Gender and Hemispheric Differences in Epilepsy Diagnosed by Voxel-based Morphometry (VBM) Method: a Pilot Cortical Thickness Study

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ABSTRACT
Introduction: Voxel-based morphometry (VBM) is a neuroimaging analysis technique that allows investigation of focal differences in brain anatomy, using the statistical approach of statistical parametric mapping. Gender changes are probably expressed in the human brain in the form of functional and anatomical organization. Aim: Our aim was to study gender differences and anatomical abnormalities in epilepsy patients (EP) by voxel-based morphometry (VBM) methods. Methods: Cortical thickness analysis of whole brain was performed in 28 patients with EP and 30 controls for gender and hemispheric differences. Results: Cortical thickness abnormalities were more widespread in left side of the brain in EP; while in female changes were mostly seen in temporal areas, frontal regions were more affected in male. Conclusion: Our study confirmed that gender and laterality are important factors determining the brain damage in EP.

Keywords: Gender, Epilepsy, Voxel-based morphometry (VBM).

1. INTRODUCTION
Gender differences are predictable in the functional and anatomical organization of the human brain early in life (1-6). In 1960s, Taylor proposed the biological basis for a higher vulnerability of the male brain and of the left hemisphere (2). According to Taylor hypothesis in 1960, in female cerebral maturation would be more rapid, so that boys would be at a greater risk for a longer time in such a way that a potential seizure-producing insult would affect the less functionally active side, the left hemisphere. The temporal lobe epilepsy with mesial temporal sclerosis (TLE-MTS) has already been described in relation Sexual dimorphism (3, 4, 5).

Voxel-based morphometry (VBM), is a fully automated computerized quantitative MRI analysis technique, which provides comprehensive analysis of global brain structure (9, 10)

2. AIM
Our aim was to study gender differences and anatomical abnormalities in epilepsy patients (EP) by voxel-based morphometry (VBM) methods.

3. METHODS
Subjects
Twenty-eight patients diagnosed with Epilepsy were included in this study. This evaluation consisted of a detailed clinical history, neurolog-
ical examination, 3T brain MRI and neuropsychological assessment.

30 age and gender-matched healthy control subjects (15 males), members of the hospital personnel with no history of head injury or significant medical or psychiatric illnesses were submitted to 3T brain MRI under conditions identical to patients. All controls had normal MRI on visual inspection.

The Ethics Committee approved the study, and written informed consent was obtained from all participants before their inclusion in this protocol.

2.3. MRI data acquisition

A Siemens Magnetom Verio 3T MRI clinical scanner (Siemens AG, Healthcare Sector, Erlangen, Germany) and 12-channel phased-array head coil were used to acquire: (1) T1-weighted 3D magnetization-prepared rapid gradient-echo imaging (MPRAGE): TR=1600 ms, TE=2.19 ms, inversion time=900 ms, flip angle=9°, acquisition plane=sagittal, voxel size=1×1×1 mm3, FOV=256 mm, acquired matrix=256×256, acceleration factor (iPAT)=2; (2) Fluid attenuated inversion recovery (FLAIR): TR=9000 ms, TE=128 ms, inversion time=2500 ms, flip angle=150°, acquisition plane=axial, slice thickness=5 mm, FOV=220 mm, acquired matrix=256×196, acceleration factor (iPAT)=2.

2.5. Statistics

2.5.1. Clinical analysis

Descriptive analyses of quantitative variables were reported by mean and standard deviation (SD).

Prior to conducting analyses, measures were tested for normal distribution using Kolmogorov–Smirnov test. All categorical and quantitative variables were assessed according to side and gender using Chi-square and Mann–Whitney test, respectively. The level of statistical significance was set at p < 0.05.

Cortical thickness analysis

In order to investigate possible gender and hemispheric differences between males and females, right and left-EP patients, and control group, we employed the ANOVA with age and brain volume as covariates of no interest for all cortical thickness analyses.

4. RESULTS

4.1. Demographics

A total number of 58 patients have been enrolled in the study. Mean age for the study population (6.24 ± 0.39). Among these cases the mean age was (6.28 ± 0.60) while in the control group the mean age was (6.20 ± 0.51). There was no statistical difference in the age between groups with p-value 0.91. Most of the patients in the population were male 60.3%, while female patients were 39.7%. Among cases the male were 71.4% and female 28.6%. While in the control group male were 60.3%, while female patients were 39.7%.

4.2. Gender differences

Areas of the brain with statistically significant in male compared to female patients for all 58 patients are summarized in Table 1.

When comparing between genders across all areas of the brain for all the population we found that there is statistically significant in: Cortex Volume (p=0.001, Table 1), Left and Right Hemisphere Cortex Volume (p=0.001 and p=0.001 respectively, Table 1), Cortical White Matter Volume (p=0.007, Table 1), Left and Right Hemisphere Cortical White Matter Volume (p=0.009 and p=0.005 respectively), Sub-Cortical Gray Matter Volume (p=0.018), Total Gray Matter Volume (p=0.000, Table 1), Left Lateral Ventricle (p=0.034), Left and Right Choroid Plexus (p=0.018 and p=0.016 respectively), Left Caudate (p=0.022), Right Accumbens Area (p=0.015), Left Putamen (p=0.039), Left Thalamus Proper (p=0.046), Left and Right Amygdala (p=0.003 and p=0.026 respectively), Left and Right Hippocampus (p=0.021 and p=0.027 respectively), Supra-Tentorial Volume with Ventricles (p=0.001), Supra-Tentorial Volume without Ventricles (p=0.001), Supra-Tentorial Volume Voxel Count (p=0.001), 4th Ventricle (p=0.040), Left and Right Cerebellum Cortex (p=0.012 and p=0.011 respectively, Table 1), Left Cerebellum White Matter (p=0.033), Mask Volume (p=0.001), Brain Segmentation Volume (p=0.001), Brain Segmentation Volume without Ventricles (p=0.001), Brain Segment Volume without Ventricles from Surface (p=0.001), Non White Matter Hypointensities (p=0.006), Right Hemisphere Surface Holes (p=0.017), Surface Holes (p=0.034) and Estimated Total Intracranial Volume (p=0.001).

We also found areas of near statistical significant: Right Lateral Ventricle (p=0.165), Right Caudate (p=0.167), Right Putamen (p=0.080), Right Thalamus Proper (p=0.057), Left and Right Ventral Diencephalon (p=0.131 and p=0.103 respectively), 3rd Ventricle (p=0.072), Brain Stem (p=0.070), Right Cerebellum White Matter (p=0.060), Left Hemisphere Surface Holes (p=0.088) and Right Vessel (p=0.147).

4.3. Hemispheric differences

Areas of the brain with statistically significant in the right hemisphere compared to the left hemisphere for all 58 patients are summarized in Table 2.

When comparing hemispheric differences across all areas of the brain for all the population we found that there is statistically significant in: Cortex Volume (p=0.001), Left and Right Hemisphere Cortex Volume (p=0.001 and p=0.001 respectively), Cortical White Matter Volume (p=0.007), Left and Right Hemisphere Cortical White Matter Volume (p=0.009 and p=0.005 respectively), Sub-Cortical Gray Matter Volume (p=0.018), Total Gray Matter Volume (p=0.000), Supra-Tentorial Volume with Ventricles (p=0.001), Supra-Tentorial Volume without Ventricles (p=0.001), Supra-Tentorial Volume Voxel Count (p=0.001), Mask Volume (p=0.000), Brain Segmentation Volume (p=0.001), Brain Segment Volume without Ventricles (p=0.001), Brain Segment Volume without Ventricles from Surface (p=0.001), Right Hemisphere Surface Holes (p=0.017), Surface Holes (p=0.034), Estimated Total Intracranial Volume (p=0.001). There is also an area of near statistically significant Left Hemisphere Surface Holes (p=0.088).

4.4. Gender differences

Areas of the brain with statistically significant in male compared to female patients for only 28 cases patients are summarized in Table 1.

When comparing between genders across all areas of the brain for only the cases we found that there is statis-
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Comparing between genders for all cases and controls

| Group comparison | Males brain volume, mm³ | Females brain volume, mm³ | P-Value |
|------------------|-------------------------|---------------------------|---------|
| Cortex Volume    | 578919.8 ± 10334.6      | 519105.9 ± 12121.4        | 0.000   |
| Left Hemisphere Cortex Volume | 287522.9 ± 5241.8 | 258466.0 ± 6035.2 | 0.001  |
| Right Hemisphere Cortex Volume | 291396.8 ± 5116.7 | 260639.8 ± 6095.6 | 0.000  |
| Cortical White Matter Volume | 377808.3 ± 10512.0 | 330638.6 ± 13176.0 | 0.007  |
| Left Hemisphere Cortical White Matter Volume | 187620.6 ± 5322.9 | 164718.0 ± 6570.9 | 0.009  |
| Right Hemisphere Cortical White Matter Volume | 190187.6 ± 5201.7 | 165920.6 ± 6611.5 | 0.005  |
| Sub-Cortical Gray Matter Volume | 56692.6 ± 1063.4 | 52450.0 ± 1396.6 | 0.018  |
| Total Gray Matter Volume | 746028.4 ± 12795.6 | 671432.4 ± 14511.8 | 0.000  |
| Left Lateral Ventricle | 5621.0 ± 562.9 | 3878.0 ± 497.9 | 0.034  |
| Left Choroid Plexus | 979.4 ± 38.1 | 810.8 ± 62.5 | 0.018  |
| Right Choroid Plexus | 1134.3 ± 48.5 | 937.2 ± 64.5 | 0.016  |
| Left Caudate | 3611.3 ± 116.9 | 3252.3 ± 94.8 | 0.022  |
| Right Accumbens Area | 661.9 ± 15.4 | 605.4 ± 14.9 | 0.015  |
| Left Putamen | 5614.8 ± 117.5 | 5204.5 ± 158.5 | 0.039  |
| Left Thalamus Proper | 7496.9 ± 198.0 | 6875.6 ± 224.3 | 0.046  |
| Left Amygdala | 1482.8 ± 32.7 | 1287.7 ± 60.1 | 0.003  |
| Right Amygdala | 1487.9 ± 36.3 | 1339.7 ± 58.2 | 0.026  |
| Left Hippocampus | 4066.5 ± 95.3 | 3652.3 ± 159.7 | 0.021  |
| Right Hippocampus | 4221.6 ± 124.2 | 3796.7 ± 142.7 | 0.027  |
| Supra-Tentorial Volume with Ventricles | 1029002.5 ± 20266.7 | 914267.5 ± 23682.3 | 0.001  |
| Supra-Tentorial Volume without Ventricles | 1016288.7 ± 20331.2 | 904657.6 ± 23785.3 | 0.001  |
| Supra-Tentorial Volume Voxel Count | 113834.2 ± 20248.5 | 902699.9 ± 23672.0 | 0.001  |
| 4th Ventricle | 1571.5 ± 82.9 | 1320.8 ± 75.7 | 0.040  |
| Left Cerebellum Cortex | 55334.5 ± 1403.8 | 50126.8 ± 1215.2 | 0.012  |
| Right Cerebellum Cortex | 55878.9 ± 1390.3 | 50548.9 ± 1349.7 | 0.011  |
| Left Cerebellum White Matter | 13722.4 ± 533.1 | 11968.8 ± 569.3 | 0.033  |
| Mask Volume | 1514251.2 ± 28738.7 | 1350662.6 ± 30442.2 | 0.000  |
| Brain Segmentation Volume | 1166828.6 ± 23019.9 | 1038452.5 ± 26016.5 | 0.001  |
| Brain Segmentation Volume without Ventricles | 1151029.7 ± 23093.8 | 1064751.7 ± 26079.1 | 0.001  |
| Brain Segmentation Volume without Ventricles from Surface | 1150495.5 ± 23082.3 | 1025502.2 ± 26138.2 | 0.001  |
| Non White Matter Hypointensities | 12.5 ± 1.2 | 7.5 ± 1.0 | 0.006  |
| Right Hemisphere Surface Holes | 68.6 ± 4.2 | 53.0 ± 4.3 | 0.017  |
| Surface Holes | 135.0 ± 8.3 | 107.3 ± 9.1 | 0.034  |
| Estimated Total Intracranial Volume | 1403577.0 ± 25831.8 | 1265618.4 ± 27025.1 | 0.001  |
| Right Lateral Ventricle | 4619.6 ± 492.7 | 3613.3 ± 452.2 | 0.165  |
| Right Caudate | 3496.5 ± 102.6 | 3284.8 ± 101.6 | 0.167  |
| Right Putamen | 5564.7 ± 111.3 | 5232.0 ± 155.5 | 0.080  |
| Right Thalamus Proper | 6964.8 ± 142.3 | 6536.9 ± 163.4 | 0.057  |
| Left Ventral Diencephalon | 3306.4 ± 80.9 | 3096.2 ± 116.3 | 0.131  |
| Right Ventral Diencephalon | 3379.8 ± 75.8 | 3164.0 ± 112.0 | 0.103  |
| 3rd Ventricle | 873.5 ± 54.3 | 726.508 ± 53.6 | 0.072  |
| Brain Stem | 17254.5 ± 522.2 | 15738.6 ± 682.5 | 0.070  |
| Right Cerebellum White Matter | 13632.9 ± 543.3 | 12110.9 ± 517.6 | 0.060  |
| Left Hemisphere Surface Holes | 66.4 ± 4.5 | 54.2 ± 5.135 | 0.088  |
| Right Vessel | 40.0 ± 5.1 | 57.8 ± 12.697 | 0.147  |
| Cortex Volume | 578919.8 ± 10334.6 | 519105.9 ± 12121.4 | 0.000  |
| Left Hemisphere Cortex Volume | 287522.9 ± 5241.8 | 258466.0 ± 6035.2 | 0.001  |
| Right Hemisphere Cortex Volume | 291396.8 ± 5116.7 | 260639.8 ± 6095.6 | 0.000  |
| Cortical White Matter Volume | 377808.3 ± 10512.0 | 330638.6 ± 13176.0 | 0.007  |
| Left Hemisphere Cortical White Matter Volume | 187620.6 ± 5322.9 | 164718.0 ± 6570.9 | 0.009  |
| Right Hemisphere Cortical White Matter Volume | 190187.6 ± 5201.7 | 165920.6 ± 6611.5 | 0.005  |
| Sub-Cortical Gray Matter Volume | 56692.6 ± 1063.4 | 52450.0 ± 1396.6 | 0.018  |
| Total Gray Matter Volume | 746028.4 ± 12795.6 | 671432.4 ± 14511.8 | 0.000  |
| Left Lateral Ventricle | 5621.0 ± 562.9 | 3878.0 ± 497.9 | 0.034  |
| Left Choroid Plexus | 979.4 ± 38.1 | 810.8 ± 62.5 | 0.018  |
| Right Choroid Plexus | 1134.3 ± 48.5 | 937.2 ± 64.5 | 0.016  |
| Left Caudate | 3611.3 ± 116.9 | 3252.3 ± 94.8 | 0.022  |
| Right Accumbens Area | 661.9 ± 15.4 | 605.4 ± 14.9 | 0.015  |

Statistically significant in: Cortex Volume (p=0.038), Left and Right Hemisphere Cortex Volume (p=0.048 and p=0.030)
| Group comparison | Brain region | Right & Left hemisphere brain volume, mm$^3$ | P-Value |
|------------------|--------------|---------------------------------------------|---------|
| Cortex Volume    | 555200.5 ± 8715.0 | 0.000 |
| Left Hemisphere Cortex Volume | 276000.3 ± 4360.0 | 0.001 |
| Right Hemisphere Cortex Volume | 279200.1 ± 4368.3 | 0.000 |
| Cortical White Matter Volume | 359103.1 ± 8699.9 | 0.007 |
| Left Hemisphere Cortical White Matter Volume | 178538.5 ± 4359.9 | 0.009 |
| Right Hemisphere Cortical White Matter Volume | 180564.5 ± 4347.6 | 0.005 |
| Sub-Cortical Gray Matter Volume | 55013.7 ± 883.6 | 0.018 |
| Total Gray Matter Volume | 716447.3 ± 10701.7 | 0.000 |
| Supra-Tentorial Volume with Ventrices | 983504.1 ± 16998.6 | 0.001 |
| Supra-Tentorial Volume without Ventrices | 972021.2 ± 16961.5 | 0.001 |
| Supra-Tentorial Volume with Ventrices without Ventrices | 972021.2 ± 16961.5 | 0.001 |
| Supra-Tentorial Volume with Ventrices from Surface | 1115920.8 ± 19019.7 | 0.001 |
| Brain Segmentation Volume | 1100929.2 ± 19024.7 | 0.001 |
| Right Hemisphere Surface Holes | 62.4 ± 3.2 | 0.017 |
| Surface Holes | 124.0 ± 6.4 | 0.034 |
| Estimated Total Intracranial Volume | 1348069.3 ± 20781.7 | 0.001 |
| Left Hemisphere Surface Holes | 61.6 ± 3.4 | 0.088 |

Table 2.
respectively), Total Gray Matter Volume (p=0.023). We also found areas of near statistical significant: Sub-Cortical Gray Matter Volume (p=0.093), Supra-Tentorial Volume with Ventricles (p=0.083), Supra-Tentorial Volume without Ventricles (p=0.085), Supra-Tentorial Volume Voxel Count (p=0.086), Mask Volume (p=0.108), Brain Segmentation Volume (p=0.069), Brain Segmentation Volume without Ventricles (p=0.070), Brain Segment Volume without Ventricles from Surface (p=0.070), Left and Right Hemisphere Surface Holes (p=0.083 and p=0.082 respectively), Surface Holes (p=0.067) and Estimated Total Intracranial Volume (p=0.112).

4.5. Hemispheric differences

Areas of the brain with statistically significant in the right hemisphere compared to the left hemisphere for only 28 cases patients are summarized in Table 2.

When comparing hemispheric differences across all areas of the brain for the only the cases we found that there is statistically significant in: Left Choroid Plexus (p=0.039) and Left and Right Cerebellum Cortex (p=0.025 and p=0.046 respectively). There are also areas of near statistical significant: Right Choroid Plexus (p=0.095), Left Caudate (p=0.117), Left and Right Accumbens area (p=0.192 and p=0.063 respectively). Left and Right Putamen (p=0.061 and p=0.119 respectively), Right Thalamus Proper (p=0.173), Left and Right Amygdala (p=0.056 and p=0.085 respectively), Left and Right Hippocampus (p=0.140 and p=0.182 respectively, Table 2) and Non White Matter Hypointensities (p=0.098).

5. DISCUSSION

CH The result of our data showed 34 statically significant areas comparing between genders for 28 patients with TLE and 30 controls. Males have showed higher ANOVA score than females in all the significant areas. Moreover, hemispheric differences were significant for 18 areas in all cases and controls. Keller has described 26 foci in the brain which were found to be associated with volume reduction in association with TLE which could be ipsilateral and contralateral to the epileptic focus (9). However, the association between volume reduction and VBM in relation to gender was not studied. This study showed significant value of gender differentiation as an augmenting tool to be used with Voxel Based Morphometry to investigate TLE patients.

The concept of using VBM as a tool to investigate epilepsy was used before in multiple previous studies. Mueller has used Voxel-based T2 Relaxation Rate Measurements in Temporal Lobe Epilepsy (TLE) with and without Mesial Temporal Sclerosis. He found ipsilateral significant that exceeds the limits of temporal lobe and extend to extra temporal areas (11). However, using VBM N. Bernasconi found the extension of gray matter disease will involve cingulum, thalamus and frontal lobe, but white matter involvement was exclusive for ipsilateral to the elliptic focus site with involvement of temporal tracks only (REFS) (12). The result of our study showed bilateral hemispheric involvement for both hemispheres including gray and white matter changes. The gray matter changes were compatible with Mullar result, but the white matter change was involving both hemispheres as Mullar showed ipsilateral involvement. Cortex Volume, Left and Right Hemisphere Cortex and Total Gray Matter Volume are the areas which were most significant for TLE patients (11). These findings augment the previous evidence provided by Maria which showed to gender and hemispheric differences as factors representing the nature and severity of TLE with bilateral hemispheric involvement (13). Also, this study proposes TLE to have generalized pathological extension to entire brain regions. The effectivity of VBM technique to monitor brain changes were shown in many conditions including, schizophrenia, temporal lobe epilepsy (TLE), mild cognitive impairment (MCI) and Alzheimer’s disease (AD) (14).

6. CONCLUSION

Further research using VBM to study patients with TLE is recommended to understand the nature of disease and to modify the treatment plan.

- Declaration of patient consent: The authors certify that they have obtained all appropriate patient consent forms.
- Author’s contribution: Each author gave substantial contribution to the conception or design of the work and in the acquisition, analysis and interpretation of data for the work. Each author had role in drafting the work and revising it critically for important intellectual content. Each author gave final approval of the version to be published and they agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
- Conflict of interest: There are no conflicts of interest.
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REFERENCES

1. Voxel based morphometry. URL: http://voxel-based morphometry (retrieved on May 2nd, 2019).
2. Geschwind N, Galaburda AM. Cerebral lateralization, biological mechanisms, associations, and pathology: I. A hypothesis and a program for research. Arch Neurol. 1985; 42(5): 428-439.
3. Taylor DC. Differential rates of cerebral maturation between sexes and between hemispheres. Lancet. 1969; 294(7612): 140-142.
4. Rémillard GM, Andermann F, Testa GF, et al. Sexual ictal manifestations predominate in women with temporal lobe epilepsy: a finding suggesting sexual dimorphism in the human brain. Neurology. 1983; 33(3): 323-330.
5. Janszky J, Schulz R, Janszky I, et al. Medial temporal lobe epilepsy: gender differences. J Neurol Neurosurg Psychiatry. 2004 May; 75(5): 773-775.
6. Chiesa V, Gardella E, Tassi L, et al. Age-related gender differences in reporting ictal fear: analysis of case histories and review of the literature. Epilepsia. 2007; 48(12): 2361-2364.
7. Briellmann RS, Berkovic SF, Jackson GD. Men may be more vulnerable to seizure-associated brain damage. Neurology.
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2000: 55: 1479-1485.

8. Scharfman HE, MacLusky NJ. Sex differences in the neurobiology of epilepsy: a preclinical perspective. Neurobiol Dis. 2014; 72 Pt B: 180-192.

9. Doherty MJ, Rostad SW, Kraemer DL, et al. Neocortical gliosis in temporal lobe epilepsy: gender-based differences. Epilepsia. 2007 Aug; 48(8): 1455-1459.

10. Keller SS, Roberts N. Voxel-based morphometry of temporal lobe epilepsy: an introduction and review of the literature. Epilepsia. 2008 May; 49(5): 741-757.

11. Ashburner J, Friston KJ. Voxel-based morphometry – the methods. Neuroimage. 2000 Jun; 11(6 Pt 1): 805-821.

12. Mueller SG, Laxer KD, Schuff N, et al. Voxel-based T2 relaxation rate measurements in temporal lobe epilepsy (TLE) with and without mesial temporal sclerosis. Epilepsia. 2007; 48(2): 220-228.

13. Bernasconi N, Duchesne S, Janke A, et al. Whole-brain voxel-based statistical analysis of gray matter and white matter in temporal lobe epilepsy. Neuroimage. 2004 Oct; 23(2): 717-723.

14. Santana GCTM, Jackowski AP, dos Santos Britto F, et al. Gender and hemispheric differences in temporal lobe epilepsy: A VBM study. Seizure. 2014; 23: 274-279.