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Hippocampal Volume in Patients with Asthma: Results from the Dallas Heart Study

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Abstract

Introduction—Asthma is associated with an increased risk of mild cognitive impairment and dementia. Depression and oral corticosteroid use are associated with atrophy of the hippocampus and are common in asthma. However, minimal neuroimaging data are available in asthma patients.

Methods—We conducted a retrospective analysis of 1,287 adult participants from the Dallas Heart Study, an epidemiological sample of Dallas County residents. Study outcome variables were hippocampal volumes measured by FreeSurfer. ANOVA was used to examine a gender difference in hippocampal volumes. General Linear Models (GLM) were conducted to examine asthma diagnosis association with hippocampal volumes.

Results—The prevalence rate of asthma among our study sample was 10.8% with 9.6% in males and 11.7% in females. After controlling for demographic characteristics, participants with asthma had significantly smaller total, right, and left hippocampal volumes than those without asthma. The association of asthma with smaller hippocampal volume was significant among males but not among females.

Conclusion—Hippocampal volume in a large and diverse sample of adults was significantly smaller in people with asthma as compared to those without asthma. These findings suggest that asthma may be associated with structural brain differences. Thus, medical illnesses without obvious direct neurodegenerative or even vascular involvement can be associated with brain changes. Because the hippocampus is a brain region involved in memory formation, these findings may have implications for treatment adherence which could have important implications for asthma treatment. Study limitations are the reliance on a self-reported asthma diagnosis and lack of additional asthma clinical information.

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Keywords

Brain volume; magnetic resonance imaging; corticosteroid; depression; hypoxia

Introduction

Asthma is an increasingly prevalent, multifactorial chronic disease that currently affects 1 in 12 people in the U.S.(1) The prevalence of asthma in the U.S. increased by 15% between 2001 and 2010 (from 7.3% to 8.4% of the population).(2, 3). Asthma costs the U.S. over \$56 billion dollars per year in healthcare expenses, missed work and school, and early deaths.(4)

Asthma pathology may extend beyond the airways to include the brain. Psychiatric disorders, such as anxiety and depression, are more common in asthma than the general population.(5-7) Mild cognitive impairment is more common in patients with mild asthma.(8) A recent report using a national cohort sample observed a 27% increased rate of dementia in patients with asthma compared to those without asthma.(9) These behavioral and cognitive findings may be associated with neuroanatomical changes in asthma patients. Depression has been linked to volume changes in the hippocampus,(10, 11) a brain region involved in memory processes. Furthermore, asthma patients may have additional risk factors for changes in regional brain volumes. Oral corticosteroid use, which is common among moderate to severe asthma patients, has also been linked to decreased hippocampal volume.(12) A subset of patients with severe asthma exacerbations exhibit hypoxia.(13, 14) Hypoxia is associated with hippocampal neuronal death in animal models.(15, 16) Despite these possible central nervous system effects of asthma, few studies, to date, have used neuroimaging to examine brain structure or functioning in asthma patients and none have focused on the hippocampus. A small study using MRI in mild to moderate asthma found that 13 out of 21 (62%) participants had incidental brain MRI abnormalities (including deep white matter hyperintensities, perivascular space, and abnormal anatomic findings).(17) A fMRI study observed that activity in the anterior cingulate cortex and insula to asthma-specific emotional stimuli was associated with biomarkers of inflammation, as well as airway obstruction in six people with mild allergic asthma.(18) A report in 14 young adults with mild to moderate asthma observed that longer disease duration was associated with increased gray matter volume in the brainstem periaqueductal grey.(19)

In the current report we examine hippocampal volumes in people with and without asthma who participated in a large cohort study in Dallas, Texas. The hippocampus was selected for this study of people with asthma because, as discussed above, it has an important role in memory, and literature suggests that the hippocampus is smaller in people with depression, oral corticosteroid use and is sensitive to the effects of hypoxia.

Methods

Study sample

We conducted a retrospective study using the initial and follow-up Dallas Heart Study (DHS) data, collected from 2000 to 2002 and September 2007 to December 2009,

respectively. DHS materials and methods have been described elsewhere.(20) DHS includes a multistage probability sample of noninstitutionalized English- or Spanish-speaking adults living in Dallas County, TX, during the period of July 2000 and January 2002. Although the primary goal of the DHS is to study heart disease risk factors, participants were enrolled to be representative of Dallas County residents, except for oversampling of African-Americans. While the primary objective of the study was to examine heart disease risk factors, participants were not specifically enrolled based on the presence of or risk factors for heart disease. Thus, DHS-1 (the initial phase of the study) consisted of an epidemiologic sample of Dallas County residents. For additional information of the design and methods of DHS please see Victor et. al. (20) Written informed consent, approved by The University of Texas Southwestern Medical Center Institutional Review Board, was obtained from all participants. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. The study extracted 2,485 DHS participants who participated in the initial study (DHS-1) and also in the follow-up study (DHS-2). Thus, the sample of 2,485 was derived from excluding persons who only participated in DHS-1 or DHS-2. A total of 2,082 participants had MRI scans in DHS-2. Of participants who participated in both DHS-1 and DHS-2 and had MRI scans, 1,616 participants had complete and usable brain volume data using FreeSurfer. Participant brain volume data was not included in the DHS database if they were determined to be outliers by the Robust Minimum Covariance Distance analysis of brain segments, had major structural defects or had error flags during automated analysis and were reviewed by a neuroradiologist (K.S.K.). Furthermore, 329 additional participants were excluded due to non-responses (missing data) for asthma diagnosis, depressive symptom and cognitive ability assessment, or education questions on the DHS questionnaire (i.e. missing data on an independent variable used in the analysis), yielding a final sample of 1,287 participants. Those included had usable data on the dependent and independent variables of interest, did not have exclusions specific to the current analysis, and had high quality structural imaging data. Study outcome variables were total, right, and left hippocampal volumes measured using FreeSurfer.

Demographic and clinical assessment—Both DHS-1 and DHS-2 used a self-report survey instrument to collect demographic characteristics, diagnoses, and medication history. Demographic characteristic variables include gender, race, age, and years of completed education. Asthma diagnosis was obtained by asking if the participant had ever received a diagnosis of asthma from a doctor or healthcare professional with possible responses of “yes,” and “no,” from DHS-1, while medication use, including oral corticosteroids, and neuroimaging date were collected in DHS-2.

Cognitive ability was measured in DHS-2 using the Montreal Cognitive Assessment (MoCA), a cognitive screening test designed to detect mild cognitive impairment was administered.(21) The 16-item Quick Inventory of Depressive Symptomology (QIDS) Self-Report, administered at DHS-2, was used to assess the depressive symptoms in the past 7 days.(22)

MR imaging—Brain volume data were collected at DHS-2 at UT Southwestern on a 3T MR imaging scanner (Achieva; Philips Healthcare, Best, the Netherlands) by using 3D magnetization-prepared rapid acquisition of gradient echo. Images were obtained from the vertex of the skull to the foramen magnum in true axial orientation. Specifications for 3D MPRAGE were the following: axial sections reconstructed at 1.0-mm section thickness; TR, 9.6 ms; TE, 5.8 ms; TI, 1100ms; SENSE factor, 2; flip angle, 12°; FOV, 260×260mm with a voxel size of 1.0 × 0.9 × 0.9 mm. Individuals with previous surgery for brain aneurysms; metal fragments in the eyes, brain, or spinal canal; cardiac pacemaker; implantable cardioverter-defibrillators; cochlear implant; spinal cord stimulators or other internal electrical devices; pregnancy; and occupations associated with exposure to metal fragments were excluded from MRI in the DHS-2.

MRI quantification was performed by using the FreeSurfer image analysis (Version 4.4), available to download from <http://surfer.nmr.mgh.harvard.edu>. The fully automated analysis was run at the Texas Advanced Computing Center at The University of Texas at Austin. Volumes of the left and right hippocampi, along with other cortical and subcortical structures not reported here, were derived from MPRAGE sequences. The neuroimaging acquisition and analysis methods of the DHS have been described in numerous other publications. (11, 23-26)

Statistical analysis—Descriptive statistics, means, standard deviations, percentages, and 95% Confidence Intervals were presented. Two-sided t-test and chi-square test were conducted to examine a sample selection bias in demographic and clinical characteristics (Table 1). Linear regressions were used to examine the association of asthma diagnosis with total, right, and left hippocampal volumes controlling for demographic characteristics (gender, race, age, and years of completed education), total brain volume, and total MoCA score. An ANOVA was used to examine gender differences in hippocampal volumes. SPSS 23 and SAS 9.4 were used for statistical analyses and a p-value < 0.05 was set as criterion for statistical significance.

Results

Descriptive statistics of demographic and clinical characteristics of the study samples were described in Table 1. The DHS participants excluded from the study were demographically similar to our study sample except age (Table 1). The prevalence rate of lifetime asthma diagnosis among our study sample was 10.8%, with 9.6% in males and 11.7% in females. Somewhat surprisingly, the frequency of asthma was slightly higher in non-Hispanic Whites (14.6%) than in African-Americans (9.3%). While there was no difference in asthma based on gender or age, non-Hispanic White had a higher rate of asthma diagnosis than other race groups. The asthma group had slightly more years of education than the non-asthma group in our sample (Table 1). The average age of our study sample at the time of the DHS-2 assessments (e.g. MRI), which were conducted several years after DHS-1, was 50.44±10.61 for the asthma group and 50.62±10.28 for those without asthma (p=0.53).

A linear regression controlling for total brain volume and demographic characteristics revealed that an asthma diagnosis was significantly associated with total (p = 0.008), left (p

= 0.027) and right ($p = 0.005$) hippocampal volume (Table 2). Participants with an asthma diagnosis had a 1.5% smaller total, left and right hippocampal volume (Table 2). Mean MoCA scores were similar in the asthma and control groups (23.48 ± 4.23 vs. 23.19 ± 4.05 , $p = 0.10$) while mean QIDS score was slightly higher in the asthma group than controls (8.19 ± 6.08 vs. 7.23 ± 5.61 , $p = 0.015$)

An analysis revealed that there was a significant gender difference in total, right and left hippocampal volumes (total $F(1,1285) = 170.91$, $p < 0.001$; right $F(1,1285) = 145.31$, $p < 0.001$; left $F(1,1285) = 175.87$, $p < 0.001$). Therefore, the linear regression analysis was conducted separately in men and women (Table 3). Asthma diagnosis was significantly associated with total, right, and left hippocampal volumes in men, while not significantly associated among women after controlling for demographic characteristics, total brain volume, and total MoCA score. The standardized coefficient (beta) values, a unitless measure of change in the dependent variable (e.g. hippocampal volume) with change in the independent variable (asthma diagnosis) were two to four times large in men than in women, suggesting a stronger effect of asthma diagnosis on hippocampal volume in men (Table 3). Total hippocampal volumes of men with asthma diagnosis were about 3.0% smaller than men without asthma, while in women the difference was only about 0.6%.

Because depression and corticosteroid use are two possible mechanisms that might, at least in part, explain the smaller hippocampal volume in the asthma group, we examined the available DHS data related to these factors. QIDS scores assessing current depressive symptom severity, but not a diagnosis of a current or past depressive disorder, were available. The mean QIDS score was fairly low and very similar in the asthma and control groups (7.01 ± 5.12 vs. 7.08 ± 5.51 , $t = -0.16$, $p = 0.875$). Current oral corticosteroid use was very uncommon in both groups ($n = 3$ in the asthma group and $n = 13$ in the control group).

Discussion

To our knowledge, this is the first study to date to examine and demonstrate a relationship between asthma and hippocampal volume. The hippocampus is a brain region involved in memory formation that is sensitive to a variety of toxins including corticosteroid excess and hypoxia. We observed that asthma was associated with a significantly smaller total, right, and left hippocampal volumes. The mean difference of 1.5%, while not large, may be of clinical significance. The mean rate of volume decline in the adult hippocampus is about 0.86% per year.⁽²⁷⁾ Thus, the observed difference between persons with and without asthma represents about 2 years of additional aging in the group sample as a whole and 4 years in men.

The mechanisms underlying the observed reduction of hippocampal volume in asthma patients are not clear. Depression is associated with hippocampal volume reduction and is a common disorder in asthma patients. However, mean QIDS scores were low and very similar in the asthma and control groups. Chronic prednisone use is associated with poor memory and smaller hippocampal volume,⁽¹²⁾ while short-term use of oral corticosteroids is associated with reversible changes in memory^(30, 31) and hippocampal volume.⁽³²⁾ In the current study, very few DHS participants in either the asthma or control group were

currently using oral corticosteroids. This finding suggests that current oral corticosteroid use does not explain the findings. A caveat is that possible effects of cumulative past corticosteroid use (e.g. multiple bursts or periods on longer-term use) on the hippocampus in asthma patients could not be investigated using the data available in the DHS.

It is important to point out that our study finding, a smaller hippocampal volume association with asthma, was largely due to male participants. Male asthma participants demonstrated a 3.0% smaller total hippocampal volume than non-asthma males, while female asthma participants demonstrated only a 0.6% smaller total hippocampal volume than non-asthma females. This sex difference may be explained by studies in animal models suggesting greater brain vulnerability to hypoxia in males than females.(40-42) Although few human studies have explored this dichotomy, women have a better prognosis following stroke than men,(43) and one in vitro study using human hippocampal slices observed that oxygen and glucose deprivation as well as N-methyl-D-aspartic acid administration resulted in less neuronal in women than men.(44) Data from animal models indicate that the male rats may be more susceptible to dendritic atrophy due to chronic stress and increases in corticosterone,(45) while female rats show greater dendritic atrophy following a single stressor.(46) In humans, females appear to show greater changes in hippocampal volume following 3-days of oral hydrocortisone,(32) while men appear to be more vulnerable to severe cognitive changes (e.g. delirium) with prescription corticosteroids.(47) These studies corroborate prior investigations which provide evidence of sexual dimorphism in neuronal cell death pathways.(48) It is important to also consider clinical features of asthma that may explain the sex difference. Some studies suggest that adult male asthma patients have poorer pulmonary function and oxygen saturation,(49) as well as a greater hospitalization rate(50) than female asthma patients. Due to a lack of clinical data, our study was unable to assess asthma severity or control in the participants.

A strength of the study is the large sample size, including a remarkably large dataset of hippocampal volumes, and inclusion of a diverse participant sample. As discussed above, the paucity of clinical data about asthma onset, duration, treatment (e.g. medications other than oral corticosteroids) and severity or control (e.g. objective symptom ratings, lung function, hospitalizations) was a study limitation. These limitations reflect the size, scope and methods of the DHS which did not primarily focus on either asthma or brain-related outcomes. A recent report suggests that a self-report of asthma has 0.86 sensitivity and 0.99 specificity when compared to a diagnosis based on primary care physician records. (51) While these findings suggest good diagnostic agreement, we acknowledge that a diagnosis based on extensive medical history, physical examination and pulmonary function testing is the gold standard.

Conclusions/Key Findings

We found that hippocampal volume was significantly smaller in participants with asthma compared to those without asthma. This suggests that asthma may be associated with structural brain differences that may impact cognitive performance. The hippocampal volume differences were largely limited to male participants, suggesting a potential need for gender consideration in clinical assessment and treatment of asthma. Our study suggests

further investigation into the etiologies of this gender difference, as well as the mechanisms by which asthma can lead to hippocampal volume reduction and perhaps other neurotoxic/neurodegenerative effects yet to be elucidated.

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Demographic and clinical characteristics of study participants (Asthma and non-asthma groups) and excluded participants

Table 1

Variables		Study participants (n=1,287)		Asthma (n=139)		Non-asthma (n=1,148)		Asthma vs. Non-Asthma		Excluded (n=329)		Study vs. Excluded	
		n (%)	n (%)	n (%)	n (%)	p-value ²	n (%)	n (%)	p-value ²				
Gender	Male	541 (42.0)		52 (37.4)	489 (42.6)	0.242		155 (47.1)	0.097				
	Female	746 (58.0)		87 (62.6)	659 (57.4)			174 (52.9)					
Race	Non-Hispanic African-American	603 (46.9)		56 (40.3) [9.28%]	547 (47.7)	0.007 ³		147 (44.7)	0.248 ³				
	Non-Hispanic White	460 (35.7)		67 (48.2) [14.5%]	393 (34.2)			135 (41.0)					
	Hispanic	198 (15.4)		13 (9.4) [6.5%]	185 (16.1)			40 (12.2)					
	Other	26 (2.0)		3 (2.2)	23 (2.0)			7 (2.1)					
Age ¹	Mean years (SD)	42.32 (10.47)		42.31 (11.20)	42.32 (10.38)	0.994		44.38 (9.70)	0.001				
Education	Mean years (SD)	13.6 (3.02)		14.14 (2.98)	13.54 (3.02)	0.028		13.42 (2.90)	0.344				

Notes:

¹ Age at DHS-1² Two-sided t-test³ χ^2 test

Table 2

Linear Regression Analysis of Hippocampal Volume

Predictor Variable	Total Combined Data					
	Unstandardized Coefficients	Standardized Coefficients	Sig.		95.0% Confidence Interval for B	
	B	Std. Error	Beta	p	Lower Bound	Upper Bound
Total Hippocampal Volume						
Asthma Diagnosis	131.765	49.213	0.000	0.008	35.182	228.347
Education	-5.686	7.738	-0.019	0.463	-20.872	9.499
Age	-3.714	2.040	-0.043	0.069	-7.718	0.290
Drinks per week	-1.536	2.747	-0.013	0.570	-6.927	3.855
Race/Ethnicity	89.968	26.619	0.078	0.001	37.729	142.208
Sex	5.364	47.549	0.003	0.910	-87.953	98.681
Total Brain Volume	0.005	0.000	0.707	0.000	0.005	0.006
MOCA Score	7.635	6.087	0.033	0.210	-4.310	19.580
Left Hippocampal Volume						
Asthma Diagnosis	59.125	26.664	0.051	0.027	6.797	111.453
Education	-1.610	4.192	-0.010	0.701	-9.838	6.617
Age	-1.521	1.105	-0.034	0.169	-3.691	0.648
Drinks per week	-0.004	1.488	0.000	0.998	-2.925	2.917
Race/Ethnicity	34.904	14.422	0.058	0.016	6.600	63.207
Sex	-5.534	25.762	-0.006	0.830	-56.093	45.025
Total Brain Volume	0.003	0.000	0.689	0.000	0.002	0.003
MOCA Score	2.720	3.298	0.022	0.410	-3.752	9.192
Right Hippocampal Volume						
Asthma Diagnosis	72.639	25.676	0.065	0.005	22.250	123.028
Education	-4.076	4.037	-0.027	0.313	-11.999	3.846
Age	-2.193	1.064	-0.050	0.040	-4.282	-0.104
Drinks per week	-1.532	1.433	-0.025	0.285	-4.345	1.280
Race/Ethnicity	55.065	13.887	0.094	0.000	27.810	82.319
Sex	10.897	24.807	0.012	0.661	-37.788	59.583
Total Brain Volume	0.003	0.000	0.684	0.000	0.002	0.003

Total Combined Data						
Unstandardized Coefficients			Standardized Coefficients	Sig.	95.0% Confidence Interval for B	
Predictor Variable	B	Std. Error	Beta	p	Lower Bound	Upper Bound
MOCA Score	4.915	3.176	0.042	0.122	-1.317	11.147

Table 3

Linear Regression Analysis of Hippocampal Volume Separated by Gender

Predictor Variable	Men						Women					
	Unstandardized Coefficients			Standardized Coefficients			Unstandardized Coefficients			Standardized Coefficients		
	B	Std. Error	Beta		p	95.0% Confidence Interval for B	B	Std. Error	Beta		p	95.0% Confidence Interval for B
Total Hippocampal Volume												
Asthma Diagnosis	224.467	77.852	0.100		0.004	71.429 377.505	69.779	63.441	0.037		0.272	-54.859 194.417
Education	0.377	11.219	0.001		0.973	-21.676 22.430	-12.704	10.747	-0.046		0.238	-33.817 8.409
Age	-7.309	3.265	-0.083		0.026	-13.728 -0.890	-1.227	2.604	-0.017		0.638	-6.342 3.889
Drinks per week	-0.856	3.426	-0.009		0.803	-7.591 5.879	-2.018	4.760	-0.014		0.672	-11.369 7.334
Race/Ethnicity	147.596	39.015	0.134		0.000	70.901 224.291	27.634	36.521	0.026		0.450	-44.117 99.385
Total Brain Volume	0.005	0.000	0.646		0.000	0.005 0.006	0.005	0.000	0.654		0.000	0.005 0.006
MOCA Score	12.075	9.530	0.051		0.206	-6.660 30.809	5.874	7.905	0.029		0.458	-9.657 21.404
Left Hippocampal Volume												
Asthma Diagnosis	114.681	43.264	0.097		0.008	29.635 199.728	21.729	33.653	0.022		0.519	-44.386 87.845
Education	0.267	6.234	0.002		0.960	-11.988 12.523	-3.643	5.701	-0.026		0.523	-14.843 7.560
Age	-3.194	1.815	-0.068		0.079	-6.761 0.373	-0.435	1.381	-0.011		0.753	-3.148 2.279
Drinks per week	0.453	1.904	0.009		0.812	-3.290 4.196	-0.390	2.525	-0.005		0.877	-5.351 4.571
Race/Ethnicity	57.607	21.681	0.099		0.008	14.987 100.228	9.764	19.373	0.018		0.614	-28.298 47.825
Total Brain Volume	0.003	0.000	0.631		0.000	0.005 0.003	0.003	0.000	0.636		0.000	0.002 0.003
MOCA Score	5.828	5.296	0.047		0.272	-4.584 16.239	1.054	4.193	0.010		0.802	-7.184 9.293
Right Hippocampal Volume												
Asthma Diagnosis	109.786	39.959	0.097		0.006	31.235 188.337	48.050	33.542	0.049		0.153	-17.848 113.948
Education	0.110	5.758	0.001		0.985	-11.210 11.429	-9.061	5.682	-0.064		0.111	-20.224 2.102
Age	-4.115	1.676	-0.092		0.014	-7.410 -0.821	-0.792	1.377	-0.021		0.565	-3.497 1.912
Drinks per week	-1.309	1.759	-0.026		0.457	-4.766 2.148	-1.628	2.517	-0.022		0.518	-6.572 3.317
Race/Ethnicity	89.989	20.026	0.161		0.000	50.623 129.354	17.870	19.309	0.033		0.355	-20.066 55.806
Total Brain Volume	0.002	0.000	0.618		0.000	0.002 0.003	0.003	0.000	0.629		0.000	0.002 0.003
MOCA Score	6.247	4.892	0.052		0.202	-3.369 15.863	4.820	4.180	0.046		0.249	-3.392 13.031