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Temporal dynamics of medial temporal lobe activation during encoding and recognition. A magnetoencephalography study

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Abstract: The goal of this study was to examine the spatiotemporal profiles of medial temporal lobe (MTL) activation during encoding and recognition of word and picture stimuli. Activation profiles were obtained from 13 neurologically intact volunteers using whole-head Magnetic Source Imaging. While a clear preponderance of left MTL activation was noted during word encoding, and to a lesser extent during word recognition, the profile of activation during picture processing was more variable featuring greater right hemisphere contribution. This conclusion was supported by the finding of a positive correlation between the degree of right MTL activity and performance during the picture encoding task, and a negative correlation between the degree of activity in this region and accuracy of word recall. Timing data indicated that left MTL engagement in word encoding is more prominent during late processing of the stimuli, whereas left MTL activity during recognition shows an early peak soon after stimulus onset. **Key words:** memory, medial temporal lobe, magnetoencephalography, magnetic source imaging, encoding, recognition, functional brain imaging.

Dinámica de activación del lóbulo temporal durante el aprendizaje y el reconocimiento. Un estudio mediante magnetoencefalografía

Resumen: El propósito de este estudio es examinar el patrón filológico de activación del lóbulo temporal durante el aprendizaje y el reconocimiento de estímulos. Mediante un magnetoencefalógrafo registramos el patrón de activación en 13 sujetos voluntarios. Mientras que la activación del lóbulo temporal medial del hemisferio izquierdo fue preponderante durante el aprendizaje de palabras, y en menor medida durante su reconocimiento; el procesamiento de imágenes (dibujos de objetos) involucro una red de

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estructuras más diversa, predominantemente en el hemisferio derecho. Estos resultados se basan en la correlación positiva entre el grado de activación del lóbulo temporal medial derecho y la ejecución durante el aprendizaje de imágenes, mientras que la activación de esta área mantuvo una correlación negativa con el recuerdo de palabras. La activación del lóbulo temporal medial izquierdo fue más temprana durante la fase de reconocimiento que durante el aprendizaje de palabras. **Palabras clave:** Memoria, lóbulo temporal medial, magnetoencefalografía, imagen de fuente magnética, aprendizaje, reconocimiento, imagen funcional cerebral.

The contribution of medial temporal lobe (MTL) structures (i.e., the hippocampus, dentate gyrus, subicular complex, entorhinal and parahippocampal cortex) to explicit memory function is strongly supported by experimental and clinical studies (Squire & Zola-Morgan, 1991; Zola et al., 2000; Zola-Morgan, Squire, & Amaral, 1986). Clinical evidence has been especially useful, revealing explicit memory problems in patients with bilateral or even unilateral MTL lesions (Scoville & Milner, 1957). Damage to the MTL in advanced stages of certain neurological disorders (e.g., Alzheimer's disease) and some forms of epilepsy, causes an amnesic syndrome, i.e. a global impairment of the ability to acquire new memories regardless of sensory modality, and a loss of some memories from the period before amnesia began. However, since impaired memory performance in these disorders may reflect a deficit in encoding, consolidation, or retrieval processes, or a combination, lesion data do not provide clear information regarding the relative contribution of the MTL to encoding and retrieval.

With the advent of non-invasive functional brain imaging techniques it became possible to obtain measures of regional brain activation during tasks that selectively involve either encoding or recognition processes. Using techniques such as Positron Emission Tomography (PET) and functional Magnetic Resonance Imaging (fMRI), a wealth of information has been collected regarding which brain areas show increased levels of metabolic activity during the encoding and retrieval stages of tasks involving various types of stimuli (Cabeza & Nyberg, 2000a; Grady et al., 1995; Grady, McIntosh, Rajah, & Craik, 1998; Kapur et al., 1994; Ungeleider, 1995). Yet, in spite of clinical evidence implicating the MTL in encoding processes, only a few of these studies have shown medial temporal lobe activation during tasks that primarily engage such processes (Brewer, Zhao, Desmond, Glover, & Gabrieli, 1998; Martin, 1999; Schacter & Wagner, 1999; Wagner et al., 1998). Some of these studies have reported a material specific laterality effect in the MTL, with predominant left hemisphere activation for verbal stimuli and right MTL activation for non-verbal stimuli (Grady, McIntosh, Rajah, & Craik, 1998; Brewer, Zhao, Desmond, Glover, & Gabrieli, 1998). Similarly, consistent MTL activation in the context of tasks that tap directly into retrieval operations has eluded many studies thus far (Kohler, Moscovitch, Winocur, McIntosh, 2000; Wiggs, Weisberg, & Martin, 1999). Two recent studies have found bilateral activity in the hippocampal region during recognition of targets studied in a different modality, suggesting that the hippocampus proper may be involved in maintaining cross-modal associations, whereas other MTL structures may support simpler recognition memory processes (Henke, Weber, Kneifel, Wieser, & Buck, 1999; Henke, Buck, Weber, & Wieser, 1997). Schacter, Alpert, Savage, Rauch, & Albert (1996) have presented evidence arguing that the degree of hippocampal activation can predict the accuracy of subsequent retrieval.

An understanding of the brain mechanism involved in the initial processing, registering and subsequent recognition of new information requires knowledge of a) the identity of brain regions and b) the temporal profile of engagement of these areas during the performance of experimental tasks that selectively involve the cognitive functions under investigation. However, techniques that rely on indices of blood flood and/or metabolism by integrating signals over a period of time (seconds or even minutes) to provide images of the spatial configuration of brain activity do not provide much information regarding the temporal course of regional activation during the actual performance of an experimental task. Consequently, little is known about the internal dynamics of activation of the MTL during real experimental conditions that engage learning and memory processes. A description of these dynamics can provide valuable information for understanding the disorders linked to brain damage in this area.

Magnetic Source Imaging (MSI), a relatively novel functional brain imaging procedure, affords measurements of regionally elevated levels of neuronal signaling in real time during processing of stimuli with excellent temporal resolution (in the millisecond range) and adequate spatial resolution (Pantev et al., 1995; Papanicolaou, 1995). MSI involves measuring changes in magnetic flux time-locked to the presentation of a stimulus from the head surface. The sources of these magnetic fields at successive time points during stimulus processing are estimated using standard algorithms and coregistrated with structural scans (i.e. MRI) permitting precise intracranial localization of active cortical patches. This method has been used with excellent results for describing spatiotemporal profiles of activation during various cognitive operations, such as working memory (Tesche & Karhu, 2000; Wang, Sakuma, & Kakigi, 2000), phonological decoding (Breier, Simos, Zouridakis, & Papanicolaou, 1999a), reading (Simos, Breier, Fletcher, Bergman, & Papanicolaou, 2000) and naming (Salmelin, Hari, Lounasma, & Sams, 1994; Levet, Praamstra, Meyer, Helenius, & Salmelin, 1998). MSI has been successfully used for the presurgical mapping of language-specific cortex (Breier et al., 1999; Papanicolaou et al., 1999; Simos, Papanicolau, Breier, Willmore, Wheless, et al., 1999; Simos, Breier, Maggio, Gormley, et al., 1999; Castillo et al., 2001), verifying the MSI-derived maps using electrocortical stimulation, which is considered the "gold standard" procedure. MSI is not only sensitive to detect activity produced in superficial cortical areas, as well as activity originating deep within the brain (Tesche, 1997). Indeed we consistently find predominantly left MTL activation in the context of episodic and working memory tasks using verbal material (Breier, Simos, Zouridakis, & Papanicolaou, 1998), and bilateral or predominantly right MTL activation with non-verbal stimuli (Breier, Simos, Zouridakis, & Papanicolaou, 1999b).

The current study was designed to examine the contribution of the MTL to encoding and recognition processes, and the time course of its activation during these two operations. Spatiotemporal brain activation profiles were obtained from 13 neurologically intact adult volunteers in two experiments, each involving performance of two memory tasks. In Experiment 1 the experimental material consisted of spoken English words, whereas pictures of common objects served as stimuli in Experiment 2. During the Encoding task, subjects were presented with a list of 12 stimuli (words or pictures depending on the experiment) and were asked to memorize them. The word list was presented ten times during which MSI data were collected in response to each of the spoken words. After each presentation subjects were given a free-recall test. During a subsequent Recognition task, subjects were shown blocks of stimuli (either words or pictures) and were asked to discriminate among items presented during the Encoding task (targets) and new words or pictures (distractors). Activation profiles were obtained with data collection and analysis protocols developed and used extensively in our laboratory. Briefly, MSI consists of recording changes in magnetic flux time locked to the onset of external stimuli. This flux results primarily from intracellular currents in large populations of neurons, reflecting increased neuronal signaling, which is, in turn, associated with engagement of a particular neuronal population in processing these stimuli. Magnetic flux measurements are obtained from 148 locations covering the entire head surface at 4 ms intervals, so that the temporal evolution of regional neurophysiological activity can be represented in real time. To identify the intracranial origin of either type of component, the magnetic field distribution that has been recorded simultaneously over the entire head surface at each time point is analyzed. The analysis consists of the application of a mathematical model which considers the intracranial activity sources (sets of active cells) as equivalent to physical current dipoles (Papanicolaou, 1995; Sarvas, 1987). The analysis intended to provide estimates of the location and strength of these sources, the activity of which produced the recorded magnetic fields at that point in time. The location estimates of each "dipolar" source are specified with reference to a Cartesian coordinate system, anchored on three fiducial points on the head (the *nasion* and the external *meatus* of each ear). The same fiducial points were marked with vitamin pills, thus enabling superimposition of the precise location of each dipolar source on the subject's (or patient's) MRI. The capacity of these MSI protocols to provide accurate and detailed maps of cortical regions essential for the performance of particular cognitive/linguistic functions has been validated in the context of two large clinical studies against invasive cortical mapping techniques (Breier, et al., 1999; 2001; Castillo et al., 2001; Papanicolaou et al., 1999; Simos et al., 1999a; 1999b).

Method

Participants

Thirteen adult normal volunteers (8 males, 5 females) provided informed consent to participate in the study and were paid for their participation. The participants had a mean age of 26.11 years (SD = 5.78) and ranged in age from 21 to 45 years. All participants had normal vision and hearing and no history of neurological or psychiatric disorder. They participated in one experimental session involving magnetoencephalographic recordings during word and picture memory tasks, which were administered in a random order to each participant.

Procedure

Two experiments were conducted in the session, one using auditory presentation of words and one using visual presentation of pictures. Event-related fields (ERFs; i,e., evoked brain responses) were recorded to each stimulus in the manner described below. For each experiment, two conditions were defined. In the first condition ("encoding") the subject was instructed to say aloud all the stimuli that he or she could remember after the presentation of each block of 12 stimuli. The same block of 12 stimuli, always in the same sequence, was presented ten times and subjects were asked for free recall after each presentation (words that the subject heard for experiment 1 and name of the pictures that the subject saw for experiment 2).

Immediately after the encoding phase, the subjects were given a recognition task in either the auditory (Experiment 1) or the visual modality (Experiment 2). In this condition a sequence of 126 stimuli were presented and participants were asked to raise their index finger (the responding hand was counterbalanced across subjects) after the presentation of the target stimuli (i.e. any of the 12 stimuli presented during the encoding condition). In each experiment, 42 stimuli (30 distractors and 12 target words) were employed. For experiment 1, 42 abstract English nouns were used, with scores of 3.0 or lower on the Paivio concretness Scale (Paivio, Yuille, & Madigan, 1968); and for experiment 2, 42 picture drawings easy to recognize that we already employed in a previous study (Castillo et al., 2001).

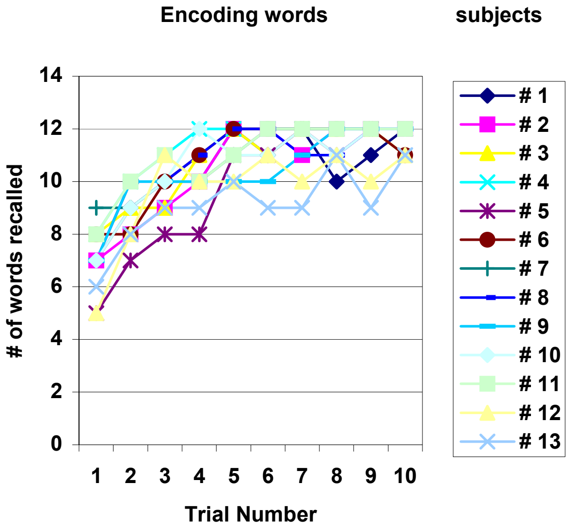
Recording and analysis of brain activity

Brain activity was recorded using a whole-head neuromagnetometer (Model WH-2500; 4-D Neuroimaging, Inc., San Diego, CA). Event-related magnetic fields (ERFs) time locked with stimulus presentation were collected during the experimental session for each participant. Only those ERFs that were evoked by stimuli that were correctly remembered during the encoding condition and correctly classified (target vs distractor) during the recognition condition were included in the final averages. A minimum of 60 epochs for each condition was used to calculate each averaged waveform (See fig 1a, b encoding words and encoding pictures waveforms). Once the averaged waveform was filtered (filter low pass 20 Hz), the analysis consisted of the application of a mathematical model that considered the intracranial sources at successive points (4 ms apart) as equivalent to physical current and the determination of the location of the magnetic flux source, also referred as “activity source”. The location estimated for each dipolar source was specified with reference to a Cartesian coordinate system, anchored on three fiducial points on the head (the nasion and the external meatus of each ear). The same fiducial points were marked with vitamin pills during the MRI scan, enabling superimposition of images and the intracranial precise location of each dipolar source (for details see Simos, Breier, Zouridakis, & Papanicolaou, 1998; Zouridakis, Simos, Breier, & Papanicolaou, 1998; Papanicolaou et al., 1999). The number of activity sources and their latency originating from the left and right MTL (including hippocampus, dentate gyrus, subicular complex and entorhinal and parahippocampal cortex) were estimated during the encoding and recognition conditions of the word and picture tasks separately. Activity sources with a correlation coefficient of 0.9 or greater and a volume of 20 or lower were considered acceptable. These parameters have been proved to ensure an accurate localization of brain activation in previous studies verifying MSI-derived maps using cortical stimulation (Simos et al., 1999).

Results

Behavioral performance

Figure 1 shows the learning curve during the encoding phase for words and pictures. All subjects showed a steep increase in the number of correctly recalled items after the first presentation, but took longer to learn the word stimuli. The subjects took a mean number of 5.15 trials (SD = 1.86) to learn all 12 pictures, compared to a mean number of 6.15 trials (SD = 2.04) to learn all 12 words. These differences were not statistically significant, however (p > .20). During the recognition task the rate of correct target identification of was over 90% for both stimulus types.



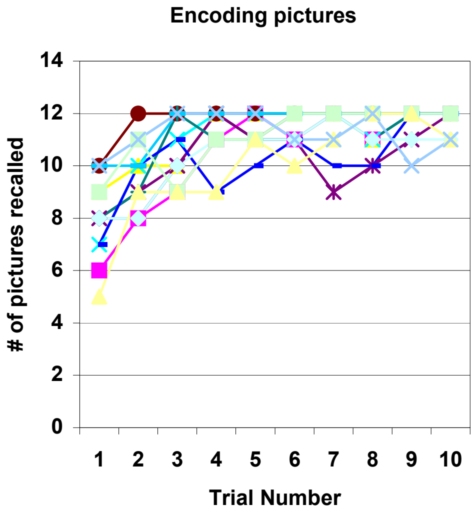


Figure 1. Learning curves for each of the 13 subjects during the Encoding tasks for words and pictures.

Hemispheric differences in MTL activation across experiments

Figure 2 displays the distribution of hemispheric asymmetries for the number of activity sources in the MTL during each of the two tasks and stimulus types. During word encoding and, albeit to a lesser extent, during word recognition, the majority of subjects showed predominantly left MTL activation. In contrast, the distribution of hemispheric asymmetries during picture processing was more variable, with 50-70 % of the subjects showing predominantly right hemisphere or bilaterally symmetric MTL activation. MTL activation profiles from two representative subjects are presented in Figure 3.

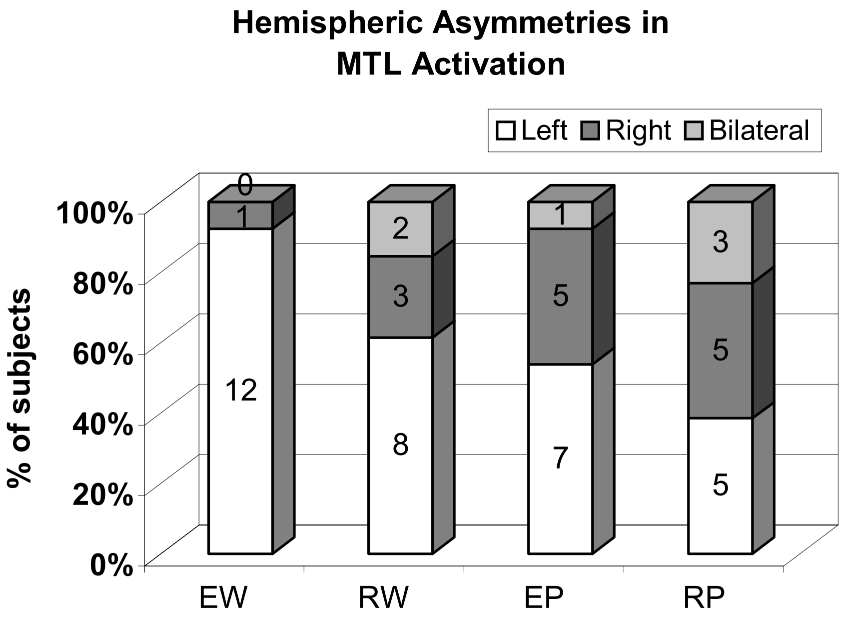


Figure 2. Percentage (and total number) of subjects showing predominantly left, right, or bilaterally symmetric MTL activation in each condition. We considered any profile featuring a difference of 20% or less between the number of sources in the left and the right MTL to be bilateral (Breier et al., 1999). A profile was considered as right hemisphere dominant if the degree of right MTL activation was at least 20% greater than the degree of left MTL activation. If the left-right asymmetry was smaller than ±20%, the activation profile was considered as bilaterally symmetric. Abbreviations: EW: encoding words; RW: recognizing words; EP: encoding pictures; RP: recognizing pictures.

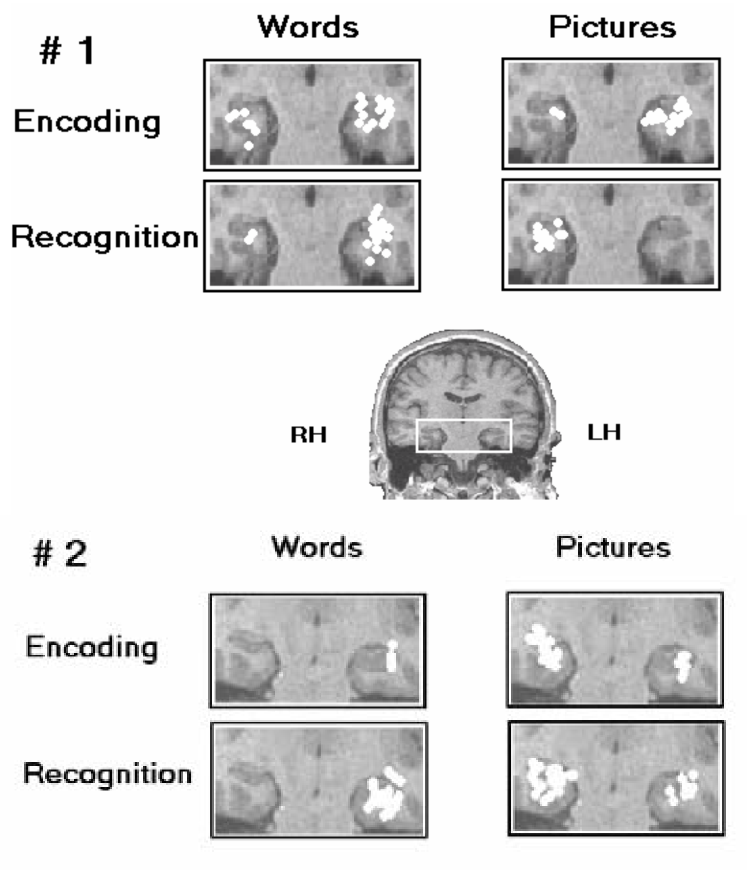


Figure 3. Profile of MTL activation in two representative subjects during the four experimental conditions. In case #1, encoding and recognition of words engaged predominantly the left MTL. Picture encoding and recognition engaged the left and right MTL, respectively. In case #2 word encoding was, again, associated with greater left than right hemisphere MTL activation, whereas picture processing was associated with predominant right MTL activity.

Experiment 1: Encoding and recognition of words

During both tasks, early activity sources (during the first 200 ms after stimulus onset) were localized in modality-specific cortex, primarily in the vicinity of the superior temporal plane, reflecting primary sensory processing of the stimuli. This activation was bilaterally symmetric in degree. In addition to medial temporal regions, late activity sources (200-

1000 ms) were found in different locations of the lateral temporal and parietal lobes in all cases, as well as the frontal lobe in some cases. This activity was observed more consistently in the posterior portion of the left superior temporal, supramarginal, and inferior frontal gyrus, and also in middle temporal gyrus bilaterally.

The number of intracranial sources localized in the left and right medial temporal lobes (MTL) were estimated during the word encoding and recognition tasks separately. Figures 4 and 5 display the temporal course of activation in each hemisphere during each task for the entire group of subjects. As shown, there is a tendency for clear laterality effects to first appear between 500 and 650 ms during word encoding, with more activity in the left than the right MTL. Laterality effects favoring the left MTL appear somewhat earlier during word recognition (around 350 ms).

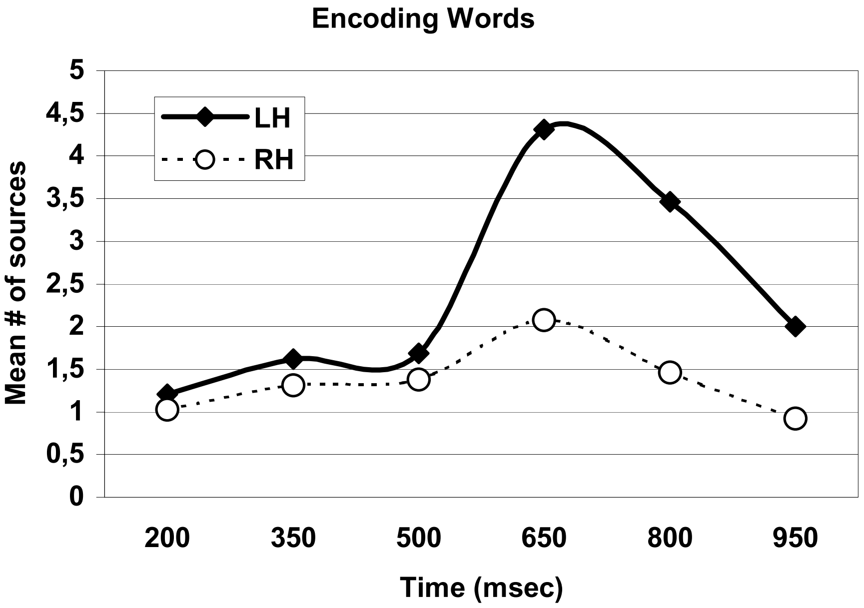


Figure 4. Temporal course of the activation (i. e. mean number of activity sources) in the left and right MTL during word encoding and recognition (each condition separately). As shown, there is a tendency for clear laterality effects to appear between 500 and 650 ms during word encoding, and earlier during word recognition, with more activity in the left than the right medial temporal lobe.

The number of intracranial sources were subjected to a two (task: encoding, recognition) by two (hemisphere: left, right) by five (time window: 200-350, 350-500, 500-650, 650-800, 800-950 ms) within-subjects ANOVA. Only sources between 200 and 1000 ms were included in the analyses to ensure that activity occurring after the expiration of the N1m component was considered. The ANOVA revealed a significant main effect of hemisphere, F (1,12) = 9.68, p < .01, as well as not significant main effect of time, F (4,48) = 2.36, p < .07. None of the other main effects or interactions were statistically significant. These findings suggest that the brain activation profiles in the MTL associated with word encoding and recognition are similar, and reveal comparable hemispheric asymmetries (LH > RH) and temporal progressions of activity. However, laterality effects (LH > RH) did appear more consistently during word encoding, with 12/13 subjects exhibiting greater amounts of activity in the left vs. right MTL compared to word recognition (8/13 subjects). Whereas the former proportion is significantly different from chance (binomial test, p < .01), the latter is not (p > .50).

The behavioral data further substantiated these hemispheric asymmetries. Hemispheric asymmetry scores were computed for each subject (LH – RH / LH + RH), indicating the relative amount of activity in the left vs. right MTL during the word encoding task. These asymmetry scores were highly correlated with the total number of words recalled across all ten learning trials, r = .75, p < .01. This finding suggests that more words were recalled as subjects evidenced more brain activity in the left MTL, but less activity in the right MTL. When the number of sources in the left and right MTL were correlated separately with the number of words recalled, the number of sources in the left hemisphere was only weakly correlated with the number of words recalled, r = -.09, p > .75, whereas the number of sources in the right hemisphere was strongly and significantly correlated with the number of words recalled, r = -.83, p < .001. Taken together, these findings suggest that activity in the right MTL may be a hindrance to word encoding, as reduced activity in this area is associated with more words recalled, and more activity is associated with fewer words recalled. Activity in the left MTL does not show a strong relationship with word encoding performance.

Experiment 2: Encoding and recognition of pictures

During both tasks, early activity sources (first 200 ms) were localized in modality-specific cortex in the occipital lobe, primarily in the vicinity of the calcarine fissure. In addition to the medial temporal activity sources, late activity sources (200-1000 ms) were found in all the participants in different locations of the lateral temporal, parietal and occipital lobes as well as the frontal lobe in some cases. Medial temporal lobe activity sources were analyzed with more detail.

Data were analyzed in a manner identical to that used in Experiment 1 with a two (task: encoding, recognition) by two (hemisphere: left, right) by five (time: 200-350, 350-500, 500-650, 650-800, 800-950 ms) within-subjects ANOVA. Figure 5 displays the temporal course of MTL activation in each hemisphere during each task for the entire group of subjects.

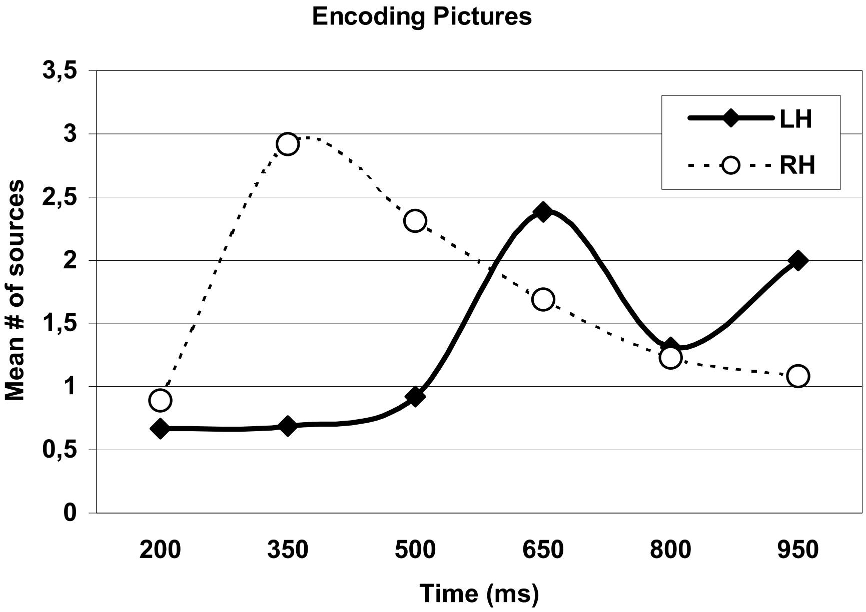


Figure 5. Temporal course of activation (i. e. mean number of activity sources) in the left and right MTL during picture processing. The tendency for predominantly left MTL activation observed during word processing is absent. Picture encoding engaged predominantly the right MTL in five subjects, with a peak of activation between 200-350 ms, and the left MTL in seven subjects, with a peak between 500-650 ms (one subject showed of bilateral activation). Picture recognition engaged predominantly the right MTL in five subjects, with a peak of activation between 500-650 ms, the left MTL in five subjects, with a peak of activation between 650-800 ms, and both the left and right MTL, symmetrically in three subjects.

The ANOVA revealed a significant three-way interaction, F (4, 48) = 20.72, p < .05. None of the other main effects or two-way interactions were significant. Planned comparisons between the left and right hemispheres for each task and time interval separately revealed significantly greater right vs. left MTL activity during the picture recognition task from 500 to 650 ms, t(12) = -2.27, $p < .05$. There were no other statistically significant differences between hemispheres at other time points, or between tasks within each hemisphere. The degree and direction of hemispheric asymmetries in did not correlate significantly across tasks ($r = -.14$, $p > .60$). Neither hemispheric asymmetry scores, nor the absolute number of sources in the left and MTL areas, correlated significantly with the total number of pictures recalled, although there was a slight trend for subjects to recall more pictures as the total amount of activity in the right MTL increased, $r = .45$, $p = .13$.

Discussion

Memory can be defined as a set of brain operations involved in the analysis, storage and retrieval of information. In the last decades, the knowledge of the brain mechanisms mediating these operations has substantially improved using non-invasive brain imaging techniques (for a review see Cabeza, & Nyberg, 2000b). A brain mechanism can be conceived as a set of neurophysiological processes that operate jointly to carry out a particular cognitive function. Each component process is subserved by one or more neuronal populations located in a particular brain area. Traditionally, investigations in human neuropsychology and cognitive neuroscience focus on the identity of areas where these operations take place. In this context, a wealth of data exist that support the contribution of the MTL to explicit memory function. Very little information exists, however, regarding the temporal profile of MTL activation in tasks that involve such functions. In our study we recorded regional brain activity using Magnetic Source Imaging, a technique that possesses the requisite temporal resolution for obtaining such information.

It should be pointed out that the stimuli presented in the encoding stage of this investigation (and in the majority of previous investigations) were familiar to the subjects and were repeated several times during the course of the experiment. “Encoding” tasks are, therefore, likely to involve initial stimulus processing, including automatic access to stored representations that leads to recognition, in addition to those operations related to storage and retention of information (consolidation). It is, nevertheless, safe to assume that the most prominent component of our “encoding” tasks was the act of learning of a particular set of a stimuli. Given the high level of success displayed by all subjects in memorizing the stimuli, we may assume that consolidation processes were active during this task. The “recognition” tasks on the other hand did not require learning or memorization, but featured, primarily, recognition (similar to the encoding tasks) and discrimination of stimuli as belonging to a learned set or not. To the extent that both processes require controlled access to stored representations of verbal and pictorial stimuli, our "recognition" tasks must also engage retrieval processes. The consistent engagement of the MTL during the encoding tasks suggests the contribution of this area to consolidation processes that can be maximized using different strategies (in this case repetition). The hippocampus itself is usually associated with consolidation of experiences into long term memory (Squire & Zola Morgan, 1991). Our findings suggest not only that left MTL engagement during the encoding phase is an important component of the brain mechanism involved in verbal learning and memory, but also that right MTL activation has detrimental effects to subsequent recall ability. The strong left MTL predominance during the encoding phase was reduced during the recognition phase, suggesting some contribution of the right MTL in word retrieval and recognition.

The clinical evidence supporting the presence of selective verbal memory deficits in patients with left MTL damage (Baxendale et al., 1998; Sass et al., 1995; Namer et al., 1999) and our findings reinforce the notion of left MTL specificity for verbal material. The association between right hippocampal function and nonverbal memory has been suggested, but remains less clear than that between left hippocampal function and verbal memory (Kilpatrick et al., 1997; Breier, Simos, Zouridakis, & Papanicolaou, 1999b; Lencz et al., 1992; Sass et al., 1995). In the present study, we did not observe a single dominant laterality profile during either picture processing tasks. One explanation for the variability of profiles across subjects during picture processing is the use of different cognitive strategies (verbal vs. visuospatial) during the encoding and/or the recognition phase. During the encoding phase the objective for the subject was to increase the number of verbal responses after each presentation of the stimuli, and this can be achieved through different strategies (i.e. verbal vs. visuospatial). Since pictures are usually remembered far better than words (Borges, Stepnowsky, & Holt, 1977) the picture superiority effect that we observed during the encoding phase (see Figure 1), can be explained by taking into account that pictures engage greater conceptual elaborative processing than words. Ongoing studies in our laboratory focus specifically on the effects of adopting different encoding and memorization strategies on the profiles of MTL activation using both meaningful (object drawings) and inherently meaningless pictorial stimuli (i.e., kaleidoscope patterns).

In addition, the two word tasks were associated with distinct (albeit not statistically significant) temporal profiles of activation. MTL activation during the encoding task showed a late left hemisphere maximum between 500 and 950 ms. In contrast, left MTL activation in the recognition task started much earlier, on average around 200 ms, and resolved by 850 ms after stimulus onset. It is tempting to hypothesize that the late phase of the engagement of the left MTL in both word tasks may reflect the initial stimulus encoding and automatic access to a stored representation, namely processes common to both tasks that are normally sufficient to support stimulus recognition. Furthermore, assuming that the right MTL plays a somewhat greater role in word retrieval, this hypothetical contribution may be more notable during the late stage of stimulus processing, i.e., between approximately 500 and 800 ms. The temporal course of *left* MTL activation during the picture encoding task was qualitatively similar to that observed during the word encoding task. In the former case, however, the group data showed a prominent peak in *right* MTL activation between 200 and 500 ms. The temporal course of *right* MTL activation during the picture recognition task was also qualitatively similar to the profile of *left* MTL activation observed in the context of the word recognition task. Both profiles featured early (i.e., around 250 ms) and late (i.e., around 650 ms) activation peaks. Finally, *left* MTL activation during the picture recognition task and *right* MTL activation in the context of the word recognition task showed a single late (i.e., after 500 ms) maximum. These qualitative observations are consistent with the notion that the right MTL plays a greater role in the brain mechanisms responsible for the initial processing, consolidation, and retrieval of information presented in pictorial form. As far as timing is concerned, the contribution of the right MTL in picture processing tasks appears to be equivalent to the role of the left MTL in word processing tasks. An important distinguishing feature that emerged from our data is that bilateral MTL involvement during memorization of pictorial material is not a disadvantage for adequate task performance. In contrast, predominant left MTL involvement during word list memorization appears to be necessary to ensure high recall performance levels.

A final issue that deserves mentioning is the consistency with which MTL activation has been observed across studies. Some studies, specifically designed to investigate cerebral activation associated with memory processes have not found task-specific MTL activation (Shallice et al., 1994; Tulving, Kapur, Craik, Moscovitch, & Houle, 1994; Grasby et al., 1993; Fletcher et al., 1995), although others have (Schacter, Alpert, Savage, Rauch, & Albert, 1996; Gabrieli, Brewer, Desmond, & Glover, 1997; Squire, 1992). Different explanations for these inconsistencies can be suggested. Most studies to date used short retention intervals (typically a few minutes) failing to ensure adequate consolidation of the material to be learned. In our case, the retention interval was short, but consolidation was maximized through repeated presentation of the stimulus lists. The tasks ensured a high level of success during the encoding and the recognition tasks, which minimized individual differences in performance. This approach, during the encoding condition, ensures a consolidation process (through repetition) that purportedly leads to a more stable memory trace.

Conclusion

MSI provides the opportunity to study the temporal dynamics of regional brain activation (including deep brain structures such as the hippocampus) with an extraordinary temporal resolution and with adequate spatial precision. The presented data extends the results of previous studies using this instrument, clarifying the spatiotemporal course of brain activation during cognitive tasks (Breier, Simos, Zouridakis, & Papanicolaou, 1998; Simos, Breier, Fletcher, Bergman, Papanicolaou, 2000). Our results reinforce the hypothesis of MTL contribution in the distributed networks implicated in memory encoding and recognition with specific left MTL engagement in verbal memory processes. The temporal course of regional activation in this area during memory processes provides novel and relevant neurophysiological information extending previous studies in this field.

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