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添付資料： 研究報告書

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内線：

1. 助 成 金 額： 300,000 円

2. 研究テーマ

痛覚刺激に対する脳反応の睡眠中の変化

3. 成果の概要 (100字程度)

表皮内電気刺激法を使って、痛覚関連体性感覚誘発脳磁場に対する睡眠の影響について検討した。痛覚刺激により誘発された SI、SII、島、帯状回と MT の脳活動は、睡眠時に小さくなったから、これらの活動は痛覚認知に関連することと考えられる。

4. 研究業績

(1) 学会における発表 無 ・ ☒ (学会名・演題)

The 8th International evoked potentials symposium・Cortical responses to noxious stimuli during sleep.

(2) 発表した論文 無 ・ ☒ (雑誌名・題名)

Neuroscience 2004;128:177-86. ・ Cortical responses to noxious stimuli during sleep.

痛覚刺激に対する脳反応の睡眠中の変化

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Abstract

We used magnetoencephalography (MEG) to study effects of sleep on cortical responses to noxious stimuli and to clarify the mechanisms underlying pain perception. For a noxious stimulus, painful intra-epidermal electrical stimulation (ES), which selectively activates A-delta fibers, was applied to the dorsum of the left hand. While awake, subjects were asked to count the number of stimuli silently (Attention) or ignore the stimuli (Control). During sleep, magnetic fields recorded in stage 1 sleep and stage 2 sleep were analyzed. One main component at a latency around 140–160 ms was identified in the awake condition. Multiple source analysis indicated that this main component was generated by activities in the contralateral primary somatosensory cortex (SI), bilateral secondary somatosensory cortex (SII) and insular cortex. The medial temporal area (MT) and cingulate cortex were activated later than the main component. Cortical responses in the contralateral SI, ipsilateral SII and MT, bilateral insula and cingulate cortex were significantly enhanced in Attention as compared with Control. The main component 1M as well as later magnetic fields were markedly attenuated during sleep, suggesting that all these cortical areas are involved in pain cognition.

Keywords: Attention, Magnetoencephalography (MEG), Pain, Sleep, Somatosensory

Introduction

Mechanisms underlying pain perception have been examined in many studies but are still not well understood. Since cerebral responses to noxious stimuli are affected by the subject's attentional and arousal levels, several studies have investigated the effects of distraction on pain-related somatosensory evoked potentials (SEPs) [1,2] to clarify the mechanism of pain perception. These studies found a decrease of pain-related SEP amplitude during distraction tasks. Examining the effects of sleep on cerebral responses to noxious stimuli is another useful way of understanding nociceptive processing. However, up to now, only a few studies have attempted to investigate the cortical responses to noxious stimuli during sleep [3, 4, 5]. Beydoun et al. [1] reported that pain-related SEPs were markedly decreased during sleep stages, which was confirmed later by Naka and Kakigi [6] and Wang et al. [7]. In the present study, we recorded magnetic fields following ES to investigate the effects of sleep on cortical responses to noxious stimuli.

Methods

Ten healthy subjects participated in this study, and informed consent was obtained from all subjects. Intra-epidermal electrical stimulation (ES), a method we recently developed [8, 9], was used in the present study. The intensity ranged 0.1–0.3 mA. The inter-stimulus interval was varied at random between 0.1–0.3 Hz. The stimulus duration was 0.5 ms. First we obtained data in the awake state. Subjects were instructed to mentally count the number of (Attention) or ignore (Control) the stimuli. After the collection of data in the awake state, subjects were left to fall asleep. We analyzed SEFs only during stage 1 sleep and stage 2 sleep in the present study. Each session was made up of an average of 60 trials.

SEFs were measured with a dual 37-channel biomagnetometer (Magnes, BTi, San Diego, CA). The two probes were centered around positions C3 and C4 according to the International 10–20 System. SEF responses were filtered with a 0.1–100 Hz bandpass filter and digitized at a sampling rate of 2083 Hz. The analysis time was 100 ms before and 400 ms after the application of each stimulus. First, the root mean square (RMS) of the evoked magnetic fields was calculated at each sampling point in order to compare the amplitude of the response among the four conditions. Second, since several cortical activities following noxious stimulation overlapped temporally, we used the brain electric source analysis (BESA) software package (NeuroScan, Inc, Mclean, VA) for the analysis of theoretical multiple source generators as described elsewhere [9]. Data were expressed as the mean \pm standard deviation (SD). A paired t-test was used to compare RMS between the control and each task condition every 0.48 ms. A P value less than 0.05 was considered significant. The source strength of each cortical activity was compared between attention and control using a two-way analysis of variance (ANOVA) (condition and source as the two factors). P values less than 0.05 were considered significant.

Results

In the recorded magnetic fields, one consistent component was identified in both Attention and Control from each hemisphere. We termed it 1M and 1M (i), recorded from the hemisphere contralateral and ipsilateral to the stimulation, respectively (Fig. 1). As shown in Fig. 1, evoked magnetic fields were enhanced in Attention as compared with Control. No clear activity was identified during sleep. The RMS in Attention was significantly larger than that in Control in both hemispheres at a latency of 130–180 ms (paired t-test, $P < 0.05$). During sleep, the RMS around 110–270 ms in stage 1 and stage 2 sleep was significantly smaller than that in Control (paired t-test, $p < 0.05$).

BESA analysis indicated multiple cortical regions including the SI, SII, insula, MT and cingulate cortex were activated by noxious stimuli (Fig 3). The peak latencies of the contralateral SI, SII, and insular activities were 152, 149 and 145 ms, respectively, in Control (Table 1), which corresponded approximately to the peak latency of 1M (148 ms). The peak latencies of the ipsilateral SII and insular activities were 159 and 155 ms, respectively, which were longer than the respective latency in the contralateral hemisphere by approximately 10 ms, and also corresponded to the peak latency of 1M (i) (157ms). To explain the magnetic fields later than 1M and 1M (i) components, sources in MT or cingulate cortex were necessary. Since evoked magnetic fields during sleep were markedly attenuated, we could not find any source activity in them. Therefore, the source strength of each source activity was compared

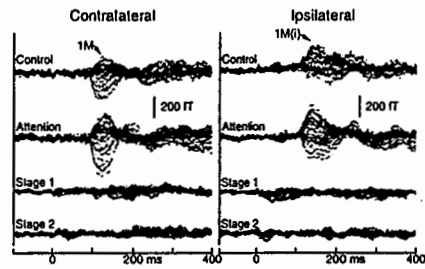


Fig 1. Magnetic fields following noxious epidermal stimulation of the dorsum of the left hand in the awake state, stage 1 sleep and stage 2 sleep in subject 1. (Attention, Stage 1 and Stage 2). The scale for the paired t-test is a common logarithm. $P < 0.05$ was considered to be significant.

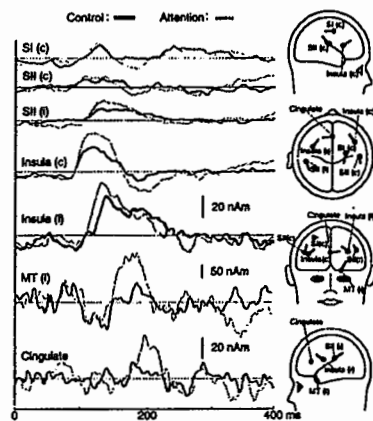


Fig. 2 The group-averaged RMS of all subjects in the four conditions and the paired t-test values at each sampling point between the control and each task condition (Attention, Stage 1 and Stage 2). The scale for the paired t-test is a common logarithm. $P < 0.05$ was considered to be significant.

	Control	Attention
SI(c) (ms)	151.6±18.2	146.7±13.3
SII(c) (ms)	148.7±17.3	142.0±12.1
SII(i) (ms)	158.6±12.8	156.6±12.8
Insula(c) (ms)	144.9±16.8	138.9±15.3
Insula(i) (ms)	154.9±14.3	152.3±17.3
MT(c) (ms)	186.7±15.4	186.9±13.9
MT(i) (ms)	192.6±15.1	190.2±10.2
Cingulate (ms)	192.7±16.1	198.1±14.2

Table 1. The source latencies and strengths of each component in the awake state. * $P < 0.05$, ** $P < 0.01$ compared with Control (Fisher' s PLSD procedure).

between Attention and Control (Table 1). The activities in the contralateral SI, bilateral insula, ipsilateral SII and MT, and cingulate cortex were significantly enhanced in Attention as compared with

Control ($p < 0.05$), whereas the change of the contralateral SII did not reach the significant level ($p = 0.12$) (Table 1).

Discussion

Multiple cortical regions including the SI, SII, insula, MT and cingulate cortex were activated by noxious stimuli. All these activities were clearly modulated by the subjects' attentional and arousal levels, suggesting that they are involved in nociceptive recognition.

Noxious stimuli applied to the skin activate cutaneous-nociceptors. The signals are conveyed through peripheral nociceptive afferents and the spinothalamic tract to reach the thalamus and then cerebral cortices. During sleep, a subject does not feel any pain after receiving the noxious stimuli, indicating the nociceptive pulses may be blocked at certain points along the neural pathway. Our results showed that all cortical activations were significantly reduced during sleep. Bushnell et al [10] reported that nociceptive neurons in the medial thalamus were modulated by changes in attentional state, suggesting that changes to cortical activities during sleep or attentional tasks are due to changes in thalamic activities. This hypothesis can explain our results that all activities of the SI, SII, insula, cingulate cortex and MT were decreased during sleep at least in part. In conclusion, the main component 1M as well as later magnetic fields were markedly attenuated during sleep, suggesting that all these cortical areas are involved in pain cognition.

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