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The relationship between mismatch negativity and arousal level. Can mismatch negativity be an index for evaluating the arousal level in infants?

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Abstract

Background: Electrophysiological and behavioral studies have shown that stimulus relevance contributes to auditory processing in sleep and auditory stimuli changes the sleep stages. So we observed changes in auditory processing due to sleep stages by recording infant mismatch negativity (MMN) during different states and investigated the arousal mechanisms.

Methods: Auditory event-related potentials (ERPs) of 26 neonates were recorded using high-density EGI EEG system. Stimuli consisted of 1000 Hz tones with 90% probability as standard and 1200 Hz with 10% probability as deviant. Study 1 was designed for the confirmation of the recording of MMN from neonates and Study 2 for investigating whether an appropriate stimulus onset asynchrony (SOA) of the stimulus would induce a clear difference in the latency or amplitude.

Results: (Study 1) MMN were obtained from all subjects. No differences of the latencies, amplitudes and distribution due to arousal or sleep stage were observed. After the MMN response occurred, a prominent negativity like Nc was seen in response to deviant stimuli in active sleep and waking state. (Study 2) No distinct differences between the difference states were seen in any SOA.

Conclusions: Only MMN did not characterize the arousal or sleep stage. But the modality of the auditory evoked potentials (AEPs) may differ according to the state, so further detailed investigation could enable the detection of the infants' state using the AEP.

Keywords: Auditory event related potential; Mismatch negativity; High density electroencephalographic system; Active and quiet sleep; Neonates

1. Introduction

Auditory evoked potential techniques have been used to investigate selective information processing during sleep. Arousal level has modality-specific effects on evoked potential (EP) amplitude. For example, EP amplitude to suprathreshold photic stimuli increases during sleep [1], while early somatosensory EP amplitude decreases form wakening to Stage II sleep [2]. Brain stem auditory evoked potential (AEP) components and the mid-latency Pa and Nb are unaffected by sleep [3].

There have been many reports on the effects of sleep and arousal level on AEP, and data from electrophysiological and behavioral studies have shown that stimulus relevance contributes to auditory processing in sleep; arousal to target sounds occurs more frequently than arousal to a variety of other familiar and unfamiliar sounds [4]. For example, subjects generate more K-complexes in response to their own names than to other names or nonsense syllables. This effect decreases in deeper sleep [5].

Based on these findings, we observed changes in auditory automatic processing during arousal and different sleep stages. Mismatch negativity (MMN) is an index of auditory automatic processing and is a kind of event-related potential (ERP) that is recorded as a negative displacement of ERPs to deviant sounds compared to those of standard sounds [6]. In short, MMN is a response to stimulus change and can be considered an outcome of a comparison process between a new deviant stimulus and a memory trace formed by the standard stimulus in the auditory system. All these MMN can be elicited in the absence of attention, i.e. when no task performance is required, which is suitable for recording young infants. The independence of MMN elicitation from attention is also indicated by results showing that MMN can be elicited in coma patients when consciousness disturbance will recur within a few days [7].

Research about MMN in infants and children containing the maturational change have already been reported [8]. These findings suggest that MMN is developmentally

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quite stable in terms of both latency and amplitude. The characteristics of the infants' MMN are as follows: latency and amplitude tend to be somewhat longer than in adulthood with a larger overall area of the MMN (peak to offset). And the MMN scalp distribution differs between adults and children. (In infants, a prominent MMN can be obtained not only over the frontal and central but also over parieta areas.) Moreover, unlike adults, MMN can be obtained from awake and sleeping infants [9].

We recorded infant MMN during different arousal and sleep stages by using the Geodesic Sensor Net which has 128 electrodes and by which it is possible to obtain detailed spatial distribution of the ERP. By these recoding, we investigated the arousal mechanisms or brain response against the auditory stimuli by detailed analysis of MMN during different arousal or sleep stages.

We planned two studies whose protocols were approved by the Ethics Committee of Tokyo Women's Medical University. Signed informed consent was obtained from the parents.

2. Study 1: MMN recording of neonates during different arousal and sleep stages

2.1. Purpose

The purpose of this study is to first confirm MMN and measure the latencies and amplitudes from the neonates. The second aim of this study is to identify differences in MMN modalities between stages.

2.2. Subjects

Auditory ERPs of eight healthy full-term neonates (five neonates of conceptional age 37–41 weeks were recorded on the 4–6th day after birth and 17 premature low-risk babies were recorded on the 30th day after birth (conceptional age 40–42 weeks). These neonates were 12 males and 13 females.

2.3. Apparatus

The neonates were laid supine in infant beds in an electric and sound-shielded room. The state of the neonates was monitored by two video cameras. One of these cameras monitored the whole body of the neonate, while the other monitored only the face. A Geodesic Sensor Net comprising 128 electrodes evenly distributed across the scalp measured the brain electrical activity of the neonates. The electrodes were connected to an EGI Net Amps amplifier through a head box located on an arm above the neonate's head.

2.4. Stimuli

Stimuli were presented in blocks of 500 tones. A stimulus block was considered acceptable for analysis if the infant remained in the same state during the majority of its duration. That is, at least 300 out of 500 stimuli had to be spent in the same sleep or waking state. Quiet sleep was classified as closed eyes, absence of rapid eye movements, behavioral quiescence, and regularity of physiological activity with electroencephalogram (EEG) showing high-voltage slow or trace alternant. Active sleep was classified as closed eyes, behavioral activity such as facial or limb movements, rapid eye movement, and low-voltage irregular or mixed pattern EEG. Open eyes characterized the waking state. Block stimulus onset asynchrony (SOA) was 1000 ms and one block consisted of a 1000 Hz standard (probability 90%) and 1200 Hz deviant (probability 10%). Stimulus duration was 100 ms with 10 ms rise and fall time, and intensity at the subject's earphones was 75 db (SPL). During measurement, stimulus was given through the earphones.

2.5. EEG recordings and analysis

Brain electrical activity was measured simultaneously at 128 locations that included electrodes at the outer canthi of the two eyes. The reference electrode was at the vertex (Cz in the international 10/20 system). The electrical potential was amplified with 0.1–40 Hz bandpass, digitized at 250 Hz sampling rate and stored on computer disk for off-line analysis.

EEG epochs used in ERP averaging were 1000 ms in duration and began 200 ms before each stimulus onset. Epochs contaminated by extracerebral artifacts (caused by eye movements, muscle activity etc.) exceeding 150 μV in any channel were automatically omitted from averaging.

Individual ERPs and difference waves obtained by subtracting ERPs to standard stimuli from those to deviant stimuli were separately calculated for each state. The latencies of the largest negative and positive peaks were measured 150–450 ms from stimulus onset from the individual difference waves at C4. This electrode was chosen because in the data from this site, MMN was approximately the same size in each state. The amplitude of these peaks was calculated at F3, C4, and P4 from the mean difference-wave amplitude during the 50 ms time window centered at the individual peak latency. These electrodes were chosen because, like in adults, the MMN amplitude to tone frequency change was slightly larger over the right than over the left hemisphere as in previous infant studies.

2.6. Results

Recordings during the waking state were obtained from seven neonates; the recordings during quiet and active sleep were from 14 and four neonates, respectively. MMN were obtained from all subjects. The distribution of MMN was mainly the frontocentral area with some parietal MMN and no distributional differences were seen due to arousal or sleep stage.

The mean latencies at C4 were as follows: waking state, 210 ± 24 ms; quiet sleep, 225 ± 26 ms; active sleep, 215 ± 20 ms. There was no significant difference between stages. The amplitude, at F3, C4, P4, was 2.0 ± 0.8 μV, showing no significant difference between each state.

After the MMN response occurred, a prominent negativity like Nc or late discriminative negativity (peak 650 ms) was seen in response to deviant stimuli in active sleep and waking state (active sleep 2/4, waking state 4/7).

3. Study 2: effect of SOA on the MMN and the difference of the appearance of the MMN during the arousal and sleep stage

3.1. Purpose

The purpose of Study 2 is investigate whether an appropriate SOA of the stimulus would induce a clear difference in the latency or amplitude of MMN.

3.2. Subjects

Subjects were six full-term neonates, comprising three males and three females.

3.3. Method

Apparatus, and EEG recording and analysis were the same as Study 1.

3.4. Stimuli

Stimuli were presented in blocks of 500 tones (same as Study 1) and in the different blocks, the SOA was either 450, 1000 or 1500 ms. With each SOA, three to four stimulus blocks, i.e., 9–12 blocks were presented. The formation of each block was the same as Study 1 (i.e. standard 1000 Hz probability 90%, deviant 1200 Hz probability 10%).

To ensure that the difference between responses to standard and deviant stimuli was caused by stimulus change, rather than just by the infrequency of the deviant stimuli, deviant stimuli were presented alone, without an intervening standard, to three subjects. All infants were in active sleep and inter-deviant intervals were similar to those in the 1000 ms SOA condition of the main experiment.

3.5. Results

With all SOAs, standard stimuli elicited low-amplitude positive waves in all sleep and waking states and there were no distinct differences between the difference states.

In all states, deviant tones elicited a prominent negative wave only with the SOA of 1000 ms. The MMNs were observed at around 180 ms and peaked at 230 ms from the stimulus onset.

When stimulus was presented with the 500 and 1500 ms SOAs, no significant negativity in response to the deviant was elicited in any state.

4. Discussion

MMN is currently the only valid objective measure of the accuracy of central auditory processing in the human brain. Electrical brain response, a negative component of the ERP elicited by any distrainable change ('deviant') in some repetitive aspect of auditory stimulation ('standard'), usually peaked at 100–200 ms from change onset. These seem to be stable developmentally.

Auditory stimulus is well known as the arousal stimulus causing K complex in EEG, so it is interesting to investigate the relationship between the appearance and the characteristics of MMN and the arousal or sleeping stage. However, there have been few reports in this area [10,11]. We investigated the relationship between arousal or sleep stage and MMN. A previous study in adults [12] demonstrated the dramatic attenuation of MMN amplitudes in sleeping subjects. However, in infants in this study, though there was a tendency of attenuation of the MMN amplitude in quiet sleep, it was not so prominent. Prolonged SOA of the auditory stimuli poses difficulties for the comparison of neonate's state.

We predicted by the prolongation of SOA a significant difference in the appearance of MMN between awake and sleep had occurred. But the results showed that MMN was irrelevant to the state. These results were almost consistent with Cheour's Report [13] and imply that the time span of auditory memory is considerably shorter in neonates than in adults. Though the arousal or sleep stages seem to have some influence on automatic auditory processing, the modality of the appearance of MMN did not change through the infants' state. Nc, which is a sign of enhanced auditory or visual attention to surprising or interesting stimuli, were observed in active sleep and waking state. So the appearance of Nc may relate to consciousness. MMN was not found to be an index of the arousal or sleeping state but more detailed observation of auditory ERP could reveal clues to detection of the state change.

5. Conclusion

The appearance or the modality of MMN did not characterize the arousal or sleep stage. But the modality of the auditory event related potential like Nc may differ according to the state, so further detailed investigation of auditory ERP could enable recoding of auditory ERP to detect the infants' state.

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