Event-related theta rhythms in cat hippocampus and prefrontal cortex during an omitted stimulus paradigm

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Abstract

In a recent study on human subjects which performed a time prediction task in an omitted stimulus paradigm we found an increase in the amplitudes of evoked potentials (EPs) for the stimulus preceding the omitted stimuli, probably due to expectancy and focused attention. The amplitude increases were dominant over frontal and parietal association areas and were mainly reflected in enhancements of the theta (3–6 Hz) components. In the present study we analyse the responses of the auditory cortex (GEA, gyrus ectosylvianus anterior), different parts of hippocampus (CA1, CA3), reticular formation (RF), and motor cortex (MC) of the cat brain using a similar paradigm. Similar theta component increases of the EPs were obtained in various parts of the hippocampus, which were dominant in pyramidal cell layers (CA3, CA4), and in motor cortex. The results are interpreted as signs of a diffuse theta response system in the brain including mainly the hippocampus and frontal and parietal association areas. The diffuse theta system is probably involved in general attention and expectancy processes.

Keywords: EEG; Event-related potentials; Theta response; Expectancy; Focused attention; Hippocampus; Association areas

1. Introduction

In a recent study Demiralp and Başar (1992) found that the time prediction task in an omitted stimulus paradigm induced considerable enhancements in the amplitudes of evoked potentials (EP) for stimuli preceding the omitted ones in human subjects. Further analyses of the EPs in the spatial and frequency domains revealed that these enhancements were dominant over frontal and parietal association areas and mainly resulting from the enhancement of the theta band (3–6 Hz) components. According to these results we concluded that parallel processes in sensory and cognitive channels could lead to event related potential (ERP) components which are overlapping in time, however which are separable by means of frequency domain analysis. The cognitive task, which can be described as a focused attention at the moment of the target onset, is

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associated with the activity of theta band generators.

The dominance of the theta response increase over frontal and parietal locations together with the well known hippocampal theta rhythm (Vanderwolf, 1969; Lopes da Silva and Arnolds, 1978; Vanderwolf and Robinson, 1981; Miller, 1991; Lopes da Silva, 1992) and many neuroanatomical studies showing the associations between hippocampus and frontal and parietal areas (Creutzfeldt, 1983; Miller, 1991; Fuster, 1991) led us to start a further analysis with the same paradigm: Elicitation of responses from deep brain structures, especially from the hippocampus, could also be examined. For this purpose we used data obtained in the cat brain by Başar-Eroğlu et al. (1991a,b), where an omitted stimulus paradigm was applied on 8 cats with chronically implanted electrodes in various parts of the hippocampus (CA1, CA3, CA4), auditory cortex (GEA, gyrus ectosylvianus anterior) and reticular formation (RF). The observation of the effects of the applied paradigm on the hippocampal field potentials is especially important in the context of the present study because of the reactivity of the well-known hippocampal theta activity during cognitive processes and studies showing increases in the coherence between the hippocampal and cortical electrical activity in the delta-theta range during conditioning (Aleksanov et al., 1986). In 4 of the cats electrodes were also placed on the motor cortex (MC), which is very close to the prefrontal cortex in the cat. This derivation has been considered as the analogue to the human frontal scalp recordings. Even if the prefrontal cortex of the cat is not well developed and has not such strong connections with other parts of the cortex as in human being, the observation of a similar theta response increase as in the human frontal scalp recordings could give information on the possible interactive mechanisms between the deep brain structures and the prefrontal cortex giving rise to the generation of the surface recorded theta responses. Additionally, there are recent studies showing that the organization between parietal and prefrontal cortex of the cat is similar to that in monkeys and that the cat prefrontal cortex has an integrative role (Criado et al., 1992). The responses of the reticular formation as a system related to the wakefulness and to attention processes were also recorded.

The results from the cat hippocampus revealed a major theta response enhancement following the stimuli preceding the omitted ones. In the light of these results, we further discuss the so-called "Diffuse Theta-Response System" introduced in our earlier studies.

2. Methods

2.1. Animals

The experiments were carried out on 8 freely moving female cats with chronically implanted electrodes. Stainless steel electrodes of 100 μm diameter were located in the auditory cortex (GEA) and mesencephalic reticular formation (RF) while the cats were under nembutal anesthesia (35 mg/kg). A multi-electrode array having four tips was placed in the right hippocampus. The diameter of the electrodes was 25 μm. The distance between the tips of the electrodes was 0.7 mm. Fig. 1 shows a schematic representation of the position of the electrode array in the right hippocampus of the cat. The electrodes were labelled as H1, H2, H3 and H4: the first electrode was located in the upper pyramidal layer of the hippocampus (CA1), the second electrode between upper pyramidal layer and gyrus dentatus, the third and fourth electrodes on or in

![Hippocampus](image)

Fig. 1. Schematic cross-section of hippocampus and the localization of multielectrodes used. CA1: upper pyramidal layer; CA3: lower pyramidal layer.
the lower pyramidal layer (CA3). In order to control the position of hippocampal multielectrodes, three cats were killed. Detailed analysis of the accuracy of the electrode position is given in references (Başar-Eroglu, 1990; Başar-Eroglu et al., 1991a,b). In one of the killed cats the HI1 electrode was bent. In four cats an electrode was also present in the motor cortex (MC). The coordinates of the electrodes (Snider and Niemer, 1964) are given in Table 1.

The derivations were against a common reference which consisted of three stainless steel screws in different regions of the skull. A David Kopf 1760 instrument was used for stereotaxic surgery.

2.2. Experimental conditions

The cats were sitting in a cage in a soundproof, echo-free dimly lit room. Long and tiring experimental sessions were avoided to eliminate the effects of adaptation.

The EEG was monitored and recorded continuously on paper during the experiments. The movements of the cats could be observed via closed circuit TV, so that the experimenter could mark the movement-rich trials during recording. It was also possible to pause the recording procedure by a button press if long lasting artifacts occurred in the EEG. An automatic on-line artefact rejection procedure based on the rejection of trials with extremely high amplitudes was also used for the elimination of global artifactual EEG epochs.

2.3. Experimental paradigms and measurements

Every experimental session consisted of three experiments in the following order: (i) Recording of spontaneous EEG for control and comparison with the omitted stimulus experiment and to make the experimental animals familiar with the experimental conditions. The spontaneous EEG traces were also used to obtain information about the signal quality and the general wakefulness of the animal at the beginning of the experiments. (ii) Recording of auditory evoked potentials. The tones were presented repetitively in order to train the cats passively for the constant interstimulus intervals also used in the event-related potential (ERP) experiments. The stimulus was a 2 kHz sound with an intensity of 80 dB and a duration of 1 s. The AEP recordings consisted of 100 epochs with ISIs of 2.5 s. (iii) Recording of ERPs. Previous investigations showed that the optimal rate for the target signal is the paradigm with every fifth tone omitted (Başar-Eroglu, 1990; Başar-Eroglu and Başar, 1987; Başar-Eroglu et al., 1991a). The ERP paradigm was applied to the cats immediately after the EP experiment, so that the training effect of the AEP recording with the same ISIs could be in play.

The design for application of the stimuli and the data acquisition intervals in the three experiments mentioned above are shown in Fig. 2.

2.4. Data acquisition and analysis

The data were amplified by means of a Schwarzer EEG apparatus with a time constant of 0.5 s and a low pass filter with cut-off frequency at 70 Hz (24 dB/octave). 1-s pre- and 1-s post-stimulus EEGs were digitized with a sampling rate of 500 points/s and stored on a computer hard disc.

The methodology for the analysis of EPs, amplitude frequency characteristics (AFCs) and digitally filtered data and its theoretical background
Spontaneous EEG

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AEP

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P300

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</table>

S = Stimulus 80 dBA, 2000 Hz
OS = omitted Stimulus

Fig. 2. Paradigm. Each experimental session consisted of 3 experiments: (a) control-EEG (b) auditory EP (c) ERP with omitted stimuli. Every 5th stimulus is omitted. The interstimulus intervals are constant (2.5 s) to induce expectancy and focussed attention on the stimulus onset.

Digital filtering. EP frequency components were computed using digital filters without phase shift (Başar and Uğan, 1973). The limits of the band-pass filters used are not arbitrarily chosen. Filters are applied only for selectivity channels, or tuning frequencies indicated by clear peakings in the amplitude frequency characteristics.

2.5. Data reduction and statistics

The averaged EPs filtered in various frequency bands are displayed on the graphics terminal of the computer. The maximal peak-to-peak amplitudes of the filtered responses in a predefined time window are obtained automatically by peak detection or by marking the peaks manually by means of graphic cursors.

The statistical evaluation of the data are carried out on the maximum peak-to-peak amplitudes of the band pass filtered responses in different frequency bands which were selected according to the bandwidths of the peaks registered in the AFCs.

The repeated measures one-way ANOVA (stimulus order) and post-hoc t-test procedure is used to test the significance of the changes in various frequency components of responses to each of the 4 stimuli.

3. Results

3.1. Time domain analysis of the responses to the 1st, 2nd, 3rd and 4th stimuli preceding the omitted stimulus

Fig. 3 shows the grand averages of evoked responses in the time domain to the four stimuli preceding the omitted stimulus in auditory cortex (GEA), reticular formation (RF), various layers of hippocampus (H12, H13, H14) (n = 8, epochs averaged = 492) and motor cortex (MC) (n = 4), respectively. Because it was observed that the H11 electrode in one of the killed cats was bent and stood in a wrong position and the signal characteristics of the H11 derivation of the three other cats deviated significantly from their other hippocampus electrodes and the homogeneous
signal characteristics of the remaining four cats, H11 derivation was excluded from the data analysis.

The unfiltered responses to the repetitive stimuli preceding the omitted stimulus did not demonstrate any additional component with a different latency. The amplitudes of the ERPs recorded from the auditory cortex (GEA) and reticular formation (RF) by 1st, 2nd, 3rd and 4th stimuli preceding the omitted stimulus (the 5th one) did not show any differences. However, in responses from the H12, H13 and H14 electrodes in hippocampus a prominent increase of the peak-to-peak amplitude was observed following the 4th stimulus (i.e., the predecessor of the omitted stimulus). Similarly, in all four cats with electrodes in the motor cortex (MC) it could be seen that the peak-to-peak amplitude of the response to the 4th stimulation was prominently higher than that to previous stimuli. In MC a slight increase in the amplitude of the response to 3rd tone could also be observed.

![Diagram](image)

**Fig. 3.** The grand averages (*n* = 8, epochs averaged 492) of the AEPs elicited by the 1st, 2nd, 3rd and 4th stimuli in the omitted stimulus paradigm with every 5th tone omitted in GEA, RF, H12, H13, H14 and MC. Positivity is over.

**Table:** Amplitude frequency characteristics

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![Graph](image)

**Fig. 4.** The amplitude frequency characteristics of the responses shown in Fig. 3.

### 3.2. Frequency domain analysis by means of AFC

**General features in the amplitude frequency characteristics (AFCs) of GEA, RF, H1 and MC**

To obtain the general frequency characteristics of the ERPs in different structures, the AFCs are calculated for the grand averages of the responses of the 1st - 4th stimuli preceding the omitted stimulus (Fig. 4). The AFCs obtained from GEA, RF, H12, H13, H14 and MC showed different weights of frequency components:

- The GEA response showed a broad peak around a center frequency in the alpha range (12 Hz) with small shoulders in theta (7 Hz), delta (3 Hz) and beta (20 Hz) bands. A small separate peak was also observed in the gamma band (40 Hz).
- In the response of the reticular formation (RF) a clearly dominant peak was observed in the alpha band (12 Hz). Secondary peaks are in theta (5 Hz), beta (20 Hz) and gamma (40 Hz) bands.
- In all hippocampal recordings (H12, H13, H14) the AFCs had similar characteristics: a compound theta-alpha-beta peak with approximately equal weights of the three frequency components at around 5–7 Hz, 8–15 Hz and 15–30 Hz and a
separate peak around 40 Hz. In motor cortex (MC) the dominant peak was in the theta band (5 Hz) followed by a secondary alpha-beta compound peak between 8 and 30 Hz and a gamma band peak around 40 Hz.

**Differences between AFCs of responses to 1st, 2nd, 3rd and 4th stimuli preceding the omitted stimulus**

As described in Section 3.1. prominent amplitude differences in the responses to stimuli preceding the omitted stimulus were only registered in hippocampal recordings and motor cortex and in the responses elicited by the 4th stimulation. The amplitude increases following the 4th stimulus were correlated with an amplitude increase in the theta frequency band in the AFCs. In HI2, HI3 and HI4 recordings a clear increase of the peak around 5 Hz (3–8 Hz) could be detected. An evident increase in the theta (5 Hz) response amplitude was observed in all of the 4 cats with an electrode in the MC in responses after the 4th stimulation. A less prominent increase in the response to 3rd stimulus was also observed. A similar theta increase could be observed in the AFCs of the responses of the reticular formation beginning on with the 2nd stimulation and gradually increasing until the 4th response, although no prominent amplitude increases could be detected in the time domain. In auditory cortex (GEA) there are no differences between the AFCs of the responses of 1st, 2nd, 3rd and 4th stimuli at all.

**3.3. Adaptive digital filtering of the responses and statistical testing of the results**

The ERPs were filtered using digital band pass filters with no phase shift. The band pass limits of the digital filters are selected according to the bandwidths of the peaks in the AFCs of the grand average waveforms. For the sake of simplicity only the theta (3–8) and alpha (8–15) band responses are shown in Figs. 5 and 6.

The significance of the differences between the maximum peak-to-peak amplitudes of filtered responses of the 1st, 2nd, 3rd and 4th stimuli preceding the omitted stimulus have been tested by a one way ANOVA analysis and post-hoc t-tests. The results of the statistics are shown in

<table>
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<tr>
<th>THETA RESPONSES</th>
<th>1. STIM.</th>
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<td>RF</td>
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<td>HI4</td>
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![Fig. 5. The theta response components (3–8 Hz) of the responses elicited by the 1st–4th stimuli preceding the omitted 5th stimulus in GEA, RF, various layers of the hippocampus and MC.](image)

Tables 2 and 3 and in Fig. 7 where the mean values of the maximal peak-to-peak amplitudes of the bandpass filtered responses are shown in histograms.

As can be seen from Figs. 5 and 6 and from the results of the test statistics (Tables 2 and 3, Fig. 7), significant differences were only obtained in the theta components of the hippocampal responses to the 4th stimulus compared with the responses of the 1st, 2nd and 3rd stimuli. The percentual values of significant theta response increases (as the percentual increase of theta response amplitude following the 4. stimulus in comparison to the mean of the theta response amplitudes after first three stimuli) are displayed on the histograms. The HI2 recording showed a mean theta increase of 36 % (1st vs 4th, $p < 0.03$; 2nd vs 4th, $p < 0.01$; 3rd vs 4th, $p < 0.02$), whereas the HI3 and HI4 recordings from the CA3 layer showed more prominent theta response increases of approximately 48% and 50% respectively (for HI3: 1st vs 4th, $p < 0.002$; 2nd vs 4th, $p < 0.0002$; 3rd vs 4th, $p < 0.0007$; for HI4: 1st vs 4th, $p < 0.0007$; 2nd vs 4th, $p < 0.01$; 3rd vs 4th, $p < 0.005$).
ALPHA RESPONSES

GEA
RF
HI2
HI3
HI4
MC

0 250 500 0 250 500 0 250 500 0 250 500 ms

Fig. 6. The alpha response components (8–15 Hz) of the responses elicited by the 1st to 4th stimuli preceding the omitted 5th stimulus in GEA, RF, various layers of the hippocampus and MC. It is given as an example for the insensitivity of other frequency components than theta to the stimulus repetition.

The consistency of the theta response increases in HI2, HI3 and HI4 and it’s dominance in HI3 and HI4 are also shown in Fig. 8 where the responses of single cats are superimposed in unfiltered form and bandpass filtered in the theta range.

In GEA and RF no significant change occurred between the responses of the 1st – 4th stimuli.

Table 2
Results from one-way ANOVA (S: stimulus order) for the maximal amplitudes in the post-stimulus period (0–250 ms) of AEPs for different frequency ranges in various brain structures

<table>
<thead>
<tr>
<th>Factor (d.f.)</th>
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<th>Theta</th>
<th>Alpha</th>
<th>Beta</th>
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<tbody>
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<td>GEA S (3,21)</td>
<td>0.34</td>
<td>0.80</td>
<td>1.38</td>
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<tr>
<td>RF S (3,21)</td>
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<td>0.21</td>
<td>1.56</td>
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<tr>
<td>HI2 S (3,21)</td>
<td>0.83</td>
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<tr>
<td>HI3 S (3,21)</td>
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<td>0.42</td>
<td>18.25</td>
<td>0.00 *</td>
</tr>
<tr>
<td>HI4 S (3,21)</td>
<td>1.42</td>
<td>0.27</td>
<td>10.77</td>
<td>0.00 *</td>
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</table>

In all four cats with the electrode in the MC, an increase in the theta component of the response to the 4th stimulation could also be very clearly observed on filtered waveforms. However, due to the small number of observations this result was not statistically analysed.

4. Discussion

4.1. Brief review of previous results on the omitted stimulus paradigm in cats and human subjects

The responses of the human brain to the omission of a stimulus in paired stimuli or in a stimulus train with regular ISIs have been reported in various studies (Sutton et al., 1967; Başar et al., 1988; Bullock et al., 1994).

The omitted stimulus responses of freely moving cats with chronically implanted electrodes in various brain structures have been studied by Başar-Eroğlu and Başar (1987) and Başar-Eroğlu

Table 3
Results from post-hoc t-test applied to the maximal amplitudes of the theta band responses in HI2, HI3 and HI4 recordings, where the overall effect of the stimulus order was significant

<table>
<thead>
<tr>
<th>d.f.</th>
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<tr>
<td></td>
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<td>p</td>
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<td>0.02 *</td>
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et al. (1991a,b). In these studies, a P300 like positivity could be observed in the auditory cortex, reticular formation and different layers of the hippocampus following the omitted stimulus in a train of repetitive stimulations with 2.5 s intervals. This result was tentatively interpreted as the ability of the cat brain to develop a type of cognitive process, namely an expectancy and focused attention to the regular stimulation intervals.

Even if most of the ERP studies on experimental animals use conditioning paradigms to obtain a meaningful target stimulus, there are a number of studies demonstrating ERPs under passive conditions in monkey (Paller et al., 1982, 1988; Neville and Foote, 1984), dolphin (Woods et al., 1986) and rat brain (O'Brien, 1982; Hurlbut et al., 1987; Yamaguchi et al., 1993). In a recent review, Paller (1994) emphasized the importance of passive paradigms in animal ERP research in search of the neural substrates of human ERPs: "Because conditioning paradigms have rarely been used in studies of P300 in humans, they provide relatively weaker evidence for validating an animal model".

Our recent study showed a considerable enhancement of the theta components of the responses to the predecessor of the omitted stimulus (Demiralp and Başar, 1992). The theta increases were significant over frontal and parietal areas in the auditory modality. In visual modality significant theta increases were more diffuse, over frontal, parietal, occipital areas and at vertex but again more pronounced at frontal and parietal sites.

In the light of results mentioned above we search now similar changes in the responses to the preceding stimuli of the omitted one on cats with chronically implanted electrodes. Certainly, the cognitive content of the omitted stimulus experiments carried out on "passively trained cats" and "instructed human subjects" are not exactly comparable. However, the presence of a P300-like response of the cat brain to the omitted stimulus (Başar-Eroğlu et al., 1991a,b) led us to the assumption that the cats probably may also to a certain extent develop "expectancy" and "focused attention" to the repetitive stimulations and the regular omission of a stimulus. The term "expectancy" here is used in a similar manner as the Bullock's description of expectation (Bullock, 1993): "I intend the term expectation here to mean an inferred state of the nervous system accounting for any of a wide variety of behavioral or physiological signs that a more or less specific sensory input has been anticipated, as a familiar

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**Fig. 7.** The mean values of the maximal amplitudes of various frequency components of AEPs elicited by 1st, 2nd, 3rd and 4th stimuli in various brain structures (in µV). Significant differences are shown. There were only significant differences between hippocampal theta responses following the 4th stimulus and those elicited by each of the 1st, 2nd and 3rd stimuli in H12, H13 and H14. The percentual values of the significant theta increases following the 4th stimulus are calculated by assuming the mean of the theta responses to 1st, 2nd and 3rd stimuli as 100%. *p < 0.05, **p < 0.01, ***p < 0.001.
event, either on schedule at a defined moment or only within broadly defined times. A surprise may be either the familiar at an unanticipated moment or an unfamiliar stimulus. I do not imply a conscious awareness of anticipation”.

4.2. Differences between responses to preceding stimuli of the omitted stimulus in the time domain

The time domain analyses of ERPs to the repetitive stimuli preceding the omitted stimulus did not demonstrate any response changes in terms of an additional component arising with a different latency. However, there were some changes in the amplitudes of the responses to the 1st, 2nd, 3rd and 4th stimuli preceding the omitted stimulus, as was the case in human studies (Demiralp and Başar, 1992; Başar-Eroğlu et al., 1992).

The most prominent amplitude changes were recorded in the hippocampal recordings (HI2, HI3, HI4) and recordings of the motor cortex (MC) close to the prefrontal area. In the time domain, the peak-to-peak amplitude of the EP to the 4th stimulus (predecessor of the omitted stimulus) increased considerably compared to the 1st, 2nd and 3rd stimuli. These results are in accordance with the results obtained from especially frontal and parietal recording sites of human subjects in our previous study (Demiralp and Başar, 1992). In the human study, we found a 44% increase in the theta response amplitudes in frontal recording site. In the present study the theta response increases in the CA3 layer of the hippocampus is also at a similar level (48–50%).

A relevant point in the comparison of the spatial distribution of the amplitude increases in both studies is that in cats the auditory cortex (GEA) is totally insensible to the repetitive application of the stimuli whereas in human study slight amplitude increases were also registered at recording sites close to the primary sensory areas (occipital derivation in visual modality) or noted to reflect the sensory processing of the input (vertex in auditory modality).

4.3. Frequency selectivity of the amplitude enhancements in hippocampus

The amplitude increase in the responses of the hippocampus and motor cortex to preceding stim-

![Fig. 8. The superimposed unfiltered (upper rows) and theta band (3–8 Hz) filtered (bottom rows) responses of HI3 and HI4 (CA3) of 8 cats.](image-url)
uli of the omitted one were correlated with a selective amplitude increase in the theta frequency band in the amplitude frequency characteristics (AFCs). In HI2, HI3 and HI4 recordings the test statistics revealed that these amplitude increases in the theta band were significant. In the motor cortex this result was not tested statistically due to the small number \( n = 4 \); however, it was consistent in all four cats with the electrode implanted in the MC. In all other recording sites and frequency bands no significant difference occurred between the responses to the 1st to 4th stimuli.

The theta enhancement in response to the preceding stimulus of the omitted one is also in accordance with the results of the human study (Demiralp and Başar, 1992), where significant increases were registered only in theta responses following the predecessor of the omitted stimulus.

The responses of the primary auditory cortex (GEA) in the cat brain showed no significant changes, which seems to partly contradict results obtained in human subjects, where a slight theta increase could also be observed in scalp locations reflecting the activities of the primary sensory areas, even though the most prominent theta enhancement was over frontal and parietal areas. However, considering the spatial smearing (blurring) effect of scalp recorded EEG and the refined recording method of the present study using implanted electrodes, it can be stated that the slight theta increases in human scalp recordings were possibly due to the reflection from frontal and parietal association areas. Accordingly, we assume that the cat experiments shed some light on the question about the location of the theta increase.

4.4. Theta rhythm as a common feature of limbic structures is also involved in mechanism of selective attention

The hippocampal electrical rhythm in the theta frequency range (4–7 Hz) has been one of the most studied rhythmic activities of the mammalian brain (Vanderwolf, 1969; Lopes da Silva and Arnolds, 1978; Vanderwolf and Robinson, 1981). All limbic areas are capable of displaying theta rhythm. The appearance of the hippocampal theta activity correlates in different ways with large body movements, the alert posture in the immobile animal, the specific orienting movements (in the absence of larger body movements), during eye movements and during fixed staring in various species (for a review see Miller, 1991). Therefore, it is one of the important examples, which lead to the general conclusion that oscillation in neural networks are not a by-product, but may have a functional significance in brain function (Lopes da Silva, 1992).

Important results on the functional significance of the hippocampal theta rhythm are experimental observations showing that the theta activity in hippocampus can facilitate the transmission of information between the hippocampus and target structures, such as the nucleus accumbens (Lopes da Silva et al., 1984), that stimulation at the theta frequency may induce LTP in hippocampal formation (Larson and Lynch, 1988; Rose and Dunwiddie, 1986; Greenstein et al., 1988), and that during the course of conditioning and at the time of presentation of the conditioned stimulus the coherence between hippocampus and prefrontal cortex increased in the delta and theta frequency ranges (Aleksanov et al., 1986).

By measuring the unit responses in hippocampus during a short-delay conditioning paradigm, it has been shown that pyramidal neurones in fields CA3 and CA1 increase their activity very rapidly and form a “temporal model” of the learned behavioral response (Berger et al., 1976; Berger and Thompson, 1977, 1978). The learning and LTP is enhanced if the delay between the pair of stimuli is in the range of theta period. The fact that in our findings the increase of the theta response is highly prominent in the CA3 location is in parallel with these findings.

The resonant theta response of the hippocampus elicited by auditory and visual stimuli was explained in detail as a component analysis of hippocampal EPs (Başar and Üngan, 1973).

Furthermore, Başar-Eroğlu et al. (1991b) have shown that the P300-like response in the cat hippocampus to omitted stimuli has a strong theta
response component, again with a dominance in the CA3 layer. Accordingly, the hippocampal theta response, which is especially dominant in the CA3 layer, seems to have a general functional role in processes of expectancy and focused attention.

There is no strong evidence showing that the phasic ERP theta components and the tonic state-dependent theta waves recorded in the hippocampus have the same origin. However, there are studies showing a strong relationship between the frequency components of the ongoing EEG and the ERP (Başar, 1980) on one side and hippocampal responses obtained by transient stimulus pairs applied with the theta period on the other (Berger et al., 1976; Berger and Thompson, 1977, 1978), pointing to possible relations between these two phenomena.

4.5. Comments on the anatomical and physiological links between the hippocampal formation and the association areas of the neocortex

The main thalamic projection nucleus to the prefrontal cortex is the nucleus medio-dorsalis. The medial magnocellular part of the nucleus medio-dorsalis gets the main input from nuclei amygdalae and the temporobasal cortex inclusive the hippocampus. Hence, the main thalamic input to the orbitofrontal cortex stems from the limbic system (Nauta, 1971, 1972). Also, lateral parts of the nucleus medio-dorsalis and, by this way, the dorsal part of the prefrontal cortex gets input from hippocampus-septum system (Creutzfeldt, 1983).

There are direct efferents of the hippocampal formation, which reach the isocortex (for a review see Miller, 1991). The CA1 sends efferent which reach the perirhinal cortex, retrosplenial cortex and various parts of frontal and temporal regions (Schwertfeger, 1979; Swanson, 1981). The subicular components also project back to the posterior cingulate cortex, dorsal prefrontal cortex, temporal and prepiriform cortex (Irle and Markowitsch, 1982a,b; Cavada et al., 1983). It was also shown that the main output of the entorhinal cortex to isocortex projects to the medial surface and convexity of the prefrontal cortex. In addition, a number of afferent connections from the isocortex to the limbic system are shown (for a review see Miller, 1991), which stem mainly from polysensory association areas.

The hippocampal formation is most directly linked with the cingulate cortex and the prefrontal areas, which send and receive many connections to the rest of the cortex: efferents from the posterior cingulate cortex have been seen projecting to the inferior and posterior parietal cortex, dorsal and lateral prefrontal cortex, orbito-frontal cortex, parieto-temporal cortex, medial and temporal cortex (Mesulam et al., 1977; Pandya et al., 1981; Baleydier and Mauguière, 1980). Each sector of parietal cortex is connected in parallel with a particular sector of the principal sulcus and presumably transposes some of its sensory-limbic specializations to these areas accordingly (Goldman-Rakic, 1988). Areas of the temporal neocortex also project topographically to the inferior convexity and orbital prefrontal cortex (Pandya and Kuypers, 1969; Jones and Powell, 1970; Markowitsch et al., 1985; Moran et al., 1987). Additionally, there are some recent findings showing the functional integrity of prefrontal and parietal cortices in cat (Criado et al., 1992).

Aleksanov et al. (1986) showed that during the course of alimentary conditioning, and at the time of presentation of the conditioned stimulus (CS), the coherence between hippocampus and prefrontal cortex increased. This increase of coherence was observed especially in the delta and theta frequency ranges. Some recent evidence that the midline prefrontal region of the cortex can generate theta activity was supported by Mizuki et al. (1980) in certain cognitive states. Lang et al. (1987), like Westphal et al. (1990) used spectral analysis of frontal EEG and showed that theta frequencies (3–7 Hz) were increased during motor or verbal learning tasks.

In light of the findings described above we come to the following conclusion: The theta response increases in hippocampus and frontal cortex from the cat brain and theta response increases in human frontal and parietal locations reflect possibly the general responsiveness of hip-
pocampal-frontal-parietal system during focused attention and expectancy.

Recently, the concept of theta resonance has extensively been analysed by Miller (1991) who proposed that Hebbian processes of synaptic strengthening select patterns of loops passing from hippocampus to cortex and back to the hippocampus. "The total conduction delay time round each one of these patterns of loops is envisaged to correspond to the theta period. Such resonance between hippocampus and cortex is envisaged to have an important functional role in registration and retrieval of information in the cortex." According to the anatomical and physiological evidence Miller takes the viewpoint that theta modulated signals are likely to influence limbic and prefrontal areas, and also (directly or indirectly) other areas of (mainly association) cortex. The theta response concept presented in this report supports further the interpretation of Miller.

Striopallido-thamic system is also proposed to take a role in processes such as expectation or preparation (Birbaumer et al., 1990). With direct inputs from hippocampus and prefrontal cortex, another important component of the investigated diffuse theta system could be the basal ganglia, which remains to be investigated.

4.6. Integrative analysis of the increased theta response in the brain: diffuse theta response system in the brain

The present study indicates that a selective strong theta response component increase occurs in the cat hippocampus in responses to stimuli preceding the omitted one in an omitted stimulus paradigm, where an expectancy and focused attention is probably developed by the cat to the onset time of the repetitive stimuli similar to theta response increases in frontal and parietal responses of human subjects (Demiralp and Başar, 1992). Further, Başar-Eroğlu et al. (1991a,b) have shown that the prominent theta response at the CA3-pyramidal layer of cat hippocampus cannot be recorded in the cortex with the important weight due to volume conduction. On the other side, there are many anatomical evidences which show a strong connectivity between the limbic structures and the association areas of the neocortex (see Section 4.5).

In previous studies (Başar et al., 1991; Demiralp and Başar, 1992; Başar-Eroğlu et al., 1992), we postulated a "Diffuse Theta-Response System" in the brain which is involved in the cognitive states of focused attention and expectancy. The parallelism between the theta response increases in these studies recorded over human neocortical areas and those in the present study recorded intracranially from cat hippocampus suggest that the hippocampus plays an important role in the diffuse theta-response system. The close anatomical relationships between the hippocampus and neocortical association areas, especially the frontal and parietal association areas, and the close anatomical and functional relationships between the latter two suggest that the interaction of the hippocampus with the neocortical association areas in the theta frequency band might be the basis of the diffuse theta-response system, which possibly is involved in focused attention and expectancy.

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