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Is There a Negative Correlation between Explicit Memory and Hippocampal Volume?

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The aim of this research was to study the relationship between explicit memory and hippocampal volume. Seventy healthy adults were administered one implicit memory test and one explicit memory (EM) test and underwent magnetic resonance imaging. The major finding was a negative correlation between the EM test and the right hippocampus/brain volume ratio ($t = -0.25$, $P = 0.03$) and the left hippocampus/brain volume ratio ($t = -0.27$, $P = 0.02$). This finding is not consistent with pathologic findings, which tend to show a relationship between decrease in memory performance and hippocampal atrophy. This discrepancy is discussed.

INTRODUCTION

Explicit memory (EM) refers to conscious recollection of previous experience, and implicit memory (IM) refers to the nonconscious effects of previous experience on subsequent performance and behavior (Schacter, 1997). The relationship between memory and the volumes of various brain structures in pathology showed an association between hippocampal atrophy and defective EM (e.g., Bondi *et al.,* 1991; Köhler *et al.,* 1998). In healthy subjects, the question of a covariation between memory and hippocampus still remains without a clear answer. Studies with healthy control subjects are not in agreement on the results. One reported a positive association between the hippocampal volume and memory in elderly subjects (Golomb *et al.,* 1994), whereas another did not find an association between hippocampal volumes and explicit memory (Raz *et al.,* 1998), and one more found a trend toward a negative association between hippocampal volumes and delayed verbal recall (Köhler *et al.,* 1998). There is a lack of data for healthy subjects. One the basis of data on pathological atrophy, we expected to find a significant relationship between hippocampal volumes and EM. One may suppose that there is a relationship between brain volume (BV) and EM performances, too. In this case, it would mean that volume of structures other than the hippocampus would contribute in explaining the variation in memory performances. The aim of the present study was to investigate the relationships between memory and hippocampus and brain volumes in healthy subjects.

MATERIALS AND METHODS

Sample

Seventy healthy volunteers (mostly students in psychology or biology; 44 females and 26 males) participated in the study. Age varied from 18 to 31 years (mean 24.45; SD 4.19). None had a positive history of neurological disorder. They all gave written informed consent.

Materials

A pool of 30 words was established. We chose words having a stem of three first letters that could be completed to form at least 10 words in the French language, appearing in a French dictionary. Word selection was based on a low or medium frequency in French (from Trésor de la Langue Française, published by CNRS).

Testing Procedure

In the initial (study) phase, the subjects were shown a list of 20 words on a screen. Each item was displayed for 5 s, then the screen was cleared for 1 s before the appearance of the next item. All the items were presented randomly. The subjects were instructed to read the word aloud. Ten of the words were different in the two groups for assessment of IM. The other 10 were the same for the two groups, for assessment of EM.

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Implicit Memory

To evaluate IM, two groups had to be established. Subjects were assigned randomly to group A (38 subjects) or to group B (32 subjects). In each of these groups we evaluated two scores: priming (a process of IM) and baseline (which corresponds to each individual's knowledge and has no direct link with a priming effect). "Priming is measured as the difference in performance, usually gains in accuracy or speed, with target items relative to baseline items, a difference that is due to study-phase exposure to the target item" (Gabrieli, 1996; p. 13535). Items evaluating baseline in one group were used as target in the other group and vice versa. Each group thus was the control of the other. This is a method classically used in research in cognitive psychology (Perruchet *et al.,* 1989; Rajaram and Roediger, 1992). After presentation of the word list, the subjects were told that their memory would be evaluated in a few minutes and that in the meantime they would be asked to perform various tasks. In fact, these tasks tested IM but participants were not told that some of the test items were related to the previously studied words. Three letters forming the beginning of a word were presented and the subjects were asked to complete this stem as fast as possible to form the first word that came to mind. A total of 20 stems were proposed. Half could form words that appeared on the list presented in the study phase, whereas the other half did not. We then totaled the number of items each subject produced that belonged to the study list of his group (primed items) and the number of items belonging to the study list of the other group (unprimed items serving as baseline for the other group). For this second score, we thus counted for group A the number of items belonging to group B and vice versa.

Explicit Memory

After the IM test, the subjects performed the EM test. When a stem appeared on the screen, they were instructed to use the stem to recall words aloud from the list that had been previously presented. Ten stems were proposed to each subject. The EM score was assessed by totaling the right answers.

Magnetic Resonance Imaging Acquisition

All subjects underwent MRI performed on a 1.5-T unit. Volumetric acquisition was obtained with the spoiled gradient-recalled acquisition in a steady state (GRASS) sequence. Parameters of the sequence were 23/5/1, flip angle was 35°, field of view was 22 cm, and matrix size was 256 × 192. One hundred twenty-four contiguous sections of the entire head were obtained. Section thickness was 1.5 mm. Each acquisition was transferred to a workstation. Volumetric measurements were performed using the 3-D option software. A 3-D model of the head was obtained from the 124 sections using a low threshold of 25 and a high threshold of 400 (arbitrary units). These values limited the range of voxel intensity used in generating the 3-D model. The width of the gray scale and the level of the four windows were adjusted visually, and images were magnified by a factor of 3.4. Processing was performed with a 3-D mouse-driven cursor, which appeared simultaneously at the same location of each window.

Image Processing: Hippocampal Volume Measurement

The volumetric acquisition in a coronal plane was not perpendicular to the hippocampus. Segmentation of the hippocampal formation was performed in all subjects. The segmentation was performed on sections reformatted in the plane perpendicular to the axis of the hippocampal formation. This choice was made after comparing three measurement protocols (Hasboun *et al.,* 1996a).

The measurements included the entire rostrocaudal extent of the hippocampus (e.g., CA-1 through CA-4 sectors of the hippocampus proper, the dentate gyrus, the alveus, the fimbria, and a part of the subiculum). The increment between two segmentation planes was 2 mm. This increment was slightly greater than the section thickness, but it could be obtained with the 3-D cursor software and it was chosen to shorten the total time needed for segmentation. The first section, checked in the sagittal window, was located just 2 mm caudal to the plane intersecting the most anterior extension of the alveus, just rostral to the uncus. The most accurate anterior limit was sought with the 3-D cursor interactively in the coronal, sagittal, and axial planes. Anatomic landmarks of the hippocampal formation were defined at the level of the head, body, and tail of the hippocampus, as described below.

Hippocampal Head

Dorsally and laterally, the alveus provides a landmark for the hippocampal head. Rostrally, it allows one to differentiate the hippocampus from the overlying amygdala with the 3-D cursor. At this level, the hippocampus has a characteristic triangular shape. Caudally, at the level of the digitations of the pes hippocampus, the temporal horn appears and enhances this dorsal limit. At this level, the medial part of the hippocampal head merges dorsally with the amygdala at the level of the amygdalohippocampal transition area. The ventral limit was clearly defined by the gray–white matter junction between the white matter of the entorhinal cortex and the subiculum. Medially, the boundary of the hippocampal head was limited by the uncal sulcus and choroid fissure. The intralimbic gyrus was outlined in the most caudal planes of the pes hippocampus (Figs. 1 and 2).

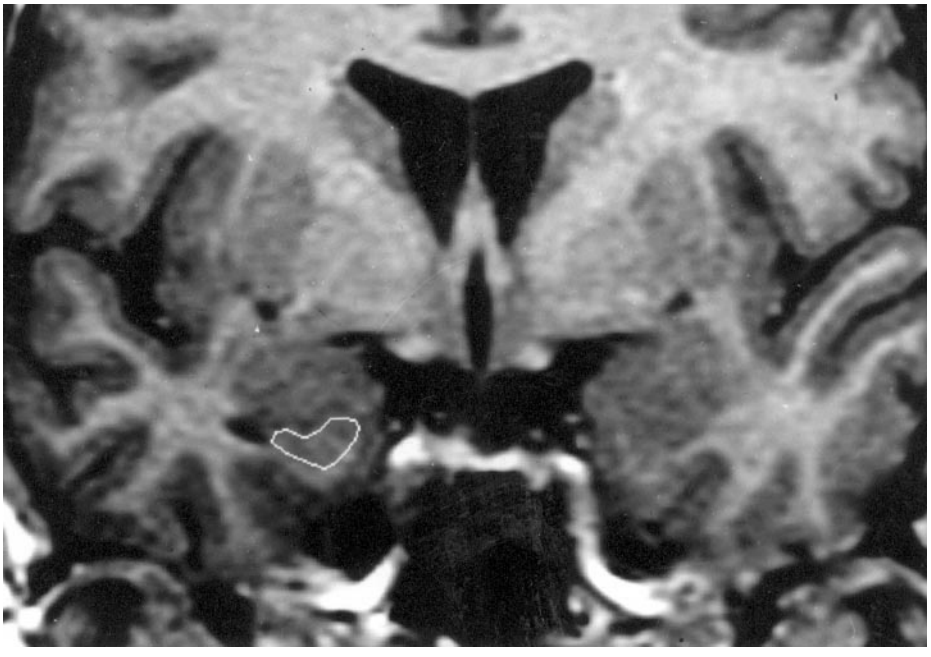

FIG. 1. Spoiled GRASS image reformatted in the coronal plane perpendicular to the long axis of the hippocampus: rostral part of the hippocampal head.

Hippocampal Body

The hippocampal body was easier to outline: dorsally and laterally we included the alveus overlying the cornu Ammonis. This boundary is well defined in the floor of the temporal horn. The fimbria was included in the measurements. Medially, we chose an arbitrary landmark located in the middle of the subiculum. The dentate gyrus was included. Ventrally and laterally, the white matter was well distinguished from the subiculum and from CA-1 (Fig. 3).

Hippocampal Tail

Caudally, the hippocampus was outlined up to the origin of the crus fornicis. The medial landmark was an

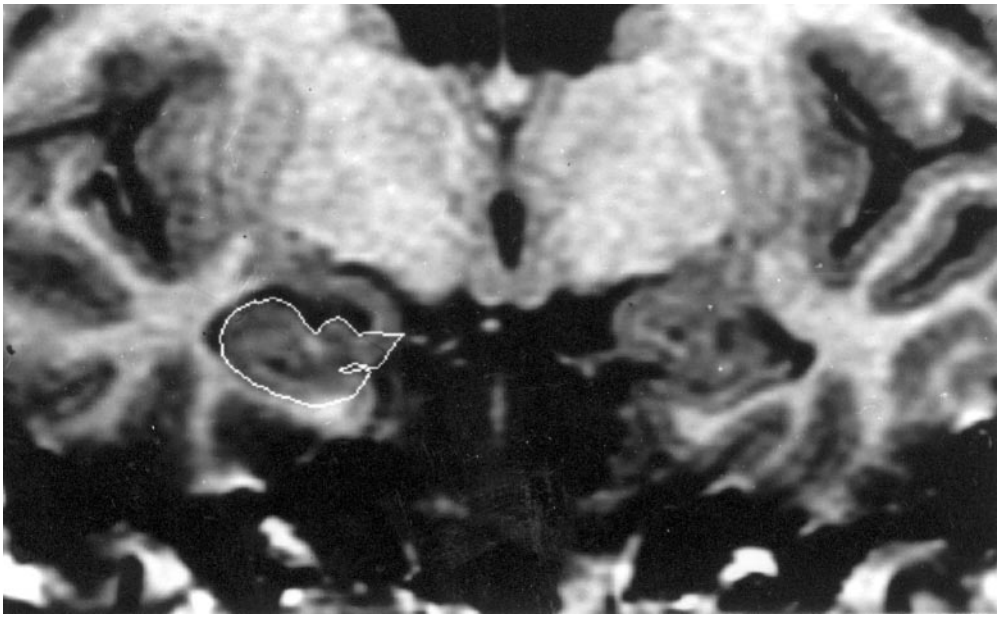

FIG. 2. Spoiled GRASS image reformatted in the coronal plane perpendicular to the long axis of the hippocampus: middle part of the hippocampal head.

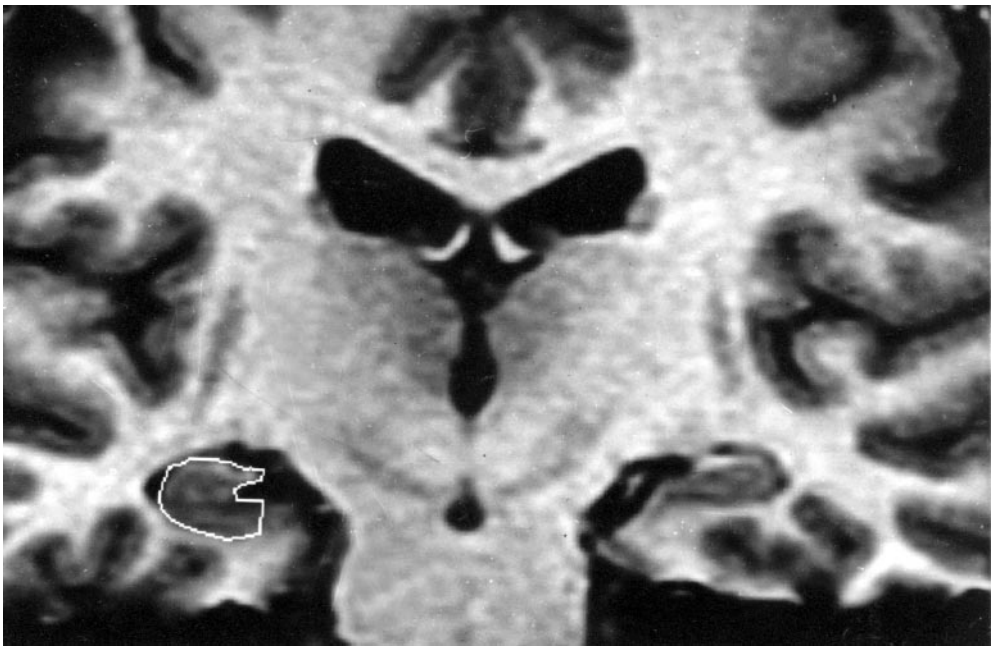

FIG. 3. Spoiled GRASS image reformatted in the coronal plane perpendicular to the long axis of the hippocampus: hippocampal body.

arbitrary vertical line traced at the level of the medial limit of the hippocampal sulcus. The section showing the entire length of the crus fornices was considered the posterior limit of the hippocampal tail and was not included in the segmentation process (Fig. 4).

After the segmentation process, the hippocampus was portrayed on a 3-D-rendered image and the numeric values of the volume obtained by the 3-D software were also displayed. Both hippocampi were studied for all subjects.

Brain Volume Measurement

According to a previous study (Hasboun *et al.,* 1996b), we measured total brain volume including the brain stem and the cerebellum. The volume occupied by the

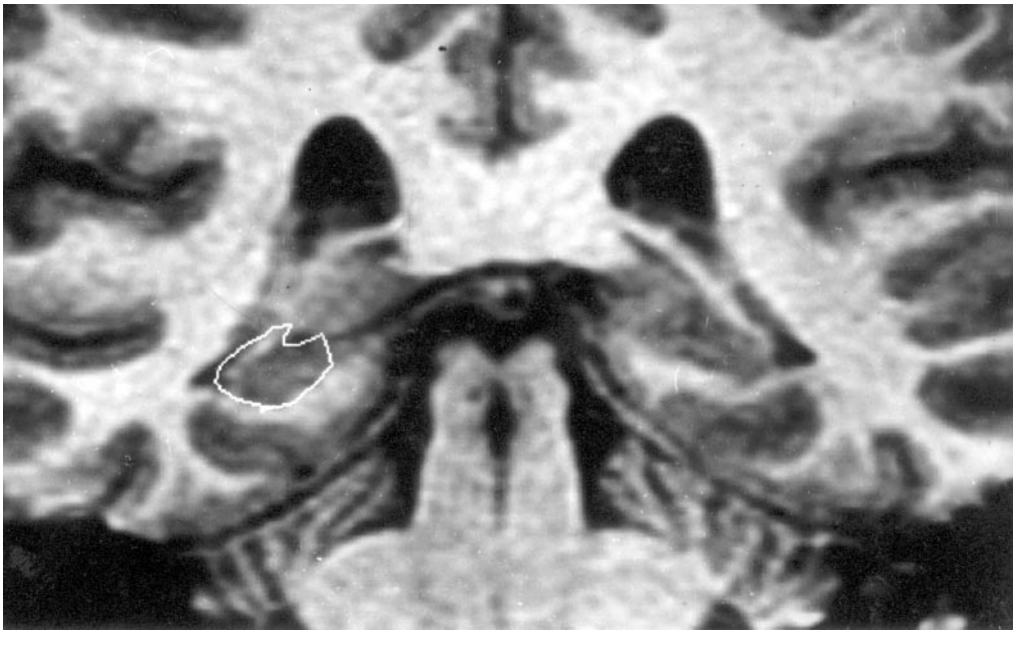

FIG. 4. Spoiled GRASS image reformatted in the coronal plane perpendicular to the long axis of the hippocampus: posterior landmark of the hippocampal segmentation. Last image before the plane of the crus fornices.

meninges and the subarachnoid space was excluded. The same acquisition as was used for the hippocampal volume was used here. The spinal cord was cut at the level of the Malgaigne line.

RESULTS

Implicit Memory

First it was verified whether the test used evaluated IM. The main results are shown in Table 1. The difference in means between primed and unprimed items for group A and for group B was significant (Student t test for independent samples). A significant priming effect was obtained. However, group B showed significantly higher scores than group A for both primed ($t = 3.44, P = 0.001$) and unprimed ($t = 3.25, P = 0.002$) items. This indicates that some words were more easily cited in one group than in the other, without relying on priming. Since the subjects were randomly distributed into the two groups, the better performance in group B could be attributed to a bias due to words that were more easily associated to the stems but did not require the priming process measured in the experiment. Therefore, to analyze the correlation between IM and hippocampal volume, the scores were separately standardized in group A and in group B ($x = (x - \bar{x})/\mathrm{SD}$). Thus, means and standard deviations of the standardized score were the same in each group. Correlation analysis between IM and hippocampal volume was performed using IM standardized scores and mixing the two groups.

Explicit Memory

The subjects recalled a mean of 3.23 words (SD = 2.18) in group A and a mean of 3.37 words (SD = 1.84) in group B. The mean for both groups was 3.30 words (SD = 2.02). Since the difference between the two groups was not significant, they were pooled for correlation analysis between the EM test and the hippocampal volume.

TABLE 1

Mean Performance on the IM Test for Primed and Unprimed (i.e., Displayed in the Study Phase) Words

Measure	Primed items	Unprimed items	Difference (priming effect)
Number of completed words for list A	1.26	0.15	1.11 $t(68) = 5.76$, $P < 0.0001$
Number of completed words for list B	2.25	0.55	1.70 $t(68) = 6.9$, $P < 0.0001$

TABLE 2

Correlations between IM and EM Performances and Brain Structures

Variable	Explicit memory test	Implicit memory test
BV	0.15 ($P = 0.22$)	−0.07 ($P = 0.53$)
RH	−0.07 ($P = 0.53$)	−0.08 ($P = 0.50$)
LH	−0.10 ($P = 0.39$)	0.06 ($P = 0.62$)
RH/BV	−0.25 ($P = 0.03$)*	−0.05 ($P = 0.64$)
LH/BV	−0.27 ($P = 0.02$)*	−0.00 ($P = 0.96$)

Note. Abbreviations used: BV, brain volume; RH, right hippocampus; LH, left hippocampus; RH/BV, right hippocampus/brain volume ratio; LH/BV, left hippocampus/brain volume ratio.
*Significant at $P = 0.05$.

Correlations between Memory Test Performance and Brain Structures

Table 2 shows the correlations between explicit and IM performance and the different brain structures. No significant correlations were obtained between the IM factor and the brain structures, and two statistically significant negative correlations were found between EM and RH/BV and LH/BV ratios.

We also performed the β multiple regression analysis coefficients with a λ for ridge regression of 0.05. It allows one to compare the relative contribution of each independent variable (RH, LH, BV) in the prediction of the dependent variable (IM or EM). For the EM, the standard model indicates that the three independent variables have a multiple regression coefficient of $R = 0.31$ (BV, $\beta = 0.37$, $P = 0.017$; RH, $\beta = -0.14$, $P = 0.549$; LH, $\beta = -0.23$, $P = 0.311$), which explains about 10% of the variance ($F(3, 67) = 2.29$, $P < 0.8$). Since this result was not significant, we then sought the best model by a stepwise multiple regression analysis. The best model was obtained with the BV and LH. These two variables have a multiple regression coefficient of $R = 0.29$ (BV, $\beta = 0.35, P < 0.01$; LH, $\beta = -0.33$, $P < 0.02$), which explains 9% of the variance ($F(2, 67) = 3.28, P < 0.04$).

DISCUSSION

Our results indicate that, in order to explain the interindividual variation of EM performance, the relationship between brain volume and hippocampal volume must be taken into account. Indeed, we found no correlation between memory and the raw values of the brain or the hippocampal volumes. But the multiple regression analysis showed that the relative contribution for EM of the left hippocampal volume was significantly negative, whereas the BV contribution was significantly positive.

First, we want to emphasize that the negative contribution from the multiple regression analysis is in

accordance with another of our results, which is the negative correlation between LH/BV ratio and EM performances. Namely, the multiple regression analysis gave results in the same way as data obtained with the ratio. That means that EM performances and hippocampal volumes varied inversely when the brain volume is taken into account.

Other works showed negative correlations between a brain structure and a cognitive activity (e.g., Squire *et al.,* 1992) and several interpretations were developed. Parks *et al.* (1988) explained it by the amount of effort provided by the subject: those who had difficulties performing the task tended to make greater effort and thus activated the associated structure(s) more, while those for whom the task was less difficult used more efficient strategies and needed less effort. On the other hand, Gur *et al.* refer to pathology, stated that ". . . poor performances may be associated with abnormally high level of activation. For example, there is some evidence for overactivation of the left hemisphere in schizophrenia, and this is accompanied by poor performances" (1994; p. 254).

Using a morphometrical approach, we can also consider the findings of prenatal studies in explaining these negative correlations. Some of these studies have indicated that problems during neuronal migration may lead to proliferation of neurons and neuronal connections and thus an increased size of the hippocampus (Jessel, 1991). This is one of the factors proposed by the works on fragile X syndrome to explain the differences in hippocampal volumes between pathologic subjects (larger volume) and healthy subjects (smaller volume) (Reiss *et al.,* 1994). This difference in size may subsequently lead to differences in the information process. Our results suggest that a large amount of neurons, neuronal connections, and glial cells could impair the information process.

Furthermore, O'Brien *et al.* (1997), comparing Alzheimer and control subjects, concluded that a strong correlation between age and temporal lobe atrophy was seen in control subjects and that the age-related increase in hippocampal atrophy should not be "interpreted as suggestive" of pathology including memory deficit (e.g., Alzheimer disease) (p. 1274). Köhler *et al.* (1998) found on their control subjects a trend toward a negative association between hippocampal volume and delayed verbal recall, whereas Raz *et al.* (1998) did not find a relationship between the volume of different limbic structures and memory. These works, including the present study, indicate that the study field of healthy adult memory is relevant to the hippocampal contribution research in memory performances.

With the positive contribution of the BV, we could expect that the increase in size of other brain structures accounts for the difference in memory performances. Some studies showed age-related strategy differences in episodic memory: in addition to the hippocampal activation, other brain areas occur (young subjects activated the anterior prefrontal region while elderly subjects activated the posterior frontal area near of the Broca's area) (Desgranges *et al.,* 1998). In memory tasks, functional imaging studies demonstrated an activation of the temporal cortex and an activation of the left frontal (Cabeza *et al.,* 1997) and the parahippocampal regions (Brewer *et al.,* 1998; Wagner *et al.,* 1998), the right frontal area (Brewer *et al.,* 1998), and the medial temporal structures (Nyberg *et al.,* 1996). Association of these structures with memory performances seems established. It is now necessary to perform, on our sample, a morphometrical approach of these structures to examine their contribution to BV increase.

CONCLUDING COMMENTS

It has long been well known that the hippocampus is involved in EM, but it is surprising to observe a negative correlation between performance in EM and hippocampal volume. This finding is counterintuitive with previous pathological studies showing a relationship between decreased memory performance and hippocampal atrophy. However, Torres *et al.* (1997) do not find significant differences in the hippocampal volumes between two healthy-subjects groups on delayed memory test (one group with low memory, $N = 10$; one group with high memory, $N = 9$). Unfortunately, they do not make a ratio with the brain volume. It would seem established that there is no positive correlation between EM performances and hippocampal volume in healthy subjects. For negative correlations between the two ratios and the EM performances, more studies performed by other teams would be necessary to confirm or to invalidate this result. If this result is confirmed by other works, it would indicate that neuropsychological processes which could explain poor EM performances in healthy subjects would be different from neuropsychological processes explaining decreased memory in pathologic subjects.

In summary, our results indicate, on the one hand, a negative contribution for the hippocampal volume and, on the other hand, a positive contribution for the BV. The negative contribution may be explained by previous studies. However, another interpretation may be considered, namely that the hippocampal volume per se has nothing to do with variance in EM. A study of the relative contribution of the hippocampus and other structures could underscore that, without correction for BV, the variance explained by the hippocampus is weak in comparison with variances explained by other structures. Subsequent studies should include several brain structures to provide the relative contribution of each of them in memory performances.

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