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(Running head: Diffusivity and memory)

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Key Words: Diffusion tensor imaging (DTI) – Medial Temporal Lobe Epilepsy – Memory – Contralateral hippocampus – Epilepsy surgery – Recovery.

Number of abstract words: 119

Number of text words: 2113

Number of figures: 1

Number of tables: 1

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ABSTRACT

This study aimed at determining if the recovery of mean diffusivity (MD) in the contralateral non sclerotic hippocampus is correlated with change in memory outcome after surgery in patients with medial temporal lobe epilepsy (MTLE). Verbal and non-verbal memory scores and MD were assessed in 23 patients with MTLE before and after surgical treatment of epilepsy. The recovery of MD in the left hippocampus was correlated with the performance on verbal memory tests and the recovery of MD in all patients was correlated with the performance on non-verbal memory tests. This finding strengthens the hypothesis that reversible diffusion abnormalities in the contralateral hippocampus in MTLE are linked to the active epileptic process that seems to interfere with memory abilities.

INTRODUCTION

Using interictal diffusion tensor imaging (DTI) in medial temporal lobe epilepsy (MTLE) patients with unilateral hippocampal sclerosis, we demonstrated bilateral hippocampal diffusion abnormalities: an increased mean diffusivity (MD) in the epileptic hippocampus and a decreased MD in the contralateral non sclerotic hippocampus.[1] Subsequently, we showed that the reduced MD in the contralateral hippocampus recovers after epilepsy surgery.[2] This result supports previous proton magnetic resonance spectroscopy studies showing that spectroscopic abnormalities tend to normalize in the postoperative period.[3-6] These neuroimaging findings suggest that contralateral abnormalities before surgery reflect neuronal dysfunction due to the epileptic process. Although we were not able to demonstrate a relationship between the recovery of MD in the contralateral non sclerotic hippocampus after surgery and the electro-clinical outcome of these patients, we hypothesised that MD recovery should be associated with changes in memory abilities.

It is well known that the hippocampus is involved in memory functions, the left and right mediating verbal and non-verbal memory functions respectively.[7] Links between MD variations in the hippocampus and neuropsychological testing have already been reported in MTLE patients[8] but there has been no study of the relationship between postoperative changes in MD and memory functions to date. The purpose of the present study is to examine correlations between the recovery of MD in the contralateral non sclerotic hippocampus and postoperative changes in memory scores. We predicted that postoperative memory outcome should be better in the patients showing a higher MD increase in the contralateral hippocampus. According to the functional lateralization of hippocampus,[8] we hypothesized that postoperative verbal memory outcome should be correlated with MD recovery in the left hippocampus (patients with right MTLE), while postoperative non-verbal memory outcome should be correlated with MD recovery in the right hippocampus (patients with left MTLE).

METHOD

Patients

The participants included 23 patients (15 women and 8 men, mean age at surgery 31.4±9.0 years, ranging from 19 to 52) with MTLE who had undergone a presurgical evaluation at the Epilepsy Unit (La Salpêtrière Hospital). Unilateral left (n = 12) or right (n = 11) hippocampal sclerosis (HS) was preoperatively diagnosed from qualitative MRI assessment. All patients, except one, were right-handed. Left cerebral lateralization of language was confirmed by Wada tests or fMRI in most of the patients (n = 15) and one patient with left HS had bilateral language representation. With the exception of four patients who underwent a selective amygdalo-hippocampectomy, they underwent anteromedial temporal lobe (ATL) resection. Systematic pathological examination of the operated tissue confirmed HS in all patients. The number of antiepileptic medications varied from one to four (mean = 3) before surgery and from zero to four (mean = 2) after surgery. The number of antiepileptic drugs taken before and after surgery was identical for 16 patients, 6 had one medication withdrawn and one had one medication added. Based on Engel's classification, 18 patients were seizure free (class Ia), and 5 had only rare persistent auras (class Ib) after surgery. The local ethics committee approved the study and informed written consent was obtained from all the patients.

Imaging protocol

Conventional MRI and DTI data were acquired on a 1.5 T scanner (GE, Milwaukee, USA). All the patients reported that they were free of seizure in the 24 hours preceding the DTI scan. The mean interval between the pre- and postoperative MRI was 451±158 days, ranging from 252 to 790 days. The mean delay between surgery and the postoperative MRI was 243±100 days, ranging from 69 to 629 days. Details on the image acquisition and the definition of regions of interest are reported in Thivard and collaborators (2007).[2]

Memory evaluation of patients

Span and supra-span learning tasks were used to assess verbal and non-verbal memory abilities. The auditory verbal span test was performed by all patients. It contains an increasing number of digits to be immediately recalled. The score corresponded to the maximum number of digits recalled in the correct order. The abstract word learning test [9] was performed by 10 left and 11 right temporal lobe patients. It contains 13 abstract visual words that have to be recalled across four successive learning trials. The score was calculated as the total number of words recalled over all trials (score max = 52). The visual spatial span test was performed by all but one left temporal lobe patient. It comprises an increasing number of blocks displayed on a board to be immediately recalled by pointing. The score corresponded to the maximum number of blocks recalled in the correct order. The Aggie figure learning test[10] was performed by 5 left and 6 right temporal lobe patients. It consists of 15 non-verbal simple line drawings that have to be recalled across five successive learning trials. The score was calculated as the total number of figures recalled over all trials (score max = 75). The mean delay between the pre- and postoperative memory evaluation of patients was 548±213 days, ranging from 256 to 984 days.

Statistical analysis

Two by two ANOVAs were performed on the contralateral hippocampal MD values and on the memory scores obtained by the two patient groups (right vs. left) before and after surgery. Furthermore, we calculated the number of patients whose performance increased after surgery in the two verbal memory scores or in the two non-verbal memory scores. Chi-square was used to compare the number of participants with postoperative improvement in the two groups of patients (right vs. left).

A percentage of postoperative recovery of contralateral MD was calculated for each patient as follows: $MD_{recov} = 100 \times ((MD_{post} - MD_{pre}) / MD_{pre})$, in which MD_{recov} is the percentage of postoperative recovery of contralateral MD whereas MD_{pre} and MD_{post} correspond to values of MD before and after surgery respectively. For each patient and each test performed, we subtracted the score before surgery from the score after surgery to obtain a $score_{post-pre}$. To allow comparison between tests, each $score_{post-pre}$ was converted to a $z\text{-}score_{post-pre}$ using the mean and standard deviation obtained by all the patients for each test. For patients who performed the two verbal memory tests, $z\text{-}scores_{post-pre}$ were averaged to obtain a global verbal memory $z\text{-}score_{post-pre}$. For patients who performed the two non-verbal memory tests, $z\text{-}scores_{post-pre}$ were averaged to obtain a global non-verbal memory $z\text{-}score_{post-pre}$.

Pearson's correlation coefficients were first calculated to assess potential associations between postoperative recovery of hippocampal contralateral diffusivity and postoperative memory outcome. However, the change in memory scores were likely to be related to the delay between the pre- and postoperative memory evaluation of patients ($delay_{post\text{-}pre}$) and to the memory scores before surgery ($z\text{-}scores_{pre}$) as observed in a recent study.[11] Thus, partial Pearson's correlation coefficients were used to adjust for $delay_{post\text{-}pre}$ and $z\text{-}scores_{pre}$. Furthermore, Mann Whitney U tests were performed to determine the effect of the type of surgery (selective amygdalo-hippocampectomy vs. anterior temporal lobectomy) on MD_{recov} and the different memory $z\text{-}scores_{post\text{-}pre}$.

RESULTS

Postoperative recovery of the hippocampal contralateral diffusivity

Contralateral hippocampal MD value increased after surgery (Mean (SD), preoperative: 895 (25) $\times 10^{-6}$ mm^2/s, postoperative: 914 (28) $\times 10^{-6}$ mm^2/s; $F(1, 21)=22.81$, $p<0.0001$). There was no significant effect of lesion laterality ($F<1$) or interaction between factors ($F<1$).

Postoperative outcome of memory scores

The score in the abstract word learning test decreased after surgery (Mean (SD), preoperative: 32.4 (7.5), postoperative: 28.8 (8.6); $F(1, 19)=8.32$, $p=0.009$) and was higher for right than for left ATL patients (right ATL patients: 34.7(6.0), left ATL patients: 26.1(6.4); $F(1, 19)=10.35$, $p=0.005$). There was no significant interaction between factors ($F(1, 19)=1.81$, $p=0.194$). The other memory scores did not significantly change after surgery and there were no significant effect of lesion laterality or interaction between factors.

The number of patients whose performance increased after surgery in the two verbal memory tests was significantly more important in the right ATL (3 out of 11) than in the left ATL (0 out of 10) group (chi-2=10.71, df=1, p=0.001). No patients demonstrated postoperative improvement in the two non-verbal memory tests.

Correlations between recovery of the hippocampal contralateral diffusivity and memory scores

Figure 1 presents scatter plots of the different memory z-scores$_{post\text{-}pre}$ against the postoperative recovery of MD in the contralateral hippocampus for the whole group of patients and for the left and right ATL patients separately. Pearson's correlation coefficients are shown in each plot. Furthermore, partial correlation coefficients adjusting for delay$_{post\text{-}pre}$ and z-scores$_{pre}$, are shown in Table 1. No significant effect of the type of surgery was found on the MD$_{recov}$ and on the different verbal and non-verbal memory z-scores$_{post\text{-}pre}$.

Verbal memory

There was no significant correlation between the postoperative recovery of MD in the contralateral hippocampus and the different verbal memory z-scores$_{post\text{-}pre}$ in all patients. When the left ATL patients were separated from the right ATL patients, the recovery of MD in the contralateral hippocampus was positively correlated with the auditory verbal span z-score$_{post\text{-}pre}$ for the right ATL patients (p=0.023). Furthermore, an almost significant positive correlation was observed with the global verbal memory score (p=0.053). For the left ATL patients, an almost significant negative correlation was observed with the auditory verbal span z-score$_{post-pre}$ (p=0.071).

In a post-hoc analysis, right ATL patients were separated in two groups: G_1 made up of the 3 patients whose performance increased after surgery in the two verbal memory tests and G_2 made up of the 8 other patients. MD_{recov} value was significantly higher for G_1 patients (Mean(SD), G_1: 4.9(1.4) %, G_2: 1.7(1.8) %, p=0.025, Mann-Whitney U-test).

Non-verbal memory

The postoperative recovery of MD in the contralateral hippocampus was positively correlated with the global non-verbal memory z-score$_{post-pre}$ (p=0.005) and with the Aggie figure learning z-score$_{post-pre}$ (p=0.007) in all patients. When the left ATL patients were separated from the right ATL patients, the recovery of MD in the contralateral hippocampus was positively correlated with the Aggie figure learning z-score$_{post-pre}$ for the left ATL patients (p=0.032), but the correlation was not significant after adjustment for delay$_{post-pre}$ and z-scores$_{pre}$. However, the number of patients within each group was very small (<7) for the Aggie figure learning z-score$_{post-pre}$ and the global non-verbal memory score$_{post-pre}$.

DISCUSSION

The results of the present study demonstrate that postoperative recovery of MD in the non sclerotic hippocampus contralateral to the resection is linked to memory outcome in patients who have undergone surgery for intractable MTLE epilepsy.

The number of patients with postoperative improvement in verbal memory was more important in the right ATL than in the left ATL group, in agreement with a recent study.[11] Furthermore, postoperative verbal memory outcome was positively correlated with MD recovery of the contralateral hippocampus only for the right ATL patients. It has been previously reported that patients with right MTLE are impaired in verbal memory before surgery and this impairment is associated with a global decrease in left hemisphere functional activity.[12] Furthermore, the MD in the left hippocampus of right-sided MTLE patients is reduced before surgery and returns to normal after surgery.[1,2] Although several explanatory hypothesises have been previously proposed,[2] the functional mechanisms leading to the recovery of MD remain speculative. The present results reveal that this return to normal is associated with better postoperative outcome in verbal memory and more specifically in the auditory verbal span score. This latter finding would be related with the role of the left hippocampus in verbal encoding.[7] This is consistent with a recent study which shows that cognitive rehabilitation has stronger effect on verbal memory after right than after left temporal lobe surgery.[13] Cognitive rehabilitation could take effect by favouring return to normal of the contralateral non sclerotic hippocampus, although only return to normal of the left hippocampus would be associated with better postoperative verbal memory outcome.

Even though not significant, increasing diffusion in the right hippocampus of the left ATL patients is associated with worse postoperative verbal memory outcome. A hypothesis is that MD recovery of the right hippocampus would improve functions of the right hemisphere at the expense of the left, which would amplify their deficit in verbal memory.

Postoperative non-verbal memory outcome was positively correlated with MD recovery of the contralateral hippocampus only when right and left ATL patients were pooled together. This is consistent with the idea that non verbal and specifically visual spatial memory depends on the integrity of both right and left hippocampi.[14] However, the absence of significant correlation in separated groups could be due to a lack of statistical power related to the large proportion of missing data.

In conclusion, these results strengthen the hypothesis that reversible diffusion abnormalities in the hippocampus contralateral to the seizure focus in MTLE are functional and linked to the active epileptic process. Furthermore, diffusion abnormalities appear to be associated with changes in memory functions, suggesting a correlation between cognitive outcome and neuronal changes measured by diffusion tensor imaging in MTLE patients who have undergone unilateral antero-mesial temporal lobe resection.

ACKNOWLEDGMENTS

The authors are grateful to Amee Baird for her helpful comments on previous version of the manuscript. This work was supported by the IFR 49, by a grant from the college des Enseignants de Neurologie (L.T.) and was part of a post-doctoral project at the Epilepsy Unit - La Salpêtrière Hospital (M.P). The authors confirm that they have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

DISCLOSURE OF CONFLICTS OF INTEREST

The corresponding author certifies that all co-authors have no financial or other conflict of interest to disclose.

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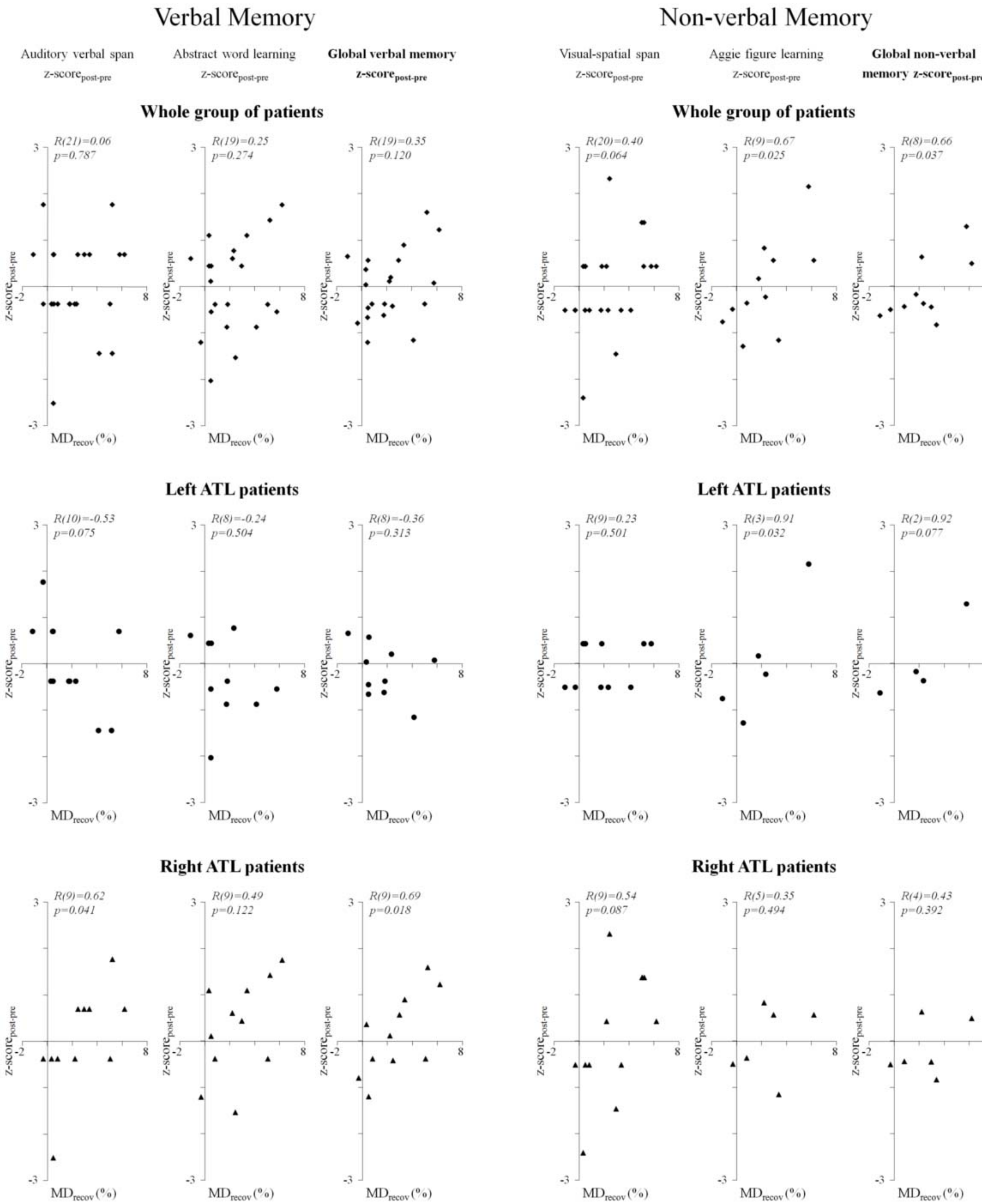
Figure Legend

Figure 1. Scatter plots of the different z-scores$_{post\text{-}pre}$ against the postoperative recovery of MD in the contralateral hippocampus (MD_{recov}) for the whole group of patients and for the left and right ATL patients separately. Pearson's correlation coefficients R(df) and p-values are presented on each plot.

Figure 1

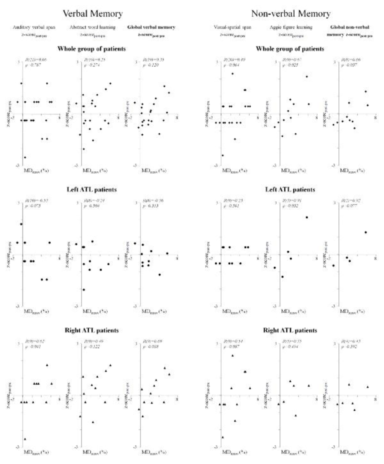


Verbal Memory
Non-verbal Memory
Auditory verbal span z-score post-pre
Abstract word learning z-score post-pre
Global verbal memory z-score post-pre
Visual-spatial span z-score post-pre
Aggie figure learning z-score post-pre
Global non-verbal memory z-score post-pre
Whole group of patients
R(21)=0.06 p=0.787
R(19)=0.25 p=0.274
R(19)=0.35 p=0.120
R(20)=0.40 p=0.064
R(9)=0.67 p=0.025
R(8)=0.66 p=0.037
Left ATL patients
R(10)=-0.53 p=0.075
R(8)=-0.24 p=0.504
R(8)=-0.36 p=0.313
R(9)=0.23 p=0.501
R(3)=0.91 p=0.032
R(2)=0.92 p=0.077
Right ATL patients
R(9)=0.62 p=0.041
R(9)=0.49 p=0.122
R(9)=0.69 p=0.018
R(9)=0.54 p=0.087
R(5)=0.35 p=0.494
R(4)=0.43 p=0.392
z-score post-pre
MD recov (%)
3
-3
-2
8

Table 1. Partial Pearson's correlation coefficients Rp(df) between the postoperative recovery of MD in the contralateral hippocampus and the different verbal and non-verbal memory z-scores$_{post-pre}$, adjusted on delay$_{post-pre}$ and z-scores$_{pre}$.

	Verbal memory			**Non-verbal memory**		
	Auditory verbal span z-score$_{post-pre}$	**Abstract word learning z-score$_{post-pre}$**	**Global verbal memory z-score$_{post-pre}$**	**Visual spatial span z-score$_{post-pre}$**	**Aggie figure learning z-score$_{post-pre}$**	**Global non-verbal memory z-score$_{post-pre}$**
Whole group of patients	Rp(19)=0.05 p=0.834	Rp(17)=0.15 p=0.539	Rp(17) =0.32 p=0.182	Rp(18)=0.29 p=0.209	Rp(7)=0.82 p=0.007**	Rp(6)=0.87 p=0.005**
Left ATL patients	Rp(8)= -0.59 p=0.071	Rp(6)=-0.25 p=0.547	Rp(6) =-0.22 p=0.594	Rp(7)=0.26 p=0.502	Rp(1)=-0.76 p=0.449	df =0
Right ATL patients	Rp(7)=0.74 p=0.023*	Rp(7)=0.40 p=0.281	Rp(7) =0.66 p=0.053	Rp(7)=0.52 p=0.140	Rp(2)=0.87 p=0.130	Rp(2)=0.83 p=0.172

*, p<0.05 and **, p<0.01.
Partial Pearson's correlation coefficients were calculated for df>0.



Verbal Memory
Non-verbal Memory
Auditory verbal span z-score post-pre
Abstract word learning z-score post-pre
Global verbal memory z-score post-pre
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Aggie figure learning z-score post-pre
Global non-verbal memory z-score post-pre
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R(8)=-0.24 p=0.504
R(8)=-0.36 p=0.313
R(9)=0.23 p=0.561
R(3)=0.91 p=0.032
R(2)=0.92 p=0.077
Right ATL patients
R(9)=0.62 p=0.041
R(9)=0.49 p=0.122
R(9)=0.69 p=0.018
R(9)=0.54 p=0.087
R(5)=0.35 p=0.494
R(4)=0.45 p=0.392
z-score post-pre
MD ratio (%)
3
-3
8

	Verbal memory			Non-verbal memory		
	Auditory verbal span **z-score$_{post\ pre}$**	**Abstract word learning** **z-score$_{post\ pre}$**	**Global verbal memory** **z-score$_{post\ pre}$**	**Visual spatial span** **z-score$_{post\ pre}$**	**Aggie figure learning** **z-score$_{post\ pre}$**	**Global non-verbal memory** **z-score$_{post\ pre}$**
Whole group of patients	Rp(19) 0.05 p=0.834	Rp(17) 0.15 p=0.539	Rp(17) 0.32 p=0.182	Rp(18) 0.29 p=0.209	Rp(7) 0.82 p=0.007**	Rp(6) 0.87 p=0.005**
Left ATL patients	Rp(8)=-0.59 p 0.071	Rp(6)=-0.25 p 0.547	Rp(6) =-0.22 p 0.594	Rp(7)=0.26 p 0.502	Rp(1)=-0.76 p 0.449	df 0
Right ATL patients	Rp(7) 0.74 p=0.023*	Rp(7) 0.40 p=0.281	Rp(7) 0.66 p=0.053	Rp(7) 0.52 p=0.140	Rp(2) 0.87 p=0.130	Rp(2) 0.83 p=0.172

*, $p<0.05$ and **, $p<0.01$.
Partial Pearson's correlation coefficients were calculated for df>0.