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Differential effects of non-REM and REM sleep on sensory gating in rats

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Abstract. Sensory gating in rats can be measured with a double click paradigm. The diminished response towards the second click is a physiological manifestation of reduced sensory input. This physiological process seems to be disturbed in human psychoses. It is thought that gating, as measured with this paradigm, is a preattentive, involuntary phenomenon which is not modulated by attention. If this is indeed the case, than it is hypothesized that gating should not be modulated by non-REM sleep. In the present experiment pairs of clicks (500 ms interval) were presented during wakefulness, non-REM as well as REM sleep and cortical auditory evoked potentials (AEP's) were recorded in chronically implanted rats. Rather similar AEP's were found after the first and second stimulus. However, the amplitudes of the various components of the second AEP were smaller than those of the first AEP, suggesting a gated response. This was the case during all three levels of vigilance. The amplitudes of both AEP's showed the more often reported changes in amplitude during sleep and REM sleep. Clear differences were seen in gating: compared to wakefulness a decrease in gating was found during REM sleep while gating was unchanged during non-REM sleep. The latter outcome seems to confirm that gating in rats is indeed a preattentive process. Finally, results were discussed in terms of neuronal properties of thalamic relay cells and it is suggested that firing properties of thalamic relay cells are not involved in this type of sensory gating.

Key words: rats, sensory gating, P50 gating, sleep, animal model of schizophrenia

INTRODUCTION

Sensory gating is a general term for describing the ability of the brain to modulate sensory information. Gating of the auditory evoked potential (AEP) can be demonstrated in man and in rats e.g. in the double click paradigm. The double click paradigm has a long research tradition, it is often used to investigate local brain inhibitory processes (Eccles 1969). Research in man and in rats has pointed out that when the interval between the first and second click, the interstimulus interval, is 500 ms, the second AEP has a substantial smaller amplitude than that of the first response (Adler et al. 1986, Nagamoto et al. 1991). This interval was proven the most optimal in demonstrating differences in gating between schizophrenic patients and normal subjects (Nagamoto et al. 1991). Sensory gating is operationalized as the ratio of the amplitude of a certain component of the second AEP to the amplitude of the same component of the first AEP (Freedman et al. 1983) or as the difference between the amplitude of a certain component of the first AEP minus the amplitude of the same component of the second AEP (Smith et al. 1994). A low ratio and a large difference reflect better inhibition and more sensory gating. Commonly the P_{50}, a small positive peak with a latency of 40-80 ms is the dependent variable in man.

The P_{50} in humans might reflect an automatic and preliminary registration of an auditory stimulus. Some authors claim that the P_{50} is preattentive, that it is not under the influence of attentional factors. This view is based on the finding that components of the AEP which are sensitive for changes in attention occur later than 50 ms Näätänen (1992) and Alho et al. (1994) found that attended auditory stimuli differed from unattended stimuli 80-120 ms after stimulus onset, later than the P_{50}. Related to the above mentioned findings are the Winter et al. (1995) results. These authors reported that sleep induced changes in the amplitude of components of the AEP's occur after 100 ms. These data suggest that in humans attention modulation including sleep affects AEP's only after 80 ms. Although an automatic, pre-attentive process might determine the amplitude of the P_{50}, it is another question whether P_{50} gating is preattentively controlled. Guterman et al. (1993) suggested that P_{50} gating is influenced by attentional processes and Cullum et al. (1993) found a high correlation between gating and a sustained attention task. However, Jerger et al. (1990) found that the amplitude of the P50 as well as P50 suppression are not affected by attentional manipulations, in contrast to the amplitude of the N100 or the P180. It seems that the amplitude of the P_{50} reflects a preattentive process which is not modulated by attention and sleep, however whether P_{50} gating is controlled by sleep and attentional processes remains to be elucidated. Recently Cardenas et al. (1997) found in man that P_{50} gating is not affected by variations in wakeful alertness.

Gating has also been studied in rats (Adler et al. 1986, 1988, Bickford-Wimer 1990, Bickford et al. 1993) with the same double click paradigm. Preliminary data from our own laboratory demonstrate that gating in rats can be found with an interclick interval of 300 to 1,000 ms (de Bruin et al., in preparation). The earliest gating studies in rats described gating for a N_{50} component of the AEP (Adler et al. 1986, 1988). Later, the hippocampal N_{40} in rats was proposed as a model system for the human P_{50} (Bickford-Wimer et al. 1990). Recent neuroanatomical and neurophysiological studies suggest that thalamic relay neurons may serve as a neuronal oscillator, i.e.. it has intrinsic properties that generate a wide range of electrical activity representing timing and gating operations (Oke and Adams 1987, Steriade and Llinas 1988).

A limited data set suggests that gating in rats occurs under chloral hydrate anesthesia (Bickford-Wimer et al. 1990). This might imply that attentional factors do not play a role in gating. However, whether gating in rats occurs during a non-pharmacological, physiological non-attentive state such as during non-REM sleep is not clear. Considering the chloral hydrate data, no major effects of non-REM sleep on sensory gating will be predicted. It is less clear whether gating occurs or will be changed during REM sleep. On the one hand REM sleep is not a uniform process, its wakening threshold is rather variable, there are many different types of phasic events such as PGO spikes and twitches, on the other hand hippocampal theta rhythm is present throughout a phase of REM sleep. What seems rather certain is that during sleep, including REM sleep a subject has limited possibilities to direct one's attention to external events. Whether gating occurs during REM sleep and whether it is similar to gating during wakefulness and non-REM sleep, will be addressed in an experiment in which in rats cortical gating will be investigated during passive wakefulness, non-REM sleep and REM sleep.

METHOD

Subjects

Random bred male Wistar rats, between 5 and 11 months of age and weighing between 360 and 452 g were used. They were born and raised in the Central Animal House of Nijmegen University, next they were moved to the vivarium of the Department of Comparative and Physiological Psychology. Subjects were housed in groups until surgery, then they were singly housed. Animals were maintained on a 12-12 h light-dark regime, with white lights on at 20.00 h under a constant room temperature of 19°C.

An EEG electrode set (Plastic One, MS303/2) was permanently implanted under 0.08 ml/100 g Hypnorm i.m. and 0.1 ml Narcovet i.p. anesthesia. Coordinates were determined with the aid of Paxinos and Watson's atlas (1988) with skull surface flat and bregma zero-zero. One cortical EEG electrode was placed in the frontal (AP 2.0, L 3.5) and one in the parietal-occipital region of left hemisphere of the cortex (AP -6.0, L 4.0), the reference electrode was placed above the cerebellum. This set up allowed one differential recording between the two active electrodes. Four screws were fixed to the skull and the electrode plugs and screws were fastened to the skull with fastacryl. Subjects were allowed to recover for at least two weeks following surgery.

Procedure

The experiment took place in freely moving animals during the dark phase of the 24 h LD cycle. The animals were placed in a transparent recording cage (25 x 30 x 35 cm) which was placed inside a sound isolated Faraday cage. The Faraday cage was provided with a window which allowed us to observe the animal. The EEG signals were filtered (only frequencies between 1 and 100 Hz were allowed to pass), amplified and digitized with a sample frequency of 512 Hz (Tektronix 2630) and stored on magneto-optical disk for subsequent off line analysis.

Auditory stimuli consisted of repeated presentation of two 1 ms duration 98 dB clicks (broad spectrum) and a fixed interclick interval of 500 ms. The interval between the pairs of clicks varied randomly between 5 and 10 s. Stimuli were presented with a loudspeaker 85 cm above the floor of the recording cage. Two hours before the actual EEG recording the rats were handled for 15 min and moved to the recording cage. Next this cage was placed into the Faraday cage, the EEG leads were connected and for 1.5 h stimuli were presented in order to habituate the animals to the stimuli. Next, EEG recordings were made.

Spontaneous behavior of the rats in their cages was closely observed. With the aid of a behavioral code (active or passive behavior) and the EEG signals active wakefulness (behavioral activity and a low amplitude fast EEG), passive wakefulness or drowsiness (passive behaviour with a small amplitude fast EEG, with less than 50% of the time intermixed with early signs of non-REM sleep), non-REM sleep (passive behavior together with large amplitude slow waves) and REM sleep (cortical theta or low amplitude fast frequencies with incidental periorial twitches) could be identified (van Luijtelaar and Coenen 1984, 1993).

Averaged auditory evoked potentials were made during passive wakefulness, non-REM and REM sleep for each subject. The number of trials was 150 to 200 for each vigilance state. All trials were checked on the presence of muscle activity, movement artifacts and 50 Hz. Only indisputable trials were used for EEG averaging. For each animal three averaged AEP's were made, one characteristic for passive wakefulness, one for non-REM sleep, one for REM sleep. All amplitude measures were determined with reference to a 100 ms prestimulus baseline. Generally, peak-to-peak amplitudes were taken except for the amplitude of the first peak or when a peak could not reliable be established then the baseline to peak amplitude was taken. Gating was defined as the absolute difference between the amplitude of a component of the first AEP minus the amplitude of the corresponding component of the second AEP (Smith et al. 1994).

Data analyses

The data originated from the three grand averaged AEP's of each subject during each of the three conditions. T-tests for dependent samples were used to establish whether gating occurred. By comparison with the data obtained during wakefulness, it was tested whether gating was affected during non-REM and REM sleep. Since lower amplitudes were anticipated for the second evoked potential, one-tail tests were used to evaluate the difference between the first and second component of the AEP.

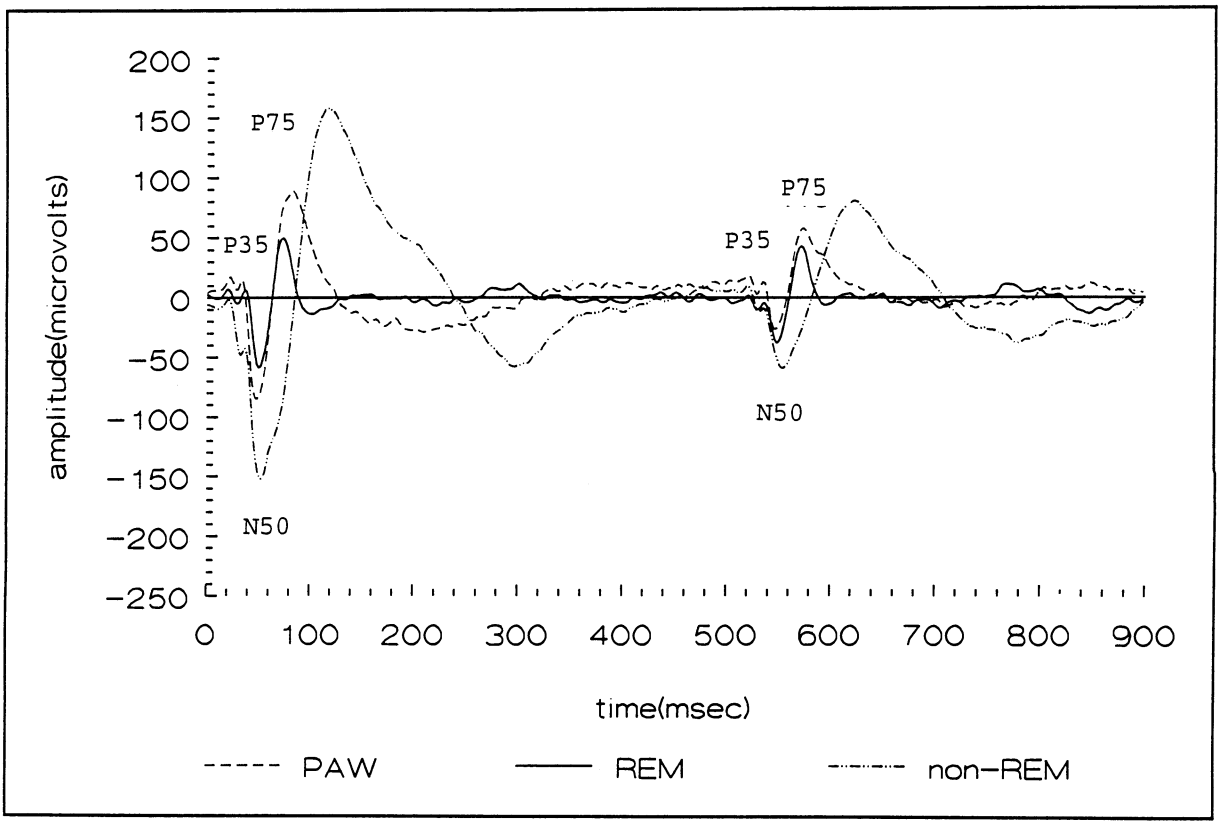

Fig. 1. Grand Averaged AEP's ($n = 5$) in the double click paradigm during passive wakefulness (PAW), REM and non-REM sleep. X-axis time in ms; Y-axis amplitude in microvolts. Continuous line represents passive wakefulness; dotted line, represents REM sleep; dashed line, represents non-REM sleep.

RESULTS

The auditory evoked potential recorded during passive wakefulness consists of three large components, a positive wave with a latency of about 35 ms (the P_{35}), a negative wave with a latency of about 50-55 ms (the N_{50}) and a large positive wave with a latency of about 75 ms, the P_{75}.

Auditory evoked potentials made during passive wakefulness, non-REM sleep and REM sleep are presented in Fig. 1. In one animal a clear P_{21} and a shoulder in its averaged evoked potentials at 35 ms was noticed. In three of the animals a P_{35} could not be assessed, therefore gating of this component could not be determined reliable. There were no difficulties with the identification of other components. The amplitudes and the latencies of the various components of both the first and second AEP are presented in Table I. The amplitudes of the second AEP were generally smaller than the amplitudes of the first AEP, suggesting that gating occurred.

From the table and the figure it can be inferred that both the components of the first and second AEP were modulated by the state of vigilance: non-REM sleep tended to increase and REM sleep tended to reduce the amplitudes of the AEP's. During non-REM sleep the amplitude of the first N_{50} was increased ($t_4 = 3.61$, $P<0.05$) and during REM sleep it was decreased ($t_4 = 3.49$, $P<0.05$). The N_{50} of the second AEP was also decreased ($t_4 = 2.64$, $P<0.05$) during REM sleep. Also for the P_{75} a decrease in the amplitude during REM sleep was found for both its component of the first ($t_4 = 3.40$, $P<0.05$) and second ($t_4 = 3.31$, $P<0.05$) AEP. Finally, an increase in latencies of the P_{75} of both the first ($t_4 = 13.3$, $P<0.001$) and second ($t_4 = -16.23$, $P<0.001$) AEP was found during non-REM sleep.

Significant gating was found for the N_{50} and P_{75} during wakefulness, non-REM sleep and REM sleep. Differences in gating between the vigilance states were found for both the N_{50} and the P_{75}: there was both less N_{50} (absolute: $t_4 = 3.43$, $P<0.05$; relative: $t_4 = 3.08$, $P<0.05$) and P_{75} (absolute: $t_4 = 2.67$, $P<0.05$; relative: t_4

TABLE I

Amplitudes in μV and latencies in ms (with standard error of the mean) of auditory evoked potentials during passive wakefulness (PAW), REM sleep (REM) and non-REM sleep. Significant gating is indicated by *, significant modulation of the amplitude and latency are indicated by $. Differences in gating between Passive wakefulness and REM sleep are indicated by #. Not done= n.d.

	PAW	REM	non-REM
P35 (n = 2)			
Amplitude First	85 ± 25	23 ± 10	69 ± 17
Amplitude Second	49 ± 15	22 ± 6	26 ± 12
Gating	36 ± 4	1 ± 8 n.d.	43 ± 31 n.d.
Latency First	38 ± 2	32 ± 4	37 ± 5
Latency Second	39 ± 2	38 ± 3	37 ± 4
N50 (n = 5)			
Amplitude First	126 ± 31	58 ± 13$^{\$}$	173 ± 43$^{\$}$
Amplitude Second	47 ± 8	38 ± 9$^{\$}$	62 ± 13
Gating	79 ± 8*	20 ± 10$^{*\#}$	111 ± 34*
Latency First	51 ± 4	50 ± 1	55 ± 4
Latency Second	50 ± 3	48 ± 0	55 ± 4
P75 (n = 5)			
Amplitude First	241 ± 53	131 ± 22$^{\$}$	325 ± 79
Amplitude Second	128 ± 26	87 ± 14$^{\$}$	149 ± 37
Gating	113 ± 33*	44 ± 16$^{*\#}$	176 ± 41*
Latency First	73 ± 3	75 ± 2	113 ± 2$^{\$}$
Latency Second	75 ± 2	74 ± 2	112 ± 4$^{\$}$

= 2.55, P<0.05) gating during REM sleep compared to wakefulness. There were no differences in gating between non-REM sleep and wakefulness.

DISCUSSION

Gating of the AEP was found during the three vigilance states in all subjects. Furthermore, the amplitudes of the AEP's were clearly modulated by the two different sleep states: they were larger during non--REM sleep, similar to what has been described by us for the amplitudes of visual evoked potentials (VEP's) (van Hulzen and Coenen 1984, Inoue et al. 1992, Meeren et al. 1998). It is thought that the non-REM sleep induced enlargements of the amplitude of evoked potentials are due to the state-dependent bursting modality of thalamo-cortical cells, which results in more synchronized periods of neuronal excitation and inhibition (Coenen 1995). The AEP's made during REM sleep are smaller than the AEP made during passive wakefulness. Earlier we (Meeren et al. 1996) compared AEP made during REM sleep with the AEP during active and passive wakefulness and we found that AEP made during REM and active wakefulness were more alike that between passive wakefulness and REM sleep, in agreement with the present data in which also smaller AEP's were found for REM sleep than during passive wakefulness. Rather long latencies, an increase of 35 ms, were found during non-REM sleep for the P_{75}. This slowing may be caused by less excitable pathways due to a hyperpolarized state of thalamic relay cells and its afferents during non-REM sleep. Also Winter et al.

(1995) found a large increase in latencies of late components of AEP as sleep deepened.

The architecture of the AEP in rats is less well described. Differences in reference and active electrode position, physical properties of the auditory stimulus and whether the animals were restrained or not might contribute to this. For example, a positive wave in the latency range from 10 and 30 is not always seen (Iwasa and Potsic 1982, Knight et al. 1985, Adler et al. 1988, Shaw 1988, Stevens et al. 1991, Simpson and Knight 1993, Shucard and Specht 1996). Therefore it is less well possible to compare the present AEP's with data from the literature, including its modulation by non-REM and REM sleep.

Sensory gating occurred for all components of the AEP during passive wakefulness. A gated response was earlier reported for the hippocampal N_{40} (Bickford--Wimer et al. 1990, Miller et al. 1992, Bickford et al. 1993, Miller and Freedman 1995). Bickford-Wimer et al. (1990) suggested that gating to auditory stimuli occurs primarily in non-lemniscal auditory pathways, including the hippocampus. Others have found that waves from the primary auditory cortex do not show a gated response (Luntz-Leybman et al. 1992). We found clear evidence for cortical gating. However, our electrodes were not aimed at the primary auditory cortex, hippocampus or vertex, and the EEG was recorded over a large cortical area. This implies that comparisons between our results and other papers are less indicative and meaningful.

Gating occurred also during non-REM and REM sleep. Although the amplitudes of the AEP's were enlarged during non-REM sleep, gating was not modulated during this vigilance state. The opposite was true for REM sleep. During this state gating was significantly reduced as can be seen by smaller differences between the amplitudes of the N_{50} and P_{75} of the two AEP's.

The lack of change in gating during non-REM sleep is in full agreement with the idea that gating is preattentive. If gating is preattentive, than it should not matter whether a subject is able or not to direct his attention to environmental stimuli as is the case during a physiological higher level of vigilance, such as wakefulness. The suggestion that gating is a preattentive, automatic phenomenon was earlier made by Jerger et al. (1990). The REM sleep data are quite different, REM sleep reduced sensory gating. This reduction in gating was not unambiguously predicted but it demonstrates that during a period of high endogenous brain activity including the continuous presence of hippocampal theta activity, gating is reduced. Whether gating is also reduced during another state with theta activity such as active wakefulness, is an interesting next step. Anyway, the reduction in gating during REM sleep suggests that during REM sleep external stimuli are modulated and that an inhibitory mechanism or a filter for external irrelevant stimuli is less active than during passive wakefulness and during non-REM sleep. It is known that during REM sleep endogenous stimuli are transferred from the pons through the thalamus and occipital cortex (PGO-spikes) and it can be speculated that there are less possibilities for preattentive gating of stimuli during this state.

Little is known about the underlying neuronal mechanism of sensory gating. However, during the last decade large progress has been made in understanding properties of thalamic relay cells (Steriade and Llinas 1988, Von Krosigk et al. 1993, McCormick and Bal 1994). Considering its anatomical position and the fact that afferent information is relayed in the specific thalamic nuclei to the cortex, it might be that the thalamus plays a major role in sensory gating. This has been proposed by Oke and Adams in 1987. Their proposal was based on both *in vivo* and *in vitro* data which demonstrated that thalamic relay units, including those of the medial geniculate and reticular thalamic nuclei show a sustained tonic firing during wakefulness and REM sleep (Steriade and Llinás 1988, McCormick and Ball 1994). During the latter two states, the voltage of the resting cell membrane of relay cells and the reticular thalamic nucleus is increased and the cells are tonically depolarized. In contrast, a bursting modus is present during non-REM sleep (Steriade and Llinas 1988). Coenen and Vendrik (1972) found in cats that during non-REM sleep the number of incoming spikes to the thalamus is not changed but that the number of outgoing spikes is reduced. This implies that during non-REM sleep less information is transferred (a reduced transfer ratio) to the cortex and that gating occurs. If the firing modality of thalamic neurons is crucial for sensory gating, than it is predicted that gating will be normal during both wakefulness and REM sleep, but reduced during non-REM sleep (Coenen 1995). And this is not what we have found. Therefore, it can be concluded that neither the thalamic firing mode nor the concept of transfer ratio can explain the present gating data. It seems that gating, as measured with the concept of transfer ratio is conceptual different from the concept of sensory gating operationalized with the double click paradigm and AEP's. The transfer ratio concept of gat-

ing may be based on cellular properties of thalamic cells and it may have a function in the reduction of cortical stimulation during non-REM sleep in order to protect us from being aroused and so that the daily need for sleep can be fulfilled. In contrast, sensory gating is not changed during non-REM sleep and might have a function in blocking truly irrelevant stimuli in order to facilitate the ongoing sleep process.

Although similar stimulus parameters were used by us as commonly found in the literature based on patient studies, it is by no means clear which component of the rat's AEP is best comparable to the P_{50} in humans. The shorter latencies in the rat's auditory evoked potential compared to human auditory evoked potential data make a comparison awkward. Knight et al. (1985) suggested that vertex waves between 50 and 130 ms in rats are comparable to human vertex waves in the range from 100 to 200. These authors based themselves mainly on similarities in topography. Also Shaw (1988) noticed that latency of the primary excitation component, which is perhaps the best reference point, is much shorter in rats than in man. Therefore it is rather likely that a putative candidate in the rat's AEP of the human P_{50} should have a shorter latency than 50 ms. Other arguments for the decision which component is best comparable to the human P50 may originate from pharmacological and sleep studies. In pharmacological studies , i.e. similar responses in man and rats towards (for example dopaminergic or glutamatergic) drugs and from sleep studies, similar vigilance induced changes. In all, it remains to be established to which component of the AEP in the rat the human P_{50} should be compared with. Parallels between human and rat AEP components might also be obscured by differences in functional organization and brain mass. Considering the ambiguity with respect to similarities and discrepancies between the human and rat's AEP on the one side and the fact that it is interesting to investigate putative gating of all components of the rat's AEP, gating was here also determined for the P_{75}.

In summary, auditory evoked potentials can be used to study sensory gating in the rat and several components of the auditory evoked potential did show a gated response. Gating was reduced during REM sleep and not during non-REM sleep. The latter outcome suggests that attentional factors are less crucial for gating of the cortical N_{50} and P_{75} and that gating might be preattentively controlled. Finally, the two different firing modes of thalamic relay cells do not seem to be involved in sensory gating.

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