WORLD JOURNAL OF PHARMACY AND PHARMACEUTICAL SCIENCES
SJIF Impact Factor 6.041
Volume 5, Issue 4, 397-413 Research Article ISSN 2278 – 4357

ROLE OF VOXEL-BASED MORPHOMETRIC ANALYSIS IN DEMONSTRATING ABNORMAL CEREBRAL STRUCTURE IN GENETIC GENERALIZED EPILEPSY: A SYSTEMATIC REVIEW

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Article Received on
02 Feb 2016,

Revised on 23 Feb 2016,
Accepted on 15 March 2016

DOI: 10.20959/wjpps20164-6463

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ABSTRACT

Background: Quantitative Magnetic Resonance Imaging such as Voxel-Based Morphometry (VBM) has made important contributions to the evaluation and management of epilepsy over the last two decades. Although VBM techniques together with histopathological studies reveal focal cerebral abnormalities in patients with Genetic Generalized Epilepsy (GGE); results of published studies are sometimes contradictory thereby limiting reasonable conclusions for effective clinical practice. This review aims to provide quantitative summary estimates of studies on role of VBM in detecting focal cerebral abnormalities in patients with GGE. **Method:** Studies were included in the systematic review if they were full texts published in English, with at least two groups (cases and controls) and sample size of not less than 15 cases. Studies were identified through three electronic databases (Pubmed EMBASE and Google scholar) from January 1995 to July 2014. Studies were systematically searched using key words (‘‘epilepsy’’ or "Idiopathic Generalized Epilepsy" or "IGE" or ‘‘juvenile myoclonic epilepsy’’ or ‘‘JME’’ or "Absences Epilepsy" or "AE" or "Juvenile Absence Epilepsy" or "JAE" or "Childhood Absence Epilepsy" or "CAE" or "Generalized Tonic-clonic seizure" or "GTCS") and (‘‘voxel-based morphometry" or ‘‘VBM’’ or ‘‘voxel-based’’ or ‘‘voxel-wise’’ or ‘‘voxel’’). The references of relevant articles were also scrutinized for additional studies. For each eligible study, data were extracted for descriptive and diagnostic variables and summaries relating to outcome. **Results:** The systematic literature search yielded six hundred and sixteen (616) published studies according to the topic and abstracts. Eighty three (83) articles were identified as potentially eligible and were

reviewed in full text. Fifteen studies (15) with a total of six hundred and forty one (641) patients with Genetic Generalized Epilepsy [Juvenile Myoclonic Epilepsy (JME) 393 (61.3%), Epilepsy with Generalized seizure on Awakening (EGA) 194 (30.3%) and Absence Epilepsy (AE)54 (8.4%)] and five hundred and five (505) healthy control subjects were selected. Some studies revealed anatomical changes such as increased Gray Matter Volume (GMV) in bilateral prefrontal cortex, while others showed decreased GMV in bilateral thalamus in patients with GGE. **Conclusion:** This systematic review reveals consistent subtle anatomical changes among patients with GGE; and support the concept of thalamocortical circuitry involvement in the pathogenesis of GGE, particularly in JME.

KEYWORDS: Epilepsy, voxel-based morphometry, Genetic Generalized Epilepsy, Gray matter volume.

1. INTRODUCTION

Voxel-based morphometry (VBM), has been described as a fully automated, quantitative Magnetic Resonance Imaging (MRI) analysis technique that is operator-independent, time efficient and unbiased to particular structure and gives an even-handed and comprehensive assessment of anatomical differences of the entire brain.[1] VBM is a structural neuroimaging method used to detect subtle changes in the brain images between groups of subjects. It compares the shape and size of brain tissues and structures by segmenting gray matter from images (segmentation), spatially normalizing all images (Normalization), smoothing the images and performing voxel-wised statistical parametric mapping (SPM) to produce a parametric map of structural regions.[2,3]

In patients with Genetic Generalized Epilepsy (GGE) MRI quantification in the cerebral gray matter using VBM can identify subtle structural changes in the brain even when MRI scans are normal on visual assessment. It has been suggested that VBM can be used as a surrogate for histology to evaluate the entire brain in detail in vivo.[4] In a study by Woermann et al.[5], an increase in cortical gray matter of the mesial frontal lobes was demonstrated in 20% of JME patients, suggesting that subtle but probably significant morphological and neurochemical alterations occur in both cortex and thalamus in GGE. These imaging findings in particular contributed to the current concept that JME involves thalamo-cortical networks,[6] in which gray matter volume (GMV) changes have been revealed through VBM studies of patients with JME compared with control group.[5,7-14]

Despite quantitative neuroimaging evidence of structural lesions enumerated above, methodological differences, process of quantification and accuracy of measurements have resulted in disparity in study findings in patients with GGE. Results of published studies are sometimes contradictory thereby, limiting reasonable conclusions for effective clinical practice. For instance, some studies found only GMV reduction in patients with JME as compared to control,[10,12] other studies reported increased GMV and reduced GMV among similar JME cohorts.[9,14] Additionally, Woermann et al. (1999) reported prefrontal lobe hypertrophy, while Tae et al. (2006) reported prefrontal lobe atrophy. Therefore, systematic review of all published VBM studies on GGE may be necessary to reveal the consistent whole-brain GMV changes in GGE.

1.1 Search strategies

A systematic literature search of Medline, EMBASE and Pubmed between January 1995 and July 2014 to obtain an up to date database was conducted. Full-length articles published in English were filtered for review. The references of relevant articles were also scrutinized for additional studies. The review question was broken down to develop a search strategy, The main search terms were. (‘‘epilepsy’’ or "Idiopathic Generalized Epilepsy" or "IGE" or ‘‘juvenile myoclonic epilepsy’’ or ‘‘JME’’ or "Absences Epilepsy" or "AE" or "Juvenile Absence Epilepsy" or "JAE" or "Childhood Absence Epilepsy" or "CAE" or "Generalized Tonic-clonic seizure" or "GTCS") and (‘‘voxel-based morphometry" or ‘‘VBM’’ or ‘‘voxel-based’’ or ‘‘voxel-wise’’ or ‘‘voxel’’). Boolean operators were used to combine search terms.

1.2 Selection criteria

Studies that met the following criteria were included in this review**:** (a) Original research published in English in a peer-reviewed journal. (b) Case-control studies with sample size not less than fifteen participants with a diagnosis of Genetic Generalized Epilepsy (isolated/mixed ILAE recognized GGE syndrome) and matched healthy control group. Studies that did not meet the inclusion criteria, duplicate studies and those with patient overlap were excluded from the review.

1.3 Data items and summary measures

The initial literature search yielded six hundred and sixteen (616), out of which eighty three (83) articles were identified as potentially eligible and were reviewed in full text. Finally fifteen studies (15) were selected for this review. The studies consist of a total of six hundred and forty one (641) patients with Genetic Generalized Epilepsy {Juvenile myoclonic epilepsy

(JME) 393 (61.3%), Epilepsy with Generalized seizure on Awakening (EGA) 194 (30.3%), Absence Epilepsy (AE) 54 (8.4%)} and five hundred and five (505) healthy control subjects.

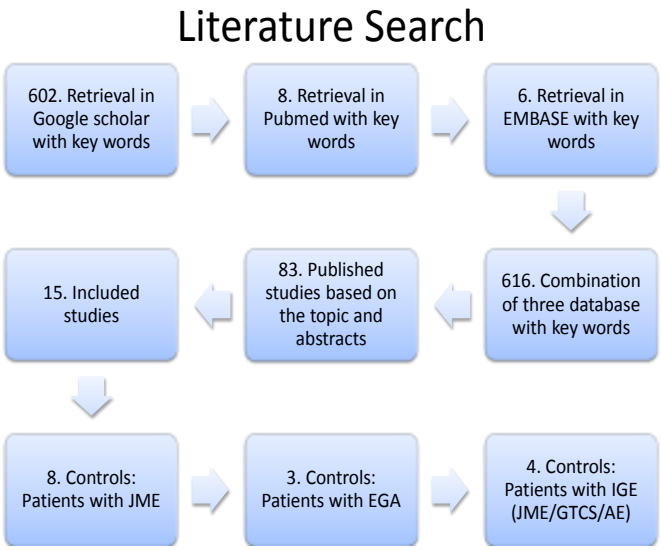

Figure 1: Chart of methodological procedure.

2. RESULTS

For each eligible study, data were extracted for descriptive and diagnostic variables (sample size, mean age, GGE-sub-syndrome) and summary relating to outcome. The technical characteristics of included studies are presented in table 1.

Table 1: Summary of the technical characteristics of included studies.

S SN N	S Study	Study Design	Type of IGE	Cases	Mean Age of cases (years)	Controls	Mean Age of controls (years)	Outcome
1.	Woermann, et al (1999).[5]	Case/ Control	JME	20	25	30	27	Increase mesial frontal GMV
2.	Betting et al (2006).[7]	Cases/ Control	GGE JME(71) AE (27) EGA (49)	147	32±12	45	32±13	Increase in total thalamic volume in JME and AE, while there was no statistical diff. in GTCS.
3.	Betting et al (2006).[8]	Case/C ontrol	GGE JME(44) AE (24) EGA (15)	83		37	32±14	JME increased GMV in frontobasal regions, AE showed increased GMV in the superior

								mesiofrontal region
4.	Tae et al.(2007).[9]	Cases/ Control	JME	19	22.6±4.9	18	22.2±6.7	Superior/middle/ medial frontal gyri and superior/ middle/inferior temporal gyri decrease thickness
5.	Kim et al. (2007).[10]	Cases/ Control	JME	25	22.7±5.1	44	23.1 ±4.3	Significant GMV reduction in the thalamus bilaterally, increase in mesiofrontal cortex bilaterally
6.	de Araujo Filho et al. (2009).[11]	Cases/ Control	JME without PD	38	27.1 ±9.5	30	30.1 ±9.0	GMV reduction bilateral thalami, insular, cerebellum
7.	Bernhardt et al. (2007).[17]	Cases/ Control	GTCS	23	35±11	46	33±11	Cortical thinning, thalamic atrophy
8.	Lin et al (2009).[17]	Cases/ control	JME PS (19) NPS (41)	60	11.3	24		Increase GMV in superior, orbito/mesial frontal regions and decrease GMV in bilateral occipital regions
9.	Roebling et al. (2009)[16]	Cases/ control	JME	19	24.2 ± 9.9	20	24.4 ±9.2	No abnormality detected
10.	Mory et al. (2011).[15]	Cases/ control	JME	21	30±9	20	31±8	Anterior thalamic atrophy
11.	O'Muircheartaigh et al. (2011).[14]	Cases/ control	JME	28	34.07	36	31.74±8.2	Increase in mesialfrontal GMV
12.	Liu et al. (2011).[13]	Cases/ control	GGE JME (15) EGA (10)	25	21±4 21±4	25 15 10		NA increase in prefrontal GMV
13.	Huang et al. (2011).[18]	Cases/ control	EGA	31	25.89±6.86	37	25.51±3.94	Significant decrease in GMV in the bilateral thalami, frontal lobe, insula and

								cerebellum
14.	Wang et al. (2012).[19]	Cases/ control	EGA	52	24.96±7.8	67	23.13±2.28	Decreased GMV, lateral thalamus mediodorsal nucleus and pulvina, orbitaofrontal cortex
15.	Kim et al (2013).[20]	Cases/ control	GGE JME (33) EGA (14) JAE (3)	50	26.0±7.2	50	26.8±5.6	GMV reduction bilateral anterior - medial thalami

[GGE – Genetic Genaralised epilepsy, JME – Juvenile myoclonic epilepsy, EGA – Epilepsy with Generalized seizure on Awakening, JAE – Juvenile absence epilepsy, AE - Absence Epilepsy, PD -Personality Disorder, PS -Photosensitivity, NPS - No-Photo Sensitivity, GTCS – Generalised tonic-clonic seizure, GMC - Gray Matter Concentration, GMV -Gray Matter Volume].

2.1 Morphometric changes in JME cohorts

2.1.1

Woermann et al.[5] using automated technique of Statistical Parametric Mapping (SPM) in analyzing structural MRI from 20 JME patients and 30 healthy controls, observed an increase in cortical gray matter in five out of 20 JME patients, four of whom had earlier been shown to have diffused cerebral abnormalities using the volume of interest technique. Result of this study suggests a significant increase in mesiofrontal cortical gray matter in JME patients compared to healthy control subjects.

2.1.2

Using VBM, Lin et al.[12] reported significant bilateral GMV reduction in thalami, decrease in gray matter volume in insula cortices and cerebellar hemispheres; whereas significant increase in GMV was found in the right superior frontal, orbitofrontal and medial frontal gyri of sixty JME (19 JME patients with photosensitivity {19JME-PS} and 41JME patients without photosensitivity {41 JME- NPS}) patients compared with 30 sex-matched healthy control subjects. Patients with JME-PS had significant reduction in GMV of visual cortices bilaterally. Furthermore, reduced left hippocampus and left inferior frontal gyrus volume was found among JME- PS group compared with JME-NPS patients. These findings revealed widespread structural abnormalities that are not limited to the frontal lobe. The study

also demonstrated the role of the occipital lobe in human PS, supporting the concept of functional-anatomic ictogenesis networks in JME.

2.1.3

Kim et al.[10] using VBM examination for structural differences in cortical and subcortical GMV among 25 JME patients and 44 age and sex-matched controls, revealed GMV increase in the superior mesiofrontal regions bilaterally and GMV reduction in the thalami in JME patients compared with controls. Correlation analysis demonstrated negative correlation between bilateral thalamic GMV and duration of epilepsy. These findings corroborate the pathophysiologic concept of the functional abnormalities in thalamocortical circuit in JME.

2.1.4

Using optimized VBM to assess volumes of the hippocampus, cerebrum, and frontal lobe and region of the corpus callosum's subdivisions in 19 JME patients compared with 19 gender/ age marched healthy control subjects. Tae et al.[9] reported significant volume decrease in the rostrum and rostral body of the corpus callosum and the left hippocampus compared with controls. Additionally, the gray matter concentration of the prefrontal lobe was found to be significantly reduced. The authors concluded that JME patients showed complex structural abnormalities in the corpus callosum, frontal lobe and hippocampus and also a decreased gray matter concentration of the prefrontal region, which suggests that there is an abnormal neural network in the brain of JME patients.

2.1.5

O'Muircheartaigh et al.[14] reported reductions in gray matter volume in the supplementary motor cortex and posterior cingulate gyrus utilising whole-brain VBM for gray matter MRI data and tract-based spatial statistics for white matter diffusion MRI data among 28 JME patients and 36 healthy controls. The authors concluded that the clinical, structural and tractography findings implicates mesial frontal cortex, especially the supplementary motor, and posterior cingulate gyrus in JME.

2.1.6

In a study using VBM to verify the possible correlation between structural abnormalities in neuroimaging and personality disorders in 38 JME patients without psychiatric disorders, sixteen JME patients with cluster B- Personality Disorder (16 JME with cluster B-PD) and 30

healthy control subjects; de Araujo Filho et al.[11] found significant reduction in thalami and increase in mesiofrontal and frontobasal regions in JME patients with PD.

Additionally, structural abnormalities of the orbitofrontal cortex were also observed. These findings support the concept of frontobasal involvement in the pathopysiology of cluster-B PD related JME.

2.1.7

In a study using a combination of multiple structural neuroimaging modalities that included VBM analysis; Mory et al.[15] found areas of anterior thalamic atrophy. Furthermore, shape analysis revealed differences between JME patients and healthy control subjects in the anterior and inferior regions of the left thalamus and in the anterior portion of the right thalamus. These results confirm the structural abnormality of anterior and inferior thalamic portions in patients with JME.

2.1.8

In an optimized VBM and two domain memory paradigms combined with functional MRI study of 19 JME patients and 20 sex-, age- and education-marched control subjects; Roebling et al.[16] found no statistically significant differences between the groups of JME patients and controls in either VBM or fMRI assessment of working memory. The authors concluded that the findings of frontal gray matter changes in JME patients from previous studies were not reproducible and that functional frontal lobe deficits in JME patients should be interpreted with caution.

2.2 Morphometric changes in GGE-EGA cohorts

2.2.1

In a study to map in vivo organization of the thalamo-cortical network in GGE patients with EGA. Bernhardt et al.[17] measured cortical thickness and thalamic volumes on MRI in 23 EGA patients and 46 control subjects. The findings revealed increased thalamo- cortical correlation network in fronto-central and parietal regions, with decreased correlation in limbic areas among EGA patients as compared with controls. Additionally, group analysis revealed that, EGA patients had bilateral thalamic atrophy and diffused cortical thinning that was more prominent in fronto-central areas compared to normal control subjects. The authors concluded that fronto-parietal atrophy in GGE is attributable to the effect of generalized seizure activity inducing thalamo-cortical network remodelling.

While, thalamic disconnection may account for the limbic abnormalities.

2.2.2

Huang et al.[18] using VBM analysis with DARTEL (differmorphic anatomical registration through exponential lie algebra) to evaluate GMV differences among 31 EGA patients compared with 37 age- and sex-matched control. They reported significant decrease in GMV in bilateral thalami, frontal cortex, insula and cerebellum in EGA patients compared with healthy controls. Additionally, voxel-based correlation analysis demonstrated that GMV in the bilateral thalami and left medial frontal gyrus had a negative correlation with duration of epilepsy. It was concluded that GMV changes in the thalamus and frontal lobe were associated with progressive epileptic seizure. These findings indicates the presence of an abnormal thalamocortical network, that reflects an underlying pathophysiological mechanism of GGE-EGA.

2.2.3

In a study to investigate alteration in anatomical and functional connectivity in the thalamic nuclei in 52 GGE-EGA patients and 67 healthy controls using VBM analysis, and resting-state blood-oxygenation level (BOLD) functional MRI analysis. Wang et al.[19] found different pattern of alteration in functional connectivity of the thalamic nuclei with reduced gray matter volume in GGE-EGA. They concluded that specific impairment of thalamic nuclei in GGE-EGA was demonstrated using anatomical and functional connectivity MRI approaches.

2.3 Morphometric changes in Mix-GGE cohorts

2.3.1

Betting et al.[7] reported increase in anterior thalamic volume of 71 JME patients with associated absence seizure compared with healthy controls. In contrast, there was no thalamic volume change seen in patients with isolated JME (without absence) and patients with GGE-EGA. These findings indicate that the anterior thalamus is different structurally in patients with JME associated with absence seizure as compared with JME patients without absence seizure.

2.3.2

In another study, investigating the presence of abnormalities on gray matter volume in 44 JME patients compared with age and gender marched healthy controls using VBM.

Betting et al.[8] demonstrated increased GMV in frontobasal region among the JME patients and increased GMV in the superior mesiofrontal region in AE patients. These results suggest the presence of different patterns of cortical abnormalities in GGE subsyndromes.

2.3.3

In a cross-sectional study using spatial extent cluster-corrected Voxel-based analysis, Liu et al.[13] found evidence suggestive of gray matter volume reduction in frontal and central regions in patients with JME and GGE-EGA. Though, initial false discovery rate-corrected VBM analysis did not reveal GMV difference between patients and healthy control groups. Additionally, tractography detected lower fractional anisotropy in some tracts including the body of corpus callosum, crus of the fornix, uncinate fasciculi, superior longitudinal fasciculi, corticospinal tracts and anterior limb of internal capsule in JME patients compared with controls. However, there were no demonstrable fractional anisotropy differences in GGE-EGA. No correlation was also found between fractional anisotropy and total lifetime seizures for either GGE-EGA or JME. The authors concluded that the absence of correlation between fractional anisotropy and lifetime seizures suggest that the white matter changes seen in JME may be secondary to seizures.

2.3.4

VBM revealed decreased in GMV in the anteromedial thalamus in GGE patients as compared with controls. Further analysis detected reduced thalamocortical FC in the bilateral medial prefrontal cortex and precuneus/posterior cingulate gyrus in GGE patients relative to healthy control subjects. The authors concluded that GGE is associated with decreased thalamocortical FC between anteromedial thalamus and medial prefrontal cortex and precuneus/posterior cingulate cortex.[20]

Table 2: Studies on Voxel-Base Morphomety in JME.

Author	Mean age (Years)	Cohort	Outcome
Woermann et al. (1999)	25	JME	Increase GMV in mesiofrontal region
Kim et al. (2007)	22±5.1	JME	Increase GMC in mesiofrontal region
Lin et al. (2009)	11.3	JME	Increase GMV in superior, orbito/mesial frontal region
O'muircheataigh et al. (2011)	34.07	JME	Increase GMV in mesiofrontal region
Tae et al. (2007)	22.6±4.9	JME	Decrease GMV in

			superior/middle/medial frontal gyri; superior/middle inferior temporal gyri
de Araujo Filho et al. (2009)	27.1±9.5	JME	Decrease GMV in cerebellum insula and bilateral thalami
Mory et al. (2011)	30±9	JME	Anterior thalamic atrophy
Roebling et al. (2009)	24.2±9.9	JME	No abnormality detected

Table 3: Studies on Voxel-Base Morphomety in GGE-EGA.

Author	Age range	Cohort	Outcome
Bernhardt et al. (2007)	35±11	GGE-EGA	Cortical thinning and thalamic atrophy
Huang et al. (2011)	25.89±6.8	GGE-EGA	Thalamic atrophy, decreased GMV in frontal lobe, insula and cerebellum
Wang et al 2012	24.96±7.8	GGE-EGA	Decreased GMV in orbitofrontal cortex, thalamic atrophy (Pulvinar and MDN)

Table 4: Studies on Voxel-Base Morphomety in GGE.

Author	Age range	Cohort	Outcome
Betting et al. (2006a)	32±12	JME/AE/EGA	Increase in thalamic volume in JME and AE, No change in EGA
Betting et al. (2006b)		JME/AE/EGA	Increase GMV in frontobasal in JME, Increase GMV in the superior mesiofrontal region in AE
Liu et al. (2011)	21±4	JME/EGA	Reduced FA was found with Spatial Cluster Extent Corrected Threshold
Kim et al. (2013)	26±7.2	JME/AE/JAE	Thalamic atrophy (AN,VA,MDN and Pulvinar)

4. DISCUSSION

This review collated fifteen (15) VBM studies for a systematic review of GMV changes between patients with GGE and healthy controls. This review strongly challenge the long held and widely accepted prevailing concept, that the patients with GGE have no structural cerebral lesion.

4.1 Morphometric changes in the thalamus

The most striking and most consistent finding in this review is thalamic atrophy (table 1), reported by greater number of included studies albeit at different sites.[17,11,15,13,18,19,20] However, Betting et al.[8] reported increase in thalamic GMV among GGE patients. Whereas two studies did not find any difference between controls and JME patients.[5,16] The discrepancies in results may be due to difference in study designs, relative small sample size, outcome measured and genetic heterogeneity.[20]

Additionally, results of VBM studies may be influenced by misregistration and gray matter volumes may vary across different scanners.[21]

4.2 Cortical morphometric changes in JME

Literature search yielded eight studies on JME (table 2). Both increased and decreased cortical GMV have been reported. Four studies found increase gray matter volume changes through VBM studies on patients with JME compared with control group,[5,10,12,14] while two studies demonstrated decreased GMV in wide cortical areas,[9,11] and one study did not find any difference between JME patients and controls.[16] The other study[15] was designed to evaluate structural abnormalities of the thalamus in JME. Methodological differences, process of quantification and accuracy of measurements may account for the observed disparity in these studies. Generally, abnormality of thalamocortical function is considered to be the most significant mechanism of JME and like other GGE sub-syndromes, JME is electrophysiologically characterized by features that show involvement of the two cerebral hemispheres from the beginning of seizures. The abnormalities of the cortical regions especially frontal gyrus reported among JME patients in VBM studies included in this review agree with the findings from other neuroimaging techniques such as MRS Screening for Occult Cancer in Unprovoked Venous Thromboembolism[22,23,24] and Positron Emission Tomography scan(PET).[25] Earlier, neuropathological studies revealed evidence of microdysgenesis in JME in the form of cortical and subcortical dystopic neurons and some other microscopic structural abnormalities. Additionally, neuropsychological and behavioural studies have suggested subtle frontal lobe dysfunction that is associated with certain personality profile.[26]

These imaging findings in particular contributed to the current concept that JME involves thalamo-cortical networks.[6]

4.3 Voxel-Based morphometric changes in GGE-EGA

Literature search yielded three papers on VBM in GGE-EGA.[17,18,19] (Table 3), despite the small number and some methodological limitations, there was consistency in their key findings of thalamic atrophy and decreased cortical GMV. Earlier study of Voxel-based morphometric analysis have revealed gray matter deficit in the thalamus and cortical structures, which may suggest neuronal loss in thalamocortical network in GGE-EGA.[27] Additionally, in a recent combined voxel-based morphometry and functional connectivity analyses in patients with GGE-EGA compared with the healthy normal subjects,

demonstrated decreased gray matter volumes in the medial dorsal nucleus (MDN) and pulvinar of the thalamus bilaterally.[20] Using multiple analytic approaches that included VBA, TBSS, probabilistic tractography and ROI analysis,[13] reported reduced FA in DTI study on GGE-EGA. The authors suggested that the reduced FA of the pyramidal tracts could be consistent with a dysfunction of the primary motor pathways in GGE. This concept is supported by the demonstration of ion channel and neurotransmitter receptor defects among first degree relatives of patients with Mendelian inherited GGE.[28]

4.4 Voxel-Based morphometric changes in Mixed-GGE

A critical appraisal of neuroimaging findings in GGE must recognize the apparent diversity of the diagnosis and heterogeneity of GGE sub-syndromes. While this systematic review provides no definite evidence for abnormal cerebral structure in GGE, focal changes have been reported within individual sub-syndromes. The search yielded four studies in GGE patients (table 4). Betting et al.[7,8], reported increase GMV at the frontobasal region in JME, in contrast abnormal thickening was demonstrated at the superior mesiofrontal region in patients with AE.[8] Similarly, both increased,[7] and decreased[20] thalamic gray matter volumes have been reported, with one study detecting white matter abnormality only after using spacial cluster extent corrected threshold statistics.[13] Although these observed neuroimaging abnormalities could be linked with covariates such as total intracranial volume, gender, age, size of control group comparison and scanner used, the possibility of the influence of genetic heterogeneity also warrant consideration. Because, normally developing adolescent brain matures with thickening or thinning of the cortex at different rates and times depending on the region, the development follows a back-to-front progression over the frontal cortex, with the last area to mature being the dorsolateral prefrontal cortex at the end of adolescence, while orbitofrontal regions continue to mature until old age.[29] Therefore, some of the discrepancies observed in the reviewed publish studies may be due to overlap of syndromes during infancy and adolescence, and patients that shift from one sub-syndrome to another as they mature.

5. Limitations

There are several limitations of this review that borders on the data from the reviewed studies. Firstly, the possible effect of AEDs on cerebral function is a confounding factor, as different AEDs administration in patients will make it difficult to estimate the effects of AEDs on functional connectivity. Secondly, the reduced functional connectivity may simply

be due to the reduced number of neurons in gray matter. Thirdly, some bias factors such as the small number of included studies cannot be completely ruled out. Fourthly, the methodological diversity in these studies, such as different preprocessing protocols, smoothing kernels and statistical threshold methods, may account for some of the noted differences. Some of these methodological limitations can be reduced by using a more consistent, reproducible and reliable VBM protocol bearing in mind the influence of both epilepsy-specific and factors such as study design, age, gender, recruitment of subjects, sample size, optimization and validation of sample size.[30]

6. CONCLUSION

This systematic review focuses on neuroimaging technologies (VBM) currently used in IGE studies. This review collated 15 VBM studies for a systematic review of GMV changes between patients with GGE and healthy controls. It reveals consistent subtle anatomical changes, such as increased GMV in bilateral prefrontal cortex and decreased GMV in bilateral thalamus in patients with GGE; supported the concept of thalamocortical circuitry involvement in the pathogenesis of GGE, particularly in JME. Therefore, the outcome of this review strongly challenge the long held and widely accepted prevailing concept, that the patients with GGE have no structural cerebral lesion. Future VBM studies in GGE should carefully control and describe sample features such as the inclusion of prospective samples drawn from community-based settings, treatment naive patients and larger samples spanning the spectrum of syndromes, particularly JAE and GGE-EGA. Together with consistent reporting of potentially confounding variables such as seizure frequency and duration of epilepsy, future studies should improve our understanding of role of VBM in GGE sub-syndromes.

Appendix A

Highlights

- There is need for establishment of relational database which could be used to determine the factors that explain conflicting results across neuroimaging studies particularly VBM. Establishment of relational database will improve the computing power needed to analyze and integrate data; and the methodological advances that are required to compare data from different GGE sub-syndromes in different centers within the network.
- There is also the need for refining the neuroimaging procedures by accounting for sources of variation between patients. The major sources of variations identified in this review are

either demographic details such as age and gender or epilepsy-specific (duration of epilepsy).

- Significant methodological diversity was apparent at the study-level in this review. Some of the heterogeneity maybe explain by sampling differences, mixtures of diagnoses or less than representative sampling. The role of neuroimaging methods such as VBM will, therefore, be proportional to the size of the database, which in turn will depend on intercenter collaborations. This recognition is important because it may open several windows for research which includes the area of diagnosis, treatment and genetic evaluation.

Authors contribution

Balarabe SA, conceived the study. Watila MM and Balarabe SA, carried out the research. Balarabe SA, prepared the first draft of the manuscript. All authors were involved in the revision of the draft manuscript and have agreed to the final content.'

Funding

None.

Conflict of interest

None.

REFERENCES

1. Ashburner, J., Friston, K.J. Voxel-based morphometry — the methods. Neuroimage., 2000; 11: 805—821.
2. Ashburner J, Friston KJ. Why voxel-based morphometry should be used. Neuroimage, 2001; 14: 1238–43.
3. Keller, S.S. and Roberts, N. Voxel-based morphometry of temporal lobe epilepsy: an introduction and review of the literature. *Epilepsia.*, 2008; *49(5): 741–57.*
4. Duncan, J.S. Brain imaging in idiopathic generalized epilepsies. *Epilepsia*, 46 Suppl, 2005; 9(10): 108–11.
5. Woermann, F.G., Free, S.L., Koepp, M.J. et al. Abnormal cerebral structure in juvenile myoclonicepilepsy demonstrated with voxel-based analysis of MRI. *Brain.*, 1999; 122: 2101—2108.
6. Koepp, M.J. & Woermann, F.G. Imaging structure and function in refractory focal epilepsy. *Lancet neurology*., 2005; 4(1): 42–53.

7. Betting LE, Mory SB, Li LM, et al. Voxel-based morphometry in patients with idiopathic generalized epilepsies. Neuroimage, 2006(a); 32: 498–502.
8. Betting, L.E, Mory SB, Lopes-Cendes I. et al. MRI volumetry shows increased anterior thalamic volumes in patients with absence seizures. *Epilepsy & behavior*, 2006(b)*;* 8(3): 575–80.
9. Tae WS, Hong SB, Joo EY, et al. Structural brain abnormalities in juvenile myoclonic epilepsy patients: volumetry and voxel-based morphometry. Korean J Radiol, 2006; 7: 162–172.
10. Kim, J.H, Lee JK, Koh SB, et al. Regional grey matter abnormalities in juvenile myoclonic epilepsy: a voxel-based morphometry study. *NeuroImage.,* 2007; *37(4): 1132–7.*
11. de Araújo Filho GM, Lin K, Lin J, et al. Are personality traits of juvenile myoclonic epilepsy related to frontal lobe dysfunctions? A proton MRS study. Epilepsia., 2009; 50(5): 1201-1209.
12. Lin, K, Jackowski AP, Carret H Jr, et al. Voxel-based morphometry evaluation of patients with photosensitive juvenile myoclonic epilepsy. *Epilepsy research*, 2009; 86(2-3): 138–45.
13. Liu, M., Concha, L., Beaulieu, C. Distinct white matter abnormalities in different idiopathic generalized epilepsy syndromes. *Epilepsia*., 2011; 52: 2267—2275.
14. O'Muircheartaigh, J., Vollmar, C., Barker, G.J. Focal structural changes and cognitive dysfunction in juvenile myoclonic epilepsy. *Neurology*., 2011; 76: 34—40.
15. Mory, S.B., Li, L.M., Guerreiro, C.A.M. Thalamic dysfunction in juvenile myoclonic epilepsy. A proton MRS study. Epilepsia., 2003; 44: 1402—1405.
16. Roebling R, Scheerer N, Uttner I, et al. Evaluation of cognition, structural and functional MRI in juvenile myoclonic epilepsy. Epilepsia, 2009; 50: 2456–2465.
17. Bernhardt, B.C. et al. Imaging structural and functional brain networks in temporal lobe epilepsy. *Frontiers in human neuroscience*., 2013; 7: 624.
18. Huang W, Lu G, Zhang Z, et al. Gray-matter volume reduction in the thalamus and frontal lobe in epileptic patients with generalized tonic-clonic seizures. *Journal of neuroradiology. Journal de neuroradiologie*., 2011; 38(5): 298–303.
19. Wang, Z, Zhang Z, Jiao Q, et al. Impairments of thalamic nuclei in idiopathic generalized epilepsy revealed by a study combining morphological and functional connectivity MRI. *PloS one,* 2012; 7(7): e39701.

20. Kim, J.H, Kim JB, Seo WK, et al. Volumetric and shape analysis of thalamus in idiopathic generalized epilepsy. *Journal of neurology*, 2013; 260(7): 1846–54.
21. Yasuda, C.L., Betting, L.E. Cendes, F. Voxel-based morphometry and epilepsy. *Expert review of neurotherapeutics*., 2010; 10(6): 975–84.
22. Koepp, M.J, Woermann F, Savic I, et al. Juvenile myoclonic epilepsy—neuroimaging findings. *Epilepsy & behavior*., 2013; *E & B*, 28(Suppl 1): S40–4.
23. Savic, I., Lekvall, A., Greitz, D. MR spectroscopy shows reduced frontal lobe concentrations of N-acetyl aspartate in patients with juvenile myoclonic epilepsy. Epilepsia., 2000; 41: 290-296.
24. Savic I, Osterman Y, Helms G. MRS shows syndrome differentiated metabolite changes in human-generalized epilepsies. Neuroimage., 2004; 21(1): 163-172.
25. Koepp MJ, Duncan J. 2000. *Positron emission tomography in idiopathic generalized epilepsy: imaging beyond structure. In: Schmitz B, Sander T, editors. Juvenile myoclonic epilepsy: The Janz Syndrome. London: Wrightson.*
26. Koepp MJ, Richardson MP, Brooks DJ, et al. Central benzodiazepine/gamma-aminobutyric acid A receptors in idiopathic generalized epilepsy: an [11C] flumazenil positron emission tomography study. *Epilepsia*., 1997; 38: 1089–97.
27. Ciumas C, Savic I. Structural changes in patients with primary generalized tonic and clonic seizures. Neurology, 2006; 67: 683–686.
28. Cossette P, Liu L, Brisebois K, et al. Mutation of GABRA1 in an autosomal dominant form of juvenile myoclonic epilepsy. *Nat Genet*., 2002; 31: 184–189.
29. Matthias J Koepp MJ, Thomas RH, Wandschneider B, et al. controversiesof juvenile myoclonic epilepsy: still an enigmatic epilepsy Expert Rev. Neurother., 2014; 14(7): 819–831.
30. Ridgway, G R, Henley SM, Rohrere JD, et al. Ten simple rules for reporting voxel-based morphometry studies Neuro Image., 2008; 40: 1429–1435.