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Structural volume and cortical thickness differences between males and females in cognitively normal, cognitively impaired and Alzheimer's dementia population

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ABSTRACT

We investigated differences due to sex in brain structural volume and cortical thickness in older cognitively normal (N=742), cognitively impaired (MCI; N=540) and Alzheimer's Dementia (AD; N=402) individuals from the ADNI and AIBL datasets (861 Males and 823 Females). General linear models were used to control the effect of relevant covariates including age, intracranial volume, magnetic resonance imaging (MRI) scanner field strength and scanner types. Significant volumetric differences due to sex were observed within different cortical and subcortical regions of the cognitively normal group. The number of significantly different regions was reduced in the MCI group, and no region remained different in the AD group. Cortical thickness was overall thinner in males than females in the cognitively normal group, and likewise, the differences due to sex were reduced in the MCI and AD groups. These findings were sustained after including cerebrospinal fluid (CSF) Tau and phosphorylated tau (pTau) as additional covariates.

1. Introduction

Evidence suggests that males and females have different prevalence rates of neuropsychiatric diseases, including the female preponderance of Alzheimer's Dementia (AD) (Filley, 1997; Fratiglioni et al., 1997; Viña and Lloret, 2010). Yet, it is less understood whether there are marked differences due to sex in the development and progression of AD-related brain atrophy. Current magnetic resonance imaging (MRI) based evidence indicates discordant findings among studies. For example, during the cognitively normal stage, some studies have shown larger brain structure volumes in males, including the basal ganglia (putamen and globus pallidus) (Rijpkema et al., 2012) amygdala, and cerebellum (Cheng et al., 2009; Good et al., 2001b) whereas other studies have shown larger hippocampal volumes (Király et al., 2016) and relatively thicker cortex (Lv et al., 2010) in females. However, other studies have also reported no sex-dependent volumetric differences for caudate and putamen (Elkattan et al., 2017; Ritchie et al., 2018), hippocampus (Ritchie et al., 2018; Scahill et al., 2003), thalamus (Ritchie et al., 2018; Sullivan et al., 2004), ventricular volumes, temporal lobe (Scahill et al., 2003), pons and cortical white matter (Sullivan et al., 2004).

Differences due to sex in the longitudinal progression of aging-related atrophy also appear discordant among studies, with some showing greater atrophy rates in males compared to females (Gur et al., 1991; Király et al., 2016; Murphy and Thomson, 1966; Ritchie

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[1] Data used in preparation of this article was obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

[2] Data used in the preparation of this article was obtained from the Australian Imaging Biomarkers and Lifestyle flagship study of ageing (AIBL) funded bythe Commonwealth Scientific and Industrial Research Organization (CSIRO) which was made available at the ADNI database (www.loni.usc.edu/ADNI). The AIBL researchers contributed data but did not participate in analysis or writing of this report. AIBL researchers are listed at www.aibl.csiro.au.

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et al., 2018) and others showing no sex-dependent differences for age related gray matter and white matter volume loss (Ge et al., 2002a; 2002b). Towards the mild cognitive impairment (MCI) and AD stages, studies have reported females experiencing greater cognitive decline (Bai et al., 2009; Ferretti et al., 2018; Henderson and Buckwalter, 1994; Laws et al., 2018; Lin et al., 2015) and atrophy (Ardekani et al., 2016; Ferretti et al., 2018; Hua et al., 2010) than males.

In order to better understand how male and female brains are differently affected during aging and towards AD, we evaluated MRI-based volume and cortical thickness from older cognitively normal, MCI and AD individuals from the Alzheimer's Disease Neuroimaging Initiative (ADNI) and the Australian Imaging Biomarkers and Lifestyle Study of Ageing (AIBL) datasets. We hypothesized that males and females have different rates of brain volume and cortical thickness change with the progression towards AD. To test this hypothesis, we assessed whether there was a pattern of change in the region-of-interests (ROIs) with significant sex-related difference among cognitively normal, MCI and AD groups, which represented stages of AD development.

2. Materials and methods

2.1. Experimental data

The data collected in this study was pooled from two publicly available datasets: Alzheimer's Disease Neuroimaging Initiative (ADNI) and Australian Imaging Biomarkers and Lifestyle Study of Ageing (AIBL).

1) Alzheimer's Disease Neuroimaging Initiative **(ADNI)**

ADNI (https://adni.loni.usc.edu) is a public-private multi-center study directed by Dr. Michael W. Weiner, which commenced in 2003 as an initiative to deploy clinical, imaging and genetic biomarkers for early identification and tracking of Alzheimer's Disease. The primary goal of ADNI has been to test whether serial MRI, PET along with other clinical assessments could be used to study the development of mild cognitive impairment (MCI) and early Alzheimer's disease (AD). ADNI protocols can be found in reports by Jack *et al.* (Jack Jr et al., 2008) and Mueller *et al.* (Mueller et al., 2005).

2) Australian Imaging Biomarkers and Lifestyle Study of Ageing **(AIBL)**

AIBL (https://aibl.csiro.au/) is a study led by Professor David Ames which was launched in 2006 to study the biomarkers, health and lifestyle factors which affect the development of symptomatic Alzheimer's Disease. AIBL has recruited over 1000 participants within cohorts - controls, Mild Cognitive Impairment (MCI) and AD. It has its two centers in Perth and Melbourne, Australia. AIBL study methodology has been previously reported by Ellis *et al.* (Ellis et al., 2009)

In this study, only stable cognitively normal subjects (sNC) [ADNI: 423, AIBL: 319], stable subjects with mild cognitive impairment (sMCI) [ADNI: 485, AIBL: 55] and stable subjects diagnosed with Dementia of Alzheimer's type (sDAT) [ADNI: 330, AIBL: 72] were used. Stable subjects were defined as those whose diagnosis did not change over time. The diagnosis used for the classification of the subjects into different cohorts (control, MCI, AD) was their given clinical diagnosis as per ADNI and AIBL. Details of demographic information for the two datasets are described in Table 1. The statistical test values (t-statistics and p-values) of the Age and MMSE scores for sNC, sMCI and sDAT groups are shown in the supplementary document Table 1, with the contrast 'Male-Female'.

Ethical protocols and procedures followed by ADNI and AIBL can be found at http://adni.loni.usc.edu/, and https://aibl.csiro.au/, respectively. Consent for publication was granted by respective Data sharing and Publication Committees from both ADNI and AIBL.

Table 1
Demographics information. Summary of ADNI and AIBL dataset demographics.

Control group (**sNC**)	ADNI		AIBL	
	Male	Female	Male	Female
N	197	226	140	179
Mean age	74.37	73.46	73.23	72.46
(SD)	(6.03)	(5.52)	(6.43)	(6.53)
Field strength (1.5T/3T)	83/114	83/143	35/105	41/138
Mean MMSE	29.04	29.08	28.82	28.75
(SD)	(1.15)	(1.14)	(1.22)	(1.15)
Ethnicity (Not Hispanic/Latino, Hispanic/Latino, Unknown)	195/2/-	209/13/4	-	-
MCI group (sMCI)	**ADNI**		**AIBL**	
	Male	Female	Male	Female
N	285	200	27	28
Mean age	73.46	72.07	75.41	75.21
(SD)	(7.51)	(7.88)	(6.07)	(8.25)
Field strength (1.5T/3T)	110/175	59/141	5/22	3/25
Mean MMSE	27.77	27.98	27.21	26.89
(SD)	(1.77)	(1.73)	(1.78)	(2.74)
Ethnicity (Not Hispanic/Latino, Hispanic/Latino, Unknown)	277/8/-	189/9/2	-	-
Dementia group (sDAT)	**ADNI**		**AIBL**	
	Male	Female	Male	Female
N	182	148	30	42
Mean age	75.76	73.91	73.36	74.88
(SD)	(7.68)	(7.92)	(8.24)	(8.13)
Field strength (1.5T/3T)	86/96	89/59	7/23	5/37
Mean MMSE	23.12	23.22	21.31	19.76
(SD)	(2.06)	(2.07)	(5.19)	(5.78)
Ethnicity (Not Hispanic/Latino, Hispanic/Latino, Unknown)	174/7/1	142/4/2	-	-

The table describes the demographics of the stable cognitively normal subjects (sNC), stable subjects with mild cognitive impairment (sMCI), and stable subjects diagnosed with Dementia of Alzheimer's type (sDAT), from the two datasets. Stable subjects are the subjects that do not change their diagnosis longitudinally. AIBL data did not have the ethnicity information.

2.2. Image processing, volume, and thickness computation

All T1-weighted MRI scans were processed through FreeSurfer (Fischl et al., 2002a; 2004b) version 5.3 to segment the whole brain into 89 cortical, subcortical, and ventricular structures. Details of the FreeSurfer pipeline can be found in studies by Fischl *et al.*(Fischl et al., 2004a; 2002a). The data was then subjected to meticulous quality control by visual inspection by trained anatomist.

Erroneous segmentations were corrected following the FreeSurfer data troubleshooting protocol[3] for 1) under-segmentation - by putting in cortical seeding points. 2) over-segmentation - by removing the excess part of the skull from the brain tissue. 3) correcting major segmentation errors of white matter and brainmask. This process of correction was repeated until the data was visually inspected and confirmed to be free of segmentation errors by expert anatomist. 16 scans that could not be salvaged by manual error corrections were removed.

[3] https://surfer.nmr.mgh.harvard.edu/fswiki/FsTutorial/TroubleshootingData.

The volumes of 89 total cortical, subcortical, and ventricular structural ROIs were computed. The intracranial volumes (ICV) of the respective subjects were estimated using Multi-Atlas Label Fusion based method (Huo et al., 2017; Ma et al., 2018). The ICV volume templates were generated as a part of the MICCAI 2012 multi-atlas labeling challenge (Landman and Warfield, 2012), using the labels from the human cortical labeling protocol (Klein and Tourville, 2012), followed by the image registration done using the large deformation diffeomorphic metric mapping (LDDMM) algorithm (Beg et al., 2005; Khan et al., 2008). Cortical thickness was estimated as the distance between white matter and pial matter at each vertex using FreeSurfer. The obtained Freesurfer cortical thickness was mapped on to a MNI152 non linear average T1 template (Grabner et al., 2006) (http://nist.mni.mcgill.ca/?p=858) and was smoothed using a 15mm full width at half maximum Gaussian kernel. The result of this mapping were thickness maps for 64 cortical regions containing 297,800 vertices. Differences in the cortical thickness between males and females were then analyzed on these thickness maps.

2.3. Experiment setup and statistical analysis

We first analyzed the volume and thickness differences due to sex using the combined pool of ADNI and AIBL datasets. Then, we confirmed the findings through the following additional sub-analyses: 1) Comparisons using each dataset (ADNI and AIBL) separately, in order to rule out the effect of dataset selection; 2) Comparisons using the same number of participants from each diagnostic group (sNC, sMCI, sDAT) in order to rule out the effect of sample size. This was done using 148 males and females from all diagnostic groups from the ADNI dataset. 148 was the smallest number available as per the data demographics for the females in the sDAT group; 3) Since ADNI data provides the CSF biomarker levels for part of the enrolled subjects, we used those participants to evaluate the differences due to sex after controlling for CSF Tau and pTau biomarker levels. For the analysis performed on volumes, linear model (lm) in R statistical software, version 3.2.0 was used. For analyzing group differences on cortical thickness, the MATLAB-based Surfstat toolbox (http://www.math.mcgill.ca/keith/surfstat/) was used.

2.3.1. Covariate determination

Age was included as a covariate, as it is a significant predictor of aging-related brain atrophy (Abedelahi et al., 2013; Courchesne et al., 2000; Király et al., 2016; Magnotta et al., 1999; Raz et al., 2005; Smith et al., 2007; Tang et al., 2001; Thambisetty et al., 2010; van Velsen et al., 2013). Further, intracranial volume was also included in the covariates to account for overall brain size and its effect on regional cortical and subcortical brain volumes (Barnes et al., 2010; Good et al., 2001a; Király et al., 2016; Ritchie et al., 2018; Scahill et al., 2003; Sullivan et al., 2004).

Additionally, ADNI and AIBL datasets include scans which have been acquired on scanners at both 1.5T and 3T. Therefore, we also controlled for scanner field strength, as it influences gray matter volume measures (Brunton et al., 2014; Chu et al., 2016; Ma et al., 2018). ADNI and AIBL datasets provide information on the scanners used, including the vendor and the model. The combination of the scanner vendor and model was used as a single covariate for the variation in the MRI acquisition hardware (Han et al., 2006).

2.3.2. Covariate regression

Statistical analyses were conducted using general linear models (GLM). Eq. 1 describes the relationship between the covariates and the dependent variables (volume, cortical thickness) for differences due to sex.

$$M_i = \beta_0 + Age_i + ICV_i + Field\ Strength_i + scanner_i + \varepsilon_i \quad (1)$$

where M_i here denotes structural volume (V) or cortical thickness(T), and the covariates used are age, intracranial volume of the subjects, and scanner field strength and the scanner type for each subject *i*. The residues of the regression model were analyzed for the differences due to sex for the contrast Male-Female. Eq. 2 further controlled for the effect of CSF Tau and pTau levels, where *i* denotes the subject, M indicates structural volume or cortical thickness, along with covariates age, ICV, field strength, scanner, CSF Tau and pTau.

$$M_i = \beta_0 + Age_i + ICV_i + Field\ Strength_i + scanner_i + Tau_i + pTau_i + \varepsilon_i \quad (2)$$

2.3.3. Volume based statistical analysis

For each FreeSurfer-parcellated structural ROI volume, differences due to sex were computed using student T-test after controlling for other covariates. The p-values obtained were corrected for multiple comparisons (Wright, 1992) using False Discovery Rate (FDR) (Benjamini and Hochberg, 1995; Benjamini and Yekutieli, 2001) of **0.05**.

2.3.4. Cortical thickness statistical analysis

The vertex-wise cortical thickness of the stable NC, MCI, and DAT subjects from ADNI and AIBL datasets was compared after the GLM-based covariate regression using the Surfstat toolbox in MATLAB. Random Field Theory (RFT) correction was used to correct for multiple comparisons ($p < 0.05$) (Chung et al., 2010).

3. Results

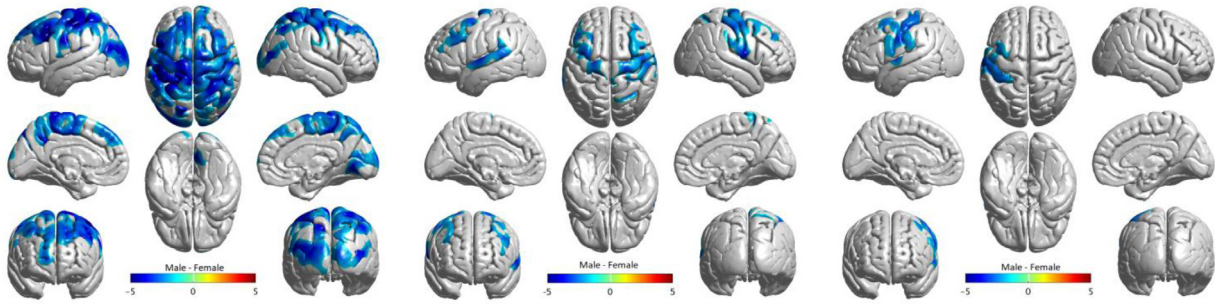
3.1. Analysis of the combined ADNI and AIBL datasets

3.1.1. Differences due to sex in structural volume

The covariate-controlled volumes in the sNC group showed significant differences in the bilateral superior parietal region, bilateral amygdala, bilateral cerebellum, 3rd and 4th ventricles, brainstem, left caudal anterior cingulate, left entorhinal, and right paracentral gyri (Table 2). Out of these regions, females showed higher volumes for bilateral superior parietal, left caudal anterior cingulate, and right paracentral gyri, as indicated by a negative t-statistic, whereas males showed higher volumes in the cerebellum, amygdala, 3rd and 4th ventricle, brainstem and the left entorhinal cortex. Significant differences in the sMCI group were found only in the left isthmus cingulate, amygdala, cerebellum, and the 3rd and 4th ventricles, with males having higher volumes than females. For the sDAT group, no significant differences in regional structural volumes between males and females were found.

3.1.2. Differences due to sex in cortical thickness

Overall, a thinner cortex was found in males in all three groups, as shown in Fig. 1 for sNC (Fig. 1a), sMCI (Fig. 1b) and sDAT (Fig. 1c). The regions in blue correspond to a negative t-statistic indicating a thinner cortex in male brains relative to female brains. In sNC group, males had a thinner cortex in the parietal, and frontal regions, as well as, some regions within the temporal and occipital lobes. The regions affected primarily corresponded to pars opercularis, precentral gyrus, paracentral gyrus, postcentral gyrus, somatosensory cortex, somatosensory association cortex (supramarginal), superior parietal lobule, inferior parietal lobule, auditory cortex with regions corresponding to superior and transverse temporal regions, pericalcarine, lingual, lateral occipital, and cuneus. As seen in Fig. 1b for the sMCI group, males showed a thinner



(a) sNC (b) sMCI (c) sDAT

Fig. 1. T-statistical map for cortical thickness difference between male and female brains for the combined ADNI+AIBL databases. Cortical thickness was analyzed for (a) 742 stable cognitively normal subjects (sNC), (b) 540 stable subjects with mild cognitive impairment (sMCI), and (c) 402 stable subjects diagnosed with Dementia of Alzheimer's type (sDAT) from the combined ADNI and AIBL databases. Stable subjects are the subjects that do not change their diagnosis longitudinally. The effect of age, ICV, field strength and scanner was controlled with a general linear model and the p-values were corrected for multiple comparisons using random field theory. Regions with significant differences in cortical thickness between males and females are noted to progressively shrink in the sMCI and sDAT groups as compared to the sNC group.

Table 2
T-statistics for structural volume difference between male vs. female for stable cognitively normal subjects (sNC) and stable subjects with mild cognitive impairment (sMCI) pooled from ADNI+AIBL databases.

ROI	sNC	sMCI
(Male-Female)	t-statistic (*p*-value)	t-statistic (*p*-value)
Left superiorparietal	-4.16 (0.002)	-
Right superiorparietal	-2.93 (0.031)	-
Left caudal anterior cingulate	-3.78 (0.003)	-
Left isthmus cingulate	-	2.98 (0.044)
Left entorhinal	3.32 (0.009)	-
Right paracentral	-2.76 (0.046)	-
Left amygdala	3.75 (0.003)	3.98 (0.0034)
Right amygdala	3.98 (0.002)	4.75 (0.002)
Left cerebellum	3.34 (0.009)	3.12 (0.034)
Right cerebellum	4.10 (0.002)	3.88 (0.0034)
3rd Ventricle	3.78 (0.003)	3.49 (0.012)
4th Ventricle	2.74 (0.046)	-
Brain-Stem	3.57 (0.005)	-

Stable subjects are the subjects that do not change their diagnosis longitudinally. GLM-based regression was used to remove the linear effect of covariates including age, ICV, scanner field strength and scanner type. This experiment analyzed the combined ADNI and AIBL databases, with contrast being male - female. Therefore, a positive t-statistic indicates higher volume in males, whereas, a negative t-statistic indicates higher volume in females. The p values are corrected for multiple comparisons using FDR with a threshold of 0.05. The table shows the results for the regions showing a significant difference. No significant difference due to sex was observed in stable subjects diagnosed with Dementia of Alzheimer's type (sDAT) in the combined ADNI+AIBL database.

cortex for regions corresponding to the precentral gyrus, paracentral gyrus, postcentral gyrus, insula, somatosensory association cortex (supramarginal), superior parietal lobule, and regions of auditory cortex, primarily the transverse temporal region. In the sDAT group, males showed a thinner cortex for regions corresponding to the precentral gyrus, postcentral gyrus, superior parietal, supramarginal, and transverse temporal regions. The statistical results for cortical thickness differences are shown in supplementary document Tables 2, 3, and 4 for the sNC, sMCI, and sDAT groups, respectively.

3.2. Evaluation on the effect of database, and sample size difference among diagnostic groups

In this section, we present the findings from the following additional sub-analyses: 1) comparisons using each dataset separately, 2) comparisons using the same number of participants from each diagnostic group, and 3) comparisons using the CSF Tau and pTau biomarker levels as additional covariates.

3.2.1. Differences due to sex analyzed separately for ADNI and AIBL datasets

Differences in structural volume

Volumetric comparisons were conducted in 89 cortical, subcortical, ventricular structures, controlling for age, ICV, field strength, and scanner.

ADNI

ADNI included 423 sNC subjects, 485 sMCI, and 330 sDAT subjects

The differences in the brain structure volume between males and females for sNC and sMCI groups are shown in Table 3. For the sNC group bilateral cerebellum (t-statistic, L: 3.01, R: 3.65), bilateral amygdala (t-statistic, L: 3.52, R: 3.93), brainstem (t-statistic, 4.18) showed higher volumes in males. In the sMCI group, right cerebellum (t-statistic, 3.52), bilateral amygdala (t-statistic, L: 3.81, R: 4.95), and 3rd ventricle (t-statistic, 3.17) showed higher volumes in males. No significant difference was observed in the sDAT group.

AIBL

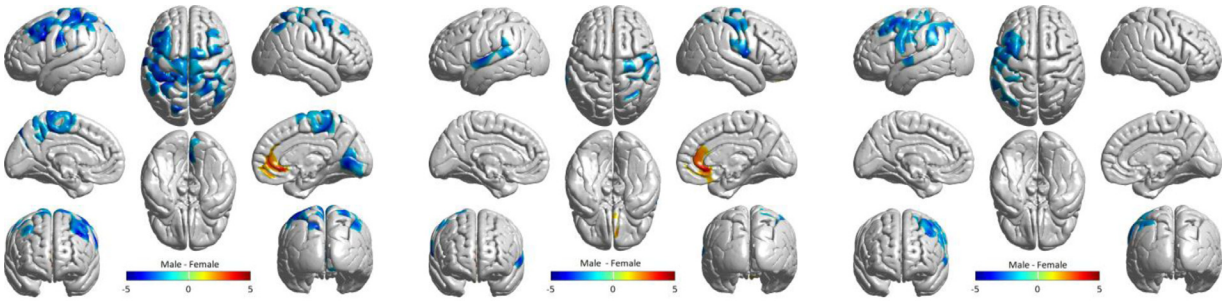
No significant volume differences were observed between males and females in the AIBL dataset for sNC (N=319), sMCI (N=55) and sDAT (N=72) groups.

Differences in cortical thickness

Cortical thickness differences due to sex were analyzed for ADNI and AIBL datasets separately, adjusting for age, ICV, field strength, and scanner.

ADNI

For ADNI dataset, Figs. 2a, 2b, and 2c show the t-statisitc maps for sNC, sMCI, and sDAT groups, respectively. The statistical results for cortical thickness differences for sNC, sMCI, and sDAT groups are shown in supplementary document Tables 5, 6, and 7 respectively. In the sNC group, thinner cortex in males (blue) was observed in regions corresponding to precentral gyrus, paracentral gyrus, postcentral gyrus, somatosensory cortex, somatosensory as-



(a) sNC (b) sMCI (c) sDAT

Fig. 2. T-statistic map for cortical thickness difference between male and female brains for subjects from the ADNI database. Cortical thickness was calculated for (a) 423 stable cognitively normal subjects (sNC), (a) 485 stable subjects with mild cognitive impairment (sMCI), and (a) 330 stable subjects diagnosed with Dementia of Alzheimer's type (sDAT) from ADNI database only. Stable subjects are the subjects that do not change their diagnosis longitudinally. The p values were corrected for multiple comparisons using random field theory and the obtained t-statistic thickness maps are thresholded with the RFT corrected p-value. Regions with significant differences in cortical thickness between males and females are noted to progressively shrink in the sMCI and sDAT groups as compared to the sNC group, in concordance with the findings when the combined ADNI+AIBL databases were analyzed as shown in Fig. 1.

Table 3
T-statistics for structural volume difference between males and females for stable cognitively normal subjects (sNC) and stable subjects with mild cognitive impairment (sMCI) in the ADNI database.

ROI (Male-Female)	sNC t-statistic (p-value)	sMCI t-statistic (p-value)
Left cerebellum	3.01 (0.048)	- -
Right cerebellum	3.65 (0.0088)	3.52 0.014
Left amygdala	3.52 (0.011)	3.81 0.007
Right amygdala	3.93 (0.0045)	4.95 $((9.41 \times 10^{-5})$
BrainStem	4.18 (0.0032)	- -
3rd ventricle	- -	3.17 (0.036)

Stable subjects are the subjects that do not change their diagnosis longitudinally. The table shows the regions with a significant difference in brain structure volumes between males and females in the ADNI dataset for sNC (N=423) and sMCI (N=485) groups. The contrast used here was Male-Female, therefore, a positive t-statistic indicates a higher volume in males. GLM based regression was used, controlling for Age, ICV, field strength and scanner. Multiple comparison correction was performed using FDR, with a threshold of 0.05. No significant differences due to sex were observed in regional volumes in stable subjects diagnosed with Dementia of Alzheimer's type (sDAT).

sociation cortex, superior parietal lobule, inferior patrietal lobule, superior temporal regions corresponding to the auditory cortex, cuneus, lingual and pericalcarine regions which are responsible for visual processing. Females exhibited a thinner cortex (orange) in prefrontal cortex regions - medial-orbito-frontal and rostral anterior cingulate. In the sMCI group, again, significant differences were observed in both males and females as seen in Fig. 2b, and supplementary document Table 6. Males showed a thinner cortex (blue) for regions corresponding to precentral gyrus, postcentral gyrus, somatosensory cortex, supramarginal, superior parietal lobule, inferior parietal lobule, and auditory cortex, as indicated by a negative t-statistic. Females had a thinner prefrontal cortex (orange). Interestingly, sMCI had smaller number of regions which showed differences due to sex compared to sNC. For the sDAT group, males (blue) had a thinner cortex for regions corresponding to left pre-frontal cortex, precentral gyrus, post central gyrus, somatosensory cortex, superior parietal lobule, and auditory cortex (Fig. 2c, supplementary document Table 7). Overall, cortical thickness differences due to sex appeared to diminish with disease progression.

AIBL

For AIBL dataset, Figs. 3a and 3b show the t-statistic maps for sNC, and sMCI groups, respectively. Supplementary document Tables 8, and 9 summarize the statistical results for cortical thickness differences in sNC, and sMCI groups, respectively. No significant sex related differences were observed in the sDAT group. This might be because of the small number of samples in the sDAT group. In the sNC group, males showed a thinner cortex in pars orbitalis, pars triangularis, pars opercularis, precentral gyrus, paracentral gyrus, postcentral gyrus, somatosensory cortex, supramarginal (somatosensory association cortex), superior parietal lobule, inferior parietal lobule, posterior cingulate, isthmus cingulate, medial temporal, transverse temporal, fusiform, cuneus, lateral occipital regions. In sMCI group, males showed a thinner cortex (blue) in precentral gyrus, paracentral gyrus (right), and postcentral gyrus (right), as seen in Fig. 3b. Again, regions with cortical thickness differences due to sex were reduced in the sMCI group compared to the sNC group. Interestingly, for AIBL dataset, cortical thickness seems to be more sensitive in detecting group differences than volumetric measures.

3.2.2. Differences due to sex based on same sample size

In this section, we made comparisons using a balanced sample, including 148 males and 148 females from the ADNI dataset. For the volume analysis, supplementary document Table 10 shows the statistical analysis results of regions with significant difference due to sex in the sNC, and sMCI groups. In the sNC group, bilateral amygdala, right cerebellum and brainstem volumes were significantly higher in males, as indicated by a positive t-statistic. In the sMCI group, only bilateral amygdala volumes showed a significant difference, with higher volume in males. No significant differences were observed in the sDAT group. Not all regions showed significant differences due to sex. However, the overall differences due to sex in sMCI and sDAT groups, in contrast to the sNC group, decreased.

For the sNC group, males showed a thinner cortex (blue) for precentral gyrus, post central gyrus, supramarginal, superior parietal, and inferior parietal lobule regions. For the sMCI group, males showed a thinner cortex for right precentral gyrus, right postcentral gyrus, right supramarginal, and right superior parietal regions, whereas, females showed a thinner cortex for prefrontal cortex regions (orange). In the sDAT group, males showed a thinner cortex in for right precentral gyrus, postcentral gyrus, regions of left prefrontal cortex, left superior and transverse temporal lobules, left superior parietal lobule and left supramarginal. Supplementary

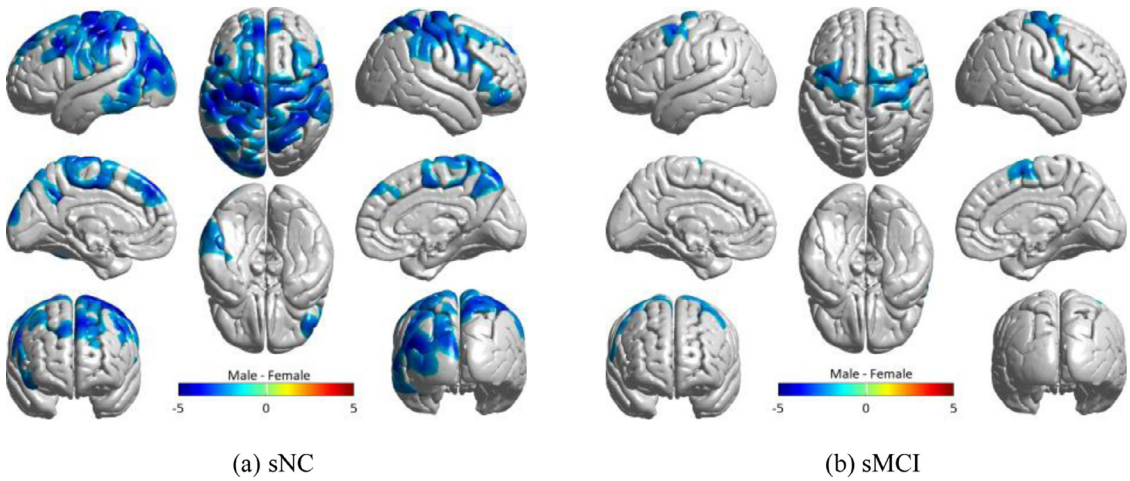


Fig. 3. T-statistic map for cortical thickness difference between male and female brains from the AIBL database. Cortical thickness was analyzed for (a) 319 stable cognitively normal subjects (sNC), and (b) 55 stable subjects with mild cognitive impairment (sMCI), controlling for age, ICV, field strength and scanner. Stable subjects are the subjects that do not change their diagnosis longitudinally. Regions with significant differences in cortical thickness between males and females are noted to progressively shrink in the sMCI group as compared to the sNC group similar to the combined ADNI+AIBL database analysis as shown in Fig. 1. No significant differences in cortical thickness between males and females were observed in the stable subjects diagnosed with Dementia of Alzheimer's type (sDAT).

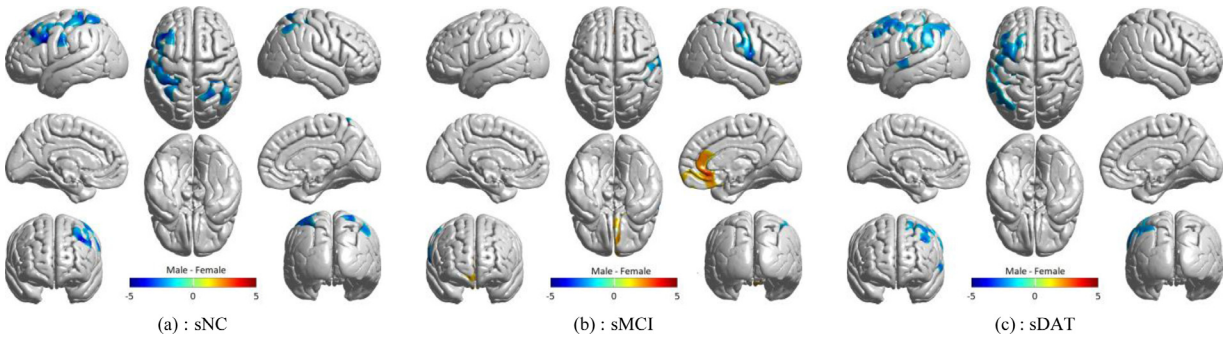


Fig. 4. T-statistical map for cortical thickness difference between male vs. female, for subjects from ADNI with same sample size for each diagnostic group. Cortical thickness was analyzed for 296 subjects (148 males, 148 females) from each diagnostic group: (a) stable cognitively normal subjects (sNC), (b) stable subjects with mild cognitive impairment (sMCI), and (c) stable subjects diagnosed with Dementia of Alzheimer's type (sDAT). Stable subjects are the subjects that do not change their diagnosis longitudinally. The regions in blue indicate a negative t-statistic, depicting a significantly thinner cortex in males. Regions in orange indicate a positive t-statistic, depicting a thinner cortex in females. The p-values were corrected for multiple comparisons using random field theory. The obtained t-statistical maps were thresholded with the RFT corrected p-value. This figure showed reduced regions with differences due to sex as the population changes from sNC to sMCI to sDAT, similar to the case for ADNI+AIBL as shown in Fig. 1.

document Table 11 summarizes the statistical results for the thickness maps shown in Figures 4a, 4b, and 4c.

3.2.3. Differences due to sex after controlling for CSF Tau and pTau levels

Here, we included CSF Tau and pTau levels as covariates in the GLM that analyzed a subset of ADNI participants with available CSF data (sNC N=305, sMCI N=364 and sDAT N=230; demographics provided in Table 4). For sNC, only the brainstem (t-statistic = 3.77, p-value = 0.018) showed a significant difference, with higher volume in males. In sMCI, right amygdala volume (t-statistic = 4.54, p-value= 0.0007) was found to be higher in males. No significant differences were observed in sDAT group.

In the sNC group, males showed a thinner cortex (blue) for prefrontal cortex regions, precentral gyrus, paracentral gyrus, postcentral gyrus, supramarginal, superior parietal lobule, inferior parietal lobule, lingual, pericalcarine, precuneus, cuneus and lateral occipital regions, as shown in Fig. 5a and supplementary document Table 12. In the sMCI group, males showed a thinner cortex for regions of precentral gyrus, postcentral gyrus, supramarginal, superior parietal lobule, inferior parietal lobule, and precuneus regions. Females showed a thinner cortex (orange) for prefrontal cortex regions, as shown in Fig. 5b and supplementary document Table 13. In the sDAT group, only males showed a thinner cortex (blue) for left precentral gyrus, left postcentral, left superior parietal lobule, and left supramarginal regions, as indicated in Fig. 5c and supplementary document Table 14.

3.2.4. Differences due sex in ICV

Leveraging both ADNI and AIBL, we have evaluated the difference due to sex in ICV, controlling for age. For both datasets, males had a significantly larger ICV than females, summarized in supplementary document Table 15.

4. Discussion

In this study, we analyzed the differences due to sex in brain structure for three groups- sNC, sMCI, and sDAT, using volume and cortical thickness measures. To verify the findings, we conducted additional analyses: 1) using the ADNI and AIBL datasets separately, 2) using a balanced sample size, and 3) adding CSF Tau and pTau biomarker levels as covariates. These additional experiments showed similar results as those for the combined pool of datasets, indicating robustness of the findings.

Table 4
Demographic Summary of the ADNI data subsets for same male-female samples and the subjects with CSF measures.

Data demographics : same sample size	sNC		sMCI		sDAT	
	Male	Female	Male	Female	Male	Female
N	148	148	148	148	148	148
Mean age	74.17	73.13	73.77	72.40	75.86	73.92
(SD)	(5.93)	(5.21)	(7.47)	(8.15)	(7.48)	(7.92)
Field strength (1.5T/3T)	54/94	52/96	67/81	56/92	93/55	89/59
Mean MMSE	29.09	29.03	27.87	27.88	23.16	23.22
(SD)	(1.13)	(1.25)	(1.71)	(1.80)	(2.05)	(2.07)
Data demographics : CSF analysis	sNC		sMCI		sDAT	
	Male	Female	Male	Female	Male	Female
N	137	168	216	148	136	94
Mean age	73.93	72.94	72.97	71.43	75.47	73.43
(SD)	(6.28)	(5.55)	(7.33)	(7.65)	(7.83)	(8.53)
Field strength (1.5T/3T)	36/101	42/126	55/161	26/122	58/78	43/51
Mean MMSE	29	29.13	27.84	28.17	23.25	23.43
(SD)	(1.26)	(1.10)	(1.79)	(1.66)	(1.98)	(1.98)
Mean Tau	103.27	115.22	120.36	133.65	174.44	217.77
(SD)	(57.99)	(63.84)	(68.62)	(99.46)	(101.53)	(120.24)
Mean pTau	27.16	27.56	30.05	32.89	42.20	49.40
(SD)	(11.78)	(14.84)	(15.60)	(19.25)	(18.66)	(27.55)
Mean $A\beta$	348.54	363.09	329.09	335.21	225.65	277.32
(SD)	(238.06)	(222.46)	(221.27)	(219.53)	(158.59)	(154.24)

The table describes the demographics of the stable cognitively normal subjects (sNC), stable subjects with mild cognitive impairment (sMCI), and stable subjects diagnosed with Dementia of Alzheimer's type (sDAT), from ADNI dataset. Stable subjects are the subjects that do not change their diagnosis longitudinally. The Table describes the demographics for the additional analysis on the same sample size and the demographics for the analysis including the CSF Tau and pTau as covariates.

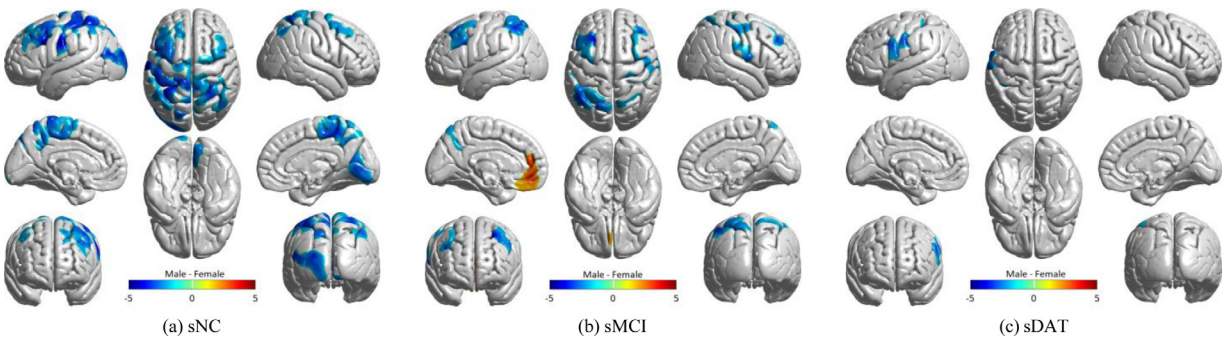


Fig. 5. T-statistical map for cortical thickness difference between male vs. female, for subjects from ADNI with CSF Tau and pTau as additional covariates. Cortical thickness was analyzed for 305 stable cognitively normal subjects (sNC), 364 stable subjects with mild cognitive impairment (sMCI), and 230 stable subjects diagnosed with Dementia of Alzheimer's type (sDAT). Stable subjects are the subjects that do not change their diagnosis longitudinally. Differences in cortical thickness were controlled for age, ICV, field strength, scanner, Tau, and pTau. The Figures above show the t-statistic map for the difference in cortical thickness between males and females in the sNC (Fig. 5a), sMCI (Fig. 5b), and sDAT (Fig. 5c) groups. The regions in blue indicate a negative t-statistic, depicting a significantly thinner cortex in males. Regions in orange indicate a positive t-statistic, depicting a thinner cortex in females. The p values were corrected for multiple comparisons using random field theory. The obtained t-statisitc thickness maps are thresholded with the RFT corrected p-value. This figure showed reduced regions with differences due to sex as the population changes from sNC to sMCI to sDAT, similar to the case for ADNI+AIBL as shown in Fig. 1.

4.1. Differences due to sex in structural volume

For the combined ADNI+AIBL analysis, in the sNC group we found males having higher volumes for bilateral cerebellum, bilateral amygdala, 3rd ventricle, 4th ventricle, brainstem, and left entorhinal. Females had higher volumes for superior parietal, left caudal anterior cingulate, and right paracentral. In the sMCI group, males had higher volumes for left isthmus cingulate, bilateral amygdala, bilateral cerebellum, and 3rd ventricle. No significant differences were observed in the sDAT group. From the volumetric findings, it can be observed that as the sample population changes from sNC to sMCI to sDAT, the differences due to sex decrease. This might be indicative of a more aggressive atrophy process in females with AD pathology.

For the sub analysis done separately on ADNI, in the sNC group, bilateral cerebellum, bilateral amygdala, and brainstem volumes were significantly higher in males. In the sMCI group, right cerebellum, bilateral amygdala, and 3rd ventricle volumes were higher in males. No significant differences were observed in the sDAT group. For AIBL, no significant differences were observed in any group. This could be due to the smaller sample size of the AIBL cohorts. For the analysis done on the same number of male female samples, males had higher volumes for bilateral amygdala, and right cerebellum in the sNC group. In the sMCI group, males had higher volumes for bilateral amygdala. No differences were observed in the sDAT group. After including CSF Tau and pTau as additional covariates, only brainstem volumes was found to be significantly higher in males in the sNC group. In the sMCI group, right amygdala volume was higher in males, and no differences were observed in the sDAT group. The additional analysis also support the hypothesis of decreasing overall differences due to sex as the disease severity increases. For the analysis including CSF Tau and pTau as additional covariates, future work includes exploring the interaction between CSF biomarker levels and sex.

Studies have reported higher cerebellar volumes (Escalona et al., 1991; Yamasue et al., 2008) in males than females. A study

by Steele *et al.* (Steele and Chakravarty, 2017) showed females having higher volumes of Crus II, which connects to the non motor regions of cerebrum and males were shown to have higher volumes of VIII A/B, which have connectivity with the motor region of cerebral cortex. Higher amygdala volumes in males have been reported in studies by Ritchie *et al.* (Ritchie et al., 2017), and Yamasue *et al.* (Yamasue et al., 2008).

In normal aging, male brains have been reported to experience greater atrophy (Gur et al., 1991; Murphy and Thomson, 1966) than female brains. Therefore, the reducing differences might be indicative of a more aggressive atrophy process in females with the increasing disease severity (from MCI to AD). Our volumteric findings are in concordance with brain areas already known to be affected in Alzheimer's Dementia. Cerebellar atrophy has been associated with Alzheimer's pathology (Baldaçara et al., 2011; Wegiel et al., 1999). Studies on Amygdala atrophy in the earlier stages of Alzheimer's Dementia have also been reported by Poulin *et al.* (Poulin et al., 2011), and Cuenod *et al.* (Cuénod et al., 1993). Ventricular dilation is also an important characteristic of Alzheimer's Dementia (Koscik et al., 2009; Luxenberg et al., 1987; Silbert et al., 2003). Cortical atrophy associated with Alzheimer's Dementia has been reported in studies done by Hubbard *et al.* (Hubbard and Anderson, 1981), and Mouton *et al.* (Mouton and Olson, 1993). Studies by Hamann *et al.* (Hamann, 2005), and Engman *et al.* (Engman et al., 2016) also suggested the possible association between estrogen and amygdala. Therefore, the role of sex hormones in the development of amygdala to its functioning in older adults needs to be understood.

For structural volume, the overall effect size of differences due to sex decreased as the sample population changed from sNC to sMCI to sDAT. It might be due to the advanced structural atrophy associated with Alzheimer's pathology that the differences due to sex were smaller if not diminished in the sDAT group.

4.2. Differences due to sex in cortical thickness

For the combined pool of ADNI and AIBL, male brains showed an overall thinner cortex compared to female brains in all three cohorts. In the sNC group, parietal and frontal regions, as well as some regions under temporal and occipital lobes showed a significant difference, with a thinner cortex in males. Significantly thinner cortex in males was also supported by previous research including Luders *et al.* (Luders et al., 2006), Sowell *et al.* (Sowell et al., 2006), Im *et al.* (Im et al., 2006), Van *et al.* (van Velsen et al., 2013) and Lv *et al.* (Lv et al., 2010). Results of our cortical thickness and volume analyses within the sNC group correspond with respect to the bilateral superior parietal and right paracentral regions, with both indicating a thinner cortex and lower volumes in male brains. The sMCI group showed a thinner cortex for males corresponding to regions within the frontal, parietal and temporal lobes. In the sDAT group, only select regions of the frontal and the parietal lobes showed a significant difference.

The motor cortex was thinner in males in all three groups. However, the differences due to sex in the motor cortex were most prominent in the sNC group, compared to sMCI and sDAT groups. The differences due to sex in the frontal cortex regions were not as evident in the sMCI and sDAT groups compared to the sNC group. Interestingly, differences in the postcentral gyrus, and the occipital lobe regions were most prominent in the sNC group, compared to sMCI and sDAT groups. The difference due to sex within the paracentral gyrus was only significant in the sNC and sMCI groups, and not in the sDAT group. Therefore, from our findings, differences due to sex in the cortical thickness were most prominent in the sNC group, and least prominent in the sDAT group. Previous studies have also associated MCI with atrophy in the superior, medial, and transverse temporal regions (Fan et al., 2008). Interestingly, differences due to sex in the left superior and transverse temporal temporal regions were found to be most prominent in the sMCI group.

For the additional analysis similar results of reducing male female differences with the increasing disease severity were observed. Interestingly, cortical thickness analysis on AIBL dataset showed a thinner cortex in males for both sNC and sMCI, with the differences decreasing the sMCI group and no differences in the sDAT group. Vertex wise cortical thickness differences seem more sensitive to differences due to sex than structural volumes. Similar to our volumetric findings, cortical thickness results showed decreasing overall differences due to sex as the sample population changed from sNC, to sMCI, to sDAT.

Our findings are in accordance with previous research demonstrating that males have greater age-related brain volume decline (Driscoll et al., 2009), while females have faster rates of brain volume change than males in the presence of symptomatic disease(Koran et al., 2017). This is additionally in line with research showing that females with Alzheimer's Dementia showed greater rates of cognitive and clinical decline than males (Filon et al., 2016; Laws et al., 2018; Malpetti et al., 2017). Lower levels of estrogen after menopause might be one of the reasons behind a higher number of older females suffer from Alzheimer's Dementia. Studies have also reported that older females taking estrogen replacement therapy (ERT) were at a lower risk of developing AD (Cholerton et al., 2002; Paganini-Hill and Henderson, 1994). Eberling *et al.* (Eberling et al., 2003) reported the protective effect of estrogen against age-related hippocampal atrophy. In a study by Yue *et al.* (Yue et al., 2005) on transgenic mice, they reported lower brain estrogen levels are related to increased amyloid plaque deposition in the brain. Therefore, in order to fully understand the differences due to sex in AD, it may be informative to study the role of estrogen in the brain.

4.3. Methodology differences with other studies

Studies of sex-related differences in the human brain are highly likely to be influenced by the methodological issues, which might explain diverging results across studies, as suggested by O'brien *et al.*(O'brien et al., 2006), Takahashi *et al.* (Takahashi et al., 2011), and Perlaki *et al.* (Perlaki et al., 2014).

The first point of difference could come from the way ICV is accounted for. Some studies tend to use the proportional method (Elkattan et al., 2017; Király et al., 2016; Scahill et al., 2003; Takahashi et al., 2011), where structural volume is divided by the ICV volume to obtain the normalized structural volume. On the other hand, some studies make use of regression methods (Chen et al., 2007; Ma et al., 2018; Pintzka et al., 2015; Ritchie et al., 2018; Schott et al., 2010b) to adjust for variations in the structural volume. We used regression method to account for ICV as studies (Ma et al., 2018; Sanchis-Segura et al., 2020) suggest regression methods to be better suited to account for ICV than normalization methods.

Secondly, differences due to sex are influenced by volume segmentation and estimation techniques. Studies conducted on differences due to sex in the brain have used a variety of methods which include FNIRT (Andersson et al., 2007a; 2007b; Ritchie et al., 2018), FAST (Ritchie et al., 2018; Zhang et al., 2001), FIRST (Király et al., 2016; Patenaude et al., 2011), MIDAS (Scahill et al., 2003; Schott et al., 2010a) along with additional thresholding, dilations and erosions (Freeborough et al., 1997) to separate brain tissue from CSF, and Freesurfer (Fischl et al., 2002b; Ritchie et al., 2018). In a study done by Elkattan *et al.* (Elkattan et al., 2017), the product of total traced area of each slice and the slice thickness was

used to obtain the volumes. Tang *et al.* (Tang et al., 2013) employed FIRST (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/first/index.html) for the segmentation part of their pipeline. Therefore, in order to understand the effect sex has on the brain, one important aspect to study is the effect that different methodologies might have on the results. A systematic comparison of these methodologies might provide an insight into this divergence of findings.

Conclusion

In our study, subjects from the sNC, sMCI, and sDAT groups were analyzed from two publicly available datasets - ADNI and AIBL, to study the differences in volume and cortical thickness due to sex. For the sNC group, volumes of bilateral superior parietal, left caudal anterior cingulate, left entorhinal, right paracentral, 3rd and 4th ventricles, brainstem, bilateral amygdala and cerebellum showed significant differences. For the sMCI group, males showed higher volumes for bilateral cerebellum, bilateral amygdala, 3rd ventricle, and left isthmus cingulate. In the sDAT group, no significant volumetric differences were observed. For cortical thickness, males showed overall thinner cortices in all three groups. However, the differences due to sex were more prevalent in the sNC group and these differences were reduced in the sMCI and sDAT groups. We also conducted additional sub-analyses, which provided similar results in terms of reduced overall differences due to sex in volume and cortical thickness with increasing disease severity.

Limitations and Future Work

One limitation of this study was the available sample size for the cohorts selected. In order to better understand the changes due to sex, it is important to establish the baseline differences in stable subjects and then extend the findings as they transition from control to MCI to AD. A future longitudinal study will help answer this. Additionally, interaction effects between sex and CSF biomarker levels will also be explored in the future studies. Another limitation of this study was that ADNI and AIBL are both multi-site studies. Technical factors like different pulse sequence, different scanners and model upgrades could complicate the analyses (Jovicich et al., 2009; Lee et al., 2019; Li et al., 2020). Finally, many studies have reported a protective effect of estrogen in Alzheimer's Dementia. One of the reasons why older females are at a greater risk for developing Alzheimer's Dementia might be in part explained by the low levels of estrogen after menopause. Future research in this domain could explore the interaction between estrogen levels and atrophy across the stages of Alzheimer's Dementia.

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Declaration of Competing Interest

There is no conflict of interest to declare from all authors.

Supplementary material

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cose.2021.102355.

CRediT authorship contribution statement

Oshin Sangha: Methodology, Data curation, Writing - original draft, Investigation, Formal analysis. **Da Ma:** Methodology, Writing - original draft, Writing - review & editing. **Karteek Popuri:** Software, Methodology. **Jane Stocks:** Writing - review & editing. **Lei Wang:** Writing - review & editing, Conceptualization. **Mirza Faisal Beg:** Writing - review & editing, Conceptualization.

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