



Differences in emotional stimuli processing in subjects with MTLE with and without depression



Lidija Preglej^{a,b,*}, Ksenija Marinković^{c,g}, Hrvoje Hećimović^{d,e,f}

^a The Accredited Private Classical High School, Zagreb, Croatia

^b University of Zagreb, Croatia

^c Department of Psychology, San Diego State University, San Diego, CA, United States

^d Neuro Center, Zagreb, Croatia

^e Neuromed Campus, J. Kepler University, Linz, Austria

^f University Nord, Varaždin, Croatia

^g Department of Radiology, University of California at San Diego, San Diego, CA, United States

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ABSTRACT

In healthy people, a preference in attention maintenance and memory for words with emotional valence comparing to neutral words has been shown. The pattern of emotional stimuli processing may be different in people with mesial temporal lobe epilepsy (MTLE) and it may be sensitive to the presence of depressive symptoms. In order to explore these possibilities, we applied the emotional spatial cueing attentional task and the free recall memory task to participants (N = 39) with MTLE and compared them with healthy controls. We hypothesized that the pattern of maintaining attention and remembering emotional words is different in people with MTLE. Current literature indicates that this pattern will change from positive bias in the controls, though no emotional bias in the participants with MTLE without depression (MTLE – d), and in this work we examined this pattern in the participants with MTLE with depressive symptoms (MTLE + d). Our results show that in both attention and memory, control subjects exhibit positive emotional bias, the subjects with MTLE – d show nonemotional bias and the subjects with MTLE + d have bias away from positive words. Participants with MTLE + d maintained attention for positive words shorter than others. Participants with MTLE + d had worse recall for positive words than the participants with MTLE – d and for all words when compared to controls. We found that faster attention disengagement from positive words and worse memory for positive words is associated with elevated levels of depressive symptoms.

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1. Introduction

Emotional stimuli processing is not well understood in persons with epilepsy. Research shows that healthy people maintain longer attention to stimuli with emotional valence than to neutral stimuli [1,2] and remember more emotional stimuli than neutral ones [3,4]. Mesial temporal structures, primarily the amygdala and the hippocampus, have an important role in the processing of emotional stimuli [5,6,7]. Patients with medication-refractory MTLE may have different patterns of emotional stimuli processing in comparison with healthy controls. In the subjects with MTLE without current depressive symptoms, recent research [4,6,8] indicates that their pattern of maintaining attention and remembering emotional and neutral stimuli is similar to patients with dysphoria. In the subjects with MTLE, a similar number of recognized negative and neutral words [4] and longer attention maintenance for

negative than for neutral words [8] was found. None of recent research [4,8] used words with positive emotional valence. Studies in patients with dysphoria [9,10,11] with no epilepsy suggest that processing of positive stimuli may represent a major difference from healthy subjects who maintain their attention longer and remember more positive stimuli than neutral or negative ones, whereas patients with dysphoria do not show this positive bias.

Studies in the subjects with dysphoria and with psychiatric depression [12,13,14,15] indicated that bias towards negative emotional stimuli in attention and memory is accompanied by elevated levels of depressive symptoms. Bourgeat et al. [12] indicated in the patients with MTLE and anxiodepressive disorders a similar negative attentional bias as in the participants with anxiodepressive disorders without epilepsy. It is, thus, possible that these changes are due to the underlying diseases. Better understanding of emotional stimuli processing in patients with MTLE could be useful in detecting potential vulnerability to depression.

In our study, we applied the attentional emotional spatial cueing task and the free recall task to evaluate whether the pattern of

* Corresponding author at: The Accredited Private Classical High School, Zagreb, Croatia.
E-mail addresses: lidija_preglej@yahoo.com (L. Preglej), kmarinkovic@ucsd.edu (K. Marinković), hrvoje.hecimovic@gmail.com (H. Hećimović).

maintaining attention and remembering emotional and neutral words in patients with MTLE is different from controls. We hypothesized that emotional stimuli processing is different in persons with MTLE and is related to presence of their depressive symptoms.

2. Materials and methods

2.1. Subjects

We evaluated 39 subjects with unilateral MTLE (54% left, 46% right). Subjects with MTLE were recruited from a single tertiary epilepsy center at the University Hospital in Zagreb, Croatia. Demographic and clinical characteristics are shown in Table 1. The inclusion criteria were age 18 years and above, MTLE defined by prolonged EEG monitoring, and seizure pharmacoresistance according to the International League Against Epilepsy [16]. Exclusion criteria were presence of any other structural brain lesion but hippocampal sclerosis and current use of any other medications, including antidepressants. Patients were evaluated for presence of depressive symptoms using the Beck Depression Inventory (BDI-II), which has been extensively applied in patients with epilepsy [17,18]. Participants with MTLE were additionally grouped according to their total BDI score: group with MTLE – d (total BDI < 15, N = 28) and group with MTLE + d (total BDI ≥ 15, N = 11). The score equal or above 15 has been used as an indicator of subclinical depression [25,33,34]. Clinical data collected included: age of seizure onset, average monthly number of seizures in the past 6 months, epilepsy duration, and number of current antiepileptic drugs (AEDs). The control group included 39 healthy subjects without epilepsy, without any other neurological disorders and with no depressive symptoms (BDI < 7), matched according to their age, sex, and years of education. All subjects had normal or corrected to normal vision. The study was approved by the Hospital Ethics Committee and a written informed consent was obtained from all participants.

2.2. Selection of stimuli

A total of 48 words in Croatian language were categorized into emotionally positive, negative, and neutral words, 16 per emotional category. Their emotional valence, as rated on Likert scale ranging from 0 to 9, was as follows (mean and standard deviation shown): negative (1.92 ± .21), neutral (5.00 ± .21), and positive (8.10 ± .20). This set of words was based on an initial rating of 602 words selected from the Dictionary of Croatian synonyms [19] carried out by 50 independent judges. Positive and negative words were selected to be

equidistant from neutral words. Negative valence words were self-concept relevant to depression (e.g., “desperate”) [20,21] referring to sadness, without reference to other negative emotions such as disgust, fear or anger and they were not related to epilepsy symptoms (e.g., “seizure”) [8]. Negative (depressive) words were additionally selected based on assessment by 20 patients with major depressive disorder. All three emotional word lists were equated with respect to word length (7.73 ± 0.792 letters) and frequency of use (.001 ± .002 words per million). The lists comprised the same number of adjectives (14) and nouns (2) per condition. Concreteness of words has also been evaluated by the same 50 independent judges. As expected, there was a significant difference in the level of abstractness ($F(2,47) = 28.48; p < 0.01$), with neutral words being more concrete (2.66 ± .71) and positive (4.66 ± .94) and negative (depressive) words (4.39 ± .78) more abstract, but comparably so, based on the 1–4 abstractness scale.

2.3. Experimental procedure

2.3.1. Attentional emotional spatial cueing task

Attentional bias for emotional valence was investigated with the emotional spatial cueing paradigm. The task was programmed in E-prime software and presented on a computer. As shown in Fig. 1, each stimulus sequence started with a fixation cross flanked by two rectangles presented for 500 ms. Words with negative, positive, and neutral valence were then presented individually in the left or right rectangle for 1500 ms. A relatively long duration of the word presentation [22] was chosen to allow sufficient time for possible engagement in depression-related elaboration of emotional information [22,23]. A target probe was a dot that was presented 50 ms after the word offset and remained on the screen until a response was provided by the participant, initiating the next stimulus sequence. Subjects were invited to pay attention to words but without explicit demands (e.g., evaluation of semantic or graphic features of words). The task was to respond to the location of the target stimulus by pressing a left or right button on the response box. Participants were asked to respond as fast as possible while maintaining accuracy. Words and targets were presented on the left and right side with equal probability and in random order. On valid trials, words provided correct cues for the target location (i.e., they appeared on the same side). Conversely, words and target probes appeared on the opposite side on invalid trials. There were an equal number of valid and invalid trials. Accuracy and response times for target detection were calculated for each condition and each participant group. A practice block preceded the experiment which comprised 96 trials with 48 emotional words appearing twice in random order. To assure that participants remain focused on the task, the fixation cross was replaced by a number presented for 100 ms on ten additional, randomly interspersed trials. Participants were instructed to acknowledge it by simply pressing a button on the response box.

2.3.2. Free recall task

A surprise (incidental) free recall task was administered immediately after the attentional task. The free recall task is suggested for the assessment of explicit memory disturbances related to mesial temporal lobe structures [24] and also in the research of the depressive mood memory bias in people with dysphoria and depression [22,25,26]. Participants were asked to write down as many words as they could recall. The number of correctly recalled words (NRW) was analyzed for each emotional category and for each participant group.

Participants provided arousal ratings for a subset of words (0 – not arousing; 5 – very arousing) in order to explore possible associations with results on the tasks of recall.

2.3.3. Data analysis

Data were analyzed using the ANOVA design with SPSS (Version 11.0, Chicago, IL). For the attentional task, trials on which reaction

Table 1
Demographic and clinical characteristics of subjects with mesial temporal lobe epilepsy (N = 39).

Age (y, mean ± SD)	35 ± 11
Education (y):	
≤ 12	75%
> 12	25%
Epileptic region lateralization:	
Left	54% (N = 21)
Right	46% (N = 18)
Hippocampal sclerosis:	2.5% (N = 1, right)
Number of seizures per month averaged for the past 6 months (mean ± SD)	1.54 ± 1.69
Epilepsy duration (y) (mean ± SD)	15.46 ± 10.81
Age of seizure onset (y) (mean ± SD)	19.10 ± 12.92
AED (mono/polytherapy, %):	56.4/43.6
Total BDI score:	
< 15 ^a	71.8%
≥ 15 ^b	28.2%

^a Total BDI score below 15.

^b Total BDI score equal or higher than 15.

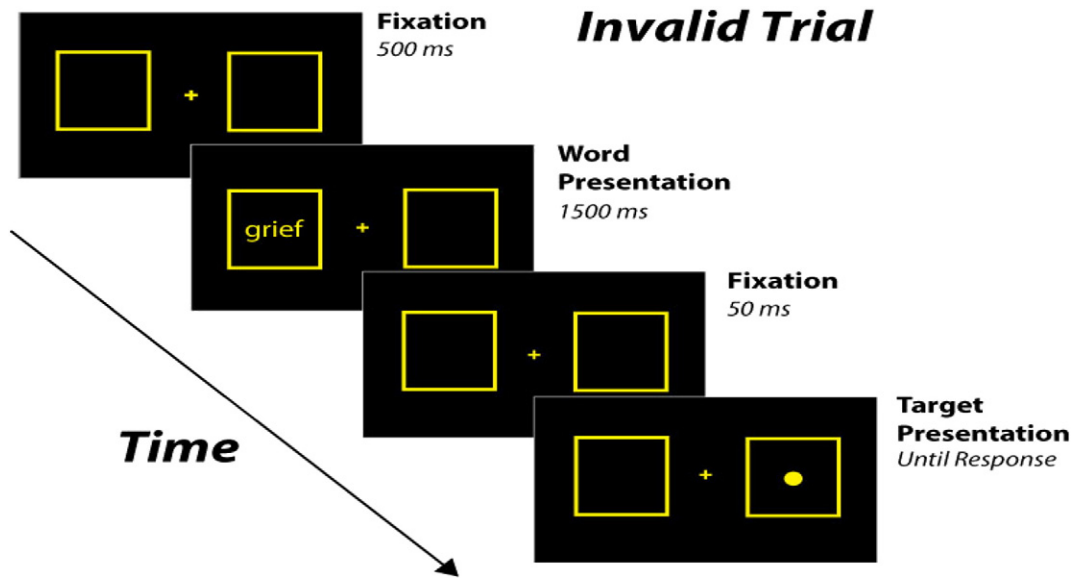


Fig. 1. Emotional spatial cueing task. Each trial starts with a fixation cross flanked by two rectangles, followed by a word presented in the left or right rectangle. Target probes appear equiprobably on the left or the right and the participant responds to the location of the target, triggering the next trial sequence. Illustrated above is an invalid trial on which the word does not correctly cue the target location.

times (RTs) were shorter than 200 ms and longer than 750 ms were excluded from the analysis [21,22]. Average RTs were calculated for each emotional valence and for each group, for invalid and valid trials separately. Cue validity index (CV) was calculated by subtracting mean RTs for each word valence according to the following formula: $RT\ invalid\ trials - RT\ valid\ trials$. Higher score on CV indicates the maintenance of attention on cues [22]. Negative scores that are significantly different from zero are taken to indicate the Inhibition of Return (IOR) effect, i.e., expected attention disengagement from words [22]. Inhibition of Return effect has been referred to a reluctance of shift attention to a previously attended location [22]. Higher (more positive) CV score for emotional compared to neutral words is taken to indicate the maintenance of attention in emotional words [22]. For the memory task, the number of correctly recalled words (NRW) was analyzed for

each emotional valence of words. Only significant effects and results are presented.

3. Results

3.1. Attention

3.1.1. Group with MTLT and the control group

Between-groups (MTLE, control) RTs were compared using ANOVA with the within-subject factors of cue validity (valid, invalid) and emotional valence of words (positive, negative, neutral). There was a main effect of cue validity [$F(1,76) = 8.45; p < 0.01$], due to faster RTs on invalid trials ($M \pm SD = 385.02 \pm 106.55$) compared to valid trials (395.73 ± 102.72), confirming the existence of the IOR effect. There

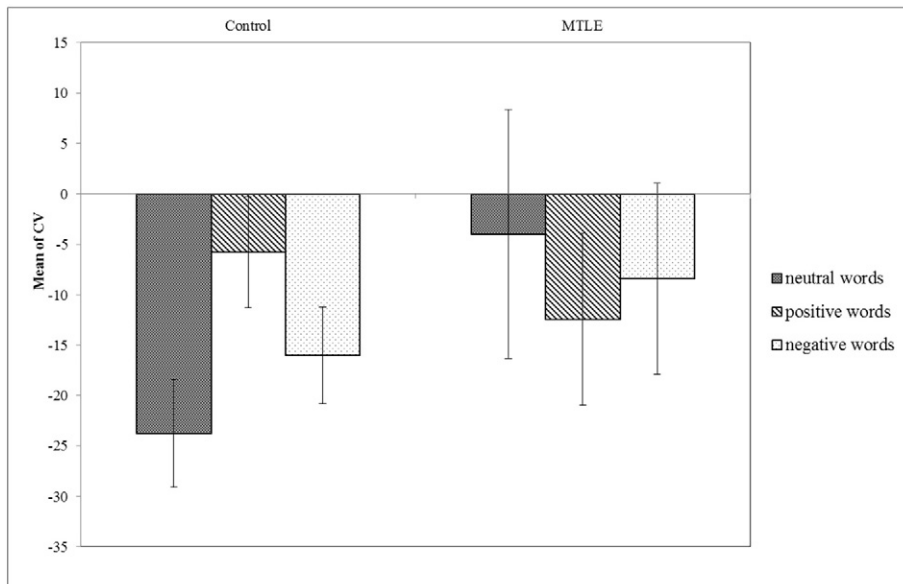


Fig. 2. CV (cue validity) index for each emotional valence of words for the control group and the group with MTLT. Error bars represent SEM values.

was also a main effect of the group [$F(1,76) = 14.47; p < 0.01$], with patients with MTLE (431.46 ± 120.00) responding slower than controls (349.29 ± 61.60).

The Cue Validity (CV) index was further analyzed in order to explore the existence of the IOR effect for each emotional valence of words separately.

In the control group, the CV index was significantly higher for positive than for neutral words [$F(2,76) = 4.55; p < 0.05$] (Fig. 2), suggesting that control participants maintained attention in positive words longer than in neutral words (positive bias). Additionally, in the same group the CV index for negative ($t(38) = 3.33; p < 0.01$) and the CV index for neutral ($t(38) = 4.46; p < 0.01$) words were significantly different from zero, confirming the IOR effect for negative and neutral words. The IOR effect was not confirmed only for positive words, suggesting that the control participants inclined to maintain attention only in the positive words.

In the group with MTLE, no significant differences among CV indexes were observed across emotional valences of words (Fig. 2), and none of the CV indexes were significantly different from zero. Participants with MTLE maintained attention in words without difference according to emotional valence and maintained attention on words of all three emotional valences, suggesting that the participants with MTLE did not show the positive bias that was found in the control group.

Between the group with MTLE and the control group, there were no significant differences in the CV index of any of the three emotional valences (positive, negative, neutral).

3.1.2. Group with MTLE – d, group with MTLE + d, and the control group

In the group with MTLE – d, as in the whole group with MTLE, there were no differences among CV indexes across emotional valences of words, and none of the CV indexes was significantly different from zero (Fig. 3).

On the contrary, in the group with MTLE + d, the CV index for negative words was higher than the CV index for positive words ($t(10) = 3.10; p < 0.05$) (Fig. 3), suggesting that participants with MTLE + d maintained attention in negative words longer than in positive words (negative bias). In the group with MTLE + d, only the CV index for positive words was significantly different from zero, ($t(10) = 2.81; p < 0.05$). The IOR effect was confirmed only for positive words, suggesting that participants with MTLE + d maintained attention in negative and

neutral, but not in positive words. When the difference in CV index of each emotional valence of words (positive, neutral, negative) was analyzed among all three groups (control, MTLE – d, MTLE + d), the difference was significant only for positive words [$F(2,75) = 3.390; p < 0.05$]. Specifically, participants with MTLE + d maintained attention in positive words shorter than participants with MTLE – d ($t(37) = 2.14; p < 0.05$) and also shorter than controls ($t(48) = 2.69; p < 0.01$) (Fig. 3).

In the complete sample of participants ($N = 78$), there was a significant correlation ($r = -0.28; p < 0.05$) between the CV index for positive words and the BDI II scores, indicating that participants reporting more depressive symptoms had higher CV index for positive words, or faster attention disengagement from positive words. Although this result is interesting, it should be noted that the r value is not very high.

3.2. Memory

3.2.1. Group with MTLE and the control group

Between groups (MTLE, control), NRWs were compared using a mixed ANOVA with the within-subject factor of emotional valence of words (positive, negative, neutral). There was a main effect of emotional valence of words [$F(2,152) = 7.45; p < 0.01$], with NRW for negative words being the lowest, and a main effect of group [$F(1,76) = 24.08; p < 0.01$] with patients showing worse recall than control subjects (Fig. 4). In the control group, there was a significant difference in NRW according to emotional valence of words [$F(2,76) = 6.71; p < 0.01$], and it was between negative and positive words ($t(38) = 2.69; p < 0.01$) and between negative and neutral words ($t(38) = -3.85; p < 0.01$). Control participants recalled less negative words than positive words and neutral words (Fig. 4).

In contrast, in the group with MTLE, there was no significant effect of Emotional Valence on NRW [$F(2,76) = 1.53; ns$].

3.2.2. Group with MTLE – d, group with MTLE + d, and the control group

In the groups with MTLE – d and MTLE + d, there were no significant differences in NRW according to emotional valence of words (Fig. 5).

Among groups (control, MTLE – d, MTLE + d), the difference in NRW of each emotional valence of words (positive, neutral, negative) was significant for all three emotional valences of words: positive

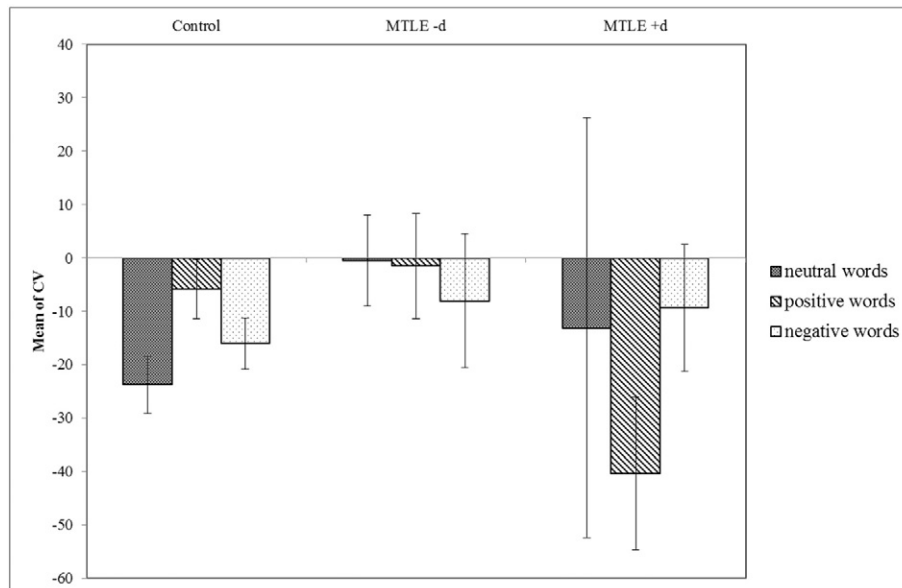


Fig. 3. CV for each emotional valence of words for the control group and the groups with MTLE – d and MTLE + d. Error bars represent SEM values.

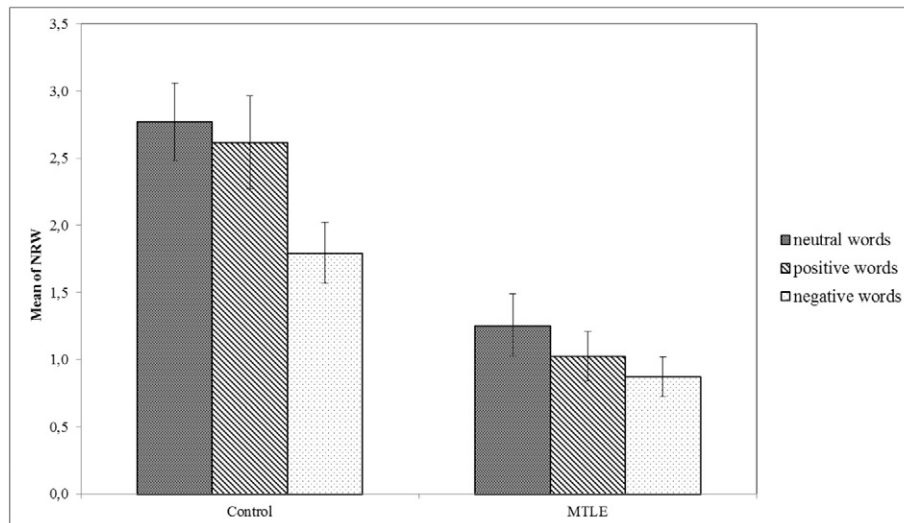


Fig. 4. NRW (number of recalled words) for each emotional valence of words for the control group and the group with MTLE. The maximum NRW of each emotional valence of words could be 16. Error bars represent SEM values.

[$F(2,75) = 3.390$; $p < 0.05$], negative [$F(2,75) = 5.86$; $p < 0.01$] and neutral [$F(2,75) = 10.09$; $p < 0.01$]. Specifically, between the control group and the group with MTLE – d, the difference was significant for all emotional valences of words: positive ($t(65) = 3.02$; $p < 0.01$), negative ($t(65) = 2.76$; $p < 0.01$), and neutral ($t(65) = 2.91$; $p < 0.01$). The same pattern was obtained between the control group and the group with MTLE + d: positive ($t(48) = 3.23$; $p < 0.01$), negative ($t(48) = 2.41$; $p < 0.01$), neutral ($t(48) = 3.99$; $p < 0.01$). Between the groups with MTLE – d and MTLE + d, the difference was shown only for positive words and only as a trend ($t(37) = 2.01$; $p = .053$). Considering the smaller number of participants in the group with MTLE + d, we additionally conducted the nonparametric Wilcoxon W-test analysis of NRW for positive, negative and neutral valence and significant difference between the groups with MTLE – d and MTLE + d was confirmed only in NRW for positive words ($z = -2.2$; $p < 0.05$).

In all participants ($N = 78$), there was a significant correlation ($r = -0.27$; $p < 0.05$) between the NRW for positive words and the BDI II scores, indicating that participants reporting more depressive

symptoms recalled smaller number of positive words. Although the r value is small again, the result indicates that the participants reporting more depressive symptoms recalled a smaller number of positive words.

Distribution of NRW for positive words in MTLE was not different when compared to seizure focus laterality, HS presence, number of AED medications, or gender.

3.2.2.1. Arousal ratings analysis. The arousal ratings of words were examined using a 3×3 ANOVA with participant group (control, MTLE – d, MTLE + d) and emotional valence (positive, neutral, negative) as factors. There was a main effect of emotional valence on arousal [$F(2,140) = 164.145$; $p < 0.01$] with positive words rated higher (3.34 ± 0.15) than negative (3.06 ± 1.23), ($t(71) = 2.01$; $p < 0.05$), and neutral words ($.62 \pm .76$), ($t(71) = 20.76$; $p < 0.01$). The group \times valence interaction [$F(4,140) = 3.71$; $p < 0.01$] mainly reflected lower arousal rating for negative words than for positive words in participants with MTLE – d ($t(24) = -3.11$, $p < 0.01$) whereas participants in the control

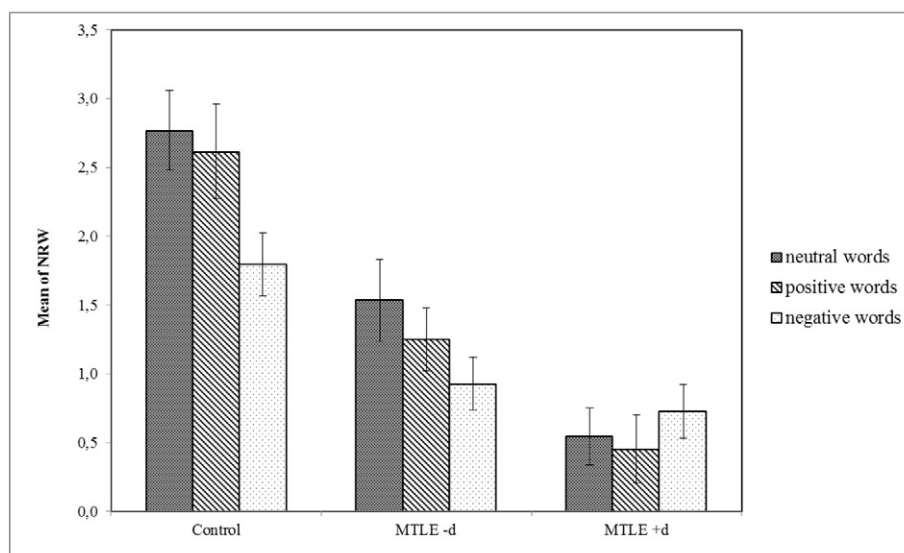


Fig. 5. NRW for each emotional valence of words for the control group and the groups with MTLE – d and MTLE + d. Error bars represent SEM values.

group and participants with MTLE + d rated negative and positive words equally. Since among groups there were not differences in the arousal rating of each kind of words, the result suggests that differences in the NRW according to emotional valence of words among participants groups cannot be solely attributed to differences in arousal ratings.

4. Discussion

We showed that the subjects with MTLE in comparison to the healthy controls manifest a different pattern of maintenance of attention and remembering emotional and neutral words. In controls, IOR effects were present for neutral and negative, but not for positive words. The attentional bias for positive words in the control group was also shown in more positive CV for positive than for neutral words. The result can be interpreted as a stronger maintenance of attention in response to positive words [22]. In our study, controls also showed a bias for positive words in memory. Specifically, they recalled more positive than negative words, and also more neutral than negative words. Thus our results confirmed previous evidence of attentional and memory bias for positive words (“towards-positive” and “away-from-negative” stimuli) in healthy cohorts [1,3,21,25]. Unlike controls, subjects with MTLE exhibited no emotional bias in pattern of maintenance of attention and remembering emotional and neutral words. None of the IOR effects was found, which indicates difficulties in disengagement of attention from words of all three emotional valences (positive, neutral, negative). Moreover, there were no differences in CVs or NRWs in the emotional valence of words. Subjects with MTLE maintained attention and recalled words of three emotional valences equally. Our results confirm the important role of the medial temporal lobe network in the processing of emotional stimuli [5,6,7] and are consistent with evidence that refractoriness of the MTLE may result in dysfunction of that network [26–29].

We evaluated whether MTLE could be an indicator of cognitive vulnerability to depression. In subjects with MTLE – d, there was neither positive nor negative emotional bias in pattern of maintenance of attention and remembering emotional and neutral words. The absence of bias for negative words confirmed earlier findings from Müller et al. in subjects with MTLE – d [4] and De Taeye et al. [30] who reported the same result on face stimuli in patients with epilepsy without psychiatric comorbidity. However previous research [11,31,32] indicated such a difference in maintenance of attention between dysphoric individuals and controls not only for negative stimuli, but also for positive stimuli. Gotlib et al. [10] found that information processing in depression was more characterized by impaired memory for positive words than by stronger memory for negative words. Thus, we assumed that the presence of bias for negative words would not be the best indicator of cognitive vulnerability to depression, especially if depressive symptoms are not clinically present. An alternative indicator may be the absence of the typical bias for positive words, and this idea motivated the introduction of positive words in our paradigm in addition to the negative and neutral words which have been classically used [4,8]. Our finding that there is no bias for positive words in maintenance of attention and remembering words in participants with MTLE – d mirrors the pattern of results previously reported in subjects without epilepsy with natural dysphoria [1], induced dysphoria [25], and in subjects with primary depression [10]. Therefore, we hypothesized that the absence of bias for positive words may be associated with cognitive vulnerability to depression also in patients with MTLE – d.

If the absence of bias for positive words is a potential indicator of cognitive vulnerability to depression, it can be assumed that bias “away-from-positive” words found in the group with MTLE should be more evident when depressive symptoms are present. The results obtained in the present study were consistent with this hypothesis, because subjects with MTLE + d exhibited a stronger maintenance of attention in response to negative and neutral, but not to positive words. This effect was reflected in MTLE + d by the IOR effect for

positive words only, which is an attentional bias pattern opposite to the one found in the control subjects. Moreover, the attentional bias for positive words moved from the “away-from-positive” to the “towards-negative” word bias. The latter was shown as the smaller CV for positive than for negative words. The maintenance of attention in the subjects with MTLE + d was therefore shorter for positive than for negative words. Similarly, bias from neutral towards negative faces was reported in subjects with epilepsy with dysphoria, but not in those without dysphoria [30]. The differences in pattern of maintenance of attention and remembering emotional and neutral words in the case of positive words were also shown by comparing the three subject groups. Specifically, the CV for positive words was more negative in the group with MTLE + d than in the control group, indicating weaker maintenance of attention in response to positive words in the subjects with MTLE + d. Subjects with MTLE + d recalled fewer words than the controls, replicating previous findings in subjects with depression without epilepsy [3,14], but more specifically, subjects with MTLE + d recalled fewer positive words than subjects with MTLE – d.

Finally, we reported a correlation between the BDI and the CV for positive words, and also between the BDI and NRW for positive words. Both correlations were negative, which indicates that the maintenance of attention to positive words and their recollection are weaker with the elevation of depressive symptoms. This is in line with previous evidence in patients without epilepsy showing that the depression-specific emotional processing bias specifically induced difficulties when processing positive stimuli [9,10,11].

In our research, for both attention and memory, control subjects showed positive emotional bias, subjects with MTLE – d showed non-emotional bias and subjects with MTLE + d exhibited bias away from positive words. The present results thus confirm previous findings from the literature [1,22].

The main limitation of our study is the relatively smaller number of subjects with MTLE + d, which reduced the statistical power. Another limitation may be a lack of testing for presence of anxiety symptoms in the subjects. In this paper, we showed that indicators of depressive symptoms and cognitive vulnerability to depression can be assessed by a linguistic attentional test in patients with MTLE.

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