Dynamic changes in white and gray matter volume are associated with outcome of surgical treatment in temporal lobe epilepsy☆

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Abstract

Background: The reasons for surgical failure in 30% of patients with unilateral mesial temporal lobe epilepsy (MTLE) are still unclear. We investigated if different outcomes could be associated to different patterns of subtle gray matter atrophy (GMA) and white matter atrophy (WMA), and searched for postoperative magnetic resonance imaging (MRI) changes.

Methods: We studied 69 controls and 67 operated patients with refractory unilateral MTLE. Patients were grouped as seizure-free (SF) group (34 patients Engel's IA), worthwhile improvement group (23 patients, Engel's IIB–IIA) and failure group (10 patients Engel's IIB–IV). We created a voxel-based morphometry/MATLAB code to mask the surgical lacuna, and performed t-test and paired t-test to evaluate preoperative and postoperative MRI scans.

Results: Failure group showed a widespread pattern of preoperative GMA. On SF and improvement groups we identified a more restricted pattern of GMA. The three groups presented a widespread, bilateral pattern of WMA. In contrast, postoperative analyses showed bilateral hemispheric recovery (a relative increase of WM concentration) on SF and improvement groups, but few changes on failure group. We also identified areas with relative postoperative increase of GM on both SF and improvement groups, more widespread on SF group.

Conclusion: Areas of subtle GMA may be related to poorer surgical outcome. In addition, we demonstrated a postoperative relative increase of WM and GM concentration associated with seizure control. These changes may represent neuroplasticity related to improvement of brain function after seizure control. Further studies with a multimodal approach may help to predict surgical outcome and improve selection of patients for surgical treatment of MTLE.

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Introduction

Surgical treatment for refractory unilateral mesial temporal lobe epilepsy (MTLE) has been indicated with a successful rate of complete seizure freedom of about 70% (Engel, 1993). Regardless restricted and uniform selection of candidates with unilateral hippocampal atrophy associated to ipsilateral EEG seizure onset, one third of patients do not become seizure-free after adequate resection of medial structures of temporal lobe (Wiebe et al., 2001; Yasuda et al., 2006). The surgical approach, selective amygdalohippocampectomy or anterior temporal lobectomy, appears to have no influence in the outcome (Arruda et al., 1996; Paglioli et al., 2004).

The perpetuation of seizures after surgery is multifactorial and results from the combination of facts that include insufficient resection of hippocampus, amygdala, parahippocampal gyrus and entorhinal cortex (Siegel et al., 1990; Bonilha et al., 2007b), bilateral hippocampal atrophy, multiplicity of potential ictal generators within the temporolimbic system (Wennberg et al., 2002), along with the postoperative persistence of extralimbic abnormalities that may also be involved in the seizures’ generation (Bertram 2003). Some preoperative factors are associated to a high probability of achieving seizure control after surgery and include: history of prolonged febrile seizures or multiple seizures in early infancy (6 months to 4 years)
(Abou-Khalil et al., 1993), unilateral hippocampal atrophy (Arruda et al., 1996), interictal temporal hypometabolism on PET scans and age at surgery (Tellez-Zenteno et al., 2007). Despite these evidences, our understanding about the functional anatomy of limbic epilepsy is incomplete and the investigation of prognostic tools remains necessary in order to predict individual's surgical outcome and simplify the selection of candidates.

The metabolic recovery of neuronal function after surgery has been described by means of proton MR spectroscopy and 18F-FDG PET (Cendes et al., 1997a; Hugg et al., 1996; Spanaki et al., 2000), but evidences of associated structural changes are still lacking. In this study we used the voxel-based morphometry (VBM) method (Good et al., 2001) to characterize distinct patterns of preoperative regions with atrophy of both gray (GM) and white matter (WM) that could be specifically associated to surgical outcome. With the same technique, we also investigated the postoperative MRI changes in WM and GM compared to preoperative MRI on patients rendered free of seizure and on those who were not free of seizures. As we had previously studied the amount of surgical resection relation to surgical outcome (Bonilha et al., 2007b) we now concentrated in investigating the in

We included 69 controls (39 women, mean age 34.3±11.0 years) and 67 patients, (41 women, mean age 34±10.4 years). We excluded 23 patients with unilateral hippocampal atrophy who had significant artifacts on volumetric (3-D) MRI sequence. Therefore, this group does not represent our surgical series of MTLE.

Surgical Procedure

The surgical approach depended on the surgeon's experience and consisted of anterior cortical resection with amygdalohippocampectomy (16 patients) and selective trans-Sylvian amygdalohippocampectomy (51 patients), both with similar surgical outcome. Hippocampal sclerosis was confirmed for all patients after histological analysis (Babb and Brown 1987).

Group Formation

Between August and November 2007 we updated the outcome of all included patients according to Engel's outcome scale (Engel, 2001) and separated them in three different groups: seizure-free (SF) group with 34 patients (Engel's: IA), worthwhile improvement group with 23 patients (Engel's: 8 IB, 3 IC, 6 ID,6 IIA) and failure group with 10 patients (Engel's 1 IIb, 6 IIbA, 3 IVA). It is important to state that patients included in this present study do not represent the final outcome of our entire surgical series as we did not include all MTLE patients submitted to surgery as described above.

This study was approved by the ethics committee of our institution and patients gave us a written informed consent.

Magnetic Resonance Imaging

Acquisition

The MRIs were acquired in a 2T scanner (Elscint Prestige, Haifa, Israel) with the following parameters: (1) sagittal $T_1$ spin echo; 6 mm thick; flip angle, 180°; repetition time (TR), 4600; echo time (TE), 12; matrix, $320 \times 320$; and field of view (FOV), 25×25 cm; (2) coronal images, perpendicular to long axis of hippocampus, defined on the sagittal images: (a) $T_2$-weighted and proton density fast spin echo; 3 mm thick; flip angle, 160°; TR, 4600; TE, 108/18; matrix, $256 \times 256$; FOV, $22 \times 22$ cm; (b) $T_1$-weighted inversion recovery; 3 mm thick; flip angle, 180°; TR 2700; TE, 14; inversion time, 860; matrix, $155 \times 256$; and FOV, $18 \times 18$ cm; (3) axial images parallel to the long axis of the hippocampi: (a) $T_2$-weighted gradient echo; 3 mm thick; flip angle, 70°; TR, 200; TE, 5.27; matrix, $230 \times 230$; and FOV, $22 \times 22$ cm; (b) FLAIR (inversion recovery fast spin echo); 5 mm thick; flip angle, 110°; TR, 10099; TE, 90; matrix, $250 \times 250$; and FOV, 24×24 cm; and (4) $T_1$-weighted 3-dimensional gradient echo with 1-mm isotropic voxels, acquired in the sagittal plane (1 mm thick; flip angle, 35°; TR, 22; TE, 9; matrix, $256 \times 220$; and FOV, $25 \times 22$ cm) (Bonilha et al., 2007a).

We used the same 3D protocol for patient's preoperative and postoperative scans as well as for healthy controls.

MRI Volumetric Analysis

In accordance with a previously described protocol (Bonilha et al., 2004a), we performed manual volumetry of hippocampi from patients and controls using DISPLAY (David McDonald, www.bic.mni.mcgill.ca/software). Besides hippocampal volume we obtained the asymmetry index (AI) for each patient and control (defined as the ratio of the smaller by the larger hippocampus). Volumes and/or AIs that were 2 standard deviations (SD) below the mean values of controls were considered as evidence of hippocampal atrophy. Both hippocampal volumes and AIs were transformed into z-scores
(standardized scores defined by the number of SDs away from the mean of control group) in order to facilitate presentation of data.

Image Preprocessing for VBM Analyses

We used MRICro (www.mricro.com) (Rorden and Brett, 2000) to transform the original format (DICOM) to ANALYSE®, mark the anterior commissure for the normalization process and flip the brains with right hippocampal atrophy in order to combine patients with right and left hippocampal atrophies, avoiding left to right cancellations on VBM analyses. We decided to flip right-sided patients to take advantage of statistical power and improve the probability of detecting areas with atrophy in relation to surgical outcome. Despite some particularities of right and left MTLE, both showed signs of similar pattern of atrophy distribution. As a result, the analysis of patients as a homogeneous group may increase the ability to identify areas with atrophy that are similar to both right and left MTLE and related to surgical results (Bonilha et al., 2006). One neurosurgeon (C.L.Y.) used the drawing tool to manually segment the surgical lacuna of each patient's postoperative volumetric MR scan, creating individual region of interest (ROI), or the mask imaging. Each individual ROI was transformed into binary mask and then smoothed to be applied during the VBM process of postoperative scan.

We used software package SPM2 (Wellcome Trust Centre for Neuroimaging, London, England; www.fil.ion.ucl.ac.uk) on MATLAB 7.0 to apply the technique of VBM to all preprocessed images, both preoperative and postoperative scans.

Voxel-Based Morphometry

Voxel-based morphometry (VBM) has been proposed in 1995 and different methods have appeared since then (Ashburner and Friston 2000). VBM is a technique that uses global information from high resolution MRI for characterizing regional cerebral volume and tissue concentration differences.

The standard VBM method can be summarized by the following sequence of steps: spatial normalization; segmentation and smoothing (Bonilha et al., 2004c; Good et al., 2001). After smoothing, each voxel of the image is a locally weighted average of GM or WM density from a region of surrounding voxels, and statistical analyses can be performed.

Previous investigators (Good et al., 2001) have identified some limitations of the segmentation used by the standard VBM protocol given that during normalization process some brain areas with atrophy can be enlarged to match the standard template. Consequently, variations in GM and WM volume from our patients could be “washed out” due to nonlinear spatial normalization process. To overcome this distortion Good et al. (2001) proposed an optimized method (optimized VBM) with an additional processing step after segmentation, in order to preserve the volume of a particular tissue (GM, WM or CSF) within a voxel. The process consists in modulating voxel values in the segmented images by determinants derived from the normalization step, compensating the tissue deformation that occurs during the normalization process. The modulated data can be tested for regional differences in volume, and may reveal more subtle abnormalities in GM than the standard version of VBM (Keller et al., 2004).

Besides correcting for volume changes, the optimized VBM takes care of extracting whole-brain from scalps in order to achieve more accurate spatial normalization and segmentation steps.

Optimized VBM and Surgical Resections

The optimized-VBM can be easily implemented by a MATLAB routine using SPM, since SPM has already efficient implementations of each step of the protocol. VBM has been widely used for the analysis of differences between individuals with different ages or gender, or differences between normal and pathological, without any surgical intervention (Good et al., 2001; Bonilha et al., 2004c). We have not found any application of VBM to study differences between the same brain prior to and subsequent to a surgical resection.

The presence of surgical lacunae or other focal lesion leads to a problem during the normalization and segmentation steps, since these steps use global information of the brain and global information of the template brain; in view of the fact that the template does not have the same lacunae as the post-surgical brain, such comparisons are not possible. The spatial normalization of images with focal lesions (as surgical lacunae) with application of automated algorithms attempts to reduce the image mismatch between the image and the template at the site of the lesion, leading to significant image distortion. The proposed solution to overcome this distortion is to use cost–function masking (masking the areas used in the calculation of the image difference) to exclude the area of the lesion during the process and avoid bias during the transformations (Brett et al., 2001b) (Supplemental Fig. 1).

The implementation of spatial normalization available in SPM2 allows the application of a mask over the lacunae, so the registration process simply ignores the information under such mask and prevents the lacunae to contribute to the normalization (Brett et al., 2001a,b). Normalization with masks has already been correctly validated and is widely used by researchers in neuroimaging (Crinion et al., 2007).

To analyze the postoperative scans we have implemented a modified version of the SPM segmentation, which accepts a mask as parameter and ignores, for global features computations, every voxel inside the region of the mask. Consequently, we have an optimized VBM-lesion, with preserved defaults settings present in the original protocol, which permits VBM to be applied to brains with lacunas or lesions.

For the controls and patient’s preoperative MR scan we applied the built-in optimized VBM routine, and for the postoperative MR scans, we applied the new routine, optimized VBM-lesion that requested individual masks for completing the process. After this step we obtained preoperative and postoperative individuals maps of GM and WM, both registered to the same stereotactic space, allowing us to compare them with those of healthy controls as well as between themselves, in a paired t-test (before and after surgery).

The MATLAB/SPM script is available online as a Supplemental material of this article.

Statistical Analysis of VBM

The whole-brain voxel analyses were corrected for multiple comparisons through false discovery rate statistical threshold of 1% (Genovese et al., 2002), with an extent threshold looking for clusters with at least 32 contiguous voxels. This implicates that approximately 1 of 100 voxels identified as statistically significant is actually a false positive.

We confirmed the stereotaxic coordinates provided in the SPM output by visual analyses and further converted them to anatomical names with the use of the MNI Space Utility and Talairach Space utility, running these routines on SPM [for the algorithms, see http://www. iibh.spb.ru/~pet_lab/MSU/MSUMain.html] (Korotkov et al., 2005).

For voxel-wise analysis we used t-test to compare patients with controls and paired t-test to compare preoperative and postoperative images from patients. All tests were performed on SPM2. The contrasts on 2-tailed paired t-test were defined to reveal areas of WM/GM increase and decrease after surgery. The analyses included proportional threshold masking (set to 0.8) and implicit masking.

The output for each comparison is a statistical parametric map of the t statistic (SPM t), which is transformed to a normal distribution map (SPM z). The maps were overlaid on a multislice display of coronal images of a smoothed T1-MRI template (simultaneous GM
and WM results) with correspondent z-score bar for each map. We used a SPM routine “display_slices” (http://imaging.mrc-cbu.cam.ac.uk/imaging/DisplaySlices) to build the structural T1 MRI slices. The smoothed brain was chosen since the results were obtained from smoothed data (Ridgway et al., 2008).

To assure the reliability of the comparisons among scans we divided the control group in two subgroups with similar age and sex distribution (Group 1: 34 individuals (19 women, 34.1±[11.3] years) and Group 2: 35 individuals (20 women, 34.4±[10.7] years of age) and performed a 2-tailed t-test between them in search of areas with either excess or atrophy of GM and WM. Absence of abnormal areas of GM and WM in this analysis gives further support against false positive findings (Supplemental Fig. 2).

With the purpose of certifying that the surgical lacuna had been properly preserved during segmentation process we also performed a t-test between the preoperative and postoperative GM extracted maps, expecting an extremely high p-value (Supplemental Fig. 3, e-Table 17).

**Statistical Analyses of Clinical Data**

We used SYSTAT 12 (San Jose, California, USA, Systat Software Inc, [SSI]) to analyze clinical variables from patients and controls. We used t-test with Bonferroni’s correction to compare continuous data between patients and controls. For categorical variables we used Pearson χ² and Fisher’s exact test. ANOVA with post hoc Turkey’s pairwise comparisons was used to compare means between the 3 groups.

**Results**

No significant differences were observed between groups of controls and patients on gender (p = 0.58) and age (p = 0.89).

Clinical data of three groups are summarized in Table 1. No significant differences between groups were identified in view of the age of the first seizure or age at surgery. In contrast, the duration of epilepsy was shorter in the improvement group compared to the SF group (p = 0.046) and the follow-up of the improvement group was shorter than both SF group (p = 0.004) and failure group (p = 0.001). Febrile seizures were also more frequent on both SF and improvement group. The failure group presented longer interval between surgery and postoperative scan than improvement group (p = 0.02). We observed differences in AI between SF group and failure group (p = 0.04) and between improvement group and failure group (p = 0.025), but not between SF group and improvement group (p = 0.89).

**Preoperative Gray Matter Atrophy (GMA)**

Compared to controls, the distribution of areas with GMA was distinct for each of the three groups. SF group showed atrophy within ipsilateral temporal lobe, caudate and insula. In frontal lobes we found atrophy within, inferior and middle frontal gyri, but ipsilaterally on superior frontal gyrus. We also identified areas of atrophy within bilateral thalamus, cuneus and cerebellum. Some areas with GM atrophy were identified in ipsilateral lingual and middle occipital gyri (e-Table 2, Fig. 1A).

A restricted pattern of GMA was identified on worthwhile improvement group. Few areas within ipsilateral temporal lobe (hippocampus and parahippocampal gyrus) and superior frontal gyrus showed significant GMA. We observed atrophy in basal ganglia, caudate, bilateral thalamus and middle frontal gyri. In occipital lobe, only contralateral cuneus showed atrophy. There was also bilateral cerebellar atrophy in this group (e-Table 3, Fig. 1B).

Failure group showed a more widespread pattern of GMA. We identified significant GMA within both temporal lobes (more extensive ipsilaterally), thalamus, insula, frontal and parietal lobes. We also observed atrophy on ipsilateral caudate, and contralateral occipital lobe and cerebellum (e-Table 4, Fig. 1C).

**Preoperative White Matter Atrophy (WMA)**

SF group showed WMA in a restricted pattern, on bilateral precentral and postcentral gyri, as well as on inferior parietal lobule and supramarginal gyrus. Some areas with WMA were also found on ipsilateral cerebellum, cingulate gyrus, parietal and occipital lobe. Contralateral atrophy was identified on insula and on superior and middle frontal gyri (e-Table 5) (Fig. 1A).

The improvement group showed WMA within bilateral middle and inferior temporal gyrus, fusiform gyrus, cuneus and precuneus, ipsilateral middle frontal gyrus and contralateral precentral gyrus. In parietal lobe we detected atrophy on ipsilateral superior parietal lobule and on contralateral postcentral gyrus, inferior parietal lobule, supramarginal and angular gyrus. We also identified WMA on ipsilateral cerebellum (e-Table 6) (Fig. 1B).

We identified significant WM atrophy on failure group involving bilateral frontal and parietal lobes, ipsilateral cerebellum, cingulate gyrus, middle occipital gyrus and cuneus. Ipsilateral temporal lobe showed more extensive WMA than the contralateral temporal lobe (e-Table 7, Fig. 1C).

**Postoperative WM Changes**

On SF group we identified areas with relative increase of WM on ipsilateral frontal lobe and cerebellum when comparing preoperative and postoperative MRI scans. The relative increase on contralateral hemisphere was more widespread, encompassing cerebellum as well as frontal, temporal, and occipital lobes (e-Table 8, Fig. 2A).

The evaluation of improvement group revealed a less extensive pattern of relative WM increase. In this particular group we identified relative increase only in the ipsilateral insula, transverse temporal gyrus, cingulated and inferior frontal gyrus. On contralateral hemisphere we observed the relative increase on cingulate gyrus, medial frontal gyrus and transverse temporal gyrus (e-Table 9, Fig. 2B).

We did not detect areas of postoperative changes of WM in the failure group with FDR1% restrictions, but with a less conservative

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Clinical data from the three groups.</th>
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<tr>
<td></td>
<td>SF group</td>
</tr>
<tr>
<td>z-Scores of asymmetry index</td>
<td>−6.8±3</td>
</tr>
<tr>
<td>First seizure (years)</td>
<td>5.2±4.0</td>
</tr>
<tr>
<td>Duration of epilepsy (years)</td>
<td>26.5±10.9</td>
</tr>
<tr>
<td>Seizure frequency (monthly)</td>
<td>10.6±7.7</td>
</tr>
<tr>
<td>Age at surgery (years)</td>
<td>31.7±10.6</td>
</tr>
<tr>
<td>Febrile seizure (number of patients)</td>
<td>10</td>
</tr>
<tr>
<td>Follow-up (years)</td>
<td>5.5±2.5</td>
</tr>
<tr>
<td>Interval of postoperative MRI(months)</td>
<td>32.2±24.7</td>
</tr>
</tbody>
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SF = seizure-free; WI = worthwhile improvement; F = failure.
Fig. 1. Areas with GM and WM atrophy on 3 groups. Statistical maps are overlaid on a multislice display of coronal images of a smoothed T1 template. Each group has 2 maps, GM (red bar) and WM (blue bar), with respective z-score bar. We used the neurological convention, i.e. the right side of the images corresponds to the right side of the brain. A (seizure-free group), B (improvement group) and C (failure group).
analysis (without FDR) we observed few areas in the bilateral frontal lobes and contralateral temporal lobe (e-Table 10).

From the 2-tailed paired \( t \)-test we also investigated areas with more atrophy in the postoperative scan, but did not identify suprathreshold results from any of the 3 groups.

**Postoperative GM Changes**

In the SF group we identified areas with relative increase of GM within the ipsilateral parietal and frontal lobes, as well as on transverse temporal gyrus. On the contralateral hemisphere the relative increase of GM encompassed more extensive regions on temporal, occipital, parietal and frontal lobes as well as on lentiform nucleus (e-Table 11) (Fig. 2A).

The improvement group showed areas with relative increase of GM within the ipsilateral superior temporal and middle frontal gyri. We also identified some areas on contralateral hemisphere, involving part of temporal and frontal lobes, as well as on basal ganglia (e-Table 12) (Fig. 2B).

In contrast, we did not identify areas with relative increase of GM in the failure group with the restrictions of FDR on statistical analysis. Due to reduced number of patients in this group, we also performed less conservative analysis (without FDR), and identified few areas with relative increase of GM concentration in contralateral temporal lobe and insula (e-Table 13).

From the 2-tailed paired \( t \)-test we also analyzed areas with more atrophy in the postoperative scan, compared to the preoperative set of scans. We identified areas with more GMA after surgery in the ipsilateral temporal lobe, on both SF group and improvement group (confirming the surgical resection of hippocampus, \( t \) statistics 6.91–11.25), and in the contralateral temporal and frontal lobes of improvement group (e-Tables 14 and 15, e-Fig. 4A, B).

Although we did not identify areas with more postoperative GMA in the failure group with restrictions of FDR 1%, we performed a less conservative analysis (without FDR) and observed a widespread pattern of postoperative GMA, involving ipsilateral hemisphere (confirming the mesial resection, \( t \) statistic 6.33–8.23), and the contralateral frontal and parietal lobes (e-Table 16, e-Fig. 4C).

We performed an additional analysis combining all patients with Engel I–II (good control group) and compared them with failure group. This analysis showed results similar to those achieved with the 3 groups’ analyses, considering both clinical and MRI data. These results are available in Supplemental data (e-Tables 18–23, e-Figs. 5–7).

**Discussion**

**WM and GM Patterns of Atrophy**

As the reasons for surgical failure remain unclear, we investigated the hypothesis that distinctive preoperative patterns of GMA and WMA would be related to different surgical outcome. The results outlined in this study revealed that patients exhibiting a more widespread and bilateral pattern of GMA presented the worst outcome.

Areas with GM and WM atrophy on patients were not restricted to the ipsilateral temporal lobe, but instead encompassed both extra-temporal and bilateral regions. As previously described by other authors we recognized areas with GM atrophy on bilateral temporal, frontal, parietal and occipital lobes, as well as on cerebellum (Babb, 1991; Cendes et al., 1997b; Bonilha et al., 2007a; Arruda et al., 1996). We also identified atrophy on subcortical regions including bilateral basal ganglia and insula (Pulsipher et al., 2007). Atrophy in the thalamus was presented in all three groups, suggesting its participation in the seizure spread (Guye et al., 2006; Labate et al., 2008).

Even though some problems concerning the use of \( T_1 \)-weighted images for white matter morphometry have been raised (as the \( T_1 \) signal intensities are not perfectly correlated to white matter integrity), VBM has been used to investigate WM abnormalities associated to aging process (Good et al., 2001) as well as to epilepsy (Bernasconi et al., 2004; Mueller et al., 2006) and other diseases (Lazaro et al., 2009). Our analyses of WM atrophy showed a bilateral temporal and extratemporal distribution, in accordance with results described with diffusion tensor imaging (DTI) (Concha et al., 2007), which provides more subtle information about white matter composition (Buchel et al., 2004) and has been used as a marker for white matter tract integrity (Smith et al., 2007). Nevertheless, the
white matter VBM results should be taken with caution due to spatial normalization issues.

In this study we confirmed previous findings (Keller et al., 2007) which described an association of refractory postoperative seizures and widespread ipsilateral and bilateral preoperative temporal lobe GM abnormalities. In addition, possibly due to a larger number of studied individuals, we could identify extratemporal areas with both GM and WM atrophy. Compared to controls, the failure group in our study showed areas of significant GM atrophy on contralateral hemisphere that were undetected by visual analysis (Araujo et al., 2006; Margerison and Corsellis 1966). We believe that this widespread GM atrophy, in particular within contralateral temporal lobe, may be at least partially involved in the persistence of seizures after adequate removal of mesial structures of temporal lobe, in accordance with previous studies that also showed a poor surgical outcome related to bilateral pathology (Arruda et al., 1996) or contralateral cortical hypometabolism on 18FDG PET (Choi et al., 2003). WM atrophy in this group was evident in the two hemispheres, sparing only contralateral occipital and part of parietal lobes. The underlying abnormality of WM is still unclear and some studies have suggested some processes like increased neuronal heterotopia (Hammers et al., 2002; Sankar et al., 2008), microdysgenesis (Thom et al., 2000), myelin dysfunction and demyelination (Mitchell et al., 2003). Another study evaluated extratemporal WM abnormalities with DTI (Gross et al., 2006) and showed evidences of myelin degradation on external capsule and corpus callosum, but was unable to associate it with a worse surgical outcome. Unlike GM atrophy, the preoperative WM atrophy in our study did not allow us to establish a specific pattern for each group. Therefore, we could not associate the pattern of widespread, bilateral WM atrophy to a poor surgical outcome.

We identified a more restricted pattern of GM atrophy on SF group, but different from a previous study (Keller et al., 2007), we found bilateral atrophy on frontal lobes. This may be, in part, due to the larger number of individuals in our study. The association between unilateral mesial atrophy and good prognosis has been described previously (Cendes et al., 1996; Arruda et al., 1996) and our results are in agreement with these, although we selected only patients with unilateral hippocampal atrophy on visual MRI analysis and hippocampal volumetry. In fact, we detected other extrahippocampal areas with GM abnormalities that may be associated with hippocampal sclerosis, but we are not able to confirm if these findings lead to seizures or are consequence of repeated seizures. A previous study showed reduction of GM concentration in these areas which were negatively correlated with duration of epilepsy (Bonilha et al., 2006). In contrast, prospective studies were unable to associate duration of epilepsy and surgical outcome (Spencer et al., 2005b). Facing these observations we believe that these differences in extrahippocampal areas with GM atrophy may result from secondary injury caused by repetitive seizures through decades and by the type and severity of the initial precipitating injury (Mathern et al., 1995). Thalamic abnormalities have also been described (Bonilha et al., 2005; Guye et al., 2006; Labate et al., 2008) and may reflect its association with limbic system in the process of generation and spread of seizures. WM atrophy in this group showed a bilateral pattern, encompassing both temporal and extratemporal areas. Our results are in agreement with a previous DTI study (Gross et al., 2006) that showed similar extensive extratemporal, bilateral WM abnormality without association with a poor surgical outcome. These findings suggest that chronic temporal lobe epilepsy is associated to WM abnormalities, although its underlying pathophysiology is yet to be determined. We can speculate that these chronic abnormalities in WM are possibly related to the cognitive dysfunction in MTLE which etiology has always been difficult to be established (Hermann et al., 2007).

The improvement group showed a peculiar pattern of GMA. Despite some similarities with SF group (for example, more restricted ipsilateral temporal atrophy), these patients persisted with some seizures after surgery. Facing the pattern of GMA in this group, one could expect the most favorable surgical outcome. We believe that the less favorable outcome in these patients is probably related to other factors, such as different sensitivity to antiepileptic drugs, alternative functional pathways of seizure generation and spread, and suboptimal surgical resection (Bonilha et al., 2004b).

When collapsing the seizure-free and improved group (Engel I–II) the results were similar to that including 3 groups of patients, confirming the clinical differences between patients with and without good seizure control.

Reversible Injury

The present data are supported by the findings from previous MRS studies (Hugg et al., 1996; Cendes et al., 1997a). By means of whole brain analysis we could detect the same pattern of WM recovery not only in temporal lobes, but within both hemispheres. Previous studies with proton MR spectroscopy were unable to assess the whole brain at once; instead, they used selected regions, as part of temporal white matter or corpus callosum, to evaluate changes after temporal surgery (Spencer et al., 2005a; Spanaki et al., 2000; Hugg et al., 1996). So far, no previous study showed similar, whole brain analysis with evidences of WM and GM postoperative changes, but one study outlined evidences of neuroplasticity by application of optimized VBM on MR scans from normal individuals pre and post-transcranial magnetic stimulation (May et al., 2007). Even though our results are in accordance with results obtained with other techniques (i.e. spectroscopy and DTI), we should consider that the use of cost-function masks for lesioned brains presents some limitations due to the lack of correspondence between the subject and the template (Crinion et al., 2007; Brett et al., 2001a).

We observed that the WM changes after surgery were related to better seizure control, as we were unable to detect areas of recovery on the failure group (Cendes et al., 1997a). Unlike our results, one previous study showed the persistence of bilateral WM diffusion changes after surgery (Concha et al., 2007) and suggests that the abnormalities on WM are probably secondary to structural damage (e.g. myelin degradation). The use of different techniques and the larger number of individuals in our study may explain these different results, although we cannot exclude the limitations of using T1-weighted images for analyzing white matter morphometry as discussed by Buchel et al. (2004). Despite these discrepancies, another study using DTI analysis found evidences of WM recovery on contralateral occipital lobe after unilateral occipital lobectomy, suggesting plasticity changes for adaptive response (Govindan et al., 2008), giving support to our results.

The reasons for reversible WM abnormalities are yet to be determined. Some possible explanations are based on evidences of reversible metabolic impairment after removal of metabolic stress, neuronal plasticity with secondary synaptogenesis and dendritic sprouting (May et al., 2007; Majewska et al., 2006). Despite the limitations of our methods, we believe that the recovery might be resultant from the combination of these hypothesis, rather than the result from a single process. Even though the mechanisms of repair are still unclear, we can hypothesize that the recovery areas are probably related to the reversible neuronal dysfunction, expressed as postoperative seizure freedom and improvement on neuropsychological tests in some of these patients (Jokeit and Ebner 1999).

In our study we identified some areas with relative increase of GM, more expressive on SF group than on improvement group. Axonal and dendritic arborization, in addition to neuronal size and number, appear to be important contributors to the density of gray matter observed in MRI (Mechelli et al., 2005). This finding reinforces the main idea that the seizure control may be related to a combination of changes in density of dendritic spines and the remodeling of connectivity through these synapses. The connections between
basal ganglia and orbitofrontal regions (Barbas, 2007) as well those between basal ganglia and medial temporal lobe (Segr, 2006) may be relieved after reduction of seizures, resulting in a functional recovery previously described in children (Gleissner et al., 2005).

Despite the evidences of recovery from chronic brain injury, we are not able to assure that this phenomenon is time independent. It is possible that the poorer performance on neuropsychological tests of elderly (Grivas et al., 2006) who undergo surgical treatment and the postoperative deteriorations are consequences of a reduced capacity of recovery.

We also observed some areas with postoperative GMA in the ipsilateral temporal lobe of the 3 groups extending beyond the mesial structures, which are probably related to the surgical manipulation and tissue shrinkage after resection (Mueller et al., 2009). In the SF group and improvement group we observed areas with more GMA after surgery, compared to the failure group, which is probably related to a wider surgical resection in the former group. This finding may be at least partially related to the better prognosis, as in accordance with previous studies reporting better surgical outcomes in patients with more extensive resection of mesial structures (Siegel et al., 1990; Bonilha et al., 2004b, 2007b) Areas with GMA on contralateral hemisphere of improvement and failure groups may result from progression of damage. Further studies with larger number of patients are necessary to evaluate the progression of damage after surgery, correlating the structural abnormalities and cognitive dysfunction.

Our results give support to the concept that an early surgical intervention for refractory patients should not be delayed (Sirven et al., 2000). It is possible that early control of seizure may not only prevent further damage but also offer patients a chance to restitute normal brain function.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2009.08.014.

References


