Impact of Dementia Severity on the Volume of the Limbic System-Related Brain Components in Women with Alzheimer's Disease

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Alzheimer's Disease (AD) is a progressive, neurodegenerative disorder where two-thirds of the affected population are women. Along with cognitive impairments, AD is associated with behavioral changes such as aggression towards caretakers. The limbic system consists of various brain structures that play a role in emotions and behavioral reactions. Some of the limbic system-related areas are the amygdala, hippocampus, thalamus, corpus collosum (CC), and white matter (WM). Cognitive changes with AD can be measured using the clinical dementia rating (CDR) scale. Physical changes in living patients require brain imaging tools, such as Magnetic Resonance Imaging (MRI). As there is currently sparse research present for these areas relating to the female brain, we used clinical data and FreeSurfer-processed imaging data from an open-access database, OASIS-3, to explore the associations between dementia severity and the volume of the limbic system-related brain components in women. A control group consisted of participants with no dementia and multiple brain scans while comparison groups consisted of participants with a single brain scan and 1) no dementia 2) mild dementia or 3) moderate/severe dementia. Hemisphere differences with increasing CDR were found for the thalamus as well as simple hemisphere differences for the hippocampus, thalamus, and WM. When using age-matched controls and normalized volume data, the amygdala, hippocampus, thalamus, and CC volumes for subjects with AD were different than those in the control group, with the amygdala and hippocampus also showing statistically significant volume loss with increasing dementia severity. As the areas included in this study are related to the limbic system, this provides insight into the physical changes occurring in the brain of women with increasing AD, who often show changes in emotions. This can be an area to longitudinally explore whether there are associated behavioral changes as physical changes at the individual level occur over time.

Abbreviations: AD – Alzheimer's Disease; CC – Corpus Collosum; CDR – Clinical Dementia Ratings; MRI – Magnetic Resonance Imaging; NFT– Neurofibrillary Tangles; WM – White Matter

Keywords: Magnetic Resonance Imaging; FreeSurfer; Sex Differences; Amygdala; Hippocampus; Thalamus

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Introduction

Alzheimer's Disease (AD), one of the leading causes of dementia, is a progressive neurodegenerative disorder (James and Bennett, 2019). AD often occurs in older people, yet it is not accepted as a normal part of aging (Irwin et al., 2018). Manifesting with cognitive impairment and personality changes, AD results in the inability to carry out the activities of daily living (Ballard et al., 2011). This disease is characterized by the presence of neritic plaques and neurofibrillary tangles (NFT) in the brain (James and Bennett, 2019). Neritic plaques in AD disrupt cell function as the beta-amyloid protein clumps between neurons to form plaques

(National Institute on Aging, n.d.). NFTs are the collection of the tau protein inside neurons which disrupt the synaptic communication between neurons. Along with these pathological changes, cognitive impairment must be present for the diagnosis of AD.

Dementia can be measured using the clinical dementia rating (CDR) scale. This is a global scale that was initially developed to be used in individuals with the AD subset of dementia (Fagundes Chaves et al., 2007). The CDR score is measured using semi-structured patient and informant interviews that assess memory, orientation, judgment, community affairs, hobbies, and personal care. The global CDR rating consists of a 5-point scale: CDR=0 (no dementia), CDR=0.5 (questionable dementia), CDR=1 (mild dementia), CDR=2 (moderate dementia), and CDR=3 (severe dementia). CDR scores have previously been correlated with physical changes in the brain, such as volume losses varying at different scores, in the amygdala, hippocampus, and thalamus (Roh et al., 2011).

Currently, the only conclusive way to diagnose AD consists of a brain autopsy. However, neuroimaging can provide insight into changes in a suspected AD brain. Neuroimaging has been used in many AD studies as it can analyze white and grey matter volumes and the presence of beta-amyloid plaques (Zhang et al., 2012). Imaging is a particularly important tool for human studies as *in-vivo* studies can be monitored. Magnetic Resonance Imaging (MRI) provides high-resolution images of the brain tissue and has been utilized in many AD studies, due to the resolution providing information about individual brain areas.

AD can also be diagnosed by the symptoms that accompany it. Commonly, memory impairments are associated with AD. However, issues in judgment, decision making, and behavioral changes can also be characteristics of AD (Centers for Disease Control and Prevention, 2020). The Alzheimer's Association notes personality changes with dementia as a large concern for caregivers and families (Alzheimer's Association, n.d.). Some of these changes include delusions, social withdrawal, paranoia, apathy, and insensitivity to others. Additionally, aggression and agitation are often accompanied with these changes. This can lead to caregivers experiencing anxiety and stress when confronted with these symptoms. Therefore, it is important to provide evidence for why these symptoms may arise, such as changes in the brain areas in AD patients compared to their counterparts.

The limbic system, which has frequently been implicated in mood disorders, consists of various brain structures that play a role in emotion and emotional expression (Price and Drevets, 2010). While this system is not universally defined, some of the common structures include the amygdala, hippocampus, thalamus, corpus collosum (CC), and white matter. The impact and importance of a normally functioning limbic system has been shown in both animal studies (Nováková et al., 1974) and human studies (Stone et al., 2002).

The amygdala is known to regulate emotions such as fear, but it also plays a role in the emotional response to smells and food choice and intake (RajMohan and Mohandas, 2007). Localized damage to the amygdala has been associated with a peaceful state, with further destruction to the ventromedian nucleus resulting in the conversion of this state to rage. The amygdala also plays a significant role in emotional memory and social interactions.

The hippocampus is a key brain region involved in long-term episodic memory as well as spatial navigation, future-thinking, and imagination (Maguire and Mullally, 2013). Hippocampal atrophy is commonly present in patients with cognitive impairment and may be used as a potential predictor of dementia (Chetelat and Baron, 2003). In a study comparing cognitively normal subjects and those with mild cognitive impairment or probable AD, it was found that hippocampal volume loss was highest in those with probable AD (Jack et al., 2000). In individuals with mild cognitive impairment, hippocampal volume reduction ranges from 10% to 15%, while early AD patients may exhibit a 15% to 30% reduction in hippocampal volume, increasing to 50% in moderate cases (Laakso et al., 1995).

AD presents with asymmetry in the hemispheres of the brain and the hippocampus has been found to show asymmetric volume loss with severity of diagnosis (Sarica et al., 2018).

The thalamus, an area consisting largely of gray matter, is the relay station between the brain and body. Thalamus atrophy has previously been associated with cognitive decline, such as in Huntington's disease and multiple sclerosis (de Jong et al., 2008). Comparing normal-aging and possible AD subjects, significant reduction in the thalamus of probable AD subjects was found and, upon cognitive testing, the investigators also found a correlation between the reduction in thalamus and cognitive testing scores for probable AD participants. Using functional MRI (fMRI), this study also found reduced functional connectivity relating to the thalamus in individuals with AD compared to mildly cognitively impaired or cognitively normal individuals.

The CC is a large fiber bundle of white matter (WM) that connects the two hemispheres in the brain. The posterior CC is involved in visual processing while the anterior CC is related to executive function, working memory, and psychomotor speed (Das et al., 2021). A study assessed CC atrophy in groups with very mild (CDR=0.5) and mild (CDR=1) dementia, compared to a control (CDR=0) group (Zhu et al., 2012). Zhu et al. detected atrophy in the very mild group and concluded that this could indicate an anterior-to-posterior-atrophic process.

WM makes up about half of the human brain. It is present under the gray matter cortex and is primarily composed of axons. WM has been correlated to learning complex skills for which WM plasticity is implied to be responsible. Previously, it was found that WM volume did not decrease significantly when comparing normally aging individuals to those with AD (Double et al., 1996). However, a meta-analysis of voxel-based morphometry studies identified that WM atrophy is present in individuals with AD. The structures affected were close to the hippocampus and amygdala (Li et al., 2012).

While normal aging shares some pathological features with AD, including NFTs and senile plaques (SP), the incidence and severity of these pathological changes are considerably lower in normal aging without any associated cognitive decline (Hof et al., 1996). NFT formation is predominantly found in the entorhinal cortex of the hippocampal formation in normal aging, while SP formation occurs in the neocortex. Neuronal loss and synaptic changes in the neocortex are also characteristic features of normal aging, with the inferior temporal cortex showing the most significant changes. Another study on cerebral atrophy related to aging has identified the temporal lobe as the region with the strongest association with age, with lower atrophy in late life compared to mid-life observed in the frontal and cingulate areas (Koenig et al., 2022).

Structurally, the male brain has more volume with more WM than the female brain, which has more grey matter (Andrew and Tierney, 2018). This may allow the male brain to show more resilience to neuronal losses. Women's hippocampus, a brain area involved in memory, is more vulnerable to decline. Genetics plays a role as recent developments have shown that an APOE gene variant, an AD risk factor, leaves women more vulnerable to developing AD relative to men. Men and women with AD experience different cognitive and psychiatric symptoms, with women exhibiting rapid cognitive decline after diagnosis of AD (Ferretti et al., 2018). Women with mild cognitive impairment also show faster brain atrophy compared to men.

While the discussed studies focus on individual structural differences in the brain, for patients with and without AD, sex differences are also present and women constitute two-thirds of the AD population (Andrew and Tierney, 2018). Andrew and Tierney reviewed the many factors that may be behind this difference including the endocrine system, brain structure, and genetics. Importantly, menopause may play a role in this disease as the relative concentrations of different estrogen types begin to alter it. Specifically, there is a change from the stronger form of estrogen, 17β-estradiol, to the weaker estrogen, estrone, in menopausal women. Estrogen offers neuroprotection by aiding the growth of cholinergic neurons and metabolizing amyloid and, specifically, 17β-estradiol is reported to support cognition. This change in estrogen levels in women is rapid relative to the change in testosterone levels in men as older men have been observed to have higher concentrations of estrogen compared to post-menopausal women.

To further explore the symptoms of AD in the female brain, the present study aims to

investigate the deviations from normal aging in atrophy of areas associated with the limbic system in AD, and its relationship with increasing dementia severity. This will be done by comparing volumes of the amygdala, hippocampus, thalamus, CC, and WM in cognitively normal women and those diagnosed with AD. The severity of the dementia will be accounted for by using the CDR scores. Furthermore, this study will explore hemispheric differences in each area.

Material and Methods

Data Collection

Data for this project was accessed in June of 2022 from the Open Access Series of Imaging Studies (OASIS, https://www.oasis-brains.org). In particular, OASIS-3 was utilized. OASIS-3 is multimodal and provides evidence of normal aging and cognitive decline longitudinally (LaMontagne et al., 2019). As of 2019, this dataset consisted of 1098 participants, 42 to 95 years old, over 30 years with 609 cognitively normal participants and 489 in cognitive decline. 1500 raw imaging scans and over 2000 MRI sessions processed by FreeSurfer are available which allows for the opportunity to do a detailed analysis. These images were processed by the Freesurfer image analysis suite by "cortical reconstruction and volumetric segmentation of T-1 weighted images" (LaMontagne et al., 2019, p. 11). This consisted of motion correction and averaging of the T-1 weighted images, non-brain tissue removal, Talairach transformation, and white and grey matter intensity normalization. Additionally, new data is added regularly to this set.

Selected Data

This study focused on female participants to avoid sex-differences and only right-handed participants were selected to avoid brain lateralization effects between right- and left-handed individuals. The control group (CDR = 0) included data from 2 MRI sessions, at least 1800 days apart with the CDR remaining zero at both instances and consisted of n = 118 participants. This group was used as a control non-AD group in assessing linear versus non-linear changes in the brain area size with age and for determining a baseline curve for age-related effects of AD on brain area size. The three comparison groups included data from one MRI session and consisted of: 1) CDR=0 (no dementia), 136 participants, ages 43 to 98; 2) CDR=1 (mild dementia), 41 participants, ages 50 to 90; 3) CDR=2 or 3 (moderate to severe dementia), 42 participants, ages 50 to 89. The included participants with a CDR score of 1 or higher were diagnosed with AD, according to the OASIS dataset.

Measurements

The OASIS-3 dataset included Freesurfer-processed data. This program measures each brain area segmentation and stores the volumes. As there was data present for both hemispheres for different areas and many segmentations of the CC, these were combined to create a single area to use in the analysis. The following areas were used: amygdala (right, left, total), hippocampus (right, left, total), thalamus (right, left, total), CC (posterior, mid-posterior, central, mid-anterior, anterior, total), and WM (right, left, total; see Figure 1 for relative locations and Figure 2 for analysis).

MATLAB, a matrix-based computing platform, was used to obtain the "residual calculations" (https://www.mathworks.com/products/matlab.html). These are values that show the difference in brain area at a single age for each subject relative to the control curve. This was done by normalizing the control group's data for each segmentation, and then creating a curve using MATLAB's "smoothing spline" fit and criteria to obtain the critical age for nonlinear curves (Nichols, 2020). The data from the three CDR comparison groups was plotted onto the graph (see Figure 3) and deviations from the control curve were measured to analyze differences from normal aging (see Figure 4).

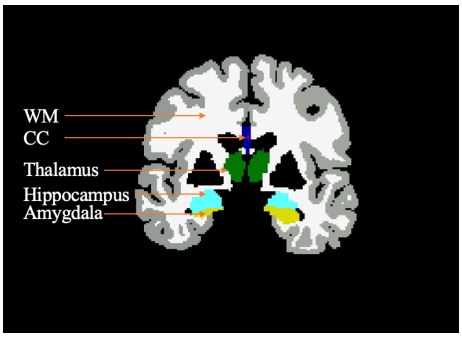

Figure 1: The locations of limbic system-related areas included in the study. This image is a screenshot from the Bert training data using FreeView.

Results

Left-Right Differences

A two-way repeated measures ANOVA was performed to analyze the effect of CDRs and hemispheres on the mean volume for brain areas (Figure 2). A statistically significant interaction between the effects of CDR and hemispheres was found only for the thalamus; F (2, 191) =6.877, p=0.001. For the left thalamus, there was an 8.13% decrease from the CDR=0 to CDR=1 group, and a 2.02% decrease from the CDR=1 to the CDR=2+ group. The right thalamus volume decreased 5.06% between the CDR=0 to CDR=1 group and 0.10% between the CDR=1 to the CDR=2+ group.

Simple main effects analysis for hemispheres showed that there was a statistically significant effect of left-right differences for the hippocampus (F (1, 191) =33.650, p<0.001), thalamus (F (1, 191) =113.074, p<0.001), and WM (F (1, 191) =5.118, p=0.025). For the hippocampus, the right hemisphere was found to be 4.75% larger than the left hemisphere, when averaging across the three CDR groups. The left thalamus was 8.54% larger than the right thalamus. The right WM was 3.41% larger than the left WM.

Main effect analysis for CDR showed statistically significant differences for the volumes of the amygdala (F (2, 191) =72.552, p<0.001), hippocampus (F (2, 191) = 92.374, p < 0.001), and thalamus (F (2, 191) =11.907, p<0.001). Compared to the CDR=0 group, there was a 21.94% decrease in combined amygdala volume in the CDR=1 group (p<0.001) and a 28.70% decrease between the CDR=0 and CDR=2 groups (p<0.001). There was also an 8.65% decrease between the CDR=1 and CDR=2 groups (p=0.041). The CDR=1 group for the hippocampus was 21.99% smaller than the CDR=0 group (p<0.001) and the CDR=2+ group was 26.89% smaller than CDR=0 group p<0.001). The thalamus had a 2.56% decrease in the CDR=1 (p<0.001) and an 8.09% decrease in the CDR=2+ (p<0.001) groups compared to the CDR = 0 group.

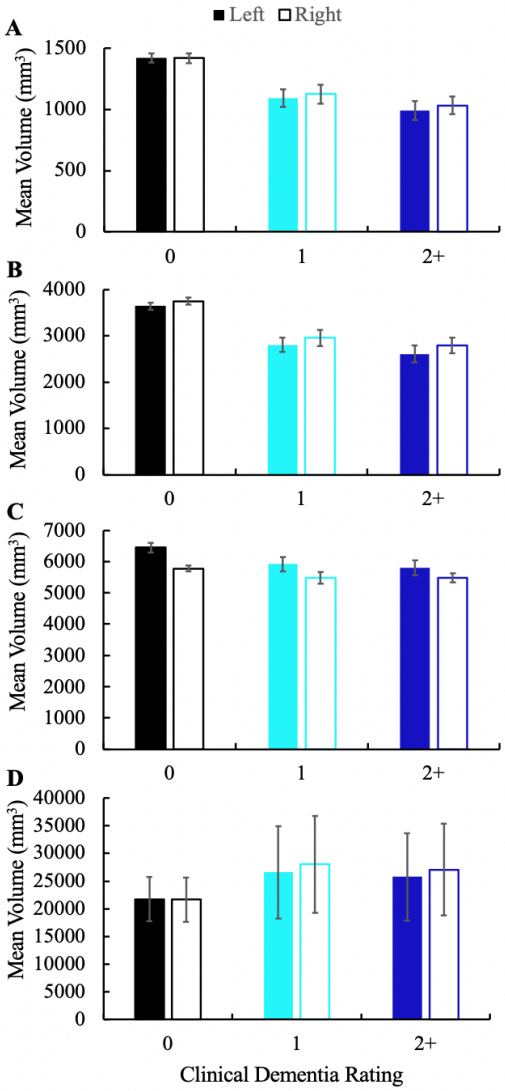

Figure 2: Hemisphere differences in total volume as a function of CDR group in the (A) Amygdala (B) Hippocampus (C) Thalamus and (D) WM. Error bars are for 95 % confidence intervals.

Curves

The control group produced age-related graphs that can be characterized into 2 types: linear decreasing and non-linear decreasing (Figure 3). These nonlinear characterizations provided information on where the critical age may be, reflecting the transition between two rates of change, as well as the rates of change for ages less than and greater than the critical age (Nichols, 2020). Overall, these show the trend in how a brain segmentation area changes over time in normal aging.

The amygdala, hippocampus, and CC show non-linear decreasing effects with age (Figure 3A, B, and D). For the control group, the mean age is 64.13 with a standard deviation of 9.61. The critical age for all nonlinear curves was 68, with rates of change above and below determined at a point roughly two standard deviations away. For the amygdala, Δvol/year (~50 years) =-7.22 and Δvol/year (~85 years) =-22.46. For the hippocampus, Δvol/year (~50 years) =-16.52 and Δvol/year (~85 years) =-82.62. For the CC, Δvol/year (~50 years) =-8.52 and Δvol/year (~85 years) =-34.99. The thalamus and WM show linear decreasing effects with age, which means there is not a critical age identified (Figure 3C and E). For the thalamus, the Δvol/year=-45.96. For WM, the Δvol/year=-2416.5.

Residuals

The residuals are a measure for assessing the differences in volume between the control group and CDR groups. As all normal aging curves showed volume decreasing with age, the residual is reported as positive if below the curve and the residual is reported as negative if above the curve (Figure 4). To assess the differences in the residuals of each brain area with respect to CDR, three groups with different CDRs were compared, using a one-way between-subjects ANOVA. Significant effects between the three

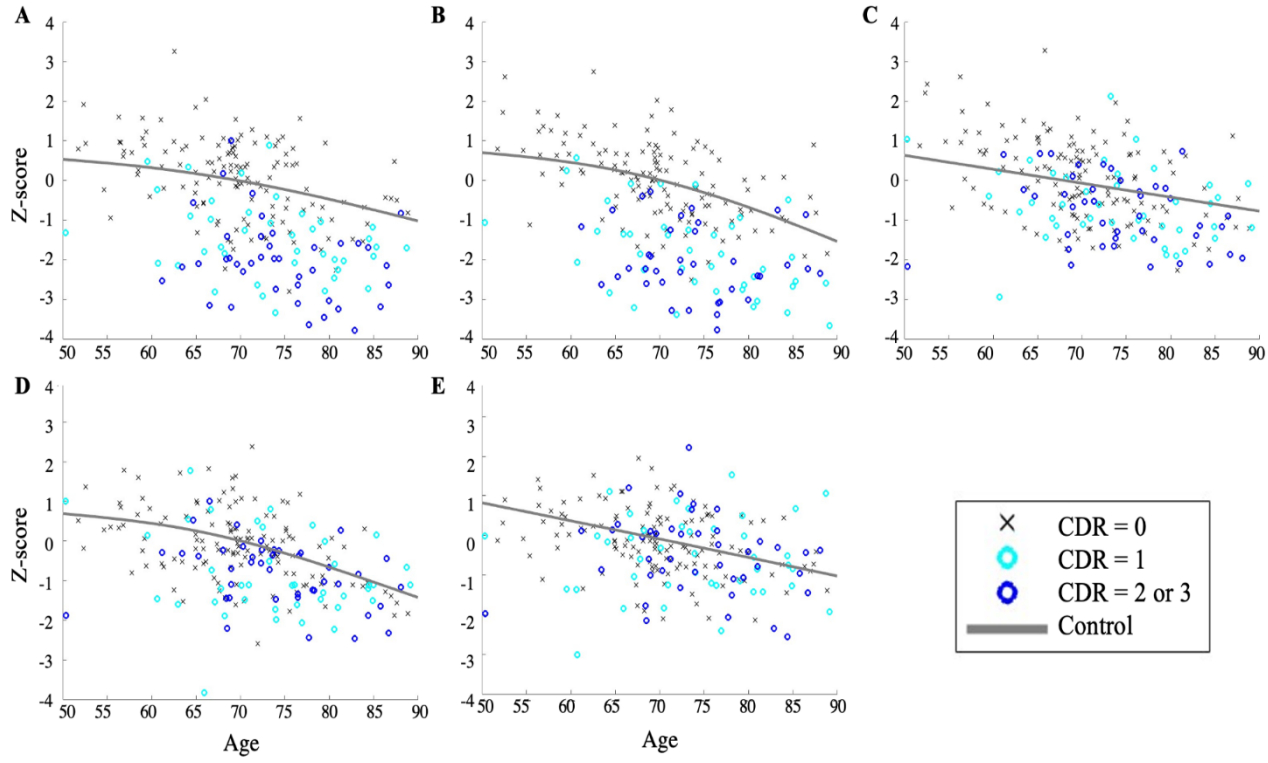

Figure 3: Normalized volume data for individual subjects plotted against a baseline curve fit to the control data. Residual values are the distance between an observed score and the control curve. Brain areas include: (A) Amygdala (B) Hippocampus (C) Thalamus (D) CC and (E) WM. Additional data exists for some areas outside the age range shown here, which is shared across areas.

CDR groups were found in the amygdala ($F(2, 216) = 84.762$, $p<0.001$), hippocampus ($F(2, 216) = 101.274$, $p<0.001$), thalamus ($F(2, 216) = 0.977$, $p<0.001$) and CC ($F(2, 216) = 9.395$, $p<0.001$). There were no significant effects seen between the three CDR groups for WM ($F(2, 216) = 0.977$, $p=0.378$).

To determine which CDR groups were different, a Tukey post-hoc test was used. The amygdalar volume was, on average, 1.35 standard deviations (540 mm^3) lower in the mild dementia group (CDR=1) compared to the control group ($p<0.001$) and 1.93 standard deviations (774.3 mm^3) lower in the moderate/severe dementia group (CDR=2+) compared to the control group ($p<0.001$). The hippocampal volume was 1.52 standard deviations (1396 mm^3) lower in the mild dementia group ($p<0.001$) and 2.03 (1864 mm^3) lower in the moderate/severe dementia group ($p<0.001$) compared to the control group. The volume of the thalamus decreased by 0.42 standard deviations (550 mm^3) in the mild dementia group ($p=0.002$) and by 0.58 standard deviations (766 mm^3) in the moderate/severe dementia group ($p<0.001$). Compared to the control group, the mild dementia group's CC volume decreased by 0.68 standard deviations (305 mm^3, $p<0.001$) and by 0.52 standard deviations (234 mm^3) in the moderate/severe dementia group ($p=0.012$).

Discussion

Many areas of the brain atrophy as one ages. Some areas are affected more than others, and this is part of normal aging. Having AD can exacerbate the atrophy seen in different brain areas. Due to the characteristic behavioral and mood changes in individuals with AD, areas associated with the limbic system were explored in this study. This was carried out by comparing the physical size of the amygdala, hippocampus, thalamus, CC, and WM in women with AD and their cognitively normal age-matched counterparts. To compare the role of dementia severity on the size of these areas, the CDR scores were utilized.

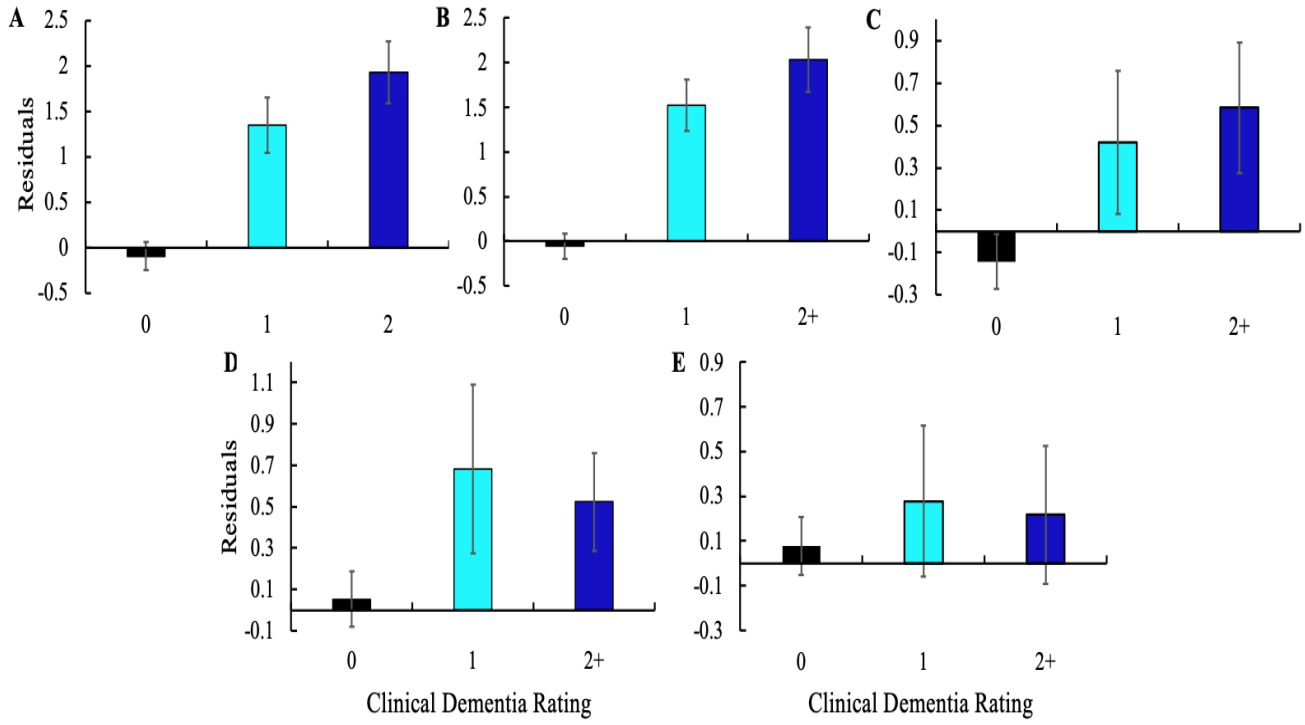

Figure 4: Deviations from the control group for different clinical dementia rating groups. Brain areas include: (A) Amygdala (B) Hippocampus (C) Thalamus (D) CC and (E) WM. Error bars are for 95 % confidence intervals.

For the thalamus, results showed hemisphere differences with increasing CDR. When comparing mild dementia to the control group, the volume of the left and right thalamus decreased differently, with the left thalamus volume starting larger and declining more.

Hemisphere differences were seen in the hippocampus, thalamus, and WM. The right hippocampus and WM were overall larger compared to the left while the left thalamus was overall larger compared to the right side. For the CC, left-right analysis could not be done as the areas were differentiated differently in FreeSurfer. Consistent with the residual analysis of combined areas, differences in hemispheres of different CDR scores were observed in the amygdala, hippocampus, and thalamus.

Analysis from curve-fitting provided information for the critical ages i.e., middle point of an acceleration in the rate of change of brain volume. For the amygdala, hippocampus, and CC, the critical age was 68 years, indicating an acceleration in the rate of brain atrophy around that point in life. Linear changes with age were found for the thalamus and WM, indicating a consistent rate of brain atrophy throughout later adulthood. Analysis of residuals from the normal curve showed changes across dementia severity in the amygdala, hippocampus, thalamus, and CC. This strengthens the argument that the differences are a result of AD, not just age. For the amygdala and hippocampus, there were significant changes noted for all three CDR groups, consistent with this test being a more sensitive measure of the impact of AD once age effects are removed.

As introduced previously, the hippocampus and amygdala have information available about differences found between cognitively normal individuals and those with AD. A small-scale study done found the amygdala volume in patients with AD to be lower compared to their age-matched controls (Cuénod, 1993). The current study supports these findings. Another study also focused on the volume of the amygdala in individuals diagnosed with early AD. While there were reductions in volume of the right and left amygdala, these were not found to be statistically significant (Laakso et al., 1995). This is replicated in the current study as there were no hemisphere differences found for the amygdala.

For the CC, Zhu et. al's (2012) study also showed that the CC exhibited atrophy in mild dementia cases. This study further extends these findings to include a moderate/severe dementia group. The previous finding was supported and it was further concluded that increasing dementia is not associated with higher atrophy in the CC. Previously, studies on WM and AD have had conflicting results, with studies introduced earlier showing changes in WM with AD and evidence that there are no changes (Double et al., 1996; Li et al., 2012). The current study supports that there are no changes in WM in the AD-affected brain.

Due to limitations in the dataset, the current study has some shortcomings. The dataset used did not include enough female individuals with severe dementia, which led to combining the moderate and severe dementia groups, based on CDR, together. This leaves the question open for whether a higher dementia level would have a different effect on the atrophy in the brain studied. Furthermore, the dataset had questionable scoring of CDR=0.5 as these would change to CDR=0 for the next scoring session sometimes. Therefore, CDR=0.5 data were excluded from the study. Of the five levels of CDR, this study included four to assess brain segmentation volume changes with increasing dementia. Additionally, since this dataset did not have sufficient longitudinal data available for AD subjects, longitudinal analysis could not be done. Future directions could entail longitudinal analysis, exploring the subparts of the amygdala, hippocampus, thalamus, CC, and WM, and adding additional brain areas included in the limbic system which have previously been associated with changes in mood and behavior.

Overall, this study concludes that the amygdala, hippocampus, thalamus, and CC are smaller in women with AD than women with normal aging. Additionally, the size of the amygdala and hippocampus were found to correlate with AD severity. This is consistent with increasing difficulties in emotional regulation and memory as AD progresses. It can also be concluded that hemisphere differences for the hippocampus, thalamus, and WM are present. As these areas are part of the limbic system, these changes provide the physical evidence for the

symptoms exhibited by AD patients. It may be beneficial to explore the subareas within each of the studied areas to examine whether a subsection is mostly decreasing in volume rather than the general area. This would aid in identifying the target area for future studies and potential therapeutic approaches for that area. Furthermore, while this study included female participants only, it would help to also include male participants into the study and identify whether there are clear sex differences present in the limbic system associated areas.

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