

Comparative study of chronic TLE patients using structural and metabolic MRI measures of hippocampal damage.

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Abstract – Chemical-shift imaging (CSI) has been applied to the evaluation of patients with temporal lobe epilepsy (TLE), but few comparisons have been made between the data obtained from quantitative structural magnetic resonance imaging (MRI) and the accuracy of CSI to identify pathological changes within the hippocampus. Our goal was to determine the discriminative capability of CSI hippocampal NAA/(Cho+Cre) ratios to distinguish between patients with lateralized epileptic foci when compared to structural MRI measures of disease.

I. INTRODUCTION

Magnetic resonance has assumed an increasingly important role in the study of patients with epilepsy that now extends beyond its demonstration of neuroanatomy and neuropathology into the fields of neurochemistry, neurometabolism and neurophysiology.

The use of chemical-shift imaging (also known as Proton multi-voxel spectroscopy – ¹H MRS) to obtain in vivo biochemical information from the brain of living, awake subjects provides a powerful tool in the investigation of tissue metabolism and complements the anatomical information delivered by MR imaging. Specifically, the pathological hallmark of the sclerotic and dysfunctional hippocampus in TLE has been analysed by the relative ratios of metabolite resonance signals such as total N-acetylaspartate (NAA), total creatine plus phosphocreatine (Cr) and choline-containing compounds (Cho).

In patients with TLE and hippocampal sclerosis (HS), CSI has frequently shown abnormalities which consist mostly in the reduction of NAA. It is believed that NAA represents a robust but unspecific marker for neuronal loss or dysfunction. According to the former hypothesis, a decrease in NAA would be directly correlated with the degree of cell loss as seen in HS, while in the latter its value would also be altered by transient metabolic states experienced by an active neuronal network, either in a disease or healthy state.

The good concordance between the side of maximal NAA reduction and the side of seizure origin is generally accepted [1, 2]. Still, the metabolic abnormality can be more extensive than the epileptogenic area defined by electroencephalography (EEG) or structural imaging [3]. It has been shown that 18% [1] -50% [3] of patients with unilateral TLE, can present a bilateral reduction in the relative metabolic ratios (either NAA/Cr or NAA/Cho+Cre) which agrees with some reported post-mortem cases [4] where asymmetric cell loss was quantitatively verified in both hippocampi, with a higher degree ipsilaterally but affecting also the opposite hippocampus.

Thus, caution is necessary while interpreting the spectroscopic profile obtained from TLE as bilateral abnormalities can obscure the relevant epileptogenic and surgically resectable lesion.

Volumetric measures of the hippocampal formation (Hvol) has provided a well established technique to assess focal atrophies within any part of the hippocampus [5, 6]. A high degree of pathological specificity is associated with the finding of even minor volume asymmetries [7, 8] and a good correlation between hippocampal atrophies and surgical outcome has been reported [9]. Comparatively with CSI-data, MRI volume measurements had highlighted few bilateral damaged hippocampi (9-18%) in the majority of reported surgical series [10, 11], which happens to have no clear relation with the clinical outcome [11]. Still, verbal memory outcome was seriously prejudiced if bilateral atrophy was associated with left focus TLE [12].

The principal MRI features of HS are volume loss and increased T2 weighted signal intensity. In general, the increased signal is thought to be related to reactive gliosis occurring within a damaged brain area. In the epileptogenic hippocampus, increased T2-relaxometry (HT2) has been specifically associated with gliosis in the dentate gyrus [13].

Since abnormal T2 signal intensity may be difficult to detect visually, HT2 has been validated as an objective

technique to quantify signal abnormality by averaging the T2 decay of a multi-echo MR sequence [14-16]. This method has allowed the identification of bilateral signal abnormalities with greater consistency in up to 44% of selected TLE patients [17, 18] based on the two standard deviations (SD) from the mean control values.

Although the surgical extraction of an unilaterally damaged amygdalo-hippocampal formation is the only current procedure to cure refractory TLE, the outcome of these patients can vary if bilateral damage is to be found [19, 20]. Thus, it is essential to separate patients with multifocal foci from those with a single seizure focus, identifying the area of the brain enclosing the focus and characterizing its pathology.

Using a multimodal MR-based quantitative evaluation, we studied a cohort of patients referred for possible surgical treatment of TLE. Our purpose was to investigate the potential added value of Hvol, HT2 and CSI to typify hippocampal damage and compare the metabolic variations with other structural determinants of disease.

II. METHODS

Images were obtained from 31 control subjects, with no history of neurological disorders (and a normal neurological examination) and 46 patients with mesial TLE, the majority of which studied at the 'Hospital Egas Moniz' (HEM) program for epilepsy surgery.

The diagnosis of these patients is based on the clinical picture of TLE [21] and on the data obtained from our standard pre-surgical evaluation criteria (Table 1).

Table 1

The presurgical selection procedure employed at HEM

1. Initial patient selection
 - Clinical evidence of temporal lobe seizures
 - Therapeutic intractability
 - Inter-ictal EEG
 - Baseline neuro-psychology
2. Imaging evaluation
 - Standard, conventional diagnostic imaging to exclude structural lesion other than HS
 - Quantitative MRI to characterize HS and the involvement of other limbic-related areas
3. Ictal recording by combined video-EEG
 - If seizures are of bilateral or extra-temporal origin, invasive monitoring is required
4. WADA test
 - For HS on the dominant hemisphere
5. Surgery

MRI images were obtained at 1.5T on a GE CV/i-NV/i. Hvol and HT2 were performed as described [16, 22]. Briefly, volumetric (figure 1) data was acquired using a coronal 3D SPGR T1 sequence with a high spatial

resolution and optimized T1-contrast. The volumetric assessment included the entire brain. The hippocampus was quantified postero-anteriorly, based on its intrinsic para-sagittal signal by the same observer. Absolute volumes were normalized to the intracranial area at the level of the anterior commissure [23] as this has been demonstrated as an accurate parameter of volume standartization [24].



Fig 1 - Hippocampal-based volumetry was performed on oblique coronal slices perpendicular to the main axis of the temporal lobe. Volumes were calculated by outlining manually the entire length of the correspondent hippocampal T1 signal and summing the values of the cross-sectional areas times the slice thickness.

T2-relaxometry (figure 2) was obtained with a 4-echo protocol. T2 values result from a mono-exponential data fit obtained at the level of the body (averaging the regions of interest [ROI] from 3 subsequent slices).

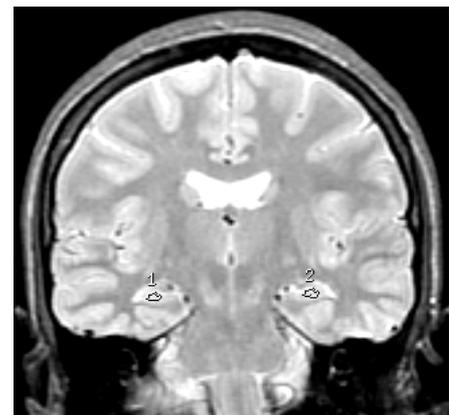


Fig 2 - T2-relaxometry over the hippocampal body. ROIs of 20mm² were placed bilaterally, tailoring the shape to the hippocampal morphology.

In order to minimize partial volume effects, both sequences were oriented perpendicular to the main temporal lobe axis using a mid-sagittal landmark (posterior commissure-obex line) [25].

CSI was performed on the axial plane, parallel to the reference line (figure 3).

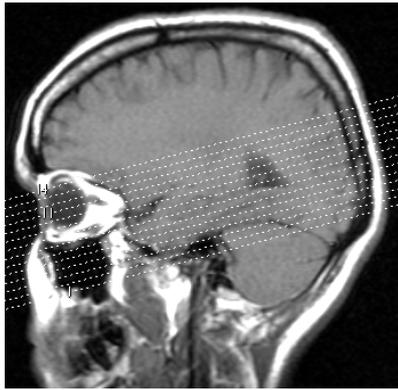


Fig 3 - Reference slices for hippocampal spectroscopy.

A T2-weighted fast spin-echo sequence with TR/TE of 4800/135 milliseconds, 2 NEX, and a matrix/FOV of 256x224mm/24x18cm was obtained for image-guided localization of the multi-voxel spectroscopic imaging.

A tilted axial slice 3.0mm thick on the hippocampus level was selected for the 2D CSI acquisition. Data was obtained using a PRESS sequence with a TR/TE of 1000/144, a FOV of 24x18cm, 1 NEX and a nominal voxel size of 7.5x7.5x9.9mm (557 mm³ volume).

Metabolite analysis was performed individually in 3 voxels placed bilaterally over the antero-posterior extent of the hippocampus (figure 4) using the manufacturers post-processing software (FuncTool, operating on a Advantage Windows 3.1)

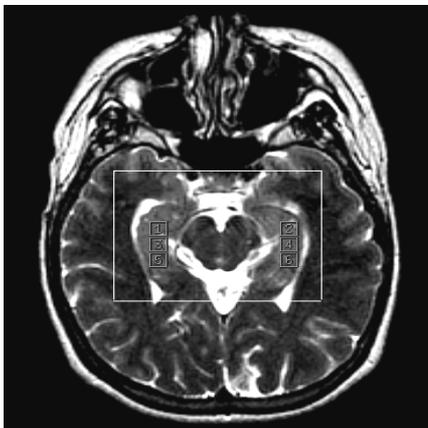


Fig 4 - A T2-weighted image is used for the tilted hippocampal reference plane. The volume of interest is placed over both hippocampi where 3 voxels are analysed.

All volumes of interest (VOIs) were studied to obtain the chemical-shift values of NAA, Cho and Cre for both populations analysed. Values for each metabolite obtained on all independent VOI were averaged to generate the metabolic profile of the hippocampus and NAA/(Cho+Cre), NAA/Cho, NAA/Cre ratios were calculated from this data. In certain cases (5/31 controls and 7/46 patients) one voxel was discarded from the analysis due to the low signal to noise obtained.

All quantitative MR data analysis was compared between groups using the StatSoft® Statistica vs.5.1 and Microsoft® Excel 2001. To assess the degree of pathology, the bilateral hippocampal values of patients were tested against control values using confidence ellipses of 99%. In order to compare the metabolic abnormalities with the structural findings, absolute asymmetry indexes were calculated accordingly to the formula [26]:

$$\frac{(\text{Right Hippocampus} - \text{Left Hippocampus})}{(\text{Right Hippocampus} + \text{Left Hippocampus})/2} \times 100$$

and correlated.

III. RESULTS

Clinical data identified 24 patients with right, 20 with left and other 2 with bilateral temporal seizure focus. Bilateral TLE subjects were identified on the basis of the recognition that seizures would arise independently from both temporal lobes.

Bilateral TLE were not included on the correlative analysis of asymmetry indexes.

Right TLE patients revealed a mean decrease of ipsilateral/contralateral normalized Hvol of 24%/5%, a mean increase of HT2 of 10%/5% and a mean decrease of NAA/(Cho+Cre) of 29%/22% (Tables 1,2,3).

Left TLE patients showed a mean decrease of ipsilateral/contralateral normalized Hvol of 34%/4%, a mean increase of HT2 of 15%/0% and a mean decrease of NAA/(Cho+Cre) of 27%/12% (Tables 1,2,3).

Bilateral TLE exhibited a mean decrease of right/left normalized Hvol of 9%/8%, a mean increase of HT2 of 17%/19% and a mean decrease of NAA/(Cho+Cre) of 24%/17% (Tables 1,2,3).

Volume	Right	Left	Δ
Control (31)	3560 ± 305	3431 ± 293	4.6 ± 2.6
Right TLE (24)	2720 ± 656	3249 ± 506	28.3 ± 13.4
Left TLE (20)	3444 ± 367	2255 ± 625	44.1 ± 25.5
Bilateral TLE (2)	3263 ± 1079	3151 ± 216	18.9 ± 1.2

Table 1 - Mean±ISD of normalized volume (mm³) in the populations studied for both right and left hippocampus. Δ represents the asymmetry index between right and left.

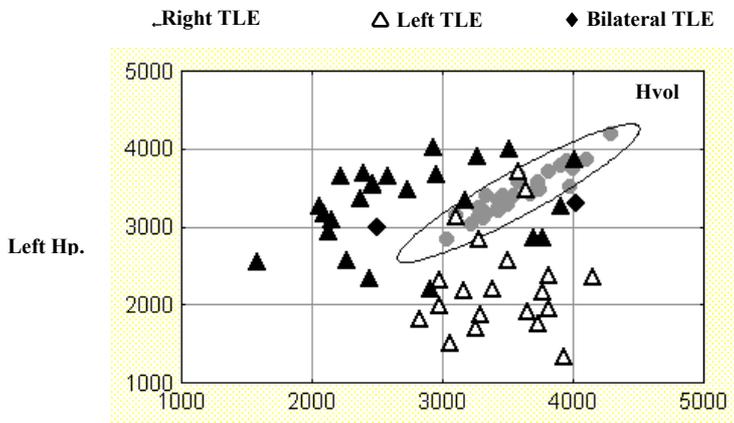
T2	Right	Left	Δ
Control (31)	83.1 ± 2.3	82.5 ± 2.5	1.8 ± 1.1
Right TLE (24)	91.2 ± 5.1	86.3 ± 6.1	8.0 ± 4.3
Left TLE (20)	83.5 ± 5.7	95.1 ± 8.3	12.8 ± 7.0
Bilateral TLE (2)	97.5 ± 8.3	98.0 ± 5.0	2.4 ± 0.8

Table 2- Mean±1SD of T2-relaxometry (ms) in the populations studied for both right and left hippocampus body. Δ represents the asymmetry index between right and left.

NAA/(Cho+Cre)	Right	Left	Δ
Control (31)	0.80 ± 0.06	0.79 ± 0.06	3.8 ± 3.6
Right TLE (24)	0.57 ± 0.10	0.62 ± 0.09	14.9 ± 7.9
Left TLE (20)	0.71 ± 0.13	0.58 ± 0.13	24.9 ± 8.6
Bilateral TLE (2)	0.60 ± 0.08	0.66 ± 0.01	11.1 ± 12.6

Table 3 - Mean±1SD of NAA/(Cho+Cre) (ppm) in the populations studied for both right and left hippocampus. Δ represents the asymmetry index between right and left.

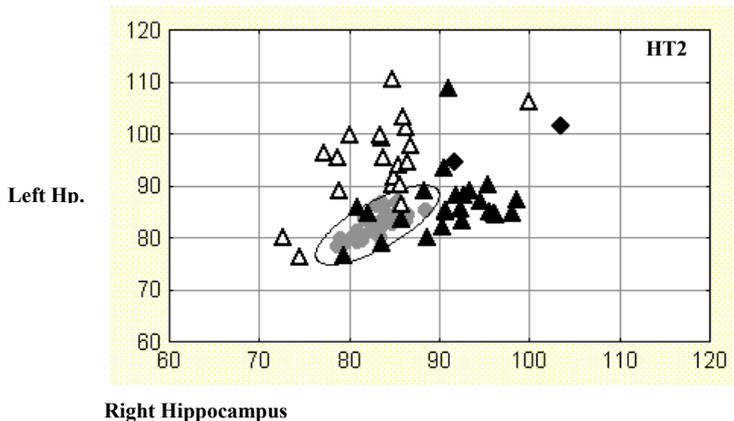
Individually, 40/46 (87%) had Hvol values outside the 99% ellipse for normal volumes (figure 5). Six right TLE patients had either a bilateral or a contralateral volume decrease. Bilateral TLE did not have a bilateral volume reduction.



Right Hippocampus

Fig 5 - Right vs. left Hvol scatterplots with 99% confidence ellipses for normal values.

85% (39/46) had HT2 values outside the 99% ellipse for normal volumes (figure 6). One right and one left TLE patients had both a bilateral T2 increase. One right TLE patients was found with a discordant lateralization. Bilateral TLE patients could be clearly distinguished by their bilateral T2 values. Unexpectedly, two pathological cases fell below the normal values.



Right Hippocampus

Fig 6 - Right vs. left HT2 scatterplots with 99% confidence ellipses for normal values.

Correlative analysis between Hvol and HT2 illustrate the high degree of specificity between MRI measures of structural damage in the ipsilateral hippocampus (r=0.74) has compared with the contralateral (r=0.27) (figure 7).

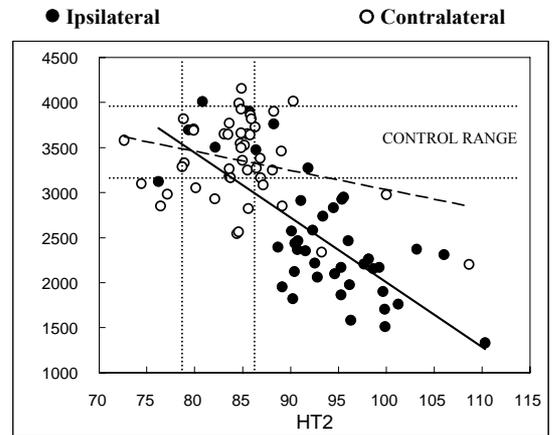
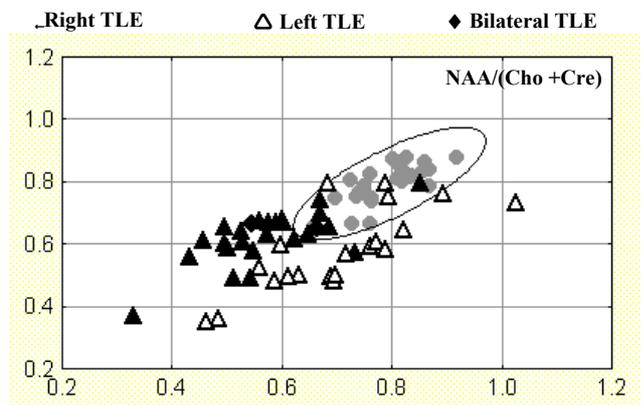


Fig 7 - Correlation data between Hvol and HT2. Ipsilateral values (●) showed a higher correlation (r=0.70) than contralateral (○) values (r=0.27). Control values are depicted (mean ± 1SD).

78% (36/46) had NAA/(Cho+Cre) values outside the 99% ellipse for normal volumes (figure 7). Of those, 15/36 (42%) had evident bilateral decreases (including the bilateral TLE) and one right TLE patient had a contralateral decrease only.



Right Hippocampus

Fig 8 - Right vs. left NAA/(Cho+Cre) scatterplots with 99% confidence ellipses for normal values.

Correlative analysis between Hvol and NAA/(Cho+Cre) did not determine any degree of relation between values obtained on both hippocampi (r=0.03 ipsilateral; r=0.13 contralateral).

The same was true for the analysis with HT2 and NAA/(Cho+Cre) on both sides (r=0.007 ipsilateral; r=0.21 contralateral).

On the contrary, correlative analysis of the asymmetry ratios for the 3 quantitative techniques used depicted an illustrative correlation between NAA/(Cho+Cre) and both Hvol and HT2 (figures 9 and 10).

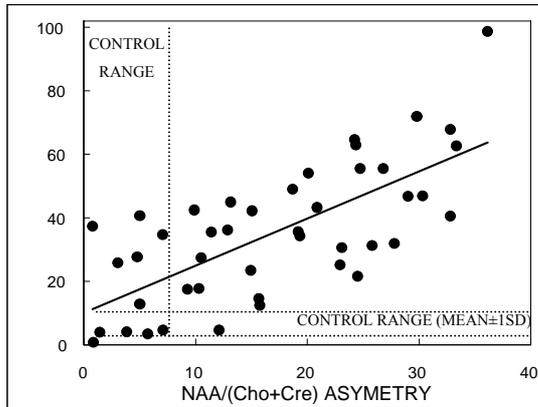


Fig 9 - Correlation data between Hvol and NAA/(Cho+Cre) asymmetry ratios ($r=0.70$). Control values are depicted (mean \pm 1SD).

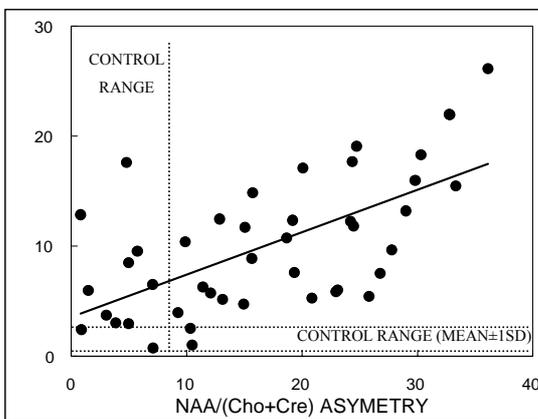


Fig 10 - Correlation data between HT2 and NAA/(Cho+Cre) asymmetry ratios ($r=0.63$). Control values are depicted (mean \pm 1SD).

To date, 18/46 well lateralized, drug-refractory patients underwent a surgical mesio-temporal resection. All had a clear cut diagnosis of histological HS, with variable neuronal loss and reactive gliosis in hippocampal sectors dentate gyrus, CA3 and CA1 with relative sparing of CA2 and subiculum.

IV. DISCUSSION

The applied MR methods described metabolic, and microstructural characteristics of an epileptogenic brain area that cannot be obtained with other noninvasive means.

The data presented were obtained from a quantitative multimodal MRI analysis performed over the same TLE patients (and age-related controls). Our objectives were to determine the relative contribution of different techniques for the detection of HS and the associated metabolic abnormalities. One advantage of such combined analysis is to integrate the complementary metabolic and structural

data acquired with MRI, the most reliable preoperative imaging technique for the detection of brain anomalies.

Hvol was able to identify ipsilateral hippocampal atrophy in 33/46 patients, including the two bilateral TLE. Still, it also identified unexpected exclusive contralateral atrophy in 4/36 patients which was not in agreement with the EEG findings.

HT2 revealed ipsilateral increased T2-relaxometry in 30/46 patients and bilateral in 4/46, including the two bilateral TLE. One patient (with contralateral atrophy) revealed a contralateral HT2 increase.

Thus, significant changes in the structural organization of the hippocampus was observed in the majority of patients with predominant lateralized EEG focus, although some cases were not in conformity with the electrophysiological data. However, due to the rapid spread of the electrical activity in the brain, bilateral electroencephalographic abnormalities are frequently present, making presurgical lateralization difficult [27] and inducing some false positives when ictal EEG is recorded [28]. Thus, the contralateral atrophic values in the four pathological cases (one with contralateral HT2) could in fact represent the original focus site which would rapidly spread its electric activity to the opposite temporal lobe when a seizure is recorded.

Still, we found that the current gold standard of clinical-EEG lateralization, Hvol, and HT2 findings were highly concordant in 32/46 patients (70%).

Measures of structural damage show an illustrative correlation on the ipsilateral hippocampus. As volume decreases, T2 values increase. Hippocampal atrophy is though to be related with neuronal cell loss [13, 29] and an increased T2-relaxometry value with gliosis [13]. Thus, our data indicates that MRI detectable structural damage has, at least, two inter-related components that act in concert to originate an area of epileptogenicity. Moreover, we have shown previously [22] that the maximal seizure frequency experienced by this group of patients was specifically related with the ipsilateral hippocampal injury.

CSI identified bilateral metabolic pathology with larger expression than Hvol or HT2 which indicates that CSI has a higher capability to detect contralateral abnormalities than MR imaging, as others had suggested [3]. In our series, it also detected less overall pathology (78% of patients) than Hvol (87%) and HT2 (85%) when compared to controls.

Pathological metabolic changes are often associated with the structural lesions of HS [27, 30] and may represent the impairment of the functional status of an altered network. Still, there is a lack of correlation between the severity of volume loss (Hvol) and the degree of metabolic disturbance (CSI, Cre/NAA ratio) [30], suggesting that the techniques examine distinct pathophysiologic processes in TLE. Our data are in agreement with these previous findings, although we used the NAA/(Cho+Cre) CSI ratio to test not only with Hvol but also with HT2. As

with Hvol, HT2 values did not show any relation with the measured NAA/(Cho+Cre).

Asymmetry ratios are interpreted as a measure of the degree of damage between the two functionally related hippocampi. Thus, we used this index to determine if the metabolic asymmetry correlated with the structural differences observed between hippocampi.

As shown, a high degree of structural asymmetry was directly related with the asymmetric metabolic profiles, despite the evidence of bilateral functional anomalies when comparing the NAA/(Cho+Cre) to the control population. This data indicates that the site of major structural impairment also shows the major functional lesion and that the metabolic abnormalities on the opposite site are not dependent on a pre-existing MRI detectable lesion.

The major functional abnormalities are more related to the existence of major structural asymmetries than to the degree of the lesion itself.

V. CONCLUSION

TLE is not invariably associated with an ipsilateral damaged hippocampus. Bilateral and contralateral pathology can be detected in a small number of cases by a combination of quantitative MRI and CSI techniques.

HS is highlighted by two inter-related MRI measures of damage: Hvol and HT2, to which the degree of clinical severity is related.

A decreased N-acetylaspartate to choline plus creatine concentration is not related with ipsilateral hippocampal atrophy and signal changes *per se*, but with the degree of structural injury in-between hippocampi.

We showed that the combination of hippocampal-based volumetry, T2 relaxation time measurements and NAA/(Cho+Cre) metabolites ratio can be used to examine the degree of ipsi- and contralateral dysfunction or injuries and their relations with the clinical severity in the presurgical evaluation of patients.

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