

**LEARNING ORTHOGRAPHY IN ADULT LIFE:
A MAGNETOENCEPHALOGRAPHY STUDY**

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INTRODUCTION

Children go to school and learn orthography, symbolic representation of algebraic calculation and line drawings, which are tools that give access to universal knowledge. Developmental studies showed us that the time for learning these early skills is related to the maturation of the brain. That means that the brain regions that are crucial to support the biologic mechanisms involved in the different competences became available for a particular function at specific moments in the maturation process. Exposure to external stimulation is known to modulate the function of these areas. In other words we can say that: 1) there is a critical period during which the learning of those several competencies is easier and 2) schooling shapes the brain both from the functional and from the structural points of view.

We have now a large amount of evidence showing differences in performing language tasks between those who learned to read and to write in the proper age and those that, for social reasons, remain illiterate all their lives (Castro-Caldas & Reis, 2000; Castro Caldas, in press).

These differences are clear in behavioural, structural and in activation terms. There are differences in specific functions like those related to the conscious mastering of phonology (Morais *et al* 1979, Reis & Castro-Caldas, 1997) which constitute a difficult task for illiterate subjects.

There are differences between literates and illiterates in the pattern of brain activation measured by means of Positron Emission Tomography (PET), while repeating pseudo words (Castro-Caldas *et al*, 1998). There are also differences in specific anatomical regions like the corpus callosum that is thinner in illiterate subjects compared to literate ones, in the regions where parietal fibres cross (Castro-Caldas *et al*, 1999).

These differences justify the discussion about the arrangement of interhemispheric distribution of competences being different as a result of schooling. Indeed the question of hemispheric dominance and literacy goes back to the time of Ernest Weber (1904) as quoted by Coppens *et al* (1998). This author considered that illiterate and semiliterate aphasic were rare on his observations. Therefore he predicted that in these low educated groups, provided the subjects were right handed, there would be a low incidence of aphasia, a greater incidence of crossed aphasia (a term coined by Byron Bramwell in 1899 meaning aphasia following a right hemisphere lesion in a right handed subject), and a better recuperation of language skills following aphasia. This first suggestion was supported in 1956 by Critchley. Discussing the outcome of aphasia this author thought that aphasia was more persistent in higher educated subjects. Later on this same idea was supported by the results of Cameron *et al* (1971) who studied patients with language disturbances following left hemisphere lesions. The authors observed that less educated subjects were less prone to become aphasic

following stroke on the left hemisphere. Our own series contradict however these last results (Damásio *et al*, 1976) in a global approach of the problem. But looking to the question of aphasia in more detail we found that repetition without comprehension was rare in illiterate aphasics due to their inability to deal consciously with phonology (Castro-Caldas *et al*, 1997). On the other hand the correlation between subcomponents of the aphasia symptomatology was different between literate and illiterate subjects (Fonseca & Castro-Caldas, 2003). Lecours *et al*. (1987a)b); 1988) suggested that the right hemisphere played a more important role in language functions in the illiterate population compared with the literate one after studying a large cohort of brain lesioned subjects and their controls.

There are also other sources of evidence, sometimes controversial, based on studies with non-brain lesioned subjects that support the concept of an influence of literacy on the interhemispheric distribution of language competencies. Studies with dichotic listening, for instance, revealed differences between literate and illiterate subjects in what concerns the dominance effect. This was found by Damásio *et al* (1979) and by Tzavaras *et al* (1981) but was absent in the study by Castro and Morais (1987). It is possible that the differences in the experimental paradigms justify the discrepant results.

Functional neuroimaging studies also brought some light into this topic. In our above mentioned PET study we also compared the role played by each cerebral hemisphere in the task of word and pseudo word repetition performed by literate and illiterate volunteers. Regions of interest of the parietal cortex were selected and we found that the pattern of inter-hemispheric balance was different for each group. The left-right difference was greater in the literate group compared to the illiterate one in the inferior parietal region being more activated on the left comparing to the right in the literate group. The reverse difference was found in the superior aspect of the parietal lobe (Castro-Caldas *et al*, 1998). Differences also became evident in relation to other cognitive functions differences also became evident. While performing a task of mental calculation of contextual magnitude, illiterate subjects activated more the right side of the brain compared to literate that used their left hemisphere to perform the task (Braga *et al*, submitted)

These works allow us to establish the importance of learning how to convert graphemes to phonemes and other mental operations in the proper age for the late functional and anatomical organization of language in the brain. We can therefore consider that there is a biologic handicap in illiterate adults compared to those that attended school in the proper age. However it is well known that it is possible to learn to read and to write in adult life. The way that this late learning is made and the mechanisms in

which its relays remain largely unknown. It is therefore important to understand if there are differences in the recruitment of cerebral structures to perform the same tasks of language processing. Then, the question that we would like to answer concerns the identification of the regions of the brain involved in the processing of orthography in subjects that learned in adult life

In order to address this topic we compared two groups of participants: one who learned to read and write in the proper age (literate) and another one who learned in adult life (late literate). Subjects were scanned by means of magnetoencephalography while reading words.

Magnetoencephalography is a method that allows us to gain information about the cerebral function with the great advantage of having a temporal resolution in the order of ms that gives us as an insight into a dynamical cortical representation. There are already a significant number of studies showing that MEG is a good method for studying mental function (Hamalainen & Hari, 2002; Maestú *et al*, 2001; 2003), particularly language (Salmelin *et al*, 1994; Breier *et al*, 1999b). The capacity of MEG to determine hemispheric dominance was tested in a series of studies with normal controls (Breier *et al*, 1998, 1999a; Papanicolaou *et al*, 1999; Simos *et al*, 1998 a, b; Simos *et al*, 2000) and patients, where the results of MEG mapping were compared with either the results of the Intracarotid Amytal Procedure (IAP) (Breier *et al*, 2001; Maestú *et al*, 2002) or to the direct

cortical stimulation mapping, done either intraoperatively (Simos *et al*, 1999 a,b) or extraoperatively through implanted electrode grids (Breier *et al*, 1999; Castillo *et al* 2001a). In general these works showed that MEG is a valid tool for mapping the cerebral regions involved in language functions.

Therefore MEG was considered a good tool for addressing the primary purpose of this study, that is, compare the performance of literates and late literates in language processing tasks in order to better understand the mechanisms that are put forward to do the learning of reading and writing outside the critical period.

MATERIAL AND METHODS

Participants: Twelve neurologically intact female adult volunteers, with no history of psychomotor developmental disabilities that would prevent normal learning in childhood, were included on the study. Present or recent psychiatric or neurological illness were ruled out on clinical basis. Before inclusion, and after the nature of the study had been properly explained to them, all participants signed consent forms. Seven women (late literates) learned to read and write in late adulthood in adult alphabetisation classes from where they were recruited for this study (mean age: 70,86 sd:7,4. The other five (literate) learned in the proper age (mean age:73- sd: 9,6).

All participants were right handed according to the Humphrey Laterality questionnaire (modified by Hecaen & Ajuriguerra, 1963) and they all scored above cut-off values for the Portuguese adaptation of Mini Mental State (MMS) (Manuela Guerreiro *et al*, 1994). The mean MMS score for literate subjects was 28,4 (sd: 1,7) and for late literates was 25,4 (sd:1,6). Their proficiency in reading was an inclusion criteria and was previously assessed by asking the subjects to read series of words similar to those that would be used in the task. Subjects were excluded if unable to read any of the words.

MEG PROCEDURE

All the recordings took place in the Center of Magnetoencephalography Dr. Pérez Mondrego in Madrid where there is already practice in the language testing procedure (Maestú *et al.*, 2002).

Stimuli and tasks

The procedures for MEG-language recordings was described in detail elsewhere (Breier *et al.*, 1998, 2001; Papanicolaou *et al.*, 1999; Maestú *et al.*, 2002), and will be briefly summarized here. For our purpose it is sufficient to emphasise that language specific brain activity was elicited using a visual recognition task. This material was first conceived in English (Simos *et al.* 2001) then adapted for the Spanish language (Maestú *et al.*, 2002). The present material was adapted from the Spanish version and the recording procedures were the same (Maestú *et al.*, 2002). A list of 63 written abstract Portuguese nouns were stored on a Neuroscan STIM stimulation system (Neurosoft, Inc., El Paso, TX). The stimuli were arranged in three lists of 43 words: 33 “target” words that were the same in all three lists, and 10 distractors that were unique in each list, for a total 129 visual events. The subjects were then asked to lift their right index finger whenever they recognize a target word (i.e. a word repeated in all three lists). All the words were familiar to the participants of both groups.

In this visual task words were projected through a Sharp LCD projector (SONY VPL-X600E) situated outside the shielded room onto a series of in-room mirrors the last of which was suspended approximately 1 meter above the subject's face.

MEG Recordings and Analysis:

In recording sessions the participants were asked to lie motionless on a bed. Recordings were made in a magnetically shielded room with a whole head magnetometer (Magnes 2500; 4D Neuroimaging, San Diego, CA) consisting of 148 magnetometer coils placed in a cryogenic dewar container. The instrument is housed in a magnetically shielded room designed to reduce environmental noise.

The signal was filtered online with a band pass filter between 0,1 and 0,5 Hz digitized for 1000 ms (250 Hz sampling rate) including a 150 ms prestimulus period and subjected to an adaptive filtering procedure that is a part of the 4-D Neuroimaging package. These steps are necessary to minimize the amount of low frequency magnetic noise that is usually present in Magnetoencephalography recordings. The single trial event related fields (ERF's) were averaged after removing those who occurred during a eye movement or blink (as indicated by a peak to peak amplitude in the electrooculogram in excess of 50 μ V). A minimum of 90 ERF

epochs were used to calculate each waveform. The averaged waveforms were digitally filtered with a lowpass 20 Hz filter.

The intracranial sources of the observed ERF's, henceforth referred to as activity sources, were modelled as single equivalent current dipole (ECD's) which were fitted at successive 4 msec intervals by using a nonlinear Levenberg-Marquardt algorithm. This algorithm used for the ECD that most probably produced the observed magnetic field at any given point in time. The ECD computation was restricted to latency periods in which a single pair of magnetic flux extreme dominated the left and/or the right half of the head surface. For any point in time the ECD fitting algorithm was applied to the magnetic flux obtained from a group of 34 to 38 magnetometers, always including both extremes.

The ECD solutions were considered satisfactory after meeting a correlation coefficient of at least 0.90 between the observed and the best predicted magnetic field distribution and a goodness of fit of at least 0.9 or higher. The ECD locations were computed with reference to a Cartesian system defined by a set of three anatomical fiducial points, one of each of the two external *meati* and the *nasion*.

In order to determine the anatomical regions where the activity sources were located, ECD coordinates were overlaid onto T1-weight, magnetic resonance (MR) images (TR 13.6 ms; TE 4.8 ms; recording matrix 256x 256 pixels, 1 excitation, 240 mm field of view, and 1.4 mm

slice thickness) obtained from every participant on a separate session. The MEG-MRI overlay was performed using the STAR program, which is part of the 4-D Neuroimaging software (see Maestú *et al*, 2002, for a detailed description of the co-registration process). Visual inspection of the resulting activation profiles showed that activity sources were computed consistently across participants in the following areas: the Medial Temporal Gyrus (MTG), Superior Temporal Gyrus (STG), Dorsal Inferior Frontal Gyrus (IFG) (Brodmann's area 44), sensorimotor (BA 1, 2, 3, 4) and the parietal lobe. The temporal course of regional activation was examined by placing activity sources in each area into two latency windows extending from the early latencies (from 150 to 400ms after stimulus onset) and late latencies (from 400 to 800ms). Early, sources related to sensory processing (i.e., those that occur during the course of the M50 and M100 components), were analyzed separately to demonstrate no visual perceptual deficits in each subject. Laterality indices were computed for each patient based on the following formula: $(LH-RH)/(LH+RH)$ where LH represents the number of activity sources in the left hemisphere and RH the number of activity sources in the right hemisphere. The data used in this formula were restricted to late activity sources (150 ms or later following stimulus onset), as it is believed that early activity reflect initial sensory processing of the word stimuli (Breier *et al*, 1998).

Results

Behavioural results:

Behavioural data revealed that both groups showed similar scores in the performance of the task without differences between them ($p= 0.14$). The literate subjects recognized 57% of the target stimuli, while the late-literate recognized 54%. The literate subjects made 6% of false-recognition responses to the non-target stimuli against 9% of the late-literate subjects.

MEG data analyses

Overall cortical involvement in the task: The first question that we raised concerns the general cortical involvement in the task. Considering the total number of activity sources (regardless of latency and topographical distribution) we found no differences between groups (mean number of sources for the late-literate: $49,8\pm 15$ and for the literate 50 ± 17 ; $p= 0.98$).

Hemispheric laterality regardless of latency and area: The second question concerned interhemispheric involvement in the task. Considering the laterality index ($LH - RH / RH+LH$) we found that while the literates group showed a mean interhemispheric asymmetry index of $0,48\pm 0,22$ the late-literate group showed $0,13\pm 0,24$, indicating a bilateral representation of operators involved in the task in late-literate (cut-off 0,25 see Maestú et

al, 2002). Furthermore, in the literate group 26% of the sources were in the right side of brain while this was the case for 41% of the sources of the late literate group ($p < .048$).

Fig. 1 about here

Anatomical distribution regardless of latency: Considering the activation sources by region, regardless of latency, we found differences between groups in two main areas (table 1). Group differences on inferior frontal gyrus (IFG), medial temporal gyrus (MTG), and superior temporal gyrus (STG) and parietal lobe were assessed using an analysis of variance (ANOVA) with Group (literate and late-literate) as the between subjects factor. The nominal significance level of .05 was corrected using the Bonferroni procedure to reduce the risk of Type 1 error. As a result, a group effect was found for the number of activity sources in the left IFG ($F_{(1, 10)} = 12,03$; $P < 0,006$) and right MTG ($F_{(1, 10)} = 9,43$; $P < 0,012$), indicating that the literate subjects showed a greater number of sources in the left IFG (BA 44) than the late literate, while the opposite effect was found for the right MTG. A similar tendency were found when collapsing the entire right temporal lobe ($F_{(1, 10)} = 12,60$; $P < 0,005$) sources or collapsing the right temporo-parietal ($F_{(1, 10)} = 7,38$; $P < 0,022$) sources,

showing the late-literates higher number of sources in those right posterior areas.

Table 1 about here

Latency effects: In order to demonstrate that the differences between groups were not due to a sensory perceptual deficit, an ANOVA was computed for the right and left occipital sources related to the M100 component (from 90 to 150ms after stimulus onset). As a result neither the right ($p=0.23$; 6.4 ± 1.51 literates; 5.4 ± 1.13 late-literates) or the left ($p=0.15$; 6.6 ± 1.5 literates; 5.14 ± 1.6 late-literates) occipital sources in the M100 time window showed differences between groups. Group differences on each of the above mentioned areas were assessed using an ANOVA with Group (literates and late-literates) as the between subjects factor. Again, the nominal significance level of .05 was corrected using the Bonferroni procedure to reduce the risk of Type 1 error. A Group effect was found for the number of activity sources over the right temporo-parietal areas in the latency window between 400 and 800 ms ($F_{(1, 10)} = 12,11$; $P < 0,006$) after the stimuli onset, indicating that the late-literate group showed greater number of sources over that region in that particular period of time than the literate group (fig. 2 and 3).

Figures 2 and 3 about here

As in the analyses regardless of latency literate subjects showed greater number of sources in the left IFG than late-literate, but here in both the early ($F_{(1, 10)} = 5.86$; $P < 0,036$) and the late ($F_{(1, 10)} = 14,16$; $P < 0,004$) latency windows

If we take in consideration the activation sources related to both occipital lobes we can see that although the difference does not reach statistical significance, there is a tendency for the late-literate subjects to have more late sources than literate (Figures 4 and 5).

Figures 4 and 5 about here

Discussion

Results showed several significant differences between subjects that learned orthography in the proper age and those who learned late in adult life. The task of reading and identifying the words within a pre-learned series is more complex than simple reading because it involves attention and memory but, as was already demonstrated in the works of the Simos *et al* (2001) and Maestú *et al* (2002), it allows us to make a comprehensive interpretation regarding the language processing.

It is important to notice first that when considering the total number of activation sources regardless of latency and regions, we found no differences between groups. Considering some of the MEG literature (Maestú *et al*, 2001) it is expected that a less efficient processing will correspond to a lower number of activity sources, this being related with brain morphological anomalies (Maestú *et al*, 2003). Following this line, when we found no differences in the total amount of activation we can assume that we are looking not to a *worst* processing of one of the groups but to a *different* processing between groups.

The second result we would like to emphasise concerns the different pattern of inter-hemispheric activity. As expected, the control group showed a left lateralization of activity based on the lateralization index (see Breier *et al*, 1998; Maestú *et al*, 2002). However, the late-literate group showed a pattern of bi-hemispheric activity due to the increased number of sources over the right hemisphere, which showed significant differences between groups. As we mentioned in the introduction there is evidence that the right hemisphere plays a more important role in language processing of illiterate subjects. This probably means that they use strategies different from those of literate subjects to solve some of the language tasks. When they start learning to read and write in adult life they support their learning procedure in their competent brain structures, that are different from those that support the same procedures when learning occurs in childhood. This

is in agreement with recent results of Stephan *et al* (2003) about hemispheric competence. It is the strategy of the processing that determines the side of the brain involved in solving the task and not the quality of the task. On the other hand previous results with MEG, showed that the brain magnetic activity could be modulated as a function of predetermined strategies of processing used by the subject (Maestú *et al*, in press Neuroimage). Thus this increased activity over the right parieto-temporal areas in late literate subjects could reflect a more holistic approach to the word rather than a phonological decoding in the late-literate subjects.

If we consider the few studies devoted to inter-hemispheric balance related to environmental influence we can say that the areas involved in inter-hemispheric asymmetry vary according to the particular task that is studied and to the strategy that is used. We know that the structure of individual neurones may change in relation to the level of education (Jacobs *et al*, 1993) but is still necessary to know the topographical distribution in the cerebral cortex of changes related with specific functions and specific strategies, and the influence of practicing to promote those changes. We have the evidence that the majority of functional changes occur in the sensorial cortex (Castro-Caldas *et al*, 1998) and in the main connection between both hemispheres (Castro-Caldas *et al*, 1999), but much more detailed studies are needed.

When we analyse the results by region and by time window the most significant difference in our study was due to excess of activity in temporo-parietal regions of the right hemisphere of late-literate subjects. More interesting is to see that the difference in this temporo-parietal region is due to sources of “very” late activity (400 to 800 ms after the stimulus onset). Previous research (Simos *et al*, 2001) already indicates that the inter-hemispheric balance of the late sources of temporo-parietal activities was judged to be a good indicator of language lateralization (Simos *et al*, 2001). This was studied comparing MEG results with electrocortical stimulation (Castillo *et al*, 2001) and Wada test (Breier *et al*, 1998; Maestú *et al*, 2002) and therefore it is possible that in late literates the differences that arise after the 400 ms period can be attributed to a biased processing towards the right hemisphere. We know that temporo-parietal cortex is an area of convergence of different sensorial modalities. Therefore when information related to written language is being processed by literate subjects it tends to be conducted to the left hemisphere very early in the process of reading. On the other hand late-literate subjects go on doing a longer and less focused process that involves right hemisphere mechanisms.

That takes us to another result that deserves comment and that concerns the occipital activity. Although not statistically significant late-literate had a tendency to have later onsets (400-800 ms) in the occipital lobe as can be seen on figures 4 and 5. We know from other image studies

that the occipital cortex of both sides is naturally involved in visual reading. However we do not know much about the distribution of this activity in time. It is possible that, for less trained readers the process of visual detection of meaning of symbolic stimuli takes longer than for trained subjects. There was also a tendency for this late activity to be located in the right side. This tendency was in accordance with the significant activity found in the right temporo-parietal cortex. It most probably corresponds to a parallel treatment of visual- information that late-literates need to activate and that expert readers do not.

Finally it was found that late-literate subjects had fewer fonts than expert readers in the left dorsal inferior frontal cortex. The interpretation, we propose for this finding is that literate subjects having a quicker access to the result of the visual decoding than late literates one. Visual decoding gives access to the phonological form of the words, which is related to left IFG (Poldrack *et al*, 1999). It is long known that auditory material gains automatic access to the phonological store (Conrad & Hull, 1964), and that, if we want to represent keep written information in the phonological store we have to reconverted it in to an auditory form .It is also known that the material visually presented relies on articulatory rehearsal in order to access to the phonological loop (Baddeley *et al*. 1984) We can assume that those subjects that are used to do this reversion of the written material in a phonological form activate phonological working memory and its

components quicker than those that are less skilled. Therefore this difference in activity may reflect the articulatory rehearsal (Fletcher & Henson, 2001).

The general interpretation that we suggest for this group of results is that the process of learning to read in adult life differs significantly on what concerns the neural support. Behaviourally the two groups performed similarly in the task but each group activated differently the brain. This is a relevant example to illustrate the theoretical discussion raised by Price and Friston (2002) concerning the relationship between mental processes and brain structures. Apparently there are, at least, two sufficient systems to produce the same outcome. We do not have yet lesion evidence for this late acquired systems to understand if a lesion in the right temporo-parietal cortex would be necessary to produce alexia in subjects that learned to read late in life or if the classical left parietal lesion would produce the same effect.

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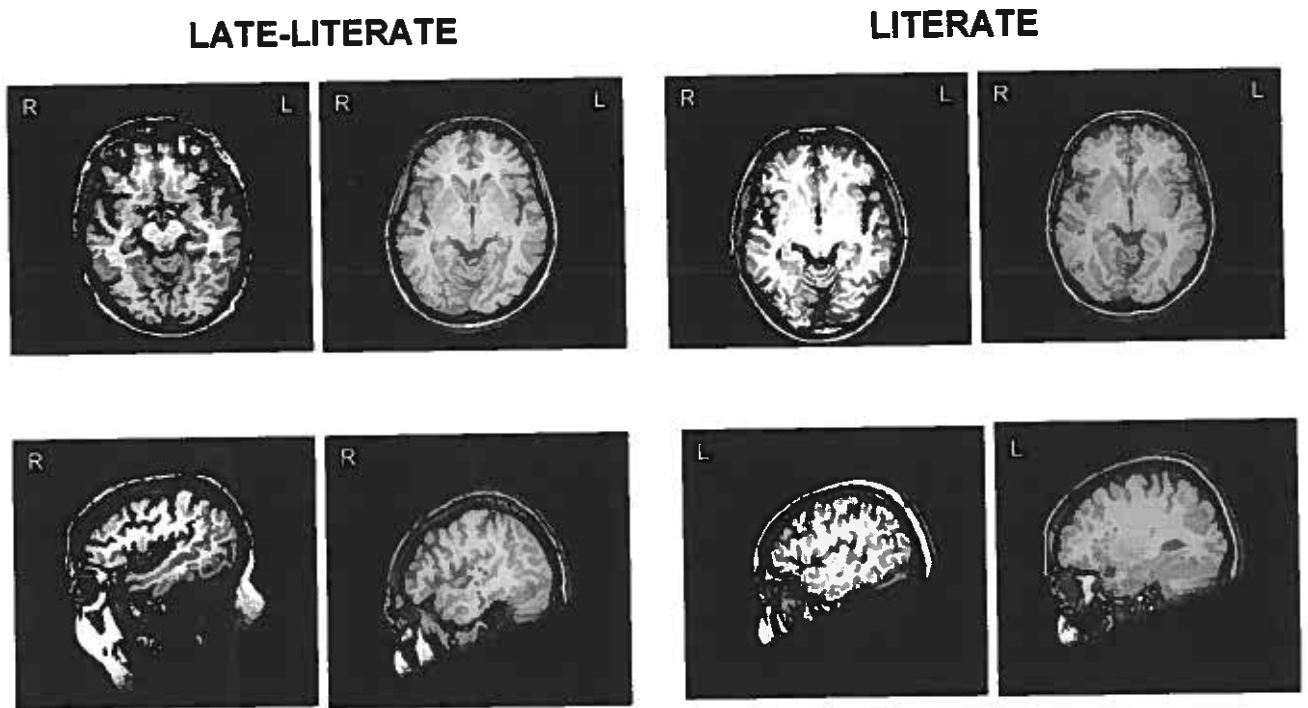


Fig. 1- Representation of right and left sources in Late literates and literates

Table 1- Differences between groups in number of sources by region independently from time window

Region	Left inferior frontal Gyrus (IFG)	Right medial temporal Gyrus (MTG)	Right temporo parietal cortex	Right temporal cortex
Literate Group	3.6±2.51	2±2.3	4.8±2.8	3±2.3
Late literate group	0.29±0.48	10.43±5.74	14.86±7.8	13.86±6.4
	P < 0.006	P < 0.012	P < 0.022	P < 0.005

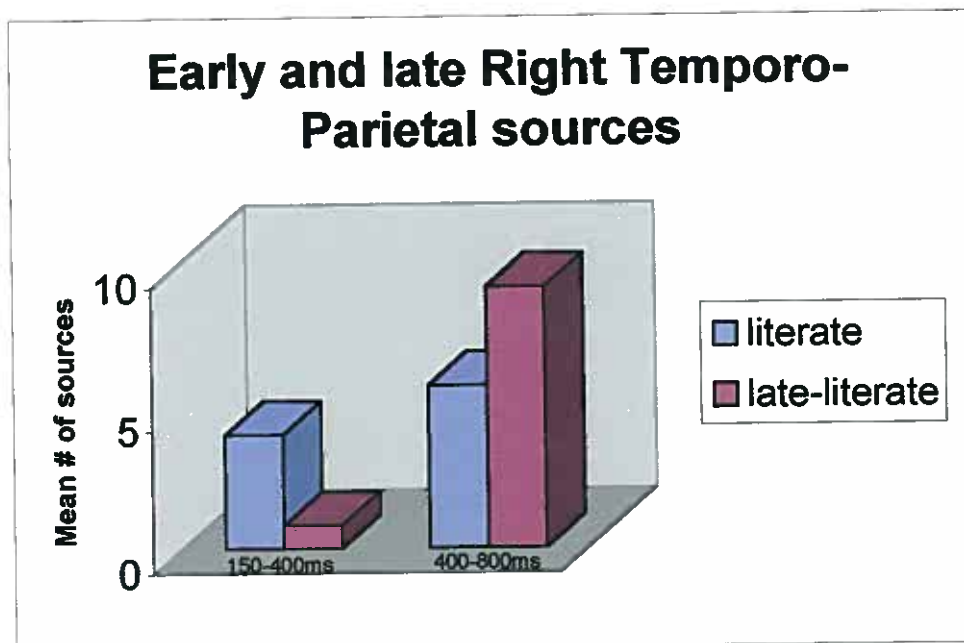


Fig.2 Mean number of sources for the two groups in the right temporo-parietal cortex in the early (from 150 to 400ms) and late (from 400 to 800ms) latency windows.

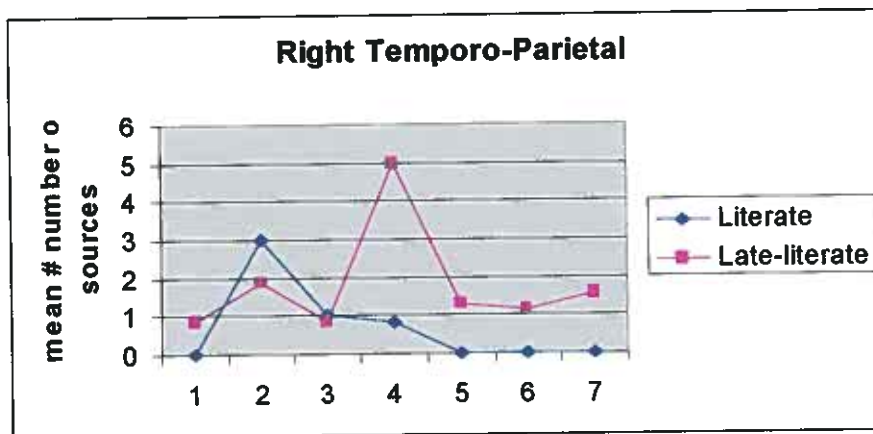


Fig.3 Temporal course of activation (from 150 to 800ms) for the two groups of subjects in Right temporo-parietal areas. 1 indicate number of sources between 150 and 200; 2 indicate number of sources between 200 and 300 ms and so on until 800ms.

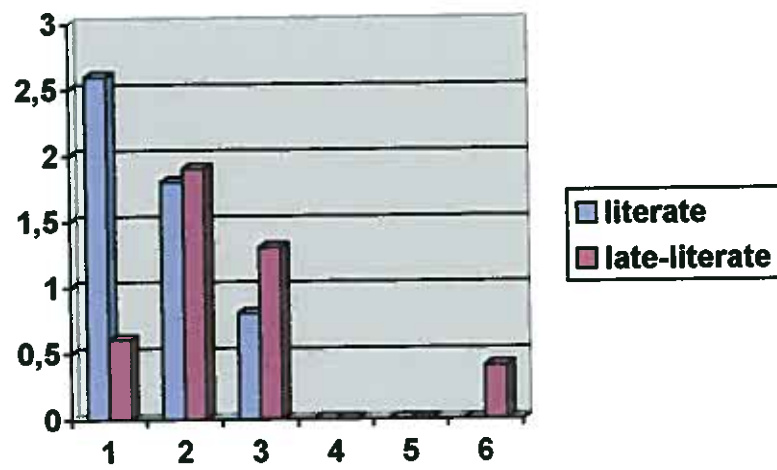


Fig.4- Activation sources in left occipital lobe. According to time window

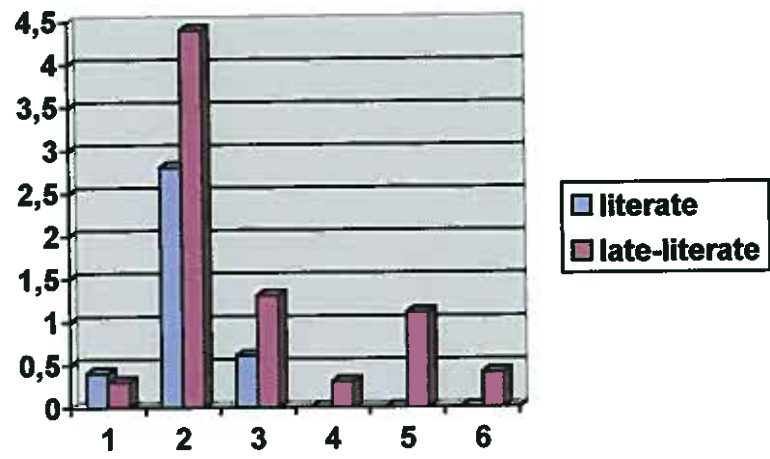


Fig. 5 – Activation sources in right occipital lobe. according to time window