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Type 2 Diabetes Affects Brain Health Differentially in Men and Women

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Abstract

Background—Type 2 diabetes mellitus (T2DM) has been shown to result in medical complications on several organ systems including the kidneys, eyes, cardiovascular system, and most recently described the brain, including the hippocampus. There is also evidence that females are disproportionately affected by these medical complications. Brain volume reductions have also been associated with chronic low grade inflammation and dyslipidemia. This study investigated the relationships between T2DM, gender, inflammation, dyslipidemia and hippocampal volumes.

Method—Participant groups consisted of 40 obese adults with T2DM and 47 lean adults group-matched on age, gender, race, and socioeconomic status. Each participant underwent medical examination including a standard panel of blood tests, an MRI, and cognitive evaluation.

Results—We show that there is a gender difference in the association of T2DM and hippocampal volumes: diabetic women are most affected despite having better glucose control than their male counterparts. There were similar gender by diabetes interactions for HDL and HbA1c but they did not explain the gender hippocampal volume differences.

Conclusions—These important findings indicate that in addition to the higher rate of traditional medical complication, females with T2DM are more likely to also suffer more brain complication than males. These observations, if supported by larger studies, suggest that in the future gender could be considered when customizing g diabetes treatment.

Introduction

The prevalence of type 2 diabetes mellitus (T2DM), a metabolic condition associated with obesity and aging, has increased sharply over the last decade [1]. A growing body of research links T2DM to damage in several organ systems; including renal disease [2], retinopathy [3], increased cardiovascular risk [4], and decreased vascular reactivity [5]. A number of studies suggest that some of these adverse effects may differ by gender, with females suffering more severe complications from T2DM than males. For example, the relative risk of cardiovascular disease associated with diabetes is greater for women than for

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men [6]. Women with T2DM also have higher mortality rates than men after acute myocardial infarction [7] and higher relative risk of general coronary heart disease mortality [8]. Furthermore, T2DM-associated end-stage renal disease leads to higher mortality in females [9]. There is also evidence of a gender difference in triglyceride and cholesterol concentrations associated with T2DM [10]. Although it remains unknown whether physiological gender differences give rise to these health disparities, more generally, women with T2DM self-report poorer quality of life and self-management behaviors than their male counterparts [11].

There are known gender differences in high density lipoprotein (HDL) levels among healthy subjects, accounting for a higher degree of HDL-associated cardiovascular protection among women [12]. It is also interesting to note that women generally have higher levels of inflammatory markers [13]. Obesity and T2DM are closely linked to dyslipidemia [14], and chronic inflammation [15]. Specifically, HDL reductions are linked to metabolic and cardiovascular health [16]. In addition, HDL modulates glucose metabolism in individuals with T2DM [17]. However, with the development of T2DM, women have a higher proportional decline in HDL concentration than men with T2DM [18]. Fibrinogen, which is a clotting factor associated with vascular dysfunction in cardiovascular disease [19], has been linked to the development of T2DM, and may be associated with the development of cerebral atrophy [20]. C-reactive protein (CRP) is another acute reactant protein marker of inflammation, which when elevated is a predictor of T2DM [21]. It is quite possible that these risk factors may play a role in damaging the brain in general, and the hippocampus in particular given its high vulnerability for injury [22–24].

Recent research show significant brain structure changes among adult subjects with T2DM, particularly hippocampal volume reductions [25]. Other imaging studies show that cognitive dysfunction is also associated with white matter lesions and brain atrophy in subjects with T2DM [26]. Work in our laboratory has shown that frontal and temporal microstructural abnormalities accompany T2DM [27]. Of great relevance to the current study, we have shown that the hippocampus is preferentially damaged in T2DM, decreasing in volume by about 12% [27]. There is no data on whether these cognitive and cerebral volumetric changes differ by gender.

The purpose of this study is to ascertain whether the hippocampal volume reductions, known to occur in T2DM, are influenced by gender. Furthermore, given the associations between brain atrophy, cardiovascular dysfunction, and the known gender differences in HDL and inflammation levels, we were also interested in ascertaining potential gender-associated brain changes mediated by those known gender differences. To the best of our knowledge, this is the first study that seeks to explore how the reductions in hippocampal volume, known to occur in T2DM, may be modulated by gender.

Materials and Methods

Participants

The study utilized eighty-seven volunteers, 40 with T2DM and 47 age-, gender-, race-, and education-matched non-insulin resistant control subjects. Study participants were evaluated consecutively as part of an NIH-sponsored study. Because educational achievement can influence cognitive performance (not the focus of this report), and measuring cognition was part of the evaluation carried out in this NIH program, all subjects needed to have a high school diploma or equivalent.

Participants with T2DM were recruited either from internet advertisements or were referred to us by collaborating endocrinologists. Control subjects were recruited from our ongoing

studies of normal aging. The exclusion criteria for this study included evidence of neurological, medical (other than T2DM, dyslipidemia, or hypertension), or active psychiatric conditions such as depression or substance abuse. This study was approved by the NYU School of Medicine Institutional Board of Research Associates. Participants were compensated for their time and inconvenience and gave informed written consent. Similar volumetric brain data and a subset of these participants were utilized in previous publications from our laboratory [25, 27–28].

Participants with T2DM

Diabetic participants met one or more of the following criteria: (1) fasting blood glucose >125 mg/dl on two separate occasions, (2) 2-hour blood glucose level >200 mg/dl during a 75-gram oral glucose tolerance test, or (3) had received a prior diagnosis of T2DM.

Control participants

The control and diabetic groups were age-, gender-, ethnicity, and education-matched. Participant selection was made blind to MRI and medical testing results. As reflected by a quantitative insulin sensitivity check index (QUICKI) ≥ 0.35 , control participants did not have evidence of overt insulin resistance [29]. The QUICKI score has been validated against dynamic assessments of insulin sensitivity [i.e. [30]].

Procedures

All participants took part in medical testing and an MRI scan of the brain. All of the evaluations used have been described in detail in previous publications [25]. Hypertension and dyslipidemia were defined per NCEP guidelines [31], which include medication use and/or meeting certain threshold values, and were assessed as binary variables.

Blood Tests and Assessment of Insulin Resistance—In order to assess glucose and insulin levels, hemoglobin A1c (HbA1c), blood count, comprehensive metabolic and lipid profiles including low density lipoproteins (LDL) and HDL, and C-reactive protein and fibrinogen levels, blood samples were taken after a 10-hour overnight fast. Glucose was measured using a glucose oxidase method (VITROS 950 AT, Amersham, England), insulin by chemiluminescence (Advia Centaur, Bayer Corporation), HbA1c was measured in blood using high performance liquid chromatography. Plasma fibrinogen concentration was measured by the prothrombin-time derived method with reference to the Clauss fibrinogen assay using ACL TOP 500 CTS coagulation analyzer with closed tube sampling (Instrumentation Laboratory, Beckman Coulter Inc.) [32].

BMI and Anthropometric Measurements—A standardized procedure was used to measure height and weight with subjects standing, wearing light clothing and without shoes; height and weight were assessed using a Seca 700 beam scale, 500 lbs capacity (with height-rod) which was calibrated prior to each individual measurement. BMI was computed as the weight in kilograms divided by the height in meters, squared. In order to estimate abdominal obesity the waist-to-height-ratio (WHtR) was calculated by dividing waist circumference by height.

Blood Pressure Assessment, Definition of Hypertension, and Cardiovascular Inclusion and Exclusion Criteria

Resting sitting blood pressure (BP) was measured twice during one of the visits to our facility with a random-zero sphygmomanometer with an appropriately sized adult cuff. The first reading was performed at the beginning of the physical exam, 30 minutes after the subjects arrived. A second reading was obtained at the end of the examination and the two

readings were then averaged. Hypertension was diagnosed using the NCEP adult criteria [31], namely by a systolic BP (SBP) ≥ 135 mmHg, a diastolic BP (DBP) ≥ 85 mmHg, and/or a history of anti-hypertensive medications at the time of examination. In addition, all participants were screened using the Rosen modification of the Hachinski ischemia scale. This scale also accounts for history of hypertension, stroke, focal neurological symptoms and focal neurological signs. The scale allows for a maximum score of 12 and we excluded those participants with scores above 3. This threshold allows for the exclusion of those participants with an indication of stroke, transient ischemic attack, or marked vascular disease. Another exclusion criterion was the presence of silent strokes on the MRI. All other participants were included in the study. All statistical analyses were performed using SPSS version 18.

Magnetic Resonance Imaging

Image Acquisition—MRI scans were obtained on either a 1.5 T GE Vision (43 controls, 27 diabetics) or 1.5 T Siemens Avanto system (4 controls, 13 diabetics), using equivalent sequences. With the GE Vision system we acquired a spoiled-gradient inversion recovery (SPGIR), as previously described in detail [25]. With the Siemens Avanto system, we used a magnetization-prepared rapid gradient echo (MPRAGE) acquisition (TR 1300 ms, TE 4.38 ms, 192 slices, slice thickness 1.2 mm, no gap; FOV 250×250 mm, matrix 256×128, flip angle 15 degrees). The SPGIR and MPRAGE images were reformatted into a standardized “pathological angle” coronal plane for the region of interest (ROI)-based volume measurements.

Manual Tracing of ROIs Used in the Volume Determinations—Tracings of the ROIs were made blind to participants' identity and diagnosis. The hippocampus was outlined on coronal images and the intracranial vault volume (ICV) was outlined on sagittal images. Please see [25] and [27] for details. Correspondence of the volumes obtained on the two scanners was ascertained by obtaining images for 10 subjects on both scanners and then assessing the intracranial vault volume obtained with the two sets of images. The volumes obtained were indistinguishable (paired t-test: $t=0.029$, $p=0.977$). The superior temporal gyrus and frontal lobe volumes were also outlined on coronal images and are used as control areas.

Statistical analyses

Descriptive demographic data were tested using a univariate analysis of variance to find significant main effects and interactions (Table 1). Covariates were used when required. Linear regression was used to account for the individual differences in overall head (brain) size by producing hippocampal volumes adjusted (residualized) to intra-cranial vault size (ICV). This adjusts for differences in head size between men and women as well as reducing the inter-individual variability in head size. The volumes shown in Figure 1 were the mean residualized hippocampal volumes split by gender and group so as to demonstrate the interaction. For the tables, the means and standard deviations for the brain volumes were reported as raw volumes in cubic centimeters, but all statistical analyses were performed utilizing the residualized volumes. Two-tailed independent samples t-tests were utilized to ascertain disease-associated brain volumes differences and then effect sizes were calculated (Table 2). Given that CRP values greater than 10 mg/l are considered to reflect acute inflammation rather than the chronic low grade inflammation that is associated with obesity, we excluded individuals with CRP values above 10 mg/l from the CRP analyses. Also given that the CRP data was skewed with a skewness statistic of 1.621, rather than utilize non-parametric statistics, we normalized the CRP data by doing a simple log transformation (resulting in a skewness statistic of 0.047) and using the log transformed data in the analyses.

Results

This study included 87 adult participants, comprised of 40 individuals with type 2 diabetes (45.0% female) and 47 matched normal-weight controls (48.9% female). The group descriptors are contained in Table 1. Males and females were well-matched on race, age, and education level for each of the two disease groups. There is a significant difference in statin use by gender in our population. However, given that as is expected for women in general, our women had higher HDL levels and better HDL/cholesterol ratios than men, this likely explained the higher statin treatment rate for men. Across all subjects there were no differences between males and females in rates of hypertension, but there were significant differences in hypertension rates between controls and diabetics ($t=4.557$, $p=0.000$). A univariate ANOVA produced a significant gender main effect for systolic blood pressure with women being higher than men (Table 1). There was only a significant group main effect for current or past use of hypertension medications.

As expected, there were differences in BMI between control and diabetic groups for both males and females. There was also a significant difference in BMI between male and female control subjects with males having higher BMIs ($t=2.108$, $p=0.041$) but there were no BMI differences for gender in the diabetic group. A univariate analysis of variance revealed a significant interaction between gender and group for BMI as well.

Relative to their counterpart control group, both male and female individuals with T2DM showed significant decreases in hippocampal volumes (Table 2). Given individual variability in head size and its possible impact on hippocampal volumes, we measured the intracranial-vault (ICV) and through the use of a regression analysis, residualized the hippocampus for ICV; after adjusting for ICV the hippocampal volumetric differences remained significant. Control men did not show significant differences in residualized hippocampal volumes relative to control women ($t=1.324$, $p=0.192$). In contrast, women with T2DM tended to have smaller ICV-adjusted hippocampal volumes than men with T2DM ($t=-1.922$, $p=0.062$). Moreover, the effect size of the hippocampal volume differences between females with and without T2DM (Cohen's $d=1.680$) was larger than that between men with and without T2DM (Cohen's $d=0.686$). No significant group or gender differences were found in head size-residualized global brain atrophy, residualized superior temporal gyrus volume, or residualized frontal volume (Table 2).

Two-way ANOVA predicting residualized hippocampal volume showed a significant gender by group interaction term ($F=5.164$, $p=0.026$, partial $\eta^2=0.059$), (Figure 1). As expected, T2DM showed a significant main effect ($F=29.887$, $p=0.000$, partial $\eta^2=0.265$) while gender did not ($F=0.162$, $p=0.688$, partial $\eta^2=0.002$). The R squared for the complete model was 0.288.

A similar, significant interaction effect (Group $\times$ Gender) was found in the prediction of HDL ($F=6.894$, $p=0.010$, partial $\eta^2=0.454$) and HbA1C ($F=5.589$, $p=0.020$, partial $\eta^2=0.065$). Both T2DM ($F=43.138$, $p=0.000$, partial $\eta^2=0.342$) and gender ($F=21.692$, $p=0.000$, partial $\eta^2=0.207$) showed significant main effects for HDL. The HDL interaction and main effects remained significant even after controlling for statin medication. HbA1C showed significant main effects for T2DM ($F=93.545$, $p=0.000$, partial $\eta^2=0.536$) and gender ($F=6.424$, $p=0.013$, partial $\eta^2=0.073$). No such effect was shown for inflammatory markers (fibrinogen and CRP). Further analysis of the residualized hippocampal volume showed that there were no significant three-way interaction effects (Group $\times$ Gender $\times$ HDL), (Group $\times$ Gender $\times$ HbA1C), or (Group $\times$ Gender $\times$ BMI). When we predicted hippocampal volume in a stepwise regression utilizing group, gender, BMI, CRP, glucose, and HDL as independent variables, BMI and group were the only significant predictors.

There were large disease (group) main effects for hippocampal volumes. As anticipated, all variables that are highly associated with diabetes (insulin level, HbA1c, or BMI), when included as covariates, eliminated the disease (group) by gender interaction in hippocampal volumes. However, those variables that differed by gender such as systolic blood pressure, statin usage, waist size, and HDL did not reduce the significance of the interaction.

Discussion

The results of this study expand upon previously described gender differences in adult T2DM pathology, highlighting a more severe impact of the disease on the brain of females. As shown in previous reports [27], hippocampal volumes are significantly reduced among individuals with T2DM after accounting for the known gender differences in head size. However, this report is the first to note that this volumetric change is much more pronounced among females (Figure 1). Moreover, as was the case across all our subjects where we found specific hippocampal volume reductions in T2DM, the gender differences in brain volumes were also restricted to the hippocampal region (Table 2). When we used group (T2DM vs. control), gender, as well as their interaction (group $\times$ gender) to predict hippocampal volume we found that both group and the group by gender interactions were statistically significant. However, gender alone was not predictive, thus indicating that females with T2DM disproportionately contribute to the T2DM-associated reductions in hippocampal volumes. Our male controls had a significantly higher BMI than their female counterparts and an increased BMI could have a negative impact on the physiology and structure of the brain. Therefore, this may result in the lack of a gender difference in brain volumes in the control group, thus potentially inflating the disease by gender interaction in hippocampal volumes. However, this is likely only a theoretical concern since there is no evidence that obesity by itself leads to hippocampal volume reductions.

T2DM is associated with blood markers of low grade chronic inflammation, such as fibrinogen [20] and CRP [21], which are also closely related to cardiovascular health [33]. In our study, females with T2DM showed significant increases in both fibrinogen ($t=-3.937$, $p=0.000$) and CRP ($t=-2.727$, $p=0.010$) relative to control females, whereas men with T2DM did not show these marked increases. This may suggest a possible mechanism for the differential changes to the brain of T2DM men and women. It is possible that gender differences in T2DM-associated inflammation may result in the higher rate of complications known to occur among diabetic women, as well as result in the more prominent hippocampal volume reductions we reported.

Both male and female diabetics showed reductions in serum HDL, which is known to occur in T2DM [14]. In our sample the magnitude of the reduction among women (32% reduction) was far greater than that for men (18% reduction). Such reductions in HDL are also known to be associated with cardiovascular abnormalities [16]. As with inflammatory factors such as fibrinogen and CRP, lowered HDL is associated with increased risk of heart disease [33], which may contribute to the gender differences we reported. When we assessed this formally by adding HDL as a covariate to the model predicting hippocampal volume, HDL did not have a significant main effect and the overall corrected model's significance remained the same and the interaction of gender by diabetes actually became slightly more significant. This suggests that gender differences in HDL do not mediate the gender effects in the association of T2DM with reductions in hippocampal volumes.

Previous data may help explain how metabolic changes associated with obesity and T2DM may impact hippocampal integrity differentially for men and women. When a region of the brain is activated (as when performing a cognitive task), there is increased synaptic activity in that region, which normally results in regional vasodilation [34]. We know that in T2DM

and IR there are clear impairments in endothelial dependent vasodilation and vascular reactivity [35–38]. Consequently, individuals with impaired vascular reactivity will likely not be able to appropriately maintain an optimal neuronal environment, particularly during periods of high demand. When faced with potentially damaging influences, the brain, and in particular those regions more vulnerable to damage, such as the hippocampus [39], [22], [23] may be preferentially affected. Diminished vascular integrity exacerbates inflammation by increasing the number of cytokine-producing cells, capable of crossing the brain barrier, [40]. Although we did not measure inflammatory cytokines, we did measure acute phase proteins CRP and fibrinogen. Our females with T2DM have the highest levels of both CRP and fibrinogen, two inflammatory markers that are associated with T2DM. Perhaps this contributes to the gender by disease group interaction we see for hippocampal volumes.

There is evidence in animals and humans of neuroprotective activity by estrogen [41–42], which appears to be the result of estrogen's anti-inflammatory properties and interactions with cytokines [43]. We have shown that females with insulin resistance (and T2DM) have lower levels of the neuroprotective factor brain-derived neurotrophic factor (BDNF) than do their healthy counterparts and that these lower levels are associated with memory problems [44]. The mean age of the women in this study was about 59 years of age; most of them were post-menopausal. It is possible that our gender effects are in part mediated by the impact of T2DM on lowering protective factors, particularly among middle-age and older females who lack the protective effects of estrogen.

This study is limited by its cross sectional design, which does not allow the assessment of cause and effect. Due to the relatively small sample size we restricted our brain analyses to those brain regions that had been previously described as affected in diabetes. It is possible that other brain areas may be also differentially affected by diabetes. Additional variability in the data may be related to the wide age range of the population studied. However, the age bracket we included is that at highest risk for the development of T2DM. This study also has important strengths. The groups are well matched on a number of important factors and the study used validated [45] and reliable hippocampal measurements.

We selected our control group so as not to have significant insulin resistance. Given that in middle age obesity and insulin resistance are inextricably linked, it was not possible to match our obese participants with T2DM with equally obese individuals without insulin resistance. Although our diabetic gender groups were well matched on fasting blood glucose levels, female diabetics had significantly lower HbA1c than their male counterparts. Higher levels of HbA1c are indicative of poorer glucose control [46], suggesting that at the time of the study the female diabetics in our sample had better glucose control than their male counterparts. This is particularly interesting, as it implies that the more prominent hippocampal volume reductions that occur in women do so despite their better glucose control. This suggests that the gender differences we are reporting here may be conservative and that even more marked gender differences are possible among more poorly controlled women.

Future studies should examine the gender-specific differences longitudinally, starting at pre-diabetic stages. In addition, future studies should also measure inflammation and MRI in more detail by including cytokines as well as more sensitive MRI measures of brain integrity. Lastly, a study comparing pre- and post-menopausal women could elucidate the contribution estrogen played on our results. Overall, this is the first study to our knowledge to investigate how gender impacts brain health among individuals with type 2 diabetes. These findings provide insight into how T2DM manifests itself differentially in men and women and if supported by future research may provide evidence that gender specific treatment approaches should be developed.

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Figure 1.

Graph of the interaction between gender and diabetes on hippocampal volume. The graph shows that hippocampal volume is disproportionately affected by diabetes in female participants.

Gender by T2DM Interaction on Residualized Hippocampal Volumes

Table 1

Descriptive data

	Control Female	T2DM Female	Control Male	T2DM Male
Age (yrs)	59.18 ± 7.5	58.91 ± 9.99	60.82 ± 8.45	58.82 ± 7.01
Count	23	18	24	22
Education (yrs)	15.48 ± 2.020	14.83 ± 2.358	16.13 ± 1.801	15.20 ± 2.364
Duration of T2DM diagnosis (Months)	n.a.	85.35 ± 52.84	n.a.	82.35 ± 89.74
Duration Range (Months)		0.83–194.97		2.70–363.50
BMI (kg/m ²) [*] †	24.34 ± 3.665	34.17 ± 7.06	26.59 ± 3.647	31.28 ± 6.34
Hypertension (%) [‡]	26.09	76.47	20.83	63.64
Systolic BP (mm Hg) [‡]	131.77 ± 22.16	132.82 ± 20.41	122.08 ± 19.03	124.50 ± 12.38
Glucose (mg/dl) [‡]	79.3 ± 8.42	127.56 ± 27.063	81.33 ± 9.092	152.00 ± 66.261
Insulin (uIU/mL) [*] †‡	5.5739 ± 1.913	17.661 ± 13.114	5.6833 ± 1.606	11.454 ± 6.993
HbA1C (%) [*] †‡	5.21 ± 0.38	7.13 ± 0.95	5.26 ± 0.38	8.44 ± 2.17
HOMA [‡]	1.09 ± 0.40	5.49 ± 4.38	1.14 ± 0.37	3.97 ± 2.36
QUICKI [‡]	0.383 ± 0.02	0.312 ± 0.03	0.379 ± 0.02	0.322 ± 0.03
HDL (mg/dl) [*] †‡	66.09 ± 11.53	44.83 ± 11.823	49.25 ± 11.81	40.14 ± 6.98
Triglycerides (mg/dl) [‡]	74.65 ± 22.58	161.83 ± 127.52	104.96 ± 41.79	155.18 ± 91.28
CRP (mg/l) [‡]	1.44 ± 1.71	3.28 ± 2.29	1.34 ± 1.77	2.36 ± 2.58
Fibrinogen (mg/dl) [‡]	279.91 ± 64.88	397.67 ± 116.75	324.22 ± 109.93	362.00 ± 119.78
Current/ past HTN meds (%) [‡]	13	66.7	16.7	54.5
Statins ^{†‡}	8.7	44.4	20.8	72.7
Anti-diabetic meds [‡]	n.a.	77.8	n.a.	77.3
Waist (cm) ^{†‡}	86.46 ± 9.36	100.68 ± 30.30	97.54 ± 8.99	112.65 ± 15.05
ICV Head Size (cc) [‡]	1157.3 ± 102.04	1118.44 ± 65.17	1314.3 ± 103.8	1264.8 ± 122.72

* Denotes significant interaction (p<0.05);

† Denotes significant gender main effect;

‡ Denotes significant group main effect

Table 2
Brain volumetric descriptive data and Diabetes Associated Brain Volume Differences by Gender

Female	Control (23)		T2DM (18)		p	Cohen's D	
	Mean	±	S.D.	Mean	±	S.D.	Utilize Res. Vol.
Avg. hipp. Volume (cc)	3.02	±	0.31	2.48	±	0.28	<0.001 1.680
Frontal volume (cc)	102.54	±	12.28	100.62	±	12.88	0.677 0.132
STG volume (cc)	24.00	±	4.79	24.14	±	4.73	0.909 0.036
Global atrophy (cc)	106.56	±	44.35	93.17	±	36.56	0.586 0.173
Male	Control (24)		T2DM (22)				
	Mean	±	S.D.	Mean	±	S.D.	Utilize Res. Vol.
Avg. hipp. Volume (cc)	3.09	±	0.33	2.84	±	0.26	0.025 0.686
Frontal volume (cc)	117.83	±	14.64	114.71	±	15.96	0.737 0.099
STG volume (cc)	24.63	±	4.48	22.87	±	3.13	0.282 0.322
Global atrophy (cc)	122.3	±	55.05	107.5	±	38.29	0.590 0.161