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Assessing functioning of the prefrontal cortical subregions with auditory evoked potentials in sleep–wake cycle

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Abstract

Our previously observations showed that the amplitude of cortical evoked potentials to irrelevant auditory stimulus (probe) recorded from several different cerebral areas was differentially modulated by brain states. At present study, we simultaneously recorded auditory evoked potentials (AEPs) from the dorsolateral prefrontal cortex (DLPFC) and the ventromedial prefrontal cortex (VMPFC) in the freely moving rhesus monkey to investigate state-dependent changes of the AEPs in the two subregions of prefrontal cortex. AEPs obtained during passive wakefulness (PW), active wakefulness (AW), slow wave sleep (SWS) and rapid-eye-movement sleep (REM) were compared. Results showed that AEPs from two subregions of prefrontal cortex were modulated by brain states. Moreover, a significantly greater increase of the peak-to-peak amplitude (PPA) of N1–P1 complexes appears in the DLPFC during PW compared to that during AW. During REM, the PPA of N1–P1 complexes presents a contrary change in the two subregions with significant difference: a significant increase in the DLPFC and a slight decrease in the VMPFC compared to that during AW. These results indicate that the modulation of brain states on AEPs from two subregions of the prefrontal cortex investigated is also not uniform, which suggests that different subregions of the prefrontal cortex have differential functional contributions during sleep–wake cycle.

Keywords: Auditory evoked potentials; Dorsolateral prefrontal cortex; Ventromedial prefrontal cortex; Sleep–wake states; Rhesus monkey

Sensory evoked brain activity varies with the sleep–wake states [14,18,19,33,35]. Those results showed that the amplitude of the sensory evoked potentials is consistently attenuated during EEG-desynchronized states, such as wakefulness and REM sleep, compared to that obtained during EEG-synchronized states, such as SWS. Our previous study showed that the amplitudes of cortical evoked potentials to irrelevant auditory stimulus (probe) recorded from several different cerebral areas (the temporal cortex, the dorsolateral prefrontal cortex and the parietal cortex) were differentially modulated by brain states, which suggests that different cerebral areas have differential functional contributions during sleep–wake cycle [29]. However, it is still not clear whether the effect of brain states on AEPs from different subregions of certainty cerebral cortex, such as the prefrontal cortex, is uniform during sleep–wake states.

The prefrontal cortex is the cortex that receives projections from the mediodorsal nucleus of the thalamus and is situated in front of the motor and premotor cortices in the frontal lobe [12]. Summarily, functions of the prefrontal cortex that are most relevant to the self-conscious awareness that is lost in sleep are commonly termed ‘executive’, mainly including self-observation, planning, prioritizing and decision-making abilities. The DLPFC involves in working memory [9,10,12,25], which has been studied intensively in monkeys. These studies indicate that the DLPFC has a role in the temporal order of information retrieval. The VMPFC consists primarily of the orbitofrontal cortex and the anterior cingulate, and is also known as the ‘limbic’ cortex. It has been demonstrated that the VMPFC plays a key role in decision-making, social cognition and social judgment [8]. Recent data indicate that in the frontal cortex, the prefrontal cortex shows the greatest change

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from waking to sleep [5]. The transition from waking to SWS is characterized by prefrontal deactivation as reported in positron emission tomography (PET) studies [16,21] and quantitative EEG studies [11,34]. Deactivation increases with the deepening of NREM sleep [15] and is maintained in the transition from SWS to REM sleep [17]. However, PET studies showed that the functioning of different subregions of prefrontal cortex is dissociated with the onset of REM sleep and the following REM sleep [5,7,21,22]: portions of the ventromedial, limbic-related prefrontal cortex and closely associated medial subcortex and cortex are reactivated, but the DLPFC still remains relatively deactivated. Up to date, there is no electrophysiological data applying evoked potentials method to explore the functioning of different subregions of the prefrontal cortex in sleep–wake cycle.

The probe-evoked potentials method, which involves recording brain response to irrelevant stimuli (probe) during performance of a wide range of cognitive tasks, is used with increasing frequency to assess patterns of regional cerebral activation mediating distinct cognitive operation [1]. The most conspicuous change in the probe-evoked potentials would be amplitude reduction in their major components when underlying cerebral region is engaging in corresponding cognitive operation [23,26,31]. As the advantages of probe-evoked potentials over traditional evoked potentials procedures in the assessment of regional cerebral engagement in cognitive operations, this method has been applied widely in variety of fields, such as task-specific hemispheric asymmetry, language processing and clinical diagnosis. Additionally, because probe-evoked potentials could be recorded when subject makes no response, this method also has been used to study the state-dependent modulation of cerebral regions during sleep–wake states [18,19,29].

As previously described [29], three healthy male rhesus monkeys, weighing 3.0–3.5 kg, were used in the present study. The surgery was performed aseptically under anesthesia after hydrochloric acidulated ketamine premedication (4 mg/kg, i.m.), then sodium pentobarbital anaesthesia (30 mg/kg) was maintained and supplementary doses were administered during the operation as needed. The scalp was incised and retracted along with the muscles overlying the skull. The surface of the skull was cleaned of all fasciae and then thoroughly dried. A Teflon-insulated epidural stainless steel recording electrode (0.2 mm in diameter) was threaded into the skull overlying the DLPFC (area 46) and a depth electrode was placed in the VMPFC (area 12) for recording signal, which were all placed in the left hemisphere. A hole was bored through the bone overlying the frontal sinus on one side and a stainless steel screw electrode was threaded into the bone that forms the rear of the orbit so that eye movement potentials could be recorded. Additional screws were placed at the lateral margins of the skull to serve as anchors for the dental cement that would be applied later. Those electrodes were connected to a D type 9-pin connector that then was fixed on the skull by applying the dental cement. Electrode locations were verified according to the geometrical relationships of the cortical gyrus and some "landmarks" of the skull by CT scanning and X-ray examination in different angles. Three monkeys were in good medical condition at the time of testing. All procedures of the present experiments have been approved by the Animal Experimental Committee, Kunming Institute of Zoology, Chinese Academy of Sciences, and were conducted in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals (NIH Guide).

Before the EEG data were collected, those monkeys were brought into a special cage (120 cm × 100 cm × 100 cm) that was situated in a large soundproof room. This allowed the monkeys to adapt to the experimental conditions and move freely in the cage. One side of the cage is made of a transparent plastic glass so that the monkeys' behaviors could be observed and filmed with an infrared video camera, which was proved useful in defining the monkeys' state in terms of the sleep–wake cycle [4]. Two audio speakers were located near the monkey cage. At the beginning, the monkeys stayed in the cage and slept throughout the night without any auditory stimulus from the speakers. Several days later, a pure tone stimulus (2000 Hz; 50 ms duration) generated by a computer was presented to the subject with constant interstimulus interval 2.0 s, and the stimulus intensity was increased gradually up to 70 db during this adaptive period (10 days). During EEG data collections, monkeys were habituated to sound stimulation for at least 1 h before each recording session started in order to guarantee that amplitude modulations would be solely caused by sleep–wake effects and not contaminated by habituation effects. There were four different brain states examined. During wakefulness, one was referred to PW in which the monkey made no or few overt actions, but without apparent signs of synchronized EEG; another was AW in which the subject was manipulating some objects, e.g., a small toy. The sleep cycle could be subdivided into two different phases: SWS and REM sleep. SWS sleep was characteristic with high-amplitude and low-frequency EEG patterns and consisted of several different stages that were not distinguished strictly in present study. REM sleep was accompanied with rapid eye movement, low-amplitude and high-frequency EEG patterns.

The EEG signals to pure sound stimulus (2000 Hz frequency, 50 ms duration, 70 db intensity and 2.0 s interstimulus interval) recorded from the DLPFC and the VMPFC during sleep–wake state were amplified, filtered (bandpass, 0.05–100 Hz), digitized (500 Hz/channel) and averaged online ($n = 300$). Each single trial AEP consisted of 100 samples, 100 ms before and 100 ms after the stimulus trigger. The average voltage of the 100 ms prestimulus activity served as baseline. The peak-to-peak amplitude (PPA) of N1–P1 complexes for every subject and subregion during sleep–wake states was analyzed and normalized according to following formula: $[(\mathrm{PPA} - \mathrm{PPA_{AW}})/\mathrm{PPA_{AW}] \times 100\%}$ (PPA: the peak-to-peak amplitude recorded during sleep–wake states; $\mathrm{PPA_{AW}}$: the peak-to-peak amplitude recorded during AW). Then, repeated-measures analysis of variance followed a post hoc test (LSD) across states (PW, AW, SWS and REM) and paired-samples *t*-test across subregions (DLPFC and VMPFC) were carried out with custom software (SPSS for windows, SPSS Inc.).

Fig. 1 illustrates grand averages of AEPs from two subregions of the prefrontal cortex during sleep–wake states that are charac-