Serial position curve and semantic facilitation in patients with mesial temporal lobe epilepsy

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ABSTRACT

We investigated the serial position curve and semantic facilitation effect in patients with left and right mesial temporal lobe epilepsy (MTLE) with hipocampal sclerosis compared to a matched control group. Subjects (L-MTLE = 19, R-MTLE = 15, and controls = 21) were assessed by recalling word lists either with the three middle words semantically related or not. The total number of words recalled from both types of lists did not differ between groups. Recency was preserved, showing that short-term memory (phonological loop) is not affected in these patients. Primacy was equally present for the lists with no semantic relationships in all groups, but was absent for lists with semantically related words. The semantic facilitation effect was seen in all groups, but with a lower magnitude in the L-MTLE group, suggesting that the spread of discharges in the left hemisphere interferes with the automatic processing of semantic networks.
Keywords: mesial temporal lobe epilepsy; serial position curve; semantic facilitation; episodic memory; semantic memory.

RESUMO

Curva de posição serial e facilitação semântica em pacientes com epilepsia de lobo temporal mesial

Nós investigamos a curva de posição serial e o efeito de facilitação semântica em pacientes com epilepsia do lobo temporal mesial (ELTM) esquerda e direita com esclerose hipocampal, comparados a um grupo controle. Os sujeitos (ELTM-E = 19, ELTM-D = 15 e controles = 21) foram submetidos ao teste de recordação livre de palavras, sendo que metade das listas de palavras continham três palavras semanticamente relacionadas inseridas nas posições intermediárias. O número total de palavras recordadas em ambos tipos de listas não diferiu entre os grupos. A recência foi preservada sugerindo que a memória de curto prazo (alça fonológica) não é afetada nestes pacientes. A primazia foi observada somente nas listas sem relacionamento semântico, independentemente do grupo. O efeito de facilitação semântica foi obtido em todos os grupos, mas com menor magnitude ao ELTM-E, sugerindo que a propagação das descargas no hemisfério esquerdo interfere com o processamento automático da rede semântica.
Palavras-chave: epilepsia do lobo temporal mesial; curva de posição serial; facilitação semântica; memória episódica; memória semântica.

RESUMEN

Curva de posición serial y facilitación semantica en pacientes con epilepsia del lóbulo temporal medial

Nosotros investigamos la curva de posición serial y el efecto de facilitación semántica en pacientes con epilepsia del lóbulo temporal medial (ELTM) izquierdo y derecho con esclerose hipocampal, comparados a un grupo controle. Los sujetos (ELTM-E = 19, ELTM-D = 15 e controles = 21) fueron submetidos al test de recordación libre de palabras, siendo que mitad de las listas de palabras contenían tres palabras semánticamente relacionadas inseridas en las posiciones intermedias. El número total de palabras recordadas en ambos los tipos de listas no difirió entre los grupos. El efecto de recencia fue preservado, sugiriendo que la memoria de corto plazo (circuito fonológico) no es afectada en eses pacientes. El efecto de primacía fue observado solamente en las listas sin relación semántica, independientemente del grupo. El efecto de facilitación semántica fue obtenido en todos los grupos, pero con menor magnitud en el grupo ELTM-E, sugiriendo que la propagación de las descargas en el hemisferio izquierdo interfiere con el procesamiento automático de la red semántica.
Palabras clave: epilepsia del lóbulo temporal medial; curva de posición serial; facilitación semántica; memoria episódica; memoria semántica.

INTRODUCTION

Epilepsy is a brain disorder characterized by recurrent and unpredictable interruption of normal brain function, called epileptic seizures. Epilepsy does not have a singular etiology and may be the result of many causes that reflect an underlying brain dysfunction (Fisher et al., 2005). Focal or partial and generalized seizures are the most common (for review see Yacubian, 2002). Mesial temporal lobe epilepsy (MTLE) is a syndrome characterized by seizures that originate in mesial temporal lobe structures such as the amygdala and hippocampal formation. The anatomic-pathological alteration found in 50-70% of patients with this syndrome is hippocampal sclerosis (HS) (Babb, Lieb, Brown, Prerotius, and Crabdall, 1984; Lee et al., 1998; Wieser, 2004), which is predominant in refractory temporal lobe epilepsy (TLE). HS is defined from an anatomic-pathological standpoint by marked loss of hilar neurons and subfields in CA1 and CA3 pyramidal cells (Babb and Brown, 1987), as well as other mesial structures, such as the amygdala, parahippocampal gyrus, and entorhinal cortex (Gloor, 1991).

Episodic declarative memory is strongly associated with mesial temporal lobe structures (Squire and Zola-Morgan, 1991; Oliveira and Bueno, 1993; Squire and Kandel, 2003), and an impairment in this type of memory is thus the most outstanding cognitive deficit in MTLE patients (e.g., Hermann, Seidenberg, Schoenfeld, and Davies, 1997; Helmstaedter and Kurthen, 2001; Alessio et al., 2006; Marques et al., 2007). Focal left TLE leads to greater impairment of verbal memory and a right TLE focus seems to affect more non-verbal and visuo-spatial information (Lee, Yip, and Jones-Gotman, 2002), but the relationship between TLE and memory seems to be more evident in patients bearing a left epileptogenic focus than a right one (Hermann et al., 1997; Helmstaedter and Kurthen, 2001; Lee et al., 2002). Semantic memory is also impaired in patients with TLE (Drane et al., 2008; Messas, Mansur, and Castro, 2008). Despite these mnemic losses, the general intellectual level is typically not impaired (Gleissner, Johanson, Helmstaedter, and Elger, 1999; Jones-Gotman, Harnadeck, and Kubu, 2000; Marques et al., 2007).

Free recall of words is a widely used task to evaluate episodic memory since each word recalled reflects its space-time context of presentation (Capitani, Della Sala, Logie, and Spinner, 1992; Bueno, 2001). In this test, lists of words are presented one at a time, and at the end of each list, the subject is required to remember as many words as possible in any order. This method gives rise to a U-shaped serial position curve in which the greater recall of the words at the beginning of the list is called the primacy effect, related to long-term memory, and the greater recall of the words at the end of the list is called the recency effect, related to short-term memory (Capitani et al., 1992; Carlesimo, Sabbadini, Fadda, and Caltagirone, 1995; Talmi, Grady, Goshen-Gottstein; and Moscovitch, 2005) (the phonological loop of the working memory framework, Baddeley, 2007). In an earlier study, Powell, Sutherland, and Agu (1984) reported that TLE patients were especially poor on the recency positions of the curve. More recently, Lespinet-Najib et al. (2004) have found that the free recall of words is impaired in TLE patients; however, these authors did not study the serial position curve in these patients.

Insertion of semantically related words at intermediate positions of the lists alters the serial position curve pattern, producing another region of increased recall in the curve (now W-shaped). This effect is called semantic facilitation (Craik and Levy, 1970; Andrade et al., 2003; Nogueira, Pompéia, Gálduroz, and Bueno, 2006). Semantic network models can to explain the semantic facilitation effect, assuming that such processing depends on a network in which concepts and words sharing semantic meaning are represented as nodes located close to each other (Collins and Loftus, 1975; Anderson, 1983; Nelson, Bennet, and Xu et al., 1997). The activation of a node automatically activates the closer nodes in such a way that does not demand the conscious attention of the individual (Collins and Loftus, 1975; Anderson, 1983). Therefore, the automatic process triggered by exposure to a word promotes the spreaded activation of the concepts strongly related to it, which, in turn, re-activate the previous node and so on, making semantically related words (e.g., "milk - cheese - butter") more accessible to conscious recovery (Vaz, 2004; Nogueira et al., 2006; Covre, Bertolucci, and Bueno, submitted; Oliveira, Vaz, Pompéia, and Bueno, submitted). The semantic facilitation effect is normal in multiple sclerosis patients (Andrade et al., 2003), and its magnitude is smaller in healthy young volunteers under the influence of a benzodiazepine (Nogueira et al., 2006). Alzheimer's patients in the moderate stage do not benefit from semantic relationships among mid-list words unless the size of the lists is reduced from 15 to 7-9 words (Bueno, Bertolucci, Oliveira, and Abrisqueta-Gomes, 2008; Covre et al., submitted), suggesting that working memory that requires controlled processing is also involved in the production of the facilitation effect beyond the automatic processing carried out by spreaded activation. In favor of this hypothesis, it was found that the magnitude of semantic facilitation is

also smaller when the word lists are presented under conditions of divided attention to young graduate students (Oliveira et al., submitted). Moreover, healthy elders show a working memory capacity-related decline in the magnitude of the semantic facilitation effect (De Luccia, Santos, and Bueno, 2005).

Given the paucity of studies addressing the serial position curve and the absence of references on the semantic facilitation effect in epilepsy, the present study aimed to investigate these memory phenomena in the free word recall of MTLE-HS patients.

METHODS AND PROCEDURES

Subjects

Subjects included 34 patients with left (L-MTLE; n = 19) and right (R-MTLE; n = 15) mesial temporal lobe epilepsy with hippocampal sclerosis (HS), without other lesions that could cause epilepsy and with medically refractory seizures (despite adequate use of at least two first-line antiepileptic drugs in monotherapy or combined therapy), who were in the process of being evaluated for epilepsy surgery at the Epilepsy Section at Hospital São Paulo, Universidade Federal de São Paulo, Brazil. Furthermore, a group matched for gender, age, and education served as a control group (CG) of healthy volunteers (n = 21). Inclusion criteria were ages between 18 and 53 years, education level of at least four years, right-handed, and no other neurological diseases or psychiatric disorders through the evaluation carried out by two professionals following the criteria of the DSM-IV (2002).

Table 1 shows the demographic data and the intellectual level (evaluated by the Progressive Matrices of Raven) of the subjects, as well as the clinical data of the patients. MTLE-HS diagnosis was defined according to previously established criteria (Commission, 1989), including seizure semiology, developmental and clinical history, consistent electro-encephalography (EEG) findings and extensive pre-surgical evaluation including prolonged noninvasive Video-EEG and neuropsychological testing. Neuro-psychological data from these patients was published elsewhere (Tudesco, 2008). The study was approved by the Ethics Committee of our institution.

Word lists. Twenty lists with 15 Portuguese common, concrete words with two or three syllables were used. Ten of these lists had three semantically related words (e.g., the Portuguese words for milk, cheese, and butter) inserted in the middle (input positions 7, 8, and 9), while the other ten lists contained only non-related words. The words, which subjects read aloud, were presented sequentially on a computer screen for three seconds each. At the end of

each list, subjects were asked to immediately recall the words in any order.

Data Analysis

All analyses were performed using STATISTICA for Windows software (Release 6.0; StatSoft Inc) and the significance level was set at 5%. A chi-square analysis was used to compare the demographic characteristics of the sample proportion and analyses of variance (ANOVAs) with group as the independent factor were conducted for other group comparisons and were followed by Tukey's *post hoc* test when appropriate.

For the primacy, recency, and semantic facilitation effects analyses, input positions of each kind of list [unrelated (UN) and related (REL)] were grouped into five different blocks of three words, containing three positions in each. The UN-1/REL-1 block corresponded to the grouping of the first three words of the lists (serial positions 1-3) and the UN-5/REL-5, to the grouping of the last three words (serial positions 13-15). The UN-2/REL-2, UN-3/REL-3, UN-4/REL-4 blocks corresponded to the grouping of the inter-mediary positions of the lists (serial positions 4-6, 7-9, and 10-12, respectively).

The primacy effect was analyzed through the comparison of the UN-1/REL-1 with UN-2/REL-2 and the recency effect, through the comparison of UN-5/REL-5 with UN-4/REL-4. The semantic facilitation effect was detected by the comparisons between REL-3 with REL-2, REL-3 with REL-4, REL-3 with UN-3, and analysed by comparing REL-3 from the three subjects groups (L-MTLE, R-MTLE, and CG).

RESULTS

Demographic Characteristics

Demographic data for each group are summarized in Table 1. There was no group difference for age ($F_{2,52} = 0.69$, p = 0.50), gender ($X^2 = 0.15$, df = 2, p = 0.92), years of education ($F_{2,52} = 1.71$, p = 0.19), duration of epilepsy ($F_{1,32} = 0.04$, p = 0.83), seizure onset age ($F_{1,32} = 0.18$, p = 0.66), and general level of intelligence (tested by the Raven test) ($F_{2,52} = 1.33$, p = 0.27).

Free Recall Test

The data for each group is shown in Tables 2, 3 and 4. ANOVA comparing the total recall of each list showed no group effect ($F_{2,52} = 0.50$, p = 0.60), but there was a list effect ($F_{1,52} = 70.25$, p < 0.0001) and interaction between group and list ($F_{2,52} = 3.21$, p < 0.05) with the REL lists being more remembered than the UN. Total free recall was not different between groups.

TABLE 1

Demographic, clinical and intellectual level data (mean ± SD) of patients with L-MTLE and R-MTLE and the CG..

	L-MTLE *(n=19)*	*R-MTLE* *(n=15)*	*CG* *(n=21)*	*p* *(value)*
Age	33.9 ± 7.5	36.7 ± 10.1	33.1 ± 9.5	0.50
Gender (F/M)	12/7	9/6	12/9	0.92
Years of Education	8.6 ± 3.1	10.4 ± 2.1	9.9 ± 2.9	0.19
Duration of epilepsy (years)	20.0 ± 9.8	20.8 ± 12.2	–	0.83
Seizures onset age (years)	14.0 ± 6.2	15.4 ± 11.7	–	0.66
Raven	36.1 ± 6.7	34.5 ± 7.0	38.8 ± 9.7	0.27

L-MTLE – left mesial temporal lobe epilepsy; R-MTLE – right mesial temporal lobe epilepsy; CG – control group; SD – standard deviation.

TABLE 2

Percentage of words correctly recalled from the serial grouped positions (UN-1/REL-1 and UN-2/REL-2)
in the lists with and without semantic relations (mean ± SD).

	UN-1 *(1-2-3)*	*UN-2* *(4-5-6)*	*Primacy effect UN-lists (p value)*	*REL-1* *(1-2-3)*	*REL-2* *(4-5-6)*	*Primacy effect REL-lists (p value)*
L-MTLE	41 ± 16	24 ± 15	<0.001	29 ± 16	22 ± 12	0.98
R-MTLE	40 ± 16	23 ± 11	<0.005	32 ± 9	24 ± 13	0.97
CG	43 ± 17	24 ± 11	<0.001	32 ± 19	23 ± 11	0.83

L-MTLE – left mesial temporal lobe epilepsy; R-MTLE – right mesial temporal lobe epilepsy; CG – control group; SD – standard deviation.

TABLE 3

Percentage of words correctly recalled from the serial grouped positions (UN-4/REL-4 and UN-5/REL-5)
in the lists with and without semantic relations (mean ± SD).

	UN-4 *(10-11-12)*	*UN-5* *(13-14-15)*	*Recency effect UN-lists (p value)*	*REL-4* *(10-11-12)*	*REL-5* *(13-14-15)*	*Recency effect REL-lists (p value)*
L-MTLE	41 ± 16	38 ± 13	<0.001	32 ± 14	68 ± 12	< 0.001
R-MTLE	40 ± 16	31 ± 8	<0.001	40 ± 13	67 ± 9	< 0.001
CG	43 ± 17	36 ± 17	<0.001	28 ± 20	70 ± 16	< 0.001

L-MTLE – left mesial temporal lobe epilepsy; R-MTLE – right mesial temporal lobe epilepsy; CG – control group; SD – standard deviation.

TABLE 4

Percentage of words correctly recalled from the serial grouped positions (UN-3 and REL-3)
in the lists with and without semantic relations (mean ± SD).

	UN-3 *(7-8-9)*	*REL-3* *(7-8-9)*	*Semantic Facilitation Effect*	
			Magnitude (%)	*p value*
L-MTLE	30 ± 11	64 ± 19	34	< 0.001
R-MTLE	29 ± 9	74 ± 19	45	< 0.001
CG	21 ± 10	77 ± 17	56	< 0.001

L-MTLE – left mesial temporal lobe epilepsy; R-MTLE – right mesial temporal lobe epilepsy; CG – control group; SD – standard deviation.

Serial Position Curve (Unrelated Lists-UN)

The data for each group are summarized in Tables 2, 3 and 4, and Figure 1A. A two-way ANOVA with repeated measures, considering group (L-MTLE, R-MTLE, and CG) and the blocks of serial positions (UN-1 to UN-5) as factors, showed no significant group effect ($F_{2,52} = 0.26$, $p = 0.76$); however, there was a serial position effect ($F_{4,208} = 120.42$, $p < 0.001$) and interaction between both factors ($F_{8,208} = 3.31$, $p < 0.002$). The Tukey test showed that the block UN-1 was more recalled than the block UN-2 for all groups [L-MTLE ($p < 0.001$), R-MTLE ($p < 0.006$), and CG ($p < 0.001$)], with no group difference for both block positions. This result characterizes the *primacy effect*.

All groups recorded more words from the block UN-5 than the block UN-4 ($p < 0.001$) and there was no difference between groups, which characterizes the presence of the *recency effect* for all groups. There was no group difference in recall of the *intermediate positions* (UN-2 to UN-4).

Legend: * The magnitude of the semantic facilitation effect (REL-3) was significantly lower in the L-MTLE group than in the CG ($p<0.03$). L-MTLE – left mesial temporal lobe epilepsy; R-MTLE – right mesial temporal lobe epilepsy; CG – control group.
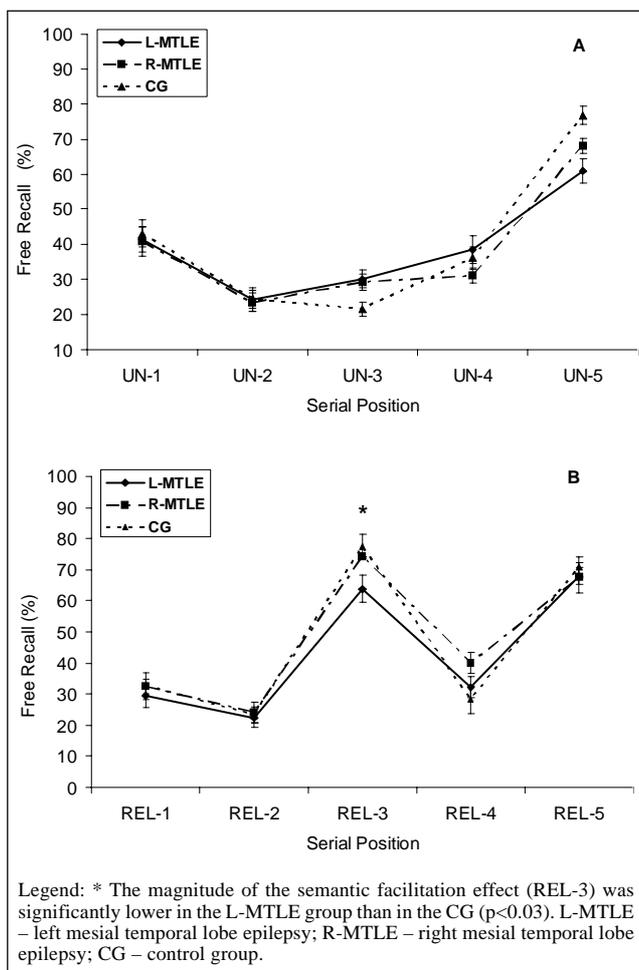
Figure 1 – Serial position curves from immediate free recall of lists containing 15 words grouped in blocks of 3 words. A - all-unrelated words; B - semantically related words in block REL-3. Mean ± Standard Error.

Serial Position Curve (Related Lists-REL)

The same procedure was performed with the lists containing words with semantic relationships; the data for each group are summarized in Tables 2, 3 and 4, and Figure 1B. The two-way ANOVA, with repeated measures for groups (L-MTLE, R-MTLE, and CG) and serial positions (REL-1 to REL-5) as factors, showed no group effect ($F_{2,52} = 1.34$, $p = 0.27$) or interaction effect between the factors ($F_{8,208} = 1.31$, $p = 0.24$); however, there was a serial position effect ($F_{4,208} = 116.81$, $p < 0.001$). The contrast analyses showed an absence of the *primacy effect* for all groups since there was no difference between REL-1 and REL-2. Groups performed similarly for both position blocks. There was no difference in *intermediate positions* (REL-2 and REL-4) between the groups. There was more recall of the REL-5 position in relation to the REL-4 position, characterizing the *recency effect* in all groups ($p < 0.001$). Again, no difference was found between the groups.

In this analysis, a *semantic facilitation effect* is found when the position REL-3 is more recalled than positions REL-2 and REL-4 for all groups ($p < 0.001$). A second analysis for the purpose of semantic facilitation was conducted considering the positions REL-3 and UN-3. There was no significant group effect ($F_{2,52} = 0.81$, $p = 0.49$), but there was a position effect ($F_{1,52} = 273.75$, $p < 0.001$) and interaction effects ($F_{2,52} = 6.21$, $p < 0.004$). The REL-3 block was more recalled than the UN-3, indicating the presence of a semantic facilitation effect for all groups. A final analysis, considering only the REL-3 position, carried out to compare the extent of the semantic facilitation effect between the groups, showed a significant difference in which L-MTLE group performance was lower than the CG ($F_{1,38} = 5.68$, $p = 0.02$), but not from the R-MTLE group ($F_{1,32} = 2.56$, $p = 0.12$). R-MTLE group did not differ from the CG group ($F_{1,34} = 0.28$, $p = 0.59$).

DISCUSSION

The purpose of this study was to investigate the serial position curve and the semantic facilitation effect in patients with L-MTLE and R-MTLE with HS compared to a control group (CG) of healthy volunteers. It is widely documented that these patients have memory episodic impairment (Hermann et al., 1997; Helmstaedter and Kurthen, 2001; Alessio et al., 2006; Marques et al., 2007) as the structures affected in this syndrome are of fundamental importance to the acquisition and consolidation of acquired information (Jones-Gotman and Milner, 1978; Squire and Zola-

Morgan, 1991; Oliveira and Bueno, 1993; Squire and Kandel, 2003). Despite this impairment, the level of general intelligence (assessed by the test of Raven) did not differ between groups; this finding is in agreement with other studies (Gleissner et al., 1999; Jones-Gotman et al., 2000; Marques et al., 2007).

Concerning the free recall test, it was observed that the total number of words recalled on both lists (related and unrelated) was not different between groups. This finding is in disagreement with the findings of Lespinet-Najib et al. (2004), who observed a difference between left-TLE and right-TLE patients and controls in their study. The lack of statistical significance in their study could be due to the reduced number of subjects, at least for the right- MTLE group. However, an effect size analysis considering the total recall (Cohen d; Rice and Harris, 2005), aiming to evaluate the magnitude of the observed effect, showed a weak relevance of this factor, turning the hypothesis of reduced sample less likely (d = 0.28 to L-MTLE × CG; d = 0.05 to R-MTLE × CG).

The effect of primacy was present on the lists with no semantic relationships in all groups and no differences between them were detected. Mid-list unrelated words were recalled in the same proportion in all groups. These findings were unexpected since these positions of the serial position curve are considered to be related to long-term memory (Capitani et al., 1992; Carlesimo et al., 1995; Talmi et al., 2005), which is typically impaired in these patients (Hermann et al., 1997; Lespinet-Najib et al., 2004; Alessio et al., 2006; Marques et al., 2007). The recency effect was also preserved in all groups, a result that runs counter to that obtained by Powell et al. (1984) and likely reflects a different strategy of our patients to recall the lists. The recency effect presented in all groups and types of lists shows the preservation of the phonological loop of working memory (short-term memory) in these patients (Frisk and Milner, 1990a,b; Cowey and Green, 1996; Abrahams et al., 1999).

The magnitude of the semantic facilitation effect (REL-3) was significantly lower in the L-MTLE group than in the CG. Lespinet-Najib et al. (2004) reported that the recall lists of words with phonetic or semantic processing was lower in patients with L-MTLE than in normal subjects, suggesting that the left temporal lobe is involved in all aspects of verbal memory. In our study, all words were intended to be semantically processed; that is, deeply processed according to the levels of processing framework (Craik and Levy, 1970). However, our results showed an impairment of the semantic facilitation only. The semantic facilitation is thought to depend on spreaded activation in semantic networks, suggesting some difficulty in this automatic process. Semantic networks are based largely on activity of the lateral temporal lobe, which is affected by the spread of seizures from the mesial temporal lobe. Therefore, the spread of seizures can be responsible for the semantic facilitation deficit found in these patients.

No differences between R-MTLE and controls were seen, a finding that was expected due to the lateralization of verbal memory (Lee et al., 2002).

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