Meta-Analysis of White Matter Voxel-Based Morphometry Studies investigating Refractory Unilateral Epilepsy

Poster No.:	C-1383
Congress:	ECR 2013
Type:	Scientific Exhibit
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Keywords:	Developmental disease, Biological effects, Experimental investigations, MR, Neuroradiology brain
DOI:	10.1594/ecr2013/C-1383

Purpose

Epilepsy is a condition experienced by many and is characterised by recurrent episodes of motor, sensory or psychological malfunction; these episodes are often referred to as epileptic seizures (Tortora, Derrickson 2006). Temporal lobe epilepsy (TLE) is a relatively common form of epilepsy, the onset of which can be either in childhood or adulthood. It refers to a form of the condition where the epileptogenic focus of the seizures occurs within the temporal lobe of the brain, this focus can be either right or left sided within the temporal lobe, allowing for the division of right sided TLE (RTLE) and left sided TLE (LTLE).

In 2012 Li, Zhang & Shang performed a meta analysis of results of voxel-based morphometry (VBM) studies in refractory TLE regarding the change in grey matter concentrations in the brain (Li, Zhang & Shang 2012), this study was comprehensive and still very current, however there was no investigation of the effects of TLE on white matter concentrations. Previous studies have shown changes in white matter volume (WMV) as a result of TLE (Alhusaini et al. 2012; Diniz et al. 2011; Coan et al. 2009). White matter concentration levels indicate the number of nerve fibres or myelinated axons (Tae et al. 2010), which means a reduction could, and has shown to mean a reduction in cognitive function (Amar et al. 1996). Previous studies (Coan et al. 2009b; Alhusaini et al. 2012; Diniz et al. 2011; Bernasconi et al. 2004; Bouilleret et al. 2008) have relatively consistently shown reductions in white matter volume, however the samples sizes have been relatively small and there have been some differences in the areas affected by the presence of TLE. If there is a clear correlation between the presence of lateralised TLE and a change in white matter concentrations in certain specific parts of the cerebrum then it will allow clinicians the advantage of knowing how patients who have been experiencing either right or left sided TLE may be affected in terms of cognitive and emotional function/ experience.

The **aim of the study** is to perform a meta-analysis of previous VBM studies that have investigated the change in concentration of white matter in the human brain as a result of the presence of unilateral temporal lobe epilepsy using ALE with a view to obtaining more accurate and complete data than any of the studies can provide alone

Methods and Materials

Data Source

Text searches were performed in the Scopus and Web of Knowledge databases, exclusions were made either in the nature of the search or manually after reading of the study. Search term key words were: ("temporal lobe epilepsy" or "TLE") and ("voxel-

based morphometry" or "VBM") and "white matter". References and citation lists of the studies found were also reviewed for further studies that met the inclusion criteria.

Inclusion and Exclusion Criteria

Table 1 shows the inclusion and exclusion criteria for studies considered for the meta-analysis.

Voxel Based Morphometry Meta-Analysis

VBM meta-analysis was performed on all the included studies by first extracting their meta-data using the BrainMap Sleuth Client and then using the ALE software (GingerALE 2.1.1, http://www.brainmap.org/) in order to compare white matter concentration changes between each of the unilateral TLE groups and their (corresponding where available) healthy control group. Coordinates were outputted in Talairach space. The full width half maximum (FWHM) was set in line with the quantitative uncertainty model demonstrated in Eickhoff et al.'s 2009 article and refined in Turkeltaub et al.'s 2012 study. The false discovery rate was set using a statistical threshold of $p<0.05$ and by clusters of total minimum volume exceeding 1,000 mm^3. Cluster analysis was performed in the Ginger ALE process, with a .txt file showing all clusters and their peak ALE values and anatomical labels. The centre of each cluster was also included in this output. The coordinate data was then transformed into a single input file and loaded into the Talairach space database using the Java based client (Talairach Client 2.4.2 http://www.talairach.org/client) in order to produce approximate (within 5mm) anatomical sites for each cluster of significant ALE values. Further to this .nii files produced by the ALE meta-analysis were viewed as overlays to the 'colin1.nii' file available from BrainMap, this underlay is a highly detailed human brain map produced by repeated computed tomography (CT), MRI and positron emission tomography (PET) scanning of Colin Holmes (volunteer at the McConnell Brain Imaging centre) combined with 27 other data sets from MRI scanning (Watson 2002).

Images for this section:

Inclusion	Exclusion
Studies using magnetic resonance imaging (MRI) to perform voxel-based morphometry studies of the brain.	Studies using other measures such as surveys of symptoms or other quantitative measures such as CT, PET or EEG exclusively.
Studies written in English.	Studies written in other languages.
Studies concerning patients with TLE.	Studies exclusively concerning patients with other forms of epilepsy.
Studies including data regarding the lateralisation of the TLE.	Studies that do not decipher between right and left sided TLE or between TLE and other forms of epilepsy, assessment of sidedness of the TLE must be performed using video EEG monitoring or another equally as highly reliable method.
Studies with available VBM data regarding white matter.	Studies without VBM data and/or not regarding white matter.
Studies published in or after January 2002	Studies published before 2002.
Studies published in peer reviewed journal.	Discursive works, published opinions, editorials and letters.
Unique data, not repeated in other included studies	Repeated data.

Key: TLE – Temporal lobe epilepsy, MRI – Magnetic resonance imaging, EEG – Electroencephalogram, CT – Computed tomography, VBM – Voxel-based morphometry, PET – Positron emission tomography.

Table 1: Inclusion and Exclusion Criteria. Key: TLE - Temporal lobe epilepsy, MRI - Magnetic resonance imaging, EEG - Electroencephalogram, CT - Computed tomography, VBM - Voxel-based morphometry, PET - Positron emission tomography.

Results

Included Studies and Demographics

A total of 55 studies were found from the search criteria, with 6 passing all the inclusion and exclusion criteria (Tae et al. 2010, Coan et al. 2009, Bernasconi et al. 2004, Bouilleret et al. 2008, McMillan et al. 2004, Pell et al. 2008). Of these 6, 3 diagnosed the lateralisation of the TLE using video electroencephalogram (EEG) monitoring (Coan et al. 2009, Bernasconi et al. 2004, McMillan et al. 2004), while 1 used the result of surgical outcome i.e. following left sided surgery, the patient's symptoms improved, therefore their TLE was likely to be left sided, clearly this must have been previously assessed in another way but it is not mentioned), this was assessed as being a reliable way of determining the sidedness of the epileptogenic focus (Tae et al. 2010) and the remaining 2 only included patients who had suffered with left sided TLE (Bouilleret et al. 2008, Pell et al. 2008). The results of the literature search are shown in Table 2 and demographics of the includied studies' patient populations in Table 3.

Regional Differences in White Matter Volume

The ALE analysis outputted 29 clustered sites of WM volume changes (23 decrease, 4 increase) for the LTLE groups when compared to healthy controls and 17 sites (13 decrease, 4 increase) in the RTLE group. All these clustered sites had volumes of at least 1,000 mm^3. In the LTLE meta-analysis 9 of the cluster sites were contributed to by two or more the included studies, the importance of these sites was reflected in them also having some of the largest peak ALE values compared to the other LTLE white matter concentration change clusters. A total of 10 of the sites affected by the presence of LTLE were located in the right side of the brain, meaning there was a considerably larger change made ipsilaterally. On the ipsilateral side there was a total affected volume of 54,696 mm^3 compared to a much lower affected volume on the contralateral side of just 23,296 mm^3. The largest area of affected white matter and the area with the highest peak ALE value were both positioned in the left temporal lobe which contains the hippocampal and parahippocampal structures as well as the specific area the LTLE is focused.

The balance of affected areas of the ipsilateral/contralateral brain was more pronounced in the RTLE meta-analysis. The total volume affected in the ipsilateral side in RLTE was 5,6984 mm^3 compared to 1,8744 mm^3 contra laterally; this ratio is considerably higher than the equivalent in the LTLE group however the sheer number of cluster sites was far less, with only 7 of the affected cluster sites being contralateral. The largest peak ALE value in the RTLE meta-analysis was ipsilateral and positioned inside the parahippocampal gyrus in the limbic lobe. Of all the cluster sites demonstrated by the RTLE analysis only two were contributed to by two or more studies, this suggests more data points would have been valuable.

Images for this section:

Title	Authors	Year Published	Pathologies studied	Number of Participants	Reference
Grey, white matter concentration changes and their correlation with heterotropic neurons in temporal lobe epilepsy.	Tae WS,, Joo EY, Kim ST, Hong, SB.	2010	LTLE and RTLE	RTLE: 15 RTLE Controls: 23 LTLE: 16 LTLE Controls: 24	(Tae et al. 2010)
Seizure frequency and lateralization affect progression of atrophy in temporal lobe epilepsy.	Coan A C, Appenzeller S, Bonilha L, Li L M, Cendes F	2009	RTLE and LTLE	RTLE: 13 LTLE: 20 Controls: 24	(Coan et al. 2009b)
Whole-brain voxel-based statistical analysis of grey matter and white matter in temporal lobe epilepsy.	Bernasconi N, Duchesne S, Janke A, Lerch J, Collins D L, Bernasconi A	2004	RTLE and LTLE	RTLE: 40 LTLE: 45 Controls: 47	(Bernasconi et al. 2004)
Voxel-based morphometry of unilateral temporal lobe epilepsy reveals abnormalities in cerebral white matter.	McMillan A B, Hermann B P, Johnson S C, Hansen R R, Seidenberg M, Meyerand M E	2004	RTLE and LTLE	RTLE: 12 LTLE: 13 Controls: 62	(McMillan et al. 2004)
Composite voxel-based analysis of volume and T2 relaxometry in temporal lobe epilepsy.	Pell G S, Briellmann R S, Pardoe H, Abbott D F, Jackson G D	2008	LTLE	LTLE: 19 Controls: 115	(Pell et al. 2008)
Basal ganglia involvement in temporal lobe epilepsy: A functional and morphologic study.	Bouilleret V, Semah F, Chassoux F, Mantzaridez M, Biraben A, Trebossen R, Ribeiro M J	2008	LTLE	LTLE: 12 Controls: 30	(Bouilleret et al. 2008)

Key: RTLE – Right temporal lobe epilepsy, LTLE – Left temporal lobe epilepsy.

Table 2: Included Key Studies

	LTLE				RTLE			
Paper Reference	No.	Average Age ±S.D (Years)	Controls	Average Age ±S.D (Years)	No.	Average Age ±S.D (Years)	Controls	Average Age ±S.D (Years)
(Tae et al. 2010)	16	32.7 ±8.47	24	32.2 ±9.05	15	28.7 ±10.59	23	29.8 ±11.42
(Coan et al. 2009b)	20	38** ±9.8	24*	36.5 ±12	13	38** ±9.8	24*	36.5 ±12
(Bernasconi et al. 2004)	45	35** ±10	47*	33 ±12	40	35** ±10	47*	33 ±12
(McMillan et al. 2004)	13	32.23** ±11.2	62*	32.4 ±12.2	12	32.23** ±11.2	62*	32.4 ±12.2
(Pell et al. 2008)	19	39.3 ±12	115	28.9 ±10	0	N/A	N/A	N/A
(Bouilleret et al. 2008)	12	31.5	30	36 ±10	0	N/A	N/A	N/A

Key: LTLE – Left temporal lobe epilepsy, RTLE – Right temporal lobe epilepsy, S.D – Standard deviation, *Controls not matched to seizure focus side groups, **Average and standard deviation data not divided into seizure focus side groups.

Table 3: Demographics of included studies patient samples

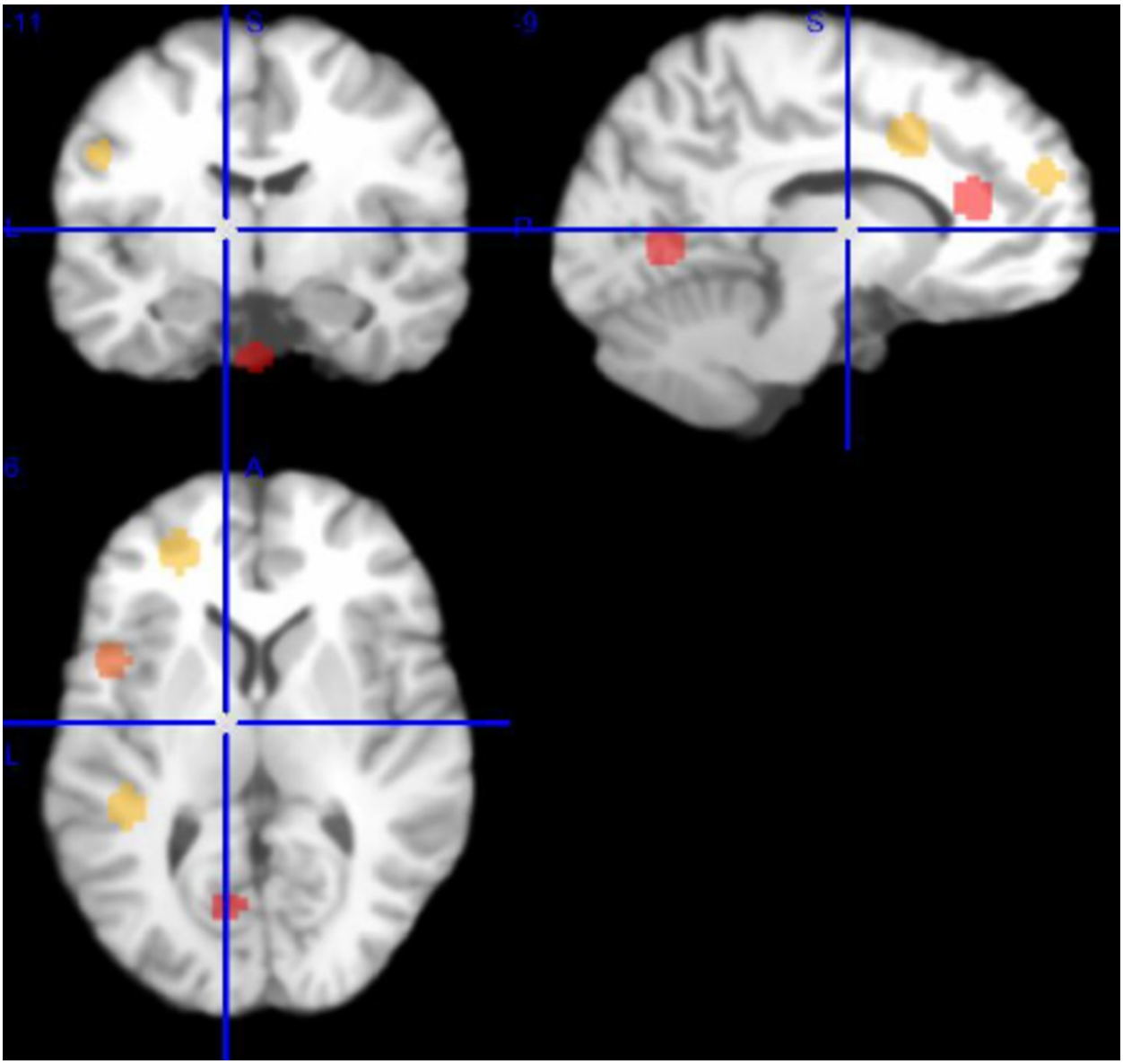

Fig. 1: Ginger ALE output for LTLE meta-analysis. Red areas show greatest changes in white matter concentration while orange and yellow show smaller and smallest changes respectively. Talairach coordinates of image: (x = -11, y = -9, z = 6). Note: more prolific disruption results on the ipsilateral (left) side and the clear extratemporal areas of white matter reduction.

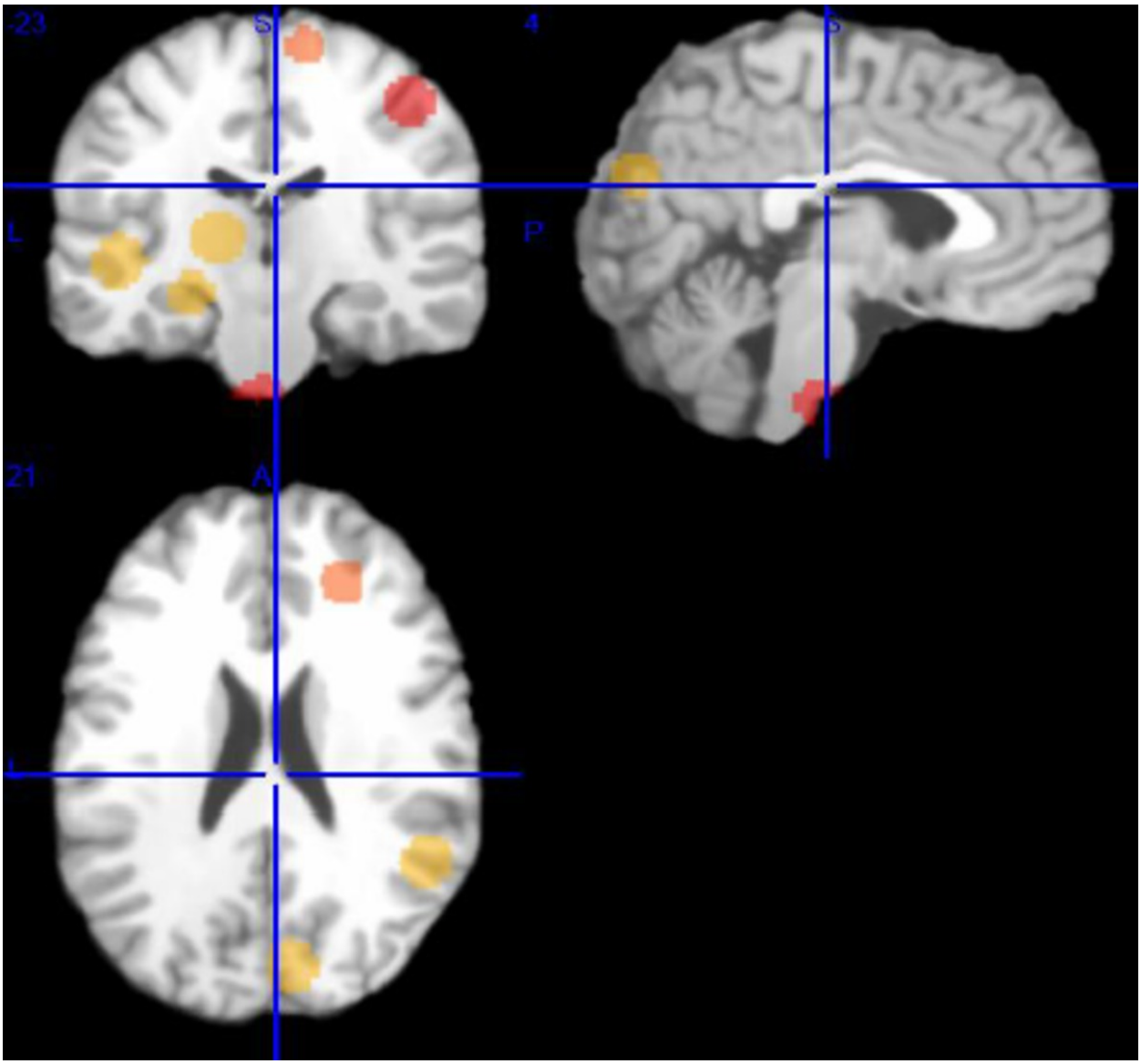

Fig. 2: Ginger ALE output for RTLE meta-analysis data. Red areas show greatest changes in white matter concentration while orange and yellow show smaller and smallest changes respectively. Talairach coordinates of image: (x = 23, y = 4, z = 21).

Conclusion

The findings of the this study clearly suggest that white matter disruption is occurring in patients with unilateral TLE, and that it is more severe ipsilateral to the epileptogenic side. Furthermore, is it clear there is extra-hippocampal and extra-temporal damage to myelinated axons in the cerebrum. While the exact reasons for the disruption to white matter are not exactly clear yet, further investigation into the areas of damage may help in revealing more about TLE as a whole and specifically how its ongoing presence and the occurrence of febrile seizures may affect cognitive and emotional function in patients 17 suffering with unilateral TLE. This is important, as having accurate and reliable information about how TLE may affect a patient's life is invaluable not only to them, but also to anyone (e.g. carers and clinicians) in considering the relative merits and risks of surgical treatments for this condition. Future studies in this area would be improved by larger sample groups and high levels of accuracy in assessment of where, preciselyy, the epileptogenic focus is located in the temporal lobe.

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Personal Information