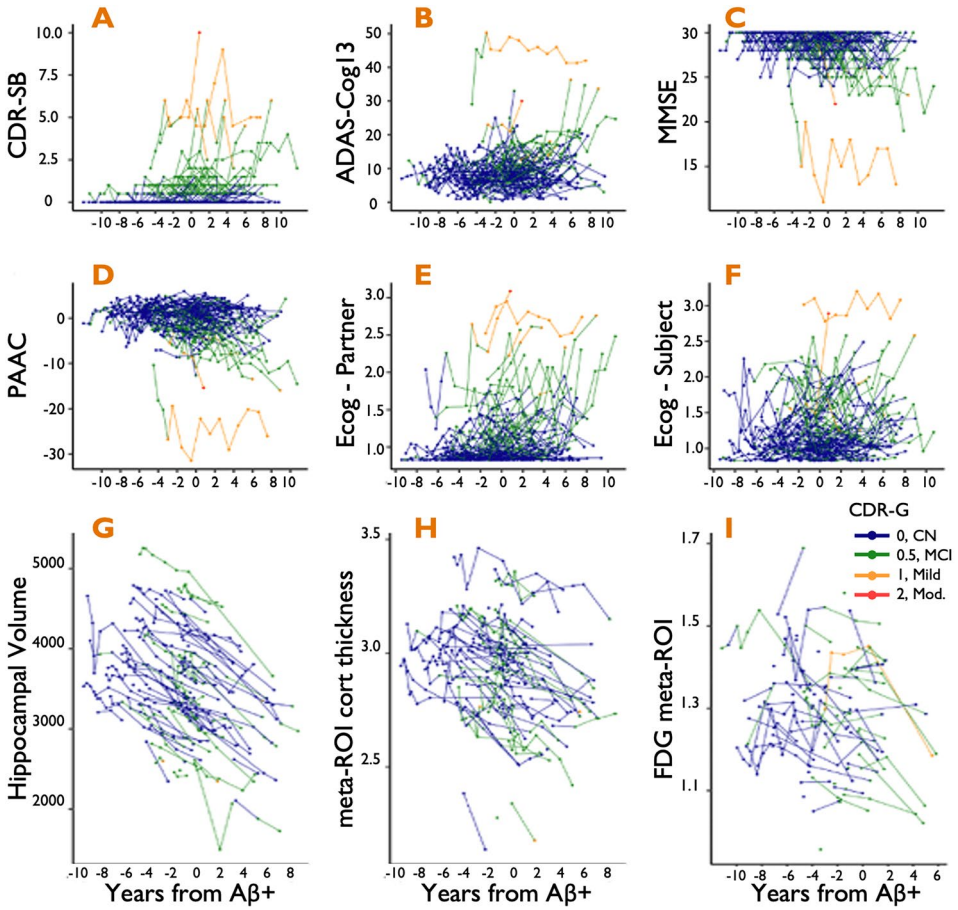

Fig. 2 Variability in trajectories of clinical outcomes versus less variable imaging outcomes—ADNI study. Data from 90 ADNI subjects who converted to positive amyloid PET during follow-up. Age range 57–93 years; 54% female individuals; 63 cognitively normal (CN); 25 with MCI and 2 with AD; genotypes were 57% APOE3/3 and 36% APOE3/4 (there were only two APOE4/4 subjects). Disease stage by baseline CDR-G: CDR-G = 0 (CN, blue lines), 0.5 (green lines, MCI), 1 (mild AD, yellow lines), and 2 (red lines, moderate AD). Adapted from Figs. 2 and 3 and Supplementary Material [15]. *Aβ* amyloid-beta, *AD* Alzheimer's disease, *ADAS-Cog13* AD Assessment Scale-Cognitive Subscale 13-item version, *ADNI* AD Neuroimaging Initiative Study, *APOE* apolipoprotein E, *CDR-SB* Clinical Dementia Rating Scale Sum of Boxes, *CN* cognitively normal, *ECog-Study Partner*, study partner-reported everyday cognition, *ECog-Subject*, subjective cognitive decline measures of self-reported everyday cognition, *MCI* mild cognitive impairment, *MMSE* Mini-Mental State Examination, *PACC* Preclinical Alzheimer Cognitive Composite, *PET* positron emission tomography

least 1 year of follow-up. Studies on familial AD, Down-syndrome-related AD, or other dementias were excluded.

Data from the identified cross-sectional and longitudinal cohort studies were summarized separately (Fig. 3). For long-running studies with multiple publications, only the most recent report with the largest sample size or longest follow-up was used in our analysis. A tabular summary was prepared for the two types of studies, detailing country of origin, basic demographics, clinical stage, main findings related to HV, and the clinical measures with corresponding correlations. Additional data included baseline HV and/or annualized HV atrophy rates and their associations with clinical decline or progression to subsequent disease stages. Some studies employed 7 Tesla MRI to investigate hippocampal subfields in relation to amyloid, tau, and neuronal loss [39, 40]. These two studies involved fewer than ten subjects per disease stage and were excluded from the tabular summary; however, their results and importance are addressed in Sect. 3.1.

2.2 Interventional Studies Reporting HV and Clinical Outcomes (Anti-amyloid Agents)

We reviewed disease-modification drug trials (> 1-year duration) that reported both clinical and HV outcomes in early AD. Since surrogate outcomes must reflect drug sensitivity and correlate with clinical efficacy, we focused on anti-amyloid agents, the only class with proven efficacy and regulatory approvals. We included phase 2 or 3 trials in early AD (includes MCI and mild AD dementia) reporting both clinical

and HV outcomes alongside vMRI methods. Data were extracted from publications and FDA documents, and treatment effects were plotted to compare HV change (percentage slowing of atrophy compared with placebo) on the *x*-axis and cognitive outcomes (percentage slowing of cognitive decline compared with placebo) on the *y*-axis over 18 months. The main cognitive outcome in these studies was the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog), and in addition, all studies included the CDR-SB.

Earlier placebo-controlled studies involving cholinesterase inhibitors or memantine were limited by short durations (≤ 1 year) and did not employ current vMRI standardized/harmonized imaging protocols and thus were not included. Given that a surrogate endpoint must demonstrate efficacy for both the surrogate *and* clinical outcomes, we focused on second-generation anti-amyloid antibodies that were tested in early AD. Our analysis excluded oral antiamyloid agents lacking demonstrated efficacy, such as gamma or beta secretase inhibitors; first-generation amyloid antibodies that were tested in mild or mild/moderate AD were also excluded. We identified four programs that showed clinical efficacy in at least one phase 2 or 3 trial and reported HV effects using vMRI [41–47]. We also identified two amyloid antibodies that did not show efficacy in early AD, gantenerumab and crenezumab (discussed further below).

2.2.1 Group-Level Relationship of Antiamyloid Drug Effects on HV and Clinical Outcomes

The group-level relationship between drug effects on HV and cognitive outcomes across these anti-amyloid studies was based on data from three approved amyloid antibodies—aducanumab, lecanemab, and donanemab [41–45]—and a phase 3 study of the oral investigational agent valiltramiprosate/ALZ-801 [46]. Valiltramiprosate/ALZ-801, an amyloid-oligomer inhibitor that stabilizes Aβ42 monomers preventing their aggregation into neurotoxic soluble oligomers, was also evaluated in an open-label phase 2 trial in APOE4 carriers [47–52]. The randomized, double-blind, placebo-controlled, multicenter trials were conducted in patients with early AD with amyloid positivity confirmed by imaging or plasma biomarkers. The 18-month antibody trials were conducted across all apolipoprotein E (APOE) genotypes [41–45], while the valiltramiprosate trial was conducted in APOE4/4 subjects [46]. Two amyloid antibodies, gantenerumab and crenezumab, did not show efficacy in 24-month trials in all APOE genotypes [53–55]. The two completed gantenerumab phase 3 trials reported both HV and cognitive effects [53, 54] and were included in this analysis (Fig. 4). The two crenezumab phase 3 trials failed interim analyses and were prematurely discontinued [55] and therefore, not included in this analysis.

All these trials employed centralized imaging vendors utilizing standardized volumetric MRI (vMRI) acquisition and quantification protocols [9, 32, 56, 57]. Imaging was performed using 1.5T or 3T MRI scanners

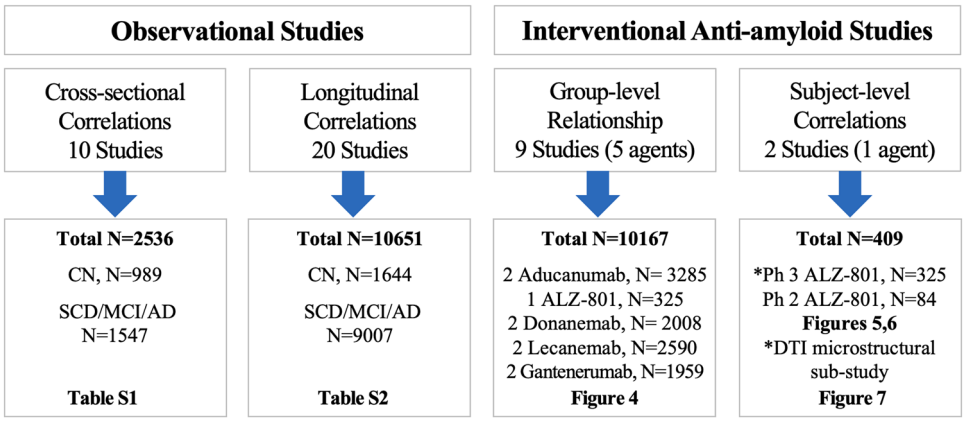

Fig. 3 Summary of clinical studies supporting correlations of HV with cognition from 30 observational and 10 interventional studies (total $N > 23{,}000$). Datasets supporting HV as surrogate outcome include correlations from observational studies and interventional studies. Observational studies: cross-sectional correlations of HV to cognitive performance and longitudinal correlations of HV atrophy to cognitive decline. Interventional studies: group-level relationship of drug effects on HV and cognitive outcomes across nine placebo-controlled drug trials; subject-level correlations of drug effects on HV atrophy and cognitive decline within two interventional trials. The nine anti-amyloid studies included in the group-level analysis were: two aducanumab phase 3 trials [43]; ALZ-801 phase 3 trial [46], lecanemab phase 2 and 3 trials [41, 42]; donanemab phase 2 and 3 trials [44, 45]; and two gantenerumab phase 3 trials [53, 54]. Two studies that reported subject-level correlations of drug effects were the valiltramiprosate phase 3 trial and a phase 2 valiltramiprosate open-label biomarker trial [46, 47]. *AD* Alzheimer's disease, *CN* cognitively normal, *HV* hippocampal volume, *MCI* mild cognitive impairment, *SCD* subjective cognitive decline

and segmentations carried out with FreeSurfer 6.0 software [58]. The antibody studies each adopted distinct approaches to measure serial changes in HV, as reported in their respective publications: lecanemab and donanemab studies assessed HV change using tensor-based morphometry [41, 42, 44, 45], whereas the methodology for aducanumab was not specified [43]. Oral valiltramiprosate (ALZ-801) utilized the boundary shift integral method to quantify HV atrophy [46, 47, 58, 59].

2.2.2 Subject-Level Correlations of HV to Clinical Outcomes in Two Interventional Studies

We conducted a literature review to identify anti-amyloid agents that demonstrated both clinical and vMRI effects in early Alzheimer's disease studies lasting at least 1 year and those that also reported subject-level correlations between HV and clinical outcomes. From these sources, we extracted the observed effects on clinical and HV measures and summarized the corresponding correlations. Two published studies in early Alzheimer's disease met these criteria, both evaluating valiltramiprosate. The first, a 104-week phase 2 open-label study, enrolled APOE4 carriers [47], while the second was the 78-week phase 3 placebo-controlled trial enrolling individuals with APOE4/4 genotype [46].

2.2.3 Assessment of Clinically Meaningful HV Effects (Protection of Neuronal Integrity)

To evaluate the clinical relevance of a drug's impact on HV atrophy, differences in HV between MCI and mild AD were assessed, as these stages reflect distinct levels of disease severity. Analyses of ADNI study publications identified the baseline HV differences between these groups [60]. In addition, data from a valiltramiprosate phase 3 trial were used to examine correlations between drug effects on HV atrophy and clinical efficacy to establish the threshold of HV preservation that aligns with a minimal clinically important difference (MCID) in cognitive outcomes [46]. Another approach to assess meaningfulness of drug effects in disease-modification trials is to estimate "time-savings." Several statistical methods that estimate time-savings on the basis of clinical outcomes have been reported, and these methods can similarly be applied to assess drug effects on volumetric measures [61, 62]. Another relevant method involves comparing the rates of HV atrophy, specifically, the divergence in slopes between drug and placebo arms, which can be translated into months or years of delaying HV atrophy/disease progression, underscoring clear clinical significance [63].

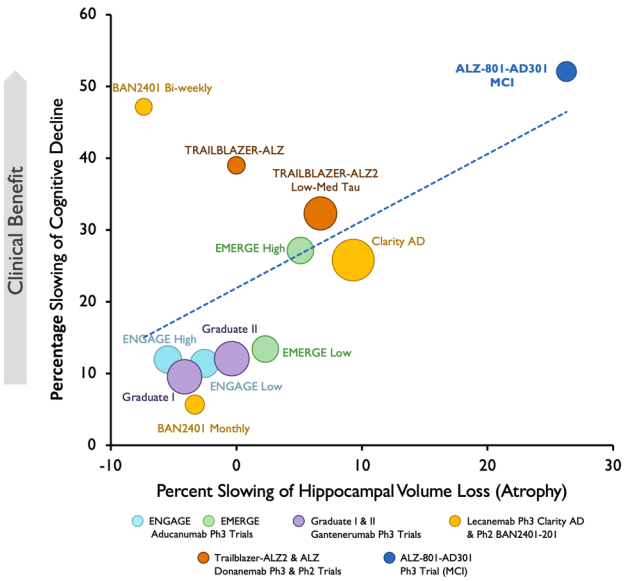

Fig. 4 Group-level relationship between drug effects on HV atrophy and slowing of cognitive decline (anti-amyloid agents). Percentage slowing of HV atrophy compared with placebo shows linear association with percentage slowing of cognitive decline. Data extracted from placebo-controlled studies of 18-month duration in early AD. Amyloid antibody studies were carried out in all APOE genotypes and included two aducanumab phase 3 trials with two active doses [43]; lecanemab phase 2 trial with two active doses [41]; lecanemab phase 3 trial with one active dose [42]; two donanemab trials; and two gantenerumab trials. The donanemab phase 3 trial had one active dose (data shown for the low-medium tau population) [44], and the phase 2 trial had one active dose [45]. The two identical gantenerumab phase 3 trials were of 24 months duration, and the datapoints were normalized to 18 months and plotted [53, 54]. The ALZ-801 phase 3 trial in APOE4/4 early AD subjects had one active dose, with data shown for the prespecified MCI population [46]. In the lecanemab phase 2 study (BAN2401), efficacy at high dose (biweekly regimen also used in the phase 3 trial) was confounded by imbalance of APOE4/4 subjects in drug versus placebo arms [41]. Percentage slowing was calculated as: [CBL placebo − CBL drug] / CBL placebo × 100. Bubble size corresponds to study sample size. Linear regression analysis including this BAN2401 dose arm shows $r = 0.54$ ($N = 12$ groups), and excluding it shows $r = 0.83$ ($N = 11$ groups). *AD* Alzheimer's disease, CBL change from baseline, *MCI* mild cognitive impairment

2.2.4 Subject-Level Correlations between HV and Brain Microstructure Using Diffusion Tensor Imaging

Diffusion tensor imaging (DTI) has been utilized in ADNI and other studies to assess microstructural brain changes in both MCI and AD [64–67]. DTI measures include mean diffusivity (MD) that quantifies extracellular water movement in gray and white matter, with higher MD indicating greater neurodegeneration [65–67]. This review examined anti-amyloid interventional studies that assessed and reported drug effects on HV and MRI–DTI as well as their correlations.

3 Subject-Level Correlations from 30 Identified Observational Studies

The literature search identified 30 observational studies (10 cross-sectional and 20 longitudinal) that met the selection criteria (Fig. 3). A total of 13,187 subjects participated in observational studies: 2536 from cross-sectional and 10,651 from longitudinal studies (follow-up up to ~10 years). Supplementary Tables S1 and S2 summarize these data. Cross-sectional studies included 989 individuals who were CN and 1547 patients with SCD, MCI, or AD. Longitudinal studies comprised 2633 individuals who were CN and 10,554 along the AD continuum. Most studies had follow-ups of 2–3 years; 6 out of 20 studies spanned 4–5 years, and one lasted ~10 years. The majority of the 30 studies showed that small HV at baseline was significantly correlated with worse cognitive scores on verbal learning and memory tests, ($r = -0.34$ to -0.62, $p < 0.01$). In four longitudinal studies, HV atrophy was associated with cognitive decline during approximately 1–5 years of follow-up ($r = 0.55$–0.84, $p < 0.05$). Baseline HV was shown to predict cognitive decline and progression to AD, with significant hazard ratios ranging from 1.6 to 3.6. The largest longitudinal analysis, which included the US Aging Brain Cohort (ABC) study (formerly NACC) cohort and two Netherlands cohorts comprising 7076 subjects, demonstrated that small HV predicted disease progression with hazard ratios from 2.15 to 4.03 over 5 years, depending on statistical model adjustments [38].

3.1 Correlations from Studies with Detailed Hippocampal Subfield Morphometry Using 7 Tesla MRI

Two observational studies evaluated detailed hippocampal subfield morphometry with 7 Tesla MRI and their relations to AD pathologies in postmortem brains [39, 40]. The Apostolova study found significant correlations of HV atrophy with Braak tau stages ($r = -0.75$, $p = 0.001$), amyloid ($r = -0.61$, $p = 0.012$), and tau burden ($r = -0.53$, $p = 0.034$). The strongest correlations of HV in this study were positive correlations of HV with neuronal counts ($r = 0.77$, $p = 0.0001$) [39], providing a direct microstructural and cellular basis of HV atrophy in AD, consistent with prior postmortem neuropathological studies showing neuronal loss [20, 21].

4 Analyses of HV–Cognitive Relationship in Anti-amyloid Interventional Trials

4.1 Group-Level Relationship of HV–Clinical Drug Effects across Nine Antiamyloid Trials

Four anti-amyloid programs showed significant efficacy in 18-month early AD trials; three were antiamyloid antibodies reported in five publications [41–45], and one was an oral amyloid antiaggregation/antioligomer agent with two publications of two early AD studies [46, 47] for a total of seven publications from these four agents (Fig. 3) [41–47]. The three antiamyloid antibodies have all received US FDA approvals on the basis of phase 3 results [42–44]; there were two studies with lecanemab [41, 42], two with aducanumab [43], and two with donanemab [44, 45]. The other two early AD studies utilized the oral amyloid-oligomer inhibitor valiltramiprosate [46–52], but only one was placebo-controlled (ALZ-801-AD301; included in Fig. 4) [46]. The gantenerumab phase 3 trials that did not show clinical efficacy had a duration of 24 months, but their plotted HV and cognitive effects were normalized to 18 months (included in Fig. 4) [53, 54].

Analysis of the relationship between drug effects on HV and cognition across the nine placebo-controlled studies demonstrated a linear association between HV effects and cognitive outcomes across study arms over 18 months (Fig. 4). The clinical trials for aducanumab yielded inconsistent findings: EMERGE showed significant clinical improvements on both the CDR-SB and ADAS-Cog at the highest dosage, whereas the ENGAGE active treatment arms did not reach statistical significance for either endpoint [43]. Notably, the four aducanumab dosing groups across these two studies reflected HV changes that corresponded with their respective cognitive outcomes. In contrast, the low-dose lecanemab arm (10 mg/kg monthly) in the phase 2 trial failed to demonstrate clinical efficacy and HV protection [41]. The high-dose lecanemab arm (10 mg/kg biweekly) in the same study showed no evidence of HV protection despite appearing to show clinical efficacy [41]. This result at the high lecanemab dose was confounded by an imbalance in the proportion of APOE4 carriers relative to the placebo group, rendering the efficacy conclusions uncertain. An alternate explanation may be that HV effects may differ depending on APOE4 genotype. Both the lecanemab phase 3 trial (Clarity AD, single high-dose arm) and the donanemab phase 3 trial (Trailblazer-ALZ2) were notable for achieving approximately 10% HV protection with statistical significance, alongside statistically significant improvement on ADAS-Cog and CDR-SB measures [42, 44]. In the donanemab trial, analysis of the prespecified low-medium tau-PET subgroup [44] was a

primary analysis and is shown in Fig. 4. Valiltramiprosate was evaluated in a phase 3 study involving APOE4/4 subjects with MCI and mild AD dementia [46]. In the combined MCI and mild dementia population, no significant effects were observed on the cognitive primary outcome (ADAS-Cog) at 18 months. However, the prespecified MCI subgroup demonstrated significant cognitive benefits, with a 52% slowing of decline (nominal $p = 0.04$), as well as marked and significant hippocampal volume protection (26% slowing of atrophy, $p = 0.004$) (Fig. 5A, B). Among individuals with MCI, valiltramiprosate produced the greatest percentage slowing of both hippocampal atrophy and cognitive decline, consistent with the observed linear relationship.

4.2 Subject-Level Correlations of HV to Clinical Outcomes in Valiltramiprosate Studies

Two interventional studies were identified that included HV measurements along with cognitive outcomes and reported their subject-level correlations, these were the phase 2 and 3 studies of valiltramiprosate [46, 47]. The phase 2 study ($N = 84$, APOE4 carriers) and the phase 3 study ($N = 325$, APOE4/4) utilized vMRI at intervals of 52 and 26 weeks, respectively. Cognitive assessments administered were the Rey Auditory Verbal Learning Test (RAVLT) total score (immediate and delayed memory) for phase 2 and ADAS-Cog13 for phase 3. Correlations between changes from baseline (CBL) in HV and CBL in clinical outcomes are shown in panel C of Figs. 5 and 6. Both studies reported statistically significant correlations between drug effects on HV and drug effects on cognitive measures: over 18 months in the phase 3 study ($r = -0.40$, $p = 0.0044$, $N = 50$), and over 24 months in the phase 2 study ($r = -0.44$, $p = 0.0002$, $N = 69$).

4.3 Determination of Clinically Meaningful Drug Effects on HV Atrophy (Neuroprotection)

In ADNI-1, baseline HV differences between MCI and mild AD in APOE3/3 patients were approximately 310 mm^3, indicating a 5% reduction from the MCI baseline value of 6260 mm^3. For APOE4/4 patients, this difference was about 640 mm^3, corresponding to a 12% reduction from the MCI baseline of 5460 mm^3 [60]. Therefore, HV reductions between 300 and 600 mm^3 represent the observed HV loss that occurs with progression from MCI to mild dementia stage over ~3–4 years, or a minimum of ~60 mm^3 per year. In the phase 3 valiltramiprosate trial [46], the HV drug effect in the MCI population associated with roughly 2.0 points of ADAS-Cog13 benefit ranged between 40 and 50 mm^3 over 18 months, representing ~10% of the placebo decline over that period. As placebo-adjusted ADAS-Cog effects ≥ 1.5 points are regarded as the MCID, a reduction in HV atrophy by around 40–50 mm^3 over 18 months may correspond to a clinically meaningful cognitive outcome in patients with MCI. In the same valiltramiprosate phase 3 study [46], an exploratory analysis of slope divergence in HV atrophy between the active and placebo arms indicated a delay in HV atrophy of about 12 months after 30 months of treatment in the MCI group [63], as shown in Supplementary Fig. S1.

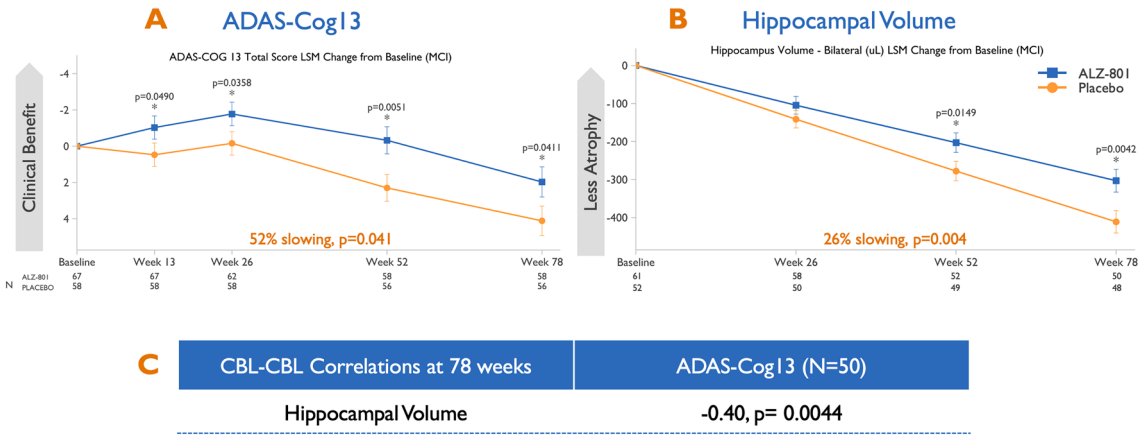

Fig. 5 Significant subject-level correlation of hippocampal volume (HV) to cognition in mild cognitive impairment (MCI): example from valiltramiprosate phase 3 study in APOE4/4 carriers. Data from valiltramiprosate (ALZ-801) phase 3 study in APOE4/4 MCI group [46]. **A** Valiltramiprosate showed significant slowing of cognitive decline versus placebo on ADAS-Cog13; placebo-active difference: least squares (LS) means $\Delta = -2.1$ (1.1) with negative ADAS difference indicating clinical benefit. **B** Significant slowing of HV atrophy versus placebo over 78 weeks; placebo-active difference: LS means $\Delta = +108$ (37.5) mm^3 with positive HV difference indicating HV preservation. **C** Pearson's correlations of change from baseline (CBL) of HV and ADAS-Cog13 CBL at 78 weeks. Percentage slowing was calculated as: [LS means CBL placebo − LS means CBL drug] / LS means CBL placebo × 100. *ADAS-Cog13* Alzheimer's Disease Assessment Scale-Cognitive Subscale 13-item version, *APOE* apolipoprotein E

4.4 Addressing Confounding Factors: Distinguishing True Neuroprotection from Pseudo-Atrophy Using DTI and Other Modalities

A key concern with anti-amyloid antibodies is that brain volume changes on vMRI may be pseudo-atrophy reflecting fluid shifts from plaque clearance; or vasogenic edema related to amyloid-related imaging abnormalities (ARIA-E) that can be misinterpreted as volume preservation and neuroprotection. This issue has been highlighted by findings from several studies with amyloid antibodies that were associated with reduced whole-brain volume (WBV) and increased ventricular volumes [68–70]. These effects were postulated to be fluid redistribution following amyloid plaque clearance from the neocortical grey matter and termed pseudo-atrophy. Notably, the hippocampus, which harbors a relatively low burden of amyloid plaque and is thus spared from fluid shifts associated with plaque clearance, demonstrated approximately 10% volume preservation with lecanemab and donanemab that achieved statistical significance [42, 44]. Furthermore, amyloid antibodies exert their effects primarily through microglial activation and inflammation that may be associated with variable degrees of cerebral edema, with ARIA-E being a severe manifestation of that spectrum [71, 72].

Distinguishing between true neuroprotective effects and these confounding phenomena can be facilitated by advanced techniques such as magnetic resonance spectroscopy (MRS), DTI, and fluid biomarkers of neurodegeneration such as plasma neurofilament light chain (NfL), thereby improving interpretation of drug-related changes in brain volumes, including HV and WBV.

MRS in AD detects brain metabolite changes, showing reduced *N*-acetyl aspartate (NAA) and increased myoinositol in patients with MCI/AD, with neuroprotective drugs expected to stabilize NAA levels [73, 74]. However, the use of MRS for this purpose requires further evaluation in disease modification trials. DTI assesses tissue integrity by measuring water diffusivity in grey and white matter, with increased mean diffusivity indicating edema or grey matter loss, reflecting synaptic or axonal damage [64–67, 75–78]. Plasma NfL increases gradually with disease progression from MCI to mild AD, signaling ongoing neurodegeneration [79, 80]. This orthogonal approach to interpreting potentially neuroprotective drug effects is illustrated in Table 1.

Effective neuroprotective drugs are expected to result in larger HV, larger WBV, decreased mean diffusivity (MD), increased fractional anisotropy (FA, another DTI measure reflecting integrity of white matter tracts), stabilized or reduced NfL and/or stabilized or increased NAA. Drugs inducing pseudo-atrophy would show a unique biomarker profile with larger HV, reduced WBV, reduced MD and either stable or improved FA, NfL and NAA levels. Neuroinflammatory drugs that cause edema are likely to increase HV, WBV, MD, and NfL, but decrease FA and NAA. Table 1 outlines this framework, which should be tested prospectively in future studies.

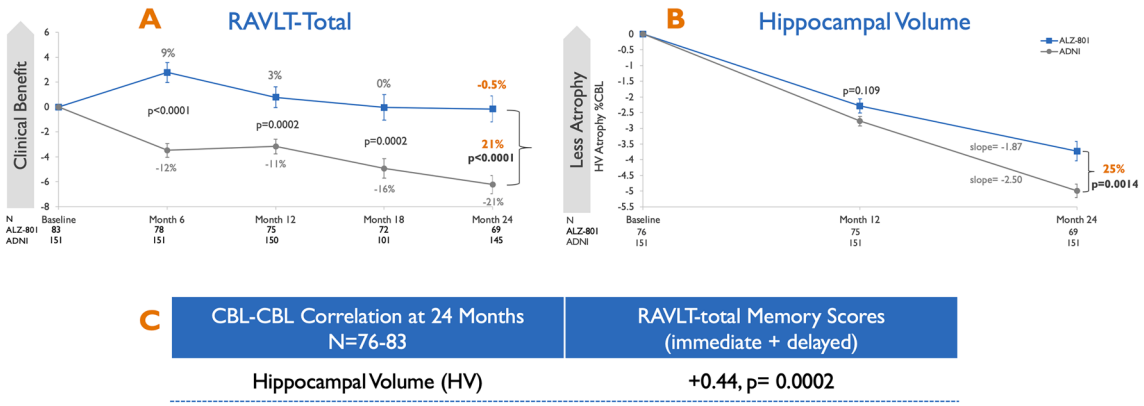

Fig. 6 Significant subject-level correlation of hippocampal volume (HV) to cognition in early Alzheimer's disease (AD): Example from valiltramiprosate phase 2 study in APOE4 carriers. Data from valiltramiprosate (ALZ-801) phase 2 study of 104 weeks duration in APOE4 carriers with early AD [47]. Drug showed early RAVLT improvement with stabilization at 2 years. Compared with matched group from ADNI (gray line), the drug showed 21% slowing of cognitive decline; with active-comparator difference: LS means Δ = +6.1, with positive difference indicating clinical benefit. For HV atrophy, valiltramiprosate showed 25% slowing compared with matched ADNI control; with active-comparator difference: LS means Δ = +1260 mm^3, with positive HV difference indicating HV preservation. CBL-CBL: Spearman's correlations of change from baseline on each outcome. Percentage slowing is calculated as: [LS means CBL placebo − LS means CBL drug] / LS means CBL placebo × 100. *CBL* change from baseline,*RAVLT* Rey Auditory Verbal Learning Test (immediate + delayed memory)

4.5 Example of a Drug Demonstrating Neuroprotective Properties on the basis of Multimodal Imaging: vMRI and DTI

DTI is being increasingly utilized in neurodegeneration studies such as in Parkinson's disease and multiple sclerosis. The phase 3 valiltramiprosate/ALZ-801 reported drug effects on HV and DTI, as well as their correlations to clinical outcomes in individuals with MCI [46, 81]. The drug's impact on DTI was assessed for grey matter and white matter effects on MD, as shown in Fig. 7. Statistically significant positive effects (MD reduction) for grey matter were observed in the cingulate cortex (155% versus placebo, $p = 0.031$), a key component of both the default mode network and the memory circuit of Papez [82], with numerically positive outcomes also noted for the hippocampus and the other cortical/subcortical grey matter regions. Significant white matter effects were identified in tracts connecting the hippocampus to the cortex that are functionally relevant in Alzheimer's disease. The most notable improvements were found in the fornix (124% versus placebo, $p = 0.032$) and the genu of the corpus callosum (92% versus placebo, $p = 0.003$), with additional positive trends across all other white matter tracts. Furthermore, MD effects in the genu of corpus callosum showed significant correlations with drug effects on HV ($r = -0.47$, $p < 0.01$), while MD in frontal cortex showed significant correlations with ADAS-Cog13 with $r = 0.33$, $p = 0.04$), where reduction in MD and ADAS-Cog indicate clinical benefit (Fig. 7C). These DTI results suggest *reduced* brain water content in the treatment group, alleviating concerns that increased hippocampal volume may be brain edema, and the significant correlations with cognition and HV suggest that these microstructural effects are clinically relevant. In addition, plasma NfL levels were also significantly correlated with HV changes ($r = -0.28$, $p < 0.05$) in the same study [46], further supporting that these reported drug effects represent true neuroprotection. Correlations of drug effects on NfL to HV effects warrant further evaluation in future AD drug trials.

5 Discussion

The US FDA recognizes amyloid plaque reduction measured with amyloid PET as a surrogate outcome reasonably likely to predict clinical benefit in AD, leading to accelerated approval or supporting traditional approval of drugs such as aducanumab, lecanemab, and donanemab [12, 13, 42–45]. However, uncertainty remains regarding its correlation with clinical efficacy in individual patients [83, 84]. Since only agents that reduce amyloid plaque can use this surrogate, alternative outcomes are needed to support new AD treatments.

5.1 Regulatory Framework for Accepting HV as Surrogate Outcome

The synthesis of this extensive body of evidence demonstrates that progressive HV atrophy is strongly linked to memory deficits, a hallmark of mild cognitive impairment (MCI) and early AD, as well as being an indicator of future cognitive deterioration. The regulatory framework for validating HV as a surrogate outcome encompasses several requirements: elucidating the role of HV atrophy in disease pathogenesis, establishing its longitudinal correlation with clinical outcomes, demonstrating HV atrophy's sensitivity to

Table 1 Differential drug effects on hippocampal volume: distinguishing neuroprotection from antibody-related pseudoatrophy or inflammation/edema/gliosis

Drug effect on hippocampal volume via[a]	vMRI HV	vMRI WB volume	DTI mean diffusivity	DTI fractional anisotropy	Plasma/CSF NfL	MRS-NAA levels
Neuroprotection, no edema[b]	↑	↑	↓	↑	↓	↑
Neuroprotective but shows pseudoatrophy due to plaque clearance/fluid shifts[c]	↔ ↑	↔ ↓	↓	↔ ↑	↔ ↓	↑
Larger HV due to ARIA/inflammation/edema/gliosis[d]	↑	↔ ↑	↑	↓	↔ ↑	↓

HV hippocampal volume, *vMRI* volumetric MRI, *WB* whole brain, *DTI* diffusion tensor imaging, *MD* mean diffusivity, *FA* fractional anisotropy, *NfL* neurofilament light, *MRS* magnetic resonance spectroscopy, *NAA N*-acetylaspartate, *ARIA* amyloid-related imaging abnormalities

[a]Framework for assessing hippocampal volume (HV) in concert with analyses of whole-brain volume (WBV), brain microstructural integrity (DTI), fluid biomarkers of ongoing neurodegeneration (NfL), and imaging of neuronal function/metabolism by MRS. Arrows indicate increase, decrease, or no change in outcome (adapted from Table 5) [70]. The following effects compared with the placebo or nontreated group suggest neuroprotection: [b]True neuroprotection: Increased HV and WBV, decreased MD with increased FA indicates less water diffusivity, stabilization/decrease in NfL indicates reduced neuroaxonal injury, and increased NAA indicates improved neuronal metabolism. [c]Pseudoatrophy: HV may be unaffected or slightly increased; WBV is reduced; decreased MD with stable or increased FA; stabilization/decrease in NfL; and stabilization or increase in NAA. [d]Inflammation/gliosis/edema: HV increased; WBV stable or increased; increased MD with decreased FA indicates increased brain water, and potentially increased NfL and decreased NAA, depending on severity of inflammation

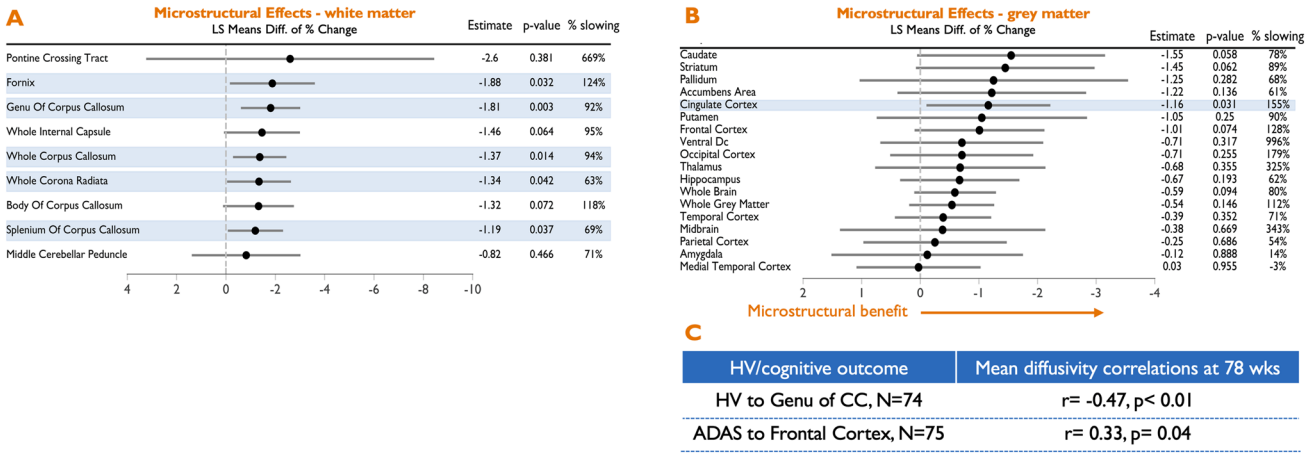

Fig. 7 Significant subject-level correlations of DTI effects to HV and cognitive effects: example from valiltramiprosate phase 3 study in APOE4/4 carriers. Data from valiltramiprosate phase 3 study in 84 individuals with APOE4/4 MCI with DTI imaging [46, 81]. Panels A and B show drug effects on white and grey matter mean diffusivity (MD), respectively. Decreasing MD indicates preservation of brain microstructure (positive drug effect). Highlighted rows in blue are regions with significant drug effect ($p < 0.05$). Cingulate cortex and five white matter tracts show significant positive effects. Estimate is LS means for % CBL between drug and placebo. LS means difference (SE) for percentage CBL for frontal cortex = 1.0% (0.6%); for genu = 1.8% (0.6%). Panel C: Correlations of drug effects on mean MD in white and grey matter to effects on HV and ADAS-Cog over 78 weeks. Frontal cortex shows highest correlation to ADAS-Cog; genu shows highest correlation to HV. Significant correlations of drug effects on DTI measures in frontal cortex and its white matter tracts with drug effects on HV and cognition support the clinical relevance of these imaging findings. *ADAS-Cog* Alzheimer's Disease Assessment Scale-Cognitive Subscale,*CBL* change from baseline, *CC* corpus callosum, *DTI* diffusion tensor imaging, *HV* hippocampal volume, *MCI* mild cognitive impairment, *R* Spearman's correlation

pharmacological intervention, and confirming that reduced rates of HV atrophy are associated with clinical improvements in interventional studies [36].

The hippocampus plays an early and central role in AD pathophysiology, showing initial amyloid-related dysfunction, tau pathology accumulation, and neuronal changes that occur before amnestic symptoms such as impaired learning and memory. Aβ oligomers, which are soluble misfolded and aggregated amyloid peptides, move through the hippocampus, causing injury to neuronal membranes, synaptic disruption, and neuronal loss, particularly within the CA1 and subiculum subfields [23–25, 39, 40]. When progressive cortical amyloid deposition reaches a critical threshold, Aβ triggers and contributes to tau hyperphosphorylation and the spread of aggregated tau tangle pathology from the hippocampus to neocortical areas, resulting in additional neurodegeneration and both cognitive and functional decline, marking the onset of dementia (Fig. 2) [4–8, 23]. Hippocampal volume (HV) atrophy appears several years before deficits in memory and learning, indicating early neurodegeneration or the "N" in A/T/N diagnostic scheme [6–8, 85] (Fig. 1).

A review of 30 observational studies (~13,000 patients) and nine anti-amyloid clinical trials (~10,000 patients with AD) found consistent, significant links between HV atrophy and cognitive decline in early AD. HV reliably predicts future decline and is also sensitive to anti-amyloid drug effects, with trials that showed significant HV benefits also demonstrating clinical efficacy. A linear association was observed between HV changes and clinical outcomes across multiple anti-amyloid drug trials (Fig. 4), supporting the role of HV as a surrogate outcome. Strong subject-level correlations between HV protection and clinical benefit were seen in two valiltramiprosate studies, including among APOE4 carriers and homozygotes (Figs. 5, 6), and confirming HV's utility across APOE4 genotypes [46, 47].

5.2 Advantages of HV Atrophy as a Surrogate Outcome

An important advantage of HV atrophy as a surrogate biomarker is its broad dynamic range across the Alzheimer's continuum and its differential sensitivity to amyloid pathology compared with normal aging. The hippocampus progressively atrophies from preclinical AD through MCI and moderate stages (Mini-Mental State Examination [MMSE] down to 15), whereas cortical thinning accelerates in early stages but slows below MMSE 21 [86]. In the Australian Imaging , Biomarkers, and Lifestyle (AIBL) study of aging, cognitively normal amyloid-negative subjects had less HV atrophy over 4 years than age-matched individuals with preclinical AD [87], while basal forebrain atrophy was greater in normal aging. HV also appears less influenced by aging than cortical sulcal width [88], indicating that it is more

specifically affected by AD pathology. In addition, vMRI is noninvasive and does not expose patients to radiation.

5.3 Standardization of vMRI Methods Across AD Trials

Serial HV assessments in multicenter trials face technical and biological challenges, mainly owing to scanner differences and segmentation methods. Standardized protocols, such as the EADC-ADNI Harmonized Protocol (HarP) have been widely adopted to reduce variability [32]. FreeSurfer segmentation shows high reliability and consistency across sites (intraclass correlation coefficient > 0.9). The HarP serves as a reference for validating tracers and automated algorithms, and its procedures have been widely validated for harmonization across scanners and field strengths [56, 89].

5.4 Challenges in Use of HV as Surrogate Outcome in AD Trials

Two main concerns with using HV as an efficacy marker are its lack of specificity for AD and ambiguity over whether larger HV reflects preserved brain tissue or fluid shifts/edema. AD diagnosis in clinical trials now relies on biomarkers, such as amyloid and tau-PET or fluid markers, which confirm AD but do not exclude comorbid conditions causing HV atrophy. HV atrophy, alongside cognitive decline, can also result from other misfolded proteins found in frontotemporal dementia or TDP-43 encephalopathy [90–92]. Although there are currently no validated clinical biomarkers to detect these pathologies, patterns of brain atrophy help differentiate them from early AD. Volumetric MRI in AD shows sequential cortical thinning starting in the entorhinal cortex and spreading to neocortical regions [4, 85]. Measuring medial temporal lobe and whole-cortex thickness is thus essential for distinguishing AD from other neurodegenerative diseases. It should also be mentioned that HV on vMRI may be affected by systemic factors such as hydration, medical comorbidities, medications, or other variables warranting further investigation. Differentiating true neuroprotective effects on HV from fluid shifts or edema is discussed in Sect. 4.4 , with an example on the use of DTI for this purpose. Notably, DTI protocols are being increasingly standardized and used for multicenter AD trials [93, 94].

5.5 Determining the Degree of HV Protection that Is Clinically Meaningful

If HV is employed as a surrogate endpoint for efficacy, it becomes necessary to evaluate the extent of HV neuroprotection that corresponds to the MCID or meaningful cognitive benefit. Our analysis indicates that preservation of ≥ 40 mm^3 HV or $\geq 10\%$ of the placebo decline over 1.5 years in MCI trials is likely to deliver clinically meaningful cognitive benefits. Histopathological comparisons between normal elderly and AD brains reveal that maintaining approximately 40 mm^3 HV equates to preserving roughly one million hippocampal neurons [20]. Given that each neuron is reported to form an estimated 15,000–80,000 synaptic connections [95], this HV preservation translates to rescuing 15–80 billion synapses, which are the neuronal substrates for learning and memory. This finding emphasizes the significance of HV atrophy and neurodegeneration—core features of AD and the "N" component in the A/T/N classification.

Further supporting HV atrophy's clinical relevance, Apostolova et al., using the harmonized EADC-ADNI vMRI protocol, demonstrated a significant and strong correlation between HV and hippocampal neuronal counts in patients with AD [39]. Additional methods for determining clinical relevance of slowing HV atrophy include analyzing the divergence of slopes, and/or calculation of time-savings, which hold clear clinical significance [61–63].

6 Summary

The technical hurdles associated with serial HV measurements are addressable. The integration of fluid biomarkers with additional volumetric measures facilitates the differentiation of AD-related HV atrophy from other etiologies, while DTI can validate pharmacologic effects on tissue microstructure and slowing of neurodegeneration. Consequently, HV on vMRI serves as a noninvasive, reproducible, and reliable metric for assessing neuroprotective effects in patients with AD.

7 Conclusions

Hippocampal volume (HV) atrophy serves as a reliable indicator of hippocampal neuron loss and neurodegeneration in AD and is recognized as an enrichment biomarker for pre-dementia stages of AD [33]. Utilizing HV measurements on standardized volumetric MRI as an accurate and dependable surrogate outcome may expedite drug approvals for therapies with innovative mechanisms that do not target plaque clearance. The endorsement of HV as a surrogate endpoint in early stage AD could also facilitate its assessment and application in prevention trials involving presymptomatic individuals, given that HV atrophy precedes cognitive decline [8, 96]. This has promising implications for evaluating interventions aimed at halting disease progression and preserving normal cognitive and functional abilities

[96]. Robust evidence from numerous observational studies conducted over the past three decades, along with recent clinical trials of anti-amyloid agents in biomarker-confirmed AD, supports the use of hippocampal atrophy detected by vMRI, when accompanied with preserved microstructure, as a dependable surrogate outcome that is reasonably likely to predict clinical benefit in early AD trials. This holds important practical value for the design of clinical trials and regulatory considerations regarding non-plaque-targeting therapeutic approaches.

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Declarations

Ethics approval Not applicable.

Consent to participate Not Applicable.

Consent for publication Not applicable.

Availability of data and materials Not applicable.

Code availability Not applicable.

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Authors and Affiliations

Susan Abushakra[1] · P. Murali Doraiswamy[2] · John A. Hey[1] · Duygu Tosun[3] · Frederik Barkhof[4,5] · Jerome Barakos[6] · Jeffrey Petrella[7] · J. Patrick Kesslak[1] · Aidan Power[1] · Marwan Sabbagh[8] · Anton Porsteinsson[9] · Sharon Cohen[10] · Serge Gauthier[11] · Craig Ritchie[12] · David Watson[13] · Emer McSweeney[14] · Merce Boada[15,16] · Earvin Liang[1] · Luc Bracoud[17] · Rosalind McLaine[1] · Susan Flint[1] · Jean F. Schaefer[1] · Jeremy Yu[1] · Margaret Bray[1] · Suzanne Hendrix[18] · Sam Dickson[18] · Abe Durrant[18] · Adem Albayrak[1] · Martin Tolar[1]

✉ Susan Abushakra
susan.abushakra@alzheon.com

1 Alzheon, Inc., 111 Speen Street, Suite 306, Framingham, MA 01701, USA

2 Departments of Psychiatry and Medicine, Duke University School of Medicine, Durham, NC, USA

3 Departments of Radiology and Biomedical Imaging, University of California, San Francisco, CA, USA

4 Department of Neuroradiology, VU University Medical Center, Amsterdam, The Netherlands

5 Queen Square Institute of Neurology and Center of Medical Imaging Computing, University College, London, UK

6 California Pacific Advanced Imaging and Sutter Health, San Francisco, CA, USA

7 Department of Radiology, Duke University School of Medicine, Durham, NC, USA

8 Department of Neurology, Barrow Neurological Institute, Phoenix, AZ, USA

9 Departments of Psychiatry, Neurology, Neuroscience, and Medicine/Geriatrics, University of Rochester School of Medicine and Dentistry, Rochester, NY, USA

10 Toronto Memory Program, Toronto, Canada

11 Departments of Neurology and Neurosurgery, Psychiatry, and Medicine, McGill University, Montreal, Canada

12 University of St. Andrews Medical School and Scottish Brain Sciences, Edinburgh, Scotland, UK

13 Alzheimer's Research and Treatment Center, Wellington, FL, USA

14 Re:Cognition Health, London, UK

15 Ace Alzheimer Center, Barcelona, Universitat Internacional de Catalunya, Barcelona, Spain

16 Networking Research Center on Neurodegenerative Diseases, Instituto de Salud Carlos III, Madrid, Spain

17 Clario Inc, Lyon, France

18 Pentara Corporation, Salt Lake City, UT, USA