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Neuroimaging in the Oldest-Old: A Review of the Literature

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Abstract

The oldest-old, those 85 years and older, are the fastest growing segment of the population and present with the highest prevalence of dementia. Given the importance of neuroimaging measures to understand aging and dementia, the objectiv of this study was to review neuroimaging studies performed in oldest-old participants. We used PubMed, Google Scholar, and Web of Science search engines to identify *in vivo* CT, MRI, and PET neuroimaging studies either performed in the oldest-old or that addressed the oldest-old as a distinct group in analyses. We identified 60 studies and summarized the main group characteristics and findings. Generally, oldest-old participants presented with greater atrophy compared to younger old participants, with most studies reporting a relatively stable constant decline in brain volumes over time. Oldest-old participants with greater global atrophy and atrophy in key brain structures such as the medial temporal lobe were more likely to have dementia or cognitive impairment. The oldest-old presented with a high burden of white matter lesions, which were associated with various lifestyle factors and some cognitive measures. Amyloid burden as assessed by PET, while high in the oldest-old compared to younger age groups, was still predictive of transition from normal to impaired cognition, especially when other adverse neuroimaging measures (atrophy and white matter lesions) were also present. While this review highlights past neuroimaging research in the oldest-old, it also highlights the dearth of studies in this important population. It is imperative to perform more neuroimaging studies in the oldest-old to better understand aging and dementia.

Keywords

aged 80 and over; aging; Alzheimer’s disease; cognitive aging; magnetic resonance imaging; memory disorders; neuroimaging; neuropathology; positron emission tomography; tomography; x-ray computed

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THE OLDEST-OLD: AN IMPORTANT POPULATION FOR STUDYING AGING AND DEMENTIA

The oldest-old (those over 85 years), are the fastest growing segment of the population, and represent a distinct group, both clinically and pathologically, compared to younger old individuals [1]. Not only are the oldest-old at the outermost extreme of human life, but they also have an increased rate of dementia (annual incidence rising to 40% for centenarians [2]). Alongside the growth of the oldest-old section of population, the development of neuroimaging technologies allowed researchers to study *in vivo* changes in the brain associated with aging and cognition. Early studies used the first widespread neuroimaging technology, computer tomography (CT), to find age- [3] and dementia-related [4] enlargement of the lateral ventricles, as well as dementia-related hippocampal atrophy [5]. Despite the increasing number and epidemiological importance of this group and the rise of neuroimaging techniques capable of assessing changes in the brain with aging and dementia, there is a dearth of neuroimaging studies dedicated to the oldest-old. For example, the Alzheimer's Disease Neuroimaging Initiative (ADNI)—which is one of the largest neuroimaging databases and ongoing research studies of Alzheimer's disease (AD) and elderly participants—excludes those who are older than 90 years of age from initial enrollment (http://adni.loni.usc.edu/study-design/). Here we provide a comprehensive review of *in vivo* neuroimaging studies in the oldest-old, to answer key questions about this rapidly growing population and to identify gaps in the literature to inform future research directions. The neuroimaging modalities of focus are magnetic resonance imaging (MRI), computed tomography (CT), and positron emission tomography (PET).

SEARCH METHODOLOGY

A literature search was performed using the following search engines: Web of Science (https://www.webofknowledge.com/), Google Scholar (https://scholar.google.com/), and PubMed (https://www.ncbi.nlm.nih.gov/pubmed/). Search terms included combinations of terms to denote oldest-old, and terms to denote neuroimaging or the specific modality of interest. Oldest-old search terms included: oldest-old, very old, old old, nonagenarian, and centenarian. These search terms for the oldest-old closely reflect the Medical Subject Headings (MeSH) for "Aged, Over 80"; however, this MeSH category was not used for searches as it did not sufficiently limit studies to the age-range of interest. Neuroimaging search terms included: neuroimaging, MRI, CT, and PET. For CT, the term "brain" was added to narrow the search results to neuroimaging studies. Search results were sorted by the appropriate relevance metric of each search engine. Only original, *in vivo* neuroimaging research articles were included. The following criteria were used to select articles: 1) the article must have focused on or had a subgroup of participants either over the age of 85 years or with a mean age over 84 years. 2) Oldest-old neuroimaging data must have been analyzed in some fashion: only acquisition of the data was insufficient for inclusion. A search was performed the week of September 3, 2018, and updated on the week of November 10, 2019. We identified 60 articles using MRI, CT, and/or amyloid PET, to examine the oldest-old, which we outline below. The main findings from the studies identified in this review are highlighted in Table 1, organized thematically.

EARLY DAYS: CT STUDIES AND THE GOTHENBERG STUDIES

The first widespread neuroimaging modality, CT, which utilizes x-ray beams to probe structures through various angles and creates cross-sectional and 3D images through tomographic reconstruction, was also the first used for neuroimaging studies in the oldest-old. Figure 1 shows an axial slice of a CT scan acquired in an oldest-old participant, which highlights the relative strengths (bone and calcification perspicacity) and limitations (poorer soft tissue contrast) of CT.

Early CT studies in the oldest-old noted a greater degree and variability of cerebral atrophy in this population. The earliest study identified in this review used CT to measure brain atrophy and found that participants aged 80–99 years had greater atrophy than those aged 60–79 years [6]. Another early CT study in the oldest-old scanned ten healthy and mentally-alert centenarians (aged 100–102 years) and noticed the presence of white matter lesions (WML) as well as a high degree of variability in atrophy patterns across the participants [7].

Infarcts and WML on CT

Some of the most prominent early neuroimaging studies in the oldest-old were performed by the longitudinal gerontological and geriatric population studies on a population-based cohort of 85-year-olds in Gothenberg, Sweden. A subset (N = 239) of the study participants underwent CT scanning. Some of the most important findings from these studies were increased prevalence of CT-detected infarcts in participants with dementia. Participants with dementia in this cohort (N = 71, 29.8%), had a higher probability of infarcts compared to those without dementia (27.9% versus 12.6%, respectively, Fisher's Exact Test p = 0.005) [8]. A later study estimated 17.1% of the total population had CT-detected infarcts, half of which were asymptomatic, and presence of infarcts increased the frequency of dementia (odds ratio [OR] = 5.5, 95% CI = 2.1–14.1 for symptomatic; OR = 2.7, 95% CI = 1.1–6.7 for silent) [9].

Other studies used the Gothenberg CT data for more refined analyses of signal abnormalities such as WML. These studies found WML to be associated with infarcts on CT as well as with dementia and worse cognitive performance. WML were more common in participants with (69.6%) than without (43.2%) CT-detected infarcts (OR = 3.00, 95% CI = 1.5–6.0) [9]. WML were also found to be more prevalent in those with (68%) than those without (33.8%) dementia (Fisher's Exact Test, $p < 0.001$), and both CT-detected infarcts and WML contributed independently to the occurrence of dementia [10]. WML graded as none, mild, and moderate-to-severe, were associated with worse performance on a wide variety of neuropsychological tests. In participants without dementia, WML were most strongly associated with performance in the identical forms (to assess perceptual speed, F = 12.3), coin (a sorting task, F =7.0), Thurstone picture memory (F = 7.0), clock (F = 5.2), and block design (F = 5.0) tests. In participants with dementia, WMLs were associated with the block design (F = 6.7), MIR memory (F = 5.4), and Mini-Mental State Examination (MMSE, F = 5.0) tests (two-way ANOVA, $p < 0.01$ for all tests) [11]. An additional study of a subset of participants (72 with dementia, 117 without) analyzed both WML and infarcts detected from CT in relation to *APOE ε*4, and found that possessing both *APOE ε*4 and WML on CT significantly increased the risk of dementia (OR = 6.8, 95% CI = 2.6–14.3), while only

having one of these did not [12]. Another study found that calcifications in the basal ganglia were more prevalent in participants without dementia who experienced hallucinations [13].

Brain atrophy on CT

Another aspect of the brain evaluable on CT is the degree of atrophy, either on a qualitative scale, as total volumes in well-defined structures such as the ventricles, or as ratios of measurements across different brain structures. Studies employing this methodology found brain and ventricular size to be associated with worse survival, increased amyloid pathology, and weakly associated with blood pressure measures. Greater temporal atrophy (OR = 1.65, 95% CI = 1.05–2.61) and larger ratio of lateral ventricle span over brain width (OR = 1.20, 95% CI = 1.00–1.44) was associated with worse 20-year survival in participants without dementia, and increased ventricle size was associated with worse survival in participants with dementia (ventricle to brain ratio, OR = 1.29, 95% CI = 1.03–1.60) [14]. A recent study in a subset of Gothenberg participants who also received lumbar punctures (23 with, 30 without dementia), found that decreased cerebrospinal fluid (CSF) $A\beta_{42}$ levels were correlated with brain atrophy only in those with dementia ($r = -0.52$ for frontal, $r = -0.70$ for temporal, $r = -0.59$ for parietal), and $A\beta_{42}$ levels were correlated with the presence of WML only in participants without dementia ($r = -0.39$) [15]. Another Gothenberg study found varied but weak correlations between lower blood pressure and brain atrophy [16]. In a study on participants from the Berlin Aging Study (BASE), the ratio of ventricle to total brain volume in the oldest-old was not significantly different between those with ($N = 8$) and without ($N = 35$) dementia (effect size of 0.2 standard deviations), but the same ratio was significantly different between participants without ($N = 196$) and with ($N = 15$) dementia in a younger (79–89 years) group (effect size of 1.3 standard deviations) [17].

THE ADVENT OF MRI: STRUCTURAL STUDIES USING ANATOMICAL MRI

MRI's greater soft tissue contrast and ability to detect more subtle lesions, as well as its flexibility for acquiring different types of imaging data, has made it the primary neuroimaging tool for both clinical and neuroscience studies. Figure 2 illustrates examples of two of the most common anatomical MRI sequences, the high-resolution T1w and fluid attenuation inversion recovery (FLAIR) scans, as well as some of the relevant metrics extracted from these, such as segmentation of cortical and subcortical structures, cortical thickness, and white matter hyperintensities (WMH), in an oldest-old participant. While MRI scans typically take a longer time than CT scans, a study using satisfaction questionnaires indicated that MRI sessions of up to an hour were feasible in this age group, where the oldest-old participants (90–93 years, $N = 13$) tolerated the procedures as well as younger-old participants (72–80 years, $N = 16$) with no statistically significant differences in satisfaction surveys between the groups [18]. One study retrospectively assessed clinical MRI scans of patients between 90 and 100 years of age for incidental findings, and reported that out of 177 patients, the most common findings were acute ischemic changes or cerebrovascular accident (20%), intracranial tumors (8%), and intracranial aneurysms (3%) [19].

MRI neuroimaging studies in the oldest-old began to leverage the improved tissue contrast to assess more regionally-specific structural changes. One of the early adopters of MRI research in the oldest-old was the Oregon Health and Science University (OHSU) through participants from various studies, most notably the Oregon Brain Aging Study (OBAS). One early study in 3 groups comprising healthy elderly participants ($N = 60$, mean age 78.2 years), participants with "incipient dementia" (CDR ≥ 0.5 in two consecutive six month follow-ups, $N = 20$, mean age 88.1 years), and participants with AD ($N = 39$, mean age 72.2 years), found that the corpus callosum was more atrophied in participants with AD compared to both healthy elderly and incipient dementia participants (ANOVA, $F = 14.1$, $p < 0.001$), while there were no significant differences between groups in pons or cerebellum size [20].

WMH and infarcts on MRI

Generally, WMH on MRI are very prevalent in the oldest-old, and the degree of WMH has been found to be weakly associated with cognitive measures, but more strongly associated with certain measures of cardiovascular health. An early study utilizing MRI to examine older participants was the Cardiovascular Health Study (CHS). Started in 1989, the CHS was an observational study of risk factors for cardiovascular disease in adults 65 years and older, and included some participants over the age of 85. Early results from the CHS suggested oldest-old participants had greater brain ventricular enlargement and sulcal widening as well as more severe WMH rating, though this report only included a small number of oldest-old participants ($N = 15$ out of 303 total) [21]. A later CHS study with more oldest-old participants ($N = 53$ out of 1,268 total) confirmed this finding, with oldest-old participants having an average WMH grade of 3.43 on a 9 point scale, compared to 2.88 for the 80–84 years group and 1.76 for the 65–69 years group [22]. Another CHS study ($N = 3,371$) found an increased prevalence of infarcts in the basal ganglia (OR = 2.62) and outside of the basal ganglia ($N = 2.94$) for the participants over the age of 85 as compared to 65–69 year olds [23]. An analysis from the Sidney Older Persons Study (SOPS, $N = 114$) reported WMH in all participants (range 81–97 years, mean 85.5 years), but noted no particularly strong associations with cognitive measures [24]. One study ($N = 24$, age range 73–96 years, mean 84 years) found decreased large and small vessel arterial elasticity indices in participants with the highest degree of WMH burden (MANOVA, $p < 0.01$ for both) [25]. Another study in 232 participants (mean age 84.4 years) found that those with high variation in self-reported systolic blood pressure had a larger increase in WMH and greater drop in cognitive assessment at follow-up [26].

Anatomical MRI and brain aging

Another benefit of MRI studies are the automated segmentation programs that facilitate neuroimaging analyses. Generally, studies employing these methods have found a relatively constant (linear) decline in volume within brain regions that persists throughout the lifespan, even in the healthy oldest-old. A study from the OBAS cohort found relatively constant rates of atrophy with age in longitudinal MRI scans in young-old (65–74 years), middle-old (75–84 years), and oldest-old (85–95 years) participants [27]. Another study, using young-old ($N = 207$, 70–89 years) and oldest-old ($N = 70$, over 90 years) participants from the Sidney Centenarian Study (SCS) and the Sidney Memory and Aging Study (SMAS), found a

constant rate of change in gray matter and hippocampal volumes. However, some quadratic trends were present for white matter volumes (atrophy rate leveling-off with age) and WMH volumes (increasing rate of accumulation with age) [28]. Another study examined cortical thickness across participants aged ≥ 18 years (N = 316) with 38 participants belonging to the old-old category (over 80 years). The study found that cortical thinning in younger ages was greater in heteromodal association cortex, but in the oldest-old cortical thinning was most pronounced in sensorimotor cortex [29].

Anatomical MRI in relation to cognition

In addition to healthy brain aging, other studies have examined the relationship between brain structure and cognitive impairment. These studies have found that brain atrophy, while related to age, is still more pronounced in participants with cognitive impairment, even in the oldest-old. In a study by OH SU, 18 participants without dementia (mean age 86.8 years) and 12 with “predementia” or “incipient dementia” (mean age 90.4 years), were scanned annually with a coronal-oblique multiecho T2 sequence. Those with predementia had significantly smaller hippocampal volumes (1.16 ± 0.1 cm^3 versus 1.34 ± 0.26 cm^3), but similar rates of atrophy, and no difference in parahippocampal volumes either cross-sectionally or longitudinally. Participants with dementia, however, had a faster rate of temporal lobe atrophy (−1.236 ± 1.43 cm^3/year versus 0.01 ± 1.67 cm^3/year)[30]. In another OHSU study, older healthy elderly individuals (N = 14, mean age 90 years) had greater prefrontal atrophy compared to younger healthy elderly (N = 14, mean age 70 years), but showed no difference compared to young elderly participants with AD (N = 14, mean age 70 years). Also, older healthy elderly participants presented with greater white matter atrophy compared to younger healthy elderly, while participants with AD had both gray and white matter atrophy [31]. Another study in 79 healthy participants followed annualy (average of 6 follow-ups), found that expansion of the ventricles (increase in expansion rate of 2.3%, 95% CI = 0.08% to 3.9%) predicted onset of mild cognitive impairment (MCI) in the oldest-old on average around 2.3 years before diagnosis [32].

A study with participants from the SCS and SMAS (N = 244, 71–103 years) found smaller overall cortex, medial temporal lobe, and corpus callosum volumes in individuals with amnestic MCI compared to cognitively normal participants, while these same measures did not differentiate amnestic MCI from those with non-amnestic MCI. Additionally, this study found that the structures that differentiated amnestic MCI from cognitively normal participants were not the same when the sample was restricted to those older than 85 years, where the hippocampus and temporal pole performed better [33]. A study utilizing data from ADNI, examined groups of young-old (60–75 years) healthy controls (HC, N = 84) and AD (N = 64), and oldest-old (≥ 85 years) HC (N = 41) and AD (N = 41) participants. While the pattern of atrophy for AD participants was similar in both the oldest-old and the younger groups (cortical thickness decreases in temporal, parietal, and cingulate cortex), the effect was less pronounced in the oldest-old [34]. An analysis of participants in *The 90 + Study* (N = 141, mean age of 94.3 years; 94 cognitively normal and 47 with cognitive impairment) found that at baseline, lower hippocampal volumes were associated with lower scores on all assessed cognitive tests ($p < 0.01$) except Digit Span Backwards and higher WMH load was associated with lower scores on California Verbal Learning Test (CVLT) immediate and

delayed recall ($p < 0.01$) and Modified Mini-Mental State exam (3MS, $p = 0.03$). This same study also looked at longitudinal neuropsychological evaluations and found lower baseline hippocampal volume to be associated with a faster decline in 3MS ($p < 0.01$), MMSE ($p = 0.02$), and CVLT tests ($p \leq 0.05$). Longitudinally, higher WMH load was only associated with faster decline on global cognitive tests (3MS, $p = 0.02$; and MMSE, $p = 0.03$). A combination of low hippocampal and high WMH volume was associated with the fastest decline on all cognitive tests [35]. Another recent study in the oldest-old found associations between volumes of hippocampal subfields and memory scores in a cohort of participants aged 95 or older ($N = 10$, mean age 97.6 years) [36].

Anatomical MRI in relation to physical function

Some structural MRI studies have examined the neural correlates of functional and motor decline in the oldest-old, finding strong associations between WMH and gait measures. One study using healthy participants of the OBAS ($N = 50$, mean age 85.1 years) found that the volume of the ventricles and periventricular WMH volume were associated with gait measures (number of steps per seconds and 30-feet walk time), with Pearson's correlations ≥ 0.54 and $p < 0.001$ [37]. In another OBAS study of participants without dementia ($N = 104$, mean age 85.1 years, mean years of follow-up 9.1 years) greater baseline WMH volume was associated with a subsequent decline in walking speed ($R^2 = 0.08$, $p = 0.0052$) and an increase in the number of steps ($R^2 = 0.12$, $p = 0.0125$) for a 30-feet walk. Greater baseline WMH volume was also associated with a faster increase in both WMH volume ($R^2 = 0.20$, $p < 0.0001$) and ventricular CSF volume ($R^2 = 0.13$, $p = 0.0022$) [38]. A study involving 106 individuals without dementia aged 80 to 94 years from the SOPS found that larger hippocampal volumes were associated with greater socializing, but not with other measures of activities of daily living, and measures of WMH were not significantly associated with any activity of daily living [39].

Additional assorted oldest-old structural MRI studies have found: an association between alcohol consumption and cerebellar size [40], association between brain volumes and nutrient biomarkers [41], association between daily computer use and hippocampal volume [42], a lack of associations between hippocampal volume and sleep quantity/quality measures [43], and associations between nocturnal blood pressure variations and WMH and cerebral microbleed burden [44].

ADVANCED AND MULTIMODAL MRI

While structural MRI is helpful in assessing macrostructural brain changes such as atrophy and the presence of WMH, more advanced MRI techniques are able to provide information about the microstructural, functional, and metabolic characteristics of the brain. Fig. 3 illustrates several of the most common metrics derived from advanced MRI in an oldest-old participant.

Diffusion tensor imaging

Studies using diffusion tensor imaging (DTI) have found lower white matter integrity in oldest-old participants, with some finding associations between decreased white matter

integrity with gait measures and perceptual speed. An investigation from *The 90 + Study* examined DTI scans from 94 participants (age 90–103 years) and found a significant decrease in fractional anisotropy (FA, a measure of white matter cohesiveness) with age (β~−0.3 for significant relationships, multiple linear regressions). However, they did not find differences in FA between cognitively normal ($N = 64$) and cognitively impaired no dementia (CIND, $N = 30$) participants [45]. Another study, utilizing longitudinal DTI scans (participants scanned twice over an average of 2.3 years) in a group with a mean age of 85.4 years (range 80–103 years, $N = 70$ at baseline, $N = 40$ at follow-up) found expected decreases in FA and increases in mean diffusivity (MD) with age. Loss of white matter integrity (decrease in FA and increased in MD) along the corticospinal tract was associated with a decline in perceptual speed, independent of gray matter changes, while other cognitive measures were not [46]. Another DTI study ($N = 90$, mean age 87.4 years, 51 with dementia or MCI) found that global preserved white matter (higher FA) was associated with more steps/day ($r = 0.272$, $p = 0.009$), greater energy expenditure/day ($r = 0.246$, $p = 0.02$), and longer exercise duration/day ($r = 0.222$, $p = 0.037$), but found no significant differences between cognitively normal and impaired participants in terms of either physical activity levels or FA [47].

Functional MRI

We found two studies that used functional MRI (fMRI) to assess memory function in cognitively normal oldest-old participants, both of which failed to find large differences between the oldest-old and younger-old participants with regards to functional activation during memory tasks. One of these studies examined differences in memory retrieval between young-old (64–76 years, $N = 18$) and old-old (84–96 years, $N = 18$) participants and found no significant differences in areas of activation even though the oldest-old performed worse on said task [48]. The other study also found relatively well-preserved functional activation during a hippocampal recognition memory task in the oldest-old (≥ 90 years, $N = 12$) compared to young-old (70–80 years, $N = 17$) participants [49].

Multimodal MRI

Unique characteristics of the brains in the oldest-old have provided an opportunity to validate or examine the relationship between multiple MRI measures. In a series of papers by OHSU, the authors take advantage of the high prevalence of WMH to study the characteristics of cerebral blood flow (CBF, as measured using arterial spin labeling) within WMH [50], and to study the relationship between CBF and DTI measures in, and adjacent to, WMH. They found a penumbra around the WMH in which DTI measures and CBF were reduced [51]. Another study compared ratings of WMH burden in T2 and FLAIR MRIs and found high inter-rater reliability for both FLAIR and T2, though FLAIR performed slightly better [52]. An early study from 2003 acquired magnetic resonance spectroscopy (MRS) scans in oldest-old participants and detected increased N-acetylaspartate to myo-inositol ratios in the parietal and temporal lobes which were associated with smaller hippocampal volumes [53].

PET TRACERS FOR ALZHEIMER'S DISEASE

In our search we only found PET studies using tracers that target amyloid (one of the two main abnormal proteins accumulating in AD) and none that used fluoro-deoxyglucose (FDG) PET (which measures cerebral metabolism). The oldest-old, having the highest prevalence and incidence of dementia and AD neuropathology, is an ideal group to study using amyloid PET. Figure 4 shows florbetapir amyloid PET scans in an amyloid positive and amyloid negative participant. The oldest-old present with the highest of amyloid PET levels, which even at this advanced age are still related to cognitive status and cognitive decline. In one of the first PET studies in the oldest-old, performed by *The 90 + Study*, the authors scanned thirteen participants without dementia with an amyloid (florbetapir) PET scan and found an association between standard uptake value ratio (SUVr) and cognitive scores (CVLT, $r = 0.71$, $p = 0.009$; 3MS $r = -0.60$, $p = 0.03$). They also found that those classified as Aβ+had a faster cognitive decline [54]. Another more recent study performed amyloid PET using the radiotracer flutemetamol in healthy and cognitively normal younger-old (age 55–80 years, $N = 36$) and oldest-old (age 85–96 years, $N = 40$) participants. In conjunction with MRI, the study found an expected decrease in brain volume and increase in amyloid beta deposition in the oldest-old compared to younger-old participants [55].

The GEM Study

A large study that has utilized amyloid PET to study the oldest-old is the Ginkgo Evaluation of Memory (GEM) study (https://nccih.nih.gov/research/results/gems). An imaging sub-study was performed in 197 participants (mean age 85.5 years, 152 cognitively normal, 38 diagnosed with MCI) who underwent brain MRI and ^{11}C-labeled Pittsburgh compound B (PiB) PET. Analyses of this data have generally found high amyloid levels in the oldest-old which are related to cross-sectional and longitudinal decreases in cognition and are relatively independent from measures of hippocampal atrophy and WMH. The first of these studies reported that 55% of those without dementia over the age of 80 were classified as PiB positive using standard cutoffs (SUVr>1.4), and this number increased to 85% when limiting to healthy participants with the *APOE ε*4 allele [56]. A study with the same participants examined their retrospective (7–9 years before PET scanning) neuropsychological data to determine whether cognitive decline preceded amyloid deposition, and only found lower performance on Stroop ($p < 0.01$) and Raven's Progressive Matrices ($p = 0.05$) executive function tests, but not any memory tests, in Aβ+participants at baseline in the study. This study also found that Aβ+participants had steeper decline on a modified Rey-Osterrieth (R-O) figure recall ($p \leq 0.02$), Trails A and B ($p \leq 0.02$), and semantic fluency ($p = 0.01$) tests [57]. Another GEM study ($N = 60$) looked at progression to dementia in the context of the PET and MRI data, and found that WMH volume (HR = 4.56, 95% CI = 1.39–14.9, $p = 0.01$) and Aβ burden (HR = 1.58, 95% CI = 1.22–2.03, $p < 0.0001$) were significant predictors of incident dementia even when including death as a competing risk [58]. Another study examined cognitive decline over a twelve-year period, with participants classified as Aβ+/− according to amyloid PET scan performed around year 5. Participants were also categorized for presence of neurodegeneration (ND)+/− based on hippocampal volume. Those who were Aβ+ND+showed the steepest cognitive decline in virtually all cognitive tests (except for phonemic fluency and Stroop tests) compared to the Aβ-ND-group. Having

only one of the biomarkers was also associated with cognitive decline in the R-O recall tests ($p \leq 0.001$ for all), but only Aβ+ND-showed additional associations with decline in CVLT, Trails B, Semantic Fluency, and Boston Naming Tests [59].

Many of the GEM imaging sub-study participants were brought back after two years for follow-up clinical assessments, MRI, and PiB PET scans ($N = 183$). These scans generally showed an increase in amyloid levels that were associated with cognitive decline. One analysis found that participants converting to dementia or MCI did not differ significantly by binary Aβ status (RR = 2.26, 95% CI = 0.83–6.10, $p = 0.14$), but did differ in terms of total Aβ burden ($p = 0.01$) compared to those who did not convert. Participants who converted to dementia differed by hippocampal atrophy (dichotomized by 25th percentile, relative risk [RR] = 3.64, 95% CI = 1.46–9.33, $p = 0.002$; continuous variable, $p < 0.001$) and had increased WMH burden (dichotomized by 75th percentile, RR = 3.41, 95% CI = 1.26–9.18, $p = 0.004$; continuous variable, $p = 0.001$) compared to those who did not convert. These three neuroimaging markers were not correlated to each other ($p \geq 0.06$), and all contributed to progression to incident dementia in a logistic model accounting for age, sex, education, and baseline MMSE scores (WMH volume, OR = 3.23, 95% CI = 1.34–7.79, $p = 0.01$; hippocampal volume, OR = 0.71, 95% CI = 0.57–0.90, $p = 0.004$; Aβ SUVr, OR = 2.94, 95% CI = 0.90–9.63, $p = 0.08$) [60]. Another subset of GEM studies were performed using participants without dementia who came for arterial stiffness assessment two years after PET ($N = 91$). One of these studies found that peripheral arterial stiffness at baseline was higher in Aβ+participants, while WMH burden was associated with central arterial stiffness [61]. A similar analysis with the two-year follow-up PET ($N = 81$) found an increase in Aβ+participants (from 48% to 75%), and reported that central arterial stiffness was significantly associated with the accumulation of Aβ [62].

ASSOCIATION OF NEUROIMAGING WITH NEUROPATHOLOGY

With the high mortality in the oldest-old, neuroimaging data in this group is usually acquired relatively close to the time of death. Additionally, the oldest-old have a higher prevalence of accumulated neuropathologies. Thus, the oldest-old provide a unique window into the association between brain structure and neuropathology. Three studies from the OH SU group have examined antemortem neuroimaging with respect to neuropathology in the oldest-old, finding that ventricular measures were related to both neuropathology and cognition, while brain and hippocampal volumes were more related to cognition. The first oldest-old neuroimaging-neuropathology study we identified was performed in 2003 in 39 oldest-old participants (mean age at entry 84.0 years, mean age at death 89.7 years; 15 without and 24 with dementia at death). In this study, for those with dementia there were associations between neurofibrillary tangles (NFTs) and final brain volume ($R^2 = 0.194$), rate of total brain atrophy ($R^2 = 0.33$), final ventricular volume ($R^2 = 0.3$), and rate of ventricular volume change ($R^2 = 0.451$). Participants with dementia showed only ventricular measures were associated with neuritic plaques (NP), which included final ventricular volume ($R^2 = 0.262$) and rate of change in ventricular volume ($R^2 = 0.451$). These measures were not significantly associated with the neuropathologies of interest in participants without dementia. Additionally, only final hippocampal atrophy ($R^2 = 0.247$), and not rate of atrophy, was related to hippocampal NFT in those with dementia [63].

A later study examined 36 participants with AD neuropathology (Braak NFT stage ≥ V and CERAD NP score ≥ 2), of whom 12 had normal cognitive function and 24 had been diagnosed with AD prior to death. They found that hippocampal and total brain volumes were significantly associated with dementia status ($p < 0.01$ for both) [64]. Another study in 71 healthy participants (average age at first MRI of 88 years; 44 participants later developed, and 27 did not develop, cognitive impairment prior to death) found ventricular expansion was related to neuropathological scores for NFT burden ($p = 0.015$), NP burden ($p = 0.001$), gross infarcts ($p < 0.001$), and diagnosis of dementia ($p < 0.001$). Also, faster total brain atrophy was associated with MCI diagnosis ($p = 0.004$), but not with dementia diagnosis, gross infarcts, and cerebral amyloid angiopathy (CAA). Finally, faster hippocampal atrophy was only associated with CAA ($p = 0.009$) [65].

SUMMARY AND FUTURE DIRECTIONS

For this review, we identified 60 *in vivo* neuroimaging studies that specifically examined oldest-old participants using one of the common neuroimaging research techniques: CT, MRI, or PET. This relatively low number of neuroimaging studies dedicated to this demographically and clinically important population highlights the need for further studies. These studies confirm that in the oldest-old, who have the greatest extent of WMH, Aβ accumulation, and brain atrophy compared to younger age groups, these measures are still important for predicting cognitive decline, survival, and clinical status outcomes. Associations with age generally suggested a relatively constant decline in volume, expansion of ventricles, decrease in white matter integrity, and increase in amyloid burden. However, these same imaging measures were also cross-sectionally associated with dementia or cognitive impairment, and a greater rate of atrophy longitudinally for these neuroimaging measures was also associated with worse cognitive outcomes and underlying neuropathology. Additionally, many of these measures relate to other risk factors: WMH load is related to cardiovascular health factors such as blood pressure and exercise, and increased arterial stiffness was found to be associated with amyloid load on PET. Out of all the *in vivo* neuroimaging studies identified in this review, we found only 14 that had groups or subgroups with an average age of 90 years or greater [7, 17-19, 28, 30, 35, 36, 43-45, 49, 54, 65]. Those 90 years and older are the group with the greatest need for targeted neuroimaging research since larger neuroimaging studies generally exclude these individuals.

Structural MRI studies in the oldest-old point toward common markers of aging and dementia: WMH, ventricular enlargement, atrophy of the hippocampus, and cortical thinning across multiple brain regions. Ideally, some of these relationships could be disambiguated using advanced MRI to reveal additional relevant neuroanatomical substrates. Studies from this review that leveraged advanced and multimodal MRI in the oldest-old used different advanced MRI modalities and examined different aspects of aging and cognition (dementia, physical performance, specific memory tasks), thus precluding generalizations of the findings. Larger, more standardized studies of the oldest-old, with emphasis on dementia and aging, are warranted to establish normative values and patterns of additional tissue characteristics as assessed through advanced MRI.

While the oldest-old provide an important window to study and understand dementia- and aging-related changes in the brain, they also represent a challenge as some of the associations with findings on neuroimaging are multifactorial and difficult to disentangle given the long and variable life courses of oldest-old individuals. For example, while in the oldest-old increasing ventricular size was found to be associated with neuropathology [63, 65], other studies have found associations with cardiovascular risk factors [66]. Thus, attempting to disentangle the relationships between neuroimaging findings, health factors, neuropathology, and cognition are an important area of future research. Additionally, there is an increasing awareness that certain age-related neuropathologies such as TAR DNA-binding protein (TDP-43) and hippocampal sclerosis of aging (HS) are of greater importance in advanced age as they are much more common and strongly related to dementia in the oldest-old. Some *in vivo* neuroimaging studies in younger cohorts have begun to identify atrophy patterns on MRI related to TDP-43 [67-69] and HS [70, 71]. However, given the importance and prevalence of TDP-43 and HS, more *in vivo* neuroimaging research focused specifically on the oldest-old and followed by pathological assessment is needed to try to identify biomarkers for these pathologies that cannot be identified during life.

One important methodological aspect of neuroimaging analysis in the oldest-old is the difficulty software programs have in appropriately processing these brain scans given the higher degree of atrophy and structural abnormalities such as WMH. This point is highlighted in a study that processed brains of participants from 71 to 103 years of age using FreeSurfer (*v5.3*), and found a high incidence of issues, including mislabeled subcortical WMH, classification of meningeal tissue as brain, and failed intensity normalization. All of these segmentation issues were especially prevalent in the oldest-old cohort, where even after manual adjustments, around 15% of the scans failed some form of quality control [28]. Additionally, the higher degree of atrophy in brains of the oldest-old means that warping the acquired images to commonly used standard spaces such as Montreal Neurological Institute (MNI) templates might not be appropriate as these are based on cognitively normal, younger adults. Developing oldest-old specific brain templates and neuroimaging pipelines should be considered a priority for the future research in this age group.

CONCLUSION

While the identified neuroimaging studies in the oldest-old have produced pertinent findings, there is a significant need for more studies specifically in nonagenarians and centenarians. Given their growing population and the valuable insights they can provide toward understanding the relationships between aging, dementia, and neurodegenerative pathologies, further neuroimaging research in the oldest-old is in dire need.

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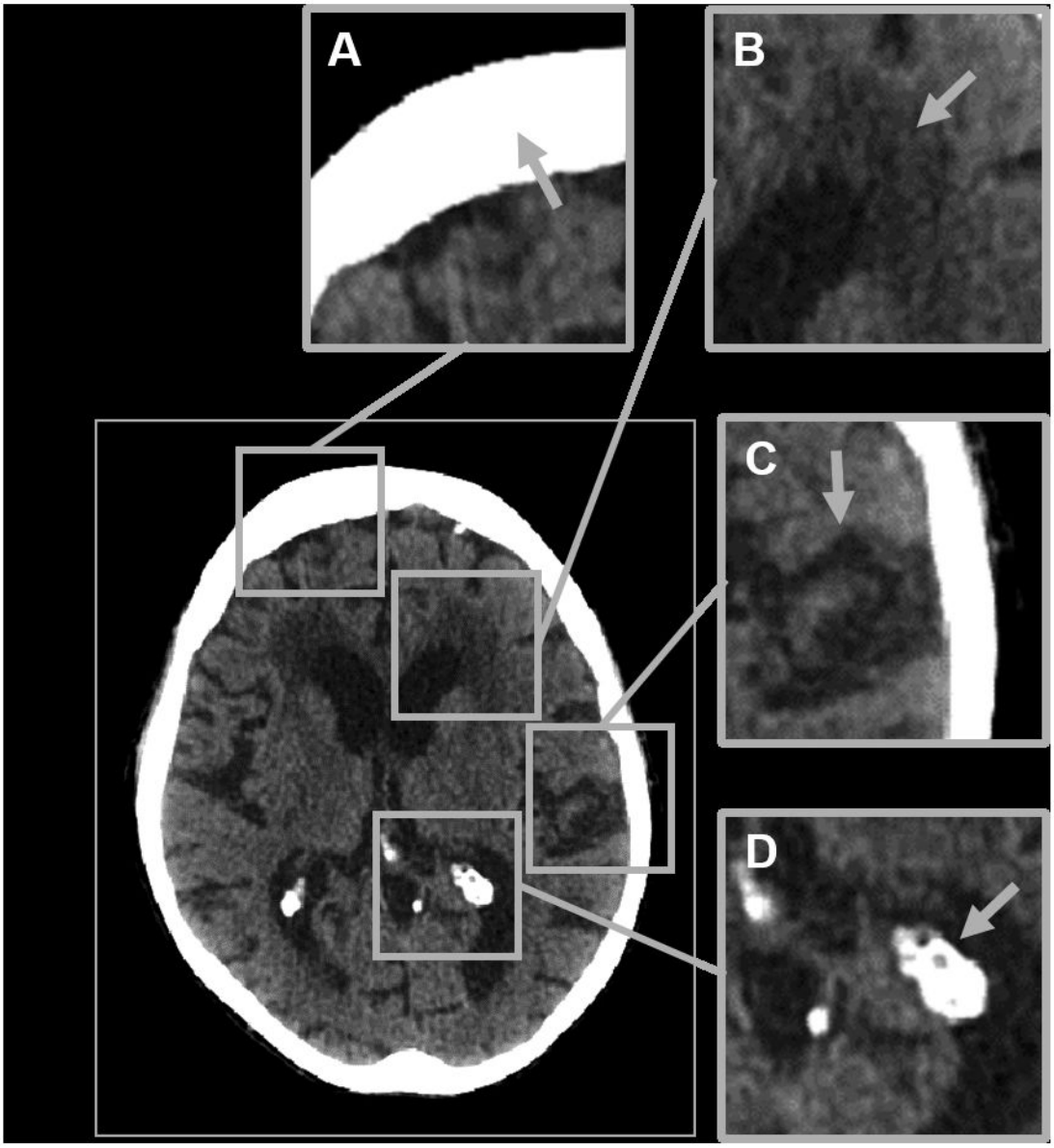

Fig. 1.

Example brain CT scan of a 96-year-old woman. A) CT possesses great ability to capture bony structures. B) CT is able to differentiate between soft tissues, such as between CSF and cerebral tissue, and white matter lesions (WML) appear hypointense on CT; however, distinction between gray and white matter is poor, and soft tissue contrast has a lower signal to noise ratio. C) Atrophy of the brain visualized by the CT scan. D) Calcification of the choroid plexus is highly conspicuous on CT images; similar calcifications are sometimes present in other structures such as the basal ganglia and may have physiological relevance.

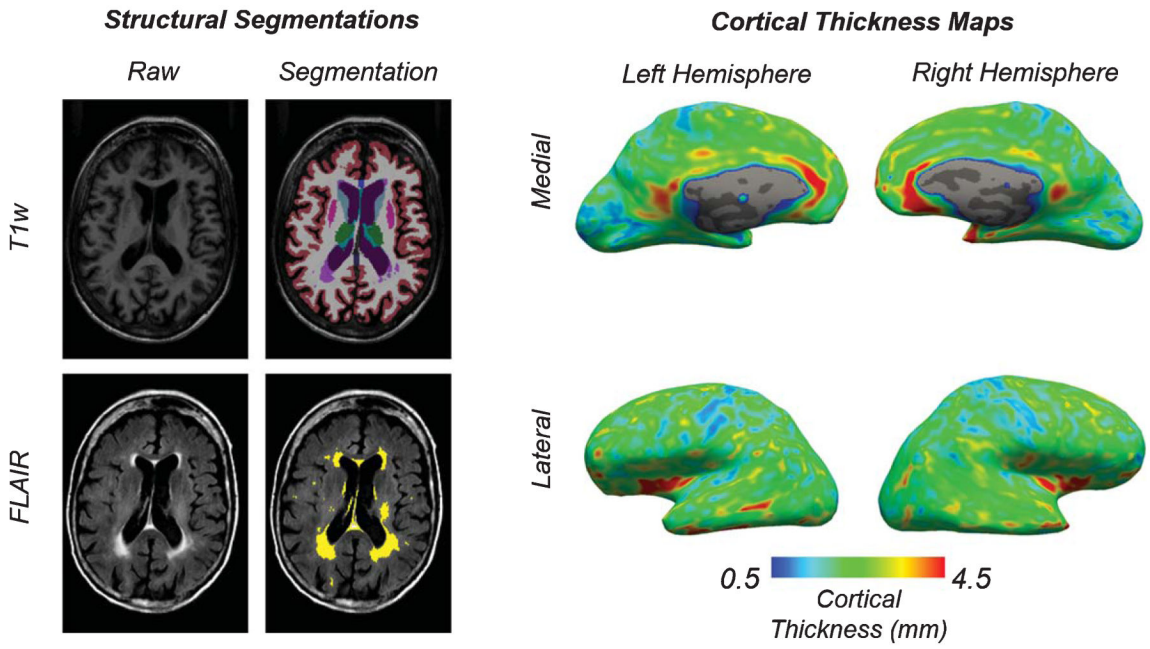

Fig. 2.

Examples of processing for structural MRI scans in a 96-year-old woman with mild age-related atrophy and white matter hyperintensities (WMH). Left image shows T1w image (top left) with segmentation (top right) performed by FreeSurfer (*v6.0*) and relevant regions such as gray matter (red), white matter (white), ventricles (dark purple), thalamus (green), caudate (light blue), and putamen (violet). Left image also shows FLAIR image (bottom left) and segmented WMH (bottom right). Right image shows cortical thickness processed from the T1w image by FreeSurfer and smoothed with a Gaussian filter at the level of 10mm full width at half maximum (FWHM).

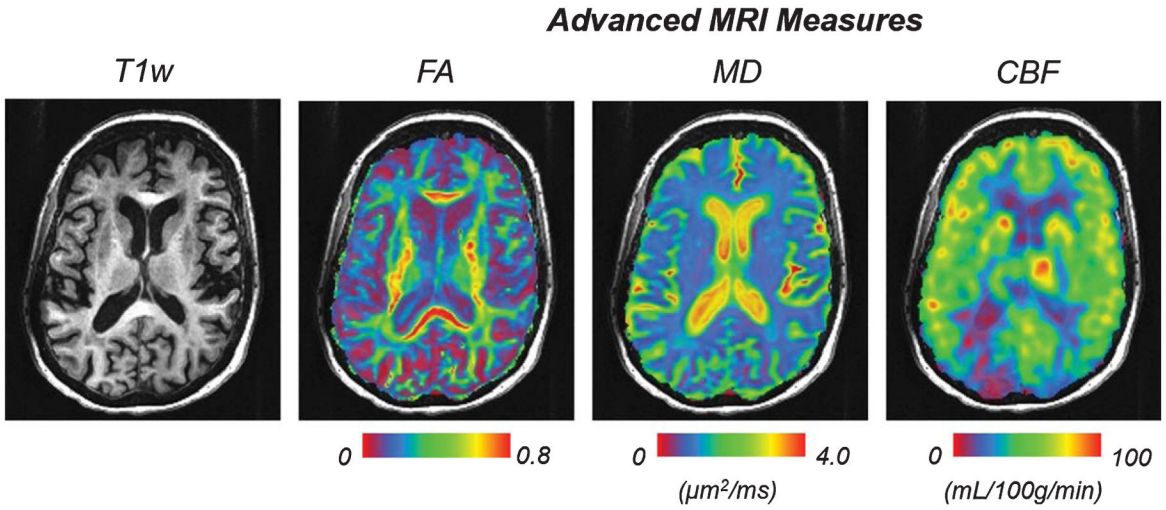

Fig. 3.

Examples of relevant measures derived from advanced MRI in a 96-year-old woman. Left to right: reference T1-weighted image (T1w), fractional anisotropy (FA) map derived from diffusion tensor imaging (DTI), mean diffusivity (MD) map derived from DTI, and cerebral blood flow (CBF) map derived from arterial spin labeling (ASL).

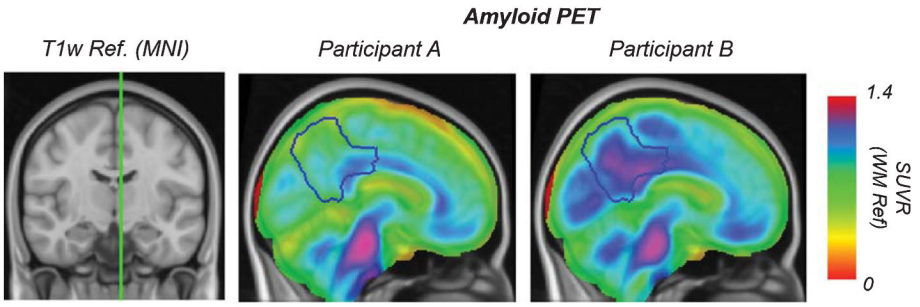

Fig. 4.

Example images of amyloid (florbetapir) PET scans for two oldest-old participants aligned to the Montreal Neurological Institute (MNI) T1w atlas. Participant A is a 98-year-old woman, and Participant B is a 96-year-old woman. From left to right: T1w reference coronal section of the MNI atlas with the green line indicating the sagittal slices used to display the amyloid PET scans, Participant A, and Participant B amyloid PET SUVr maps (normalized to cerebral white matter) overlayed on the MNI atlas with the precuneus and posterior cingulate (common regions of analysis for amyloid PET) denoted by the outline in blue. Participant A has a low SUVR of 0.65 (Aβ−) and Participant B had a high SUVr of 0.91 (A0+).

Table 1

Thematic summary of brain changes in the oldest old

Finding Summaries	Studies
Brain Atrophy	
• Variablility in brain atrophy is commonly found among the oldest-old with differing cognitive states [6, 7].	[6] Earnest et al. (1979): Cross-sectional study of 59 cognitively normal and impaired individuals, ≥ 60 years, CT scans and neuropsychology tests [7] Goldstein et al. (1985): Cross-sectional study of 10 cognitively normal centenarians, CT scans
• Healthy Aging ○ Among oldest-old participants without dementia, there was a constant decline in brain volume and thinning of the cortex [27, 29]. ○ Temporal lobe atrophy was associated with worse survival rates in the oldest-old along with greater prefrontal atrophy and decline of white matter in comparison to their healthy, young-old counterparts [14, 31]. Hippocampal volume declined at a constant rate over time in both young-old and the oldest-old [28].	[27] Mueller et al. (1998): Longitudinal study of 46 cognitively normal individuals, >65 years, MRI scans [29] McGinnis et al. (2011): Cross-sectional study of 316 cognitively normal individuals from the OASIS dataset, 18–96 years old, MRI scans [28] Yang et al. (2016): Cross-sectional study of 277 individuals without dementia from the Sydney Memory and Ageing Study and Sydney Centenarian Study,>70 years, MRI scans [14] Olesen et al. (2011): Longitudinal study of 239 cognitively normal and impaired individuals from the Longitudinal Gerontological and Geriatric Population Study, ≥ 85 years, CT scans [31] Salat et al. (1999): Cross-sectional study of 42 cognitively normal and impaired individuals from the Oregon Brain Aging Study, ≥ 60 years, MRI scans
• Cognitive Impairment ○ The pattern of atrophy was similar in cognitively impaired young-old and oldest-old participants in comparison to their healthy counterparts. There was a less pronounced effect of cortical thinning between the cognitively normal and cognitively impaired oldest-old due to similar age related atrophy, making the effects of AD related atrophy appear less severe [34]. The ratio between total brain volume to ventricular volume did not differ greatly between those with and without dementia among the oldest-old; however, there was a difference between volumes in the cognitively normal versus cognitively impaired young-old group [17]. ○ Cognitively impaired oldest-old experienced more atrophy in the corpus callosum, white matter and gray matter along with faster rates of brain atrophy in the temporal lobe [20, 30].Differences in hippocampal and temporal pole volumes distinguished individuals who had MCI versus no cognitive impairment [33]. Ventricular expansion was found to be predictive of cognitive impairment in the oldest-old [32]. Smaller hippocampal volume has been suggested to be a predictor of the incidence of dementia [58, 60]. ○ Lower hippocampal volumes were associated with a faster rate of decline in global cognition along with lower test scores in the following domains: global cognition, memory, processing speed, and executive functioning [35]. Smaller subiculum volumes were associated with lower memory scores on the ACE-III [36]. ○ Some common incidental findings found on the MRI scans of the oldest-old include ischemic changes, intracranial tumors, and intracranial aneurysms [19]. Individuals without dementia who experienced hallucinations or delusions were more often found to have calcification of the basal [13].	34] Stricker et al. (2011): Cross-sectional study of 230 cognitively normal and impaired individuals, ≥ 60 years, MRI scans and neuropsychology tests [17] Reischies et al. (2001): Cross-sectional study of 254 cognitively normal and impaired individuals from the BASE study, CT scans [20] Janowsky et al. (1996): Cross-sectional study of 119 cognitively normal and impaired individuals from the Oregon Brain Aging Study,>50 years, MRI scans [30] Kaye et al. (1997): Longitudinal study of 30 cognitively normal and preclinical AD individuals from the Oregon Brain Aging Study, ≥ 84 years, MRI scans [33] Yang et al. (2016): Cross-sectional study of 244 cognitively normal and impaired individuals from the Sydney Memory and Ageing Study and the Sydney Centenarian Study,>70 years, MRI scans [32] Carlson et al. (2008): Longitudinal study of 79 cognitively normal and impaired individuals from the Oregon Brain Aging Study, ≥ 64 years, MRI scans [58] Lopez et al. (2018): Longitudinal study of 183 individuals who were cognitively normal at baseline from the GEM study, ≥ 80 years, MRI and PET scans [60] Lopez et al. (2014): Longitudinal study of 183 cognitively normal and impaired individuals from the GEM Study, ≥ 82 years, neuropsychology tests, MRI and PET scans [35] Legdeur et al. (2019): Longitudinal study of 141 cognitively normal and impaired individuals from The 90 + Study, ≥ 90 years, MRI scans and neuropsychology tests [36] Eguchi et al. (2019): Cross-sectional study of 10 cognitively normal and impaired individuals from the Arakawa 95 + study, ≥ 95 years, MRI scans and ACE-II [19] Al-Holou et al. (2011): Cross-sectional study of 177 cognitively normal and impaired individuals, ≥ 90 years, MRI scans and medical records [13] Ostling et al. (2003): Cross-sectional study of 138 individuals without dementia from the Longitudinal Gerontological and Geriatric Population Study, 85 years, CT scans and psychological measures
• Functional ○ Systolic and diastolic blood pressure were correlated with atrophy in the frontal and parietal lobe [16]. Larger hippocampal volumes were associated with reports of higher socialization [39]. Gait was associated with smaller ventricles and periventricular WMH [37]. No associations between hippocampal volume and sleep quality or sleep quantity [43].	[16] Skoog et al. (1998): Cross-sectional study of 239 cognitively normal and impaired individuals from the Longitudinal Gerontological and Geriatric Population Study, 85 years, CT scans and blood pressure measurements [39] Bennett et al. (2006): Cross-sectional study of 106 individuals without dementia from The Sydney Older Person Study, ≥ 80 years, MRI scans and functional measures (interviews regarding daily living) [37] Camicioli et al. (1999): Cross-sectional study of 50 cognitively normal individuals from the Oregon Brain Aging Study, ≥ 64 years, MRI scans and clinical measures

Finding Summaries	Studies
Brain Atrophy	
	[43] Sabeti et al. (2018): Cross-sectional study of 144 cognitively normal and impaired individuals from The 90 + Study, ≥ 90 years, MRI scans, neuropsychology tests and Medical Outcome Study sleep questionnaire
• Pathology ○ Total brain and hippocampal volume was associated with status of dementia in participants with amyloid plaques and tau tangles [64]. ○ Neurofibrillary tanges were associated with total brain volume, rate of total brain atrophy, ventricular volume, rate of ventricular volume change [64, 65], and final hippocampal atrophy [63]. ○ Measures of ventricular atrophy were associated with neuritic plaques [65].	[64] Erten-Lyons et al. (2009): Longitudinal study of 36 cognitively normal and impaired individuals from the OSHU Layton Aging and AD Center, ≥ 75 years, MRI scans, postmortem measures and neuropsychology tests [63] Erten-Lyons et al. (2013): Longitudinal study of 71 cognitively normal and impaired individuals from the Oregon Brain Aging Study, ≥ 80 years, MRI scans and postmortem measures [65] Silbert et al. (2003): Longitudinal study of 39 cognitively normal and impaired individuals, ≥ 63 years, MRI scans and postmortem measures
White Matter Lesions/Hyperintensities	
• Healthy Aging ○ Generally, oldest-old participants were reported to have increased white matter disease [21, 22]. In one study, WMH were reported in all 114 participants [24]. WMH volumes demonstrate a trend to plateau, suggesting that accumulation may level-off with age [28]. ○ WML were associated with elevated Aβ levels detected in CSF in participants without dementia [15]. ○ WML were associated with a worse performance in the following neuropsychological tests: identical forms, coin test, Thurstone picture memory, clock test, and block design [11].	[21] Maniolo et al. (1994): Cross-sectional study of 303 cognitively normal participants from the Cardiovascular Health Study, ≥ 65 years, MRI scans [22] Heckbert et al. (1997): Cross-sectional study of 1,268 cognitively normal participants from the Cardiovascular Health Study, ≥ 65 years, MRI scans [24] Piguet et al. (2003): Cross-sectional study of 114 cognitively normal and impaired individuals from the Sydney Older Persons study, ≥ 80 years, MRI scans, clinical interviews, neuropsychology tests and apoE testing [28] Yang et al. (2016): Cross sectional study of 277 individuals without cognitive impairment from the Sydney Memory and Ageing & Sydney Centenarian study, ≥ 71 years, MRI scans [15] Skoog et al. (2018): Cross sectional study of 53 cognitively normal and impaired individuals from the Longitudinal Gerontological and Geriatric Population Study, 85 years, CT scans and CSF
• Cognitive Impairment ○ Incidence of dementia was related to having a combination of two out of three biomarkers: WMH burden, Aβ burden, and hippocampal atrophy [58, 60]. The presence of WML and having the *APOE ε*4 gene led to a higher risk of dementia [12]. ○ WML were associated with a worse performance on the following neuropsychological tests in cognitive impaired participants: block design, MIR memory test, and MMSE [11]. ○ Higher WMH volumes were associated with worse baseline scores and faster decline in 3MS and MMSE [35].	[11] Skoog et al. (1996): Cross sectional study of 232 cognitively normal and impaired individuals from the Longitudinal Gerontological and Geriatric Population Study, 85 years, CT scans and neuropsychology tests [58] Lopez et al. (2018): Longitudinal study of 183 individuals who were cognitively normal at baseline from the GEM study, ≥ 80 years, MRI and PET scans [60] Lopez et al. (2014): Longitudinal study of 183 cognitively normal and impaired individuals from the GEM Study, ≥ 82 years, neuropsychology tests, MRI and PET scans [12] Skoog et al. (1998): Cross-sectional study of 239 cognitively normal and impaired individuals from the Longitudinal Gerontological and Geriatric Population Study, 85 years, CT scans and *APOE ε*4
• Functional ○ Increased amounts of WMH was associated with decline in gait speed, increasing number of steps, and ventricular CSF volume [38]. A larger increase of WMH burden was associated with increased small and large arterial elasticity as well as high variation in self-reported systolic blood pressure [25, 26]. Cognitively normal oldest-old participants who had increased diastolic blood pressure during the nighttime had a greater average of WMH [44]. WMH burden was found to be associated with central arterial stiffness [62].	[11] Skoog et al. (1996): Cross sectional study of 232 cognitively normal and impaired individuals from the Longitudinal Gerontological and Geriatric Population Study, 85 years, CT scans and neuropsychology tests [35] Legdeur et al. (2019): Longitudinal study of 141 cognitively normal and impaired individuals from The 90+ Study, ≥ 90 years, MRI scans and neuropsychology tests [38] Silbert et al. (2008): Longitudinal study of 104 cognitively normal individuals from the Oregon Brain Aging study, ≥ 65 years, MRI scans, neuropsychology tests, and neurological assessments [25] Duprez et al. (2001): Cross-sectional study of 24 healthy individuals, ≥ 73 years, MRI scans and blood pressure measurements [26] Liu et al. (2016): Longitudinal study of 232 cognitively normal and impaired individuals, ≥ 80 years, MRI scans and blood pressure measurements
• Multimodal Imaging Associations ○ Utilizing ASL, the CBF surrounding WMH was found to predict areas that were susceptible to developing new WMH [50]. ASL was also found to be more informative in detecting areas susceptible to loss of white matter integrity in comparison to clinical MRIs [51]. Both T2 and FLAIR imaging appear to be well suited for detection of WMH in ildest-old [52].	[44] Paganini-Hill et al. (2019): Cross-sectional study of 121 cognitively normal and impaired individuals from The 90 + Study, ≥ 90 years, MRI scans, blood pressure tests, and neuropsychology assessments [62] Hughes et al. (2013): Cross-sectional study of 91 individuals without dementia from the GEM Study, ≥ 83 years, blood pressure tests, MRI and PET scans [50] Promjunyakul et al. (2015): Longitudinal study of 61 cognitively normal individuals from the Layton Aging and ADC, ≥ 65 years, MRI scans and blood pressure measurements [51] Promjunyakul et al. (2016): Cross-sectional study of 82 cognitively normal individuals from the Layton Aging and ADC, ≥ 66 years, MRI scans

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Finding Summaries	Studies
Brain Atrophy	
	[52] Piguet et al. (2005): Cross-sectional study of 111 cognitively normal and impaired individuals from the Sydney Older Persons study, ≥ 80 years, MRI scans
Infarcts	
• Cognitive Impairment ○ Infarcts more prevalent in oldest-old participants [23]. Higher incidences of infarcts were found in participants with dementia [8, 9].	[23] Sato et al. (1999): Cross-sectional study of 3,371 cognitively normal participants from the Cardiovascular Health Study, ≥ 65 years, MRI scans [8] Skoog et al. (1993): Longitudinal study of 239 individuals with dementia from the Longitudinal Gerontological and Geriatric Population Study, 85 years, CT scans, neuropsychological tests, and medical examinations
• Multimodal Imaging Associations ○ WML were more common in those who had infarcts, both of which contribute to the incidence of dementia [9, 10]. Infarcts were found to be associated with ventricular expansion [8, 9]	[9] Liebetrau et al. (2004): Cross-sectional study of 239 individuals with dementia from the Longitudinal Gerontological and Geriatric Population Study, 85 years, CT scans [10] Skoog et al. (1994): Cross-sectional study of 239 cognitively normal and impaired individuals from the Longitudinal Gerontological and Geriatric Population Study, 85 years, CT scans, neuropsychology tests, and medical examination
Diffusion Changes	
• Healthy Aging ○ FA values decreased with age, but were not different between cognitively normal and impaired oldest-old participants [45, 47].	[45] Bennett et al. (2017): Cross-sectional study of 94 individuals without dementia from The 90 + study, ≥ 90 years, MRI scans [47] Tian et al. (2015): Cross sectional study of 90 cognitively normal and impaired individuals from the Health, Aging and Body Composition study, ≥ 80 years, MRI scans and records of physical activity
• Function ○ Exercise was associated with higher FA values within the white matter [47]. Decrease in perceptual speed was associated with decreases in the white matter integrity of the corticospinal tract [46]	[46] Lovden et al. (2014): Longitudinal study of 70 individuals without dementia, from the Swedish National study on Aging and Care in Kungsholmen, ≥ 80 years, MRI scans and neuropsychology tests
Functional Activation Changes	
• Healthy Aging ○ No differences were found between cognitively normal young-old and oldest-old in regional activation during a memory retrieval fMRI task [48]. ○ Activation during a hippocampal recognition memory task was well preserved amongst oldest-old participants in comparison to the young-old [49].	[48] Wang et al. (2009): Cross-sectional study of 36 individuals without dementia, ≥ 64 years, fMRI scans with a retrieval related memory task [49] Beeri et al. (2011): Cross-sectional study of 29 cognitively normal individuals, ≥ 70 years, fMRI scans with non-verbal memory task and neuropsychology tests
Amyloid PET Changes	
• Cognitive Impairment ○ Amyloid burden is a predictor of dementia in the oldest-old [58, 60]. Being amyloid positive (by standard thresholds) does not always equate to an impaired cognitive state as 55% of participants were PiB positive and cognitively normal. 85% cognitively normal participants with the *APOE ε*4 allele were PiB positive [56]. Amongst participants without dementia, those with amyloid showed faster cognitive decline than those without amyloid [54, 57, 59]. ○ Individuals with Aβ burden at their baseline visit had higher arterial stiffness (brachial-ankle, mixed) [61]. Central arterial stiffness was associated with the accumulation of Aβ [62].	[58] Lopez et al. (2018): Longitudinal study of 183 individuals who were cognitively normal at baseline from the GEM study, ≥ 80 years, MRI and PET scans [60] Lopez et al. (2014): Longitudinal study of 183 cognitively normal and impaired individuals from the GEM Study, ≥ 82 years, neuropsychology tests, MRI and PET scans [56] Mathis et al. (2013): Cross-sectional study of 190 individuals without dementia from the GEM study, ≥ 82 years, neuropsychology tests, MRI and PET scans [54] Kawas et al. (2013): Cross-sectional and longitudinal study of 13 individuals without dementia from The 90 + study, ≥ 90 years, PET scans and neuropsychology tests [57] Snitz et al. (2013): Cross-sectional and longitudinal study of 194 individuals without dementia from the GEMS study, ≥ 82 years, PET scans and neuropsychology tests [59] Zhao et al. (2018): Longitudinal study of 175 individuals without dementia from the GEMS study, ≥ 82 years, neuropsychology tests, MRI and PET scans
• Multimodal Imaging Associations ○ Atrophy in the frontal, temporal, and parietal lobes was associated with decreased Aβ levels in the CSF of individuals with dementia [15]. ○ Increased amyloid burden was associated with decreased brain volume [55].	[61] Hughes et al. (2013): Cross-sectional study of 91 individuals without dementia from the GEM Study, ≥ 83 years, blood pressure tests, MRI and PET scans [62] Hughes et al. (2014): Longitudinal study of 81 individuals without dementia from the GEMS study, ≥ 83 years, test for arterial stiffness, MRI and PET scans

Finding Summaries	Studies
	Brain Atrophy
	[15] Skoog et al. (2018): Cross sectional study of 53 cognitively normal and impaired individuals from the Longitudinal Gerontological and Geriatric Population Study, 85 years, CT scans and CSF [55] van Bergen et al. (2018): Cross-sectional study of 80 cognitively normal individuals, ≥ 55 years, PET and MRI scans
	Miscellaneous
• Multiple studies have looked into different associations between the oldest-old and various risk factors including associations between alcohol consumption and smaller cerebellar size [40], variable brain volumes and nutrient biomarkers [41], and higher daily computer use and larger hippocampi [42]. • Increased ratio of N-acetylaspartate (NAA) to myo-inositol (mI) which was associated with smaller hippocampal volumes [53].	[40] Piguet et al. (2006): Cross-sectional study of 111 cognitively normal individuals from the Sydney Older Persons study, ≥ 81 years, MRI scans, questionnaires about alcohol consumption, medical and neurological history [41] Bowman et al. (2012): Cross-sectional study of 104 cognitively normal individuals from the Oregon Brain Aging Study, ≥ 85 years, MRI scans, neuropsychology tests, and nutrient biomarkers [42] Silbert et al. (2016): Cross-sectional study of 34 cognitively normal individuals from the Intelligent Systems of Assessing Aging Change study, ≥ 65 years, MRI scans and assessment of average computer use [53] Spencer et al. (2003): Cross-sectional study of 60 cognitively normal individuals, ≥ 85 years, MRI scans, MRS brain metabolite ration, and neuropsychology tests