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Spectral characteristics of the newborn rhesus macaque EEG reflect functional cortical activity

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ABSTRACT

Brain electrical activity is one means of assessing neural development in awake, reactive infants. The development of the electroencephalogram (EEG) in the first week of infant rhesus macaque life is poorly understood though recent work has demonstrated the utility of using this measure to assess neural responses to biologically meaningful stimuli. Here we report on the emergence of EEG rhythms in one-week-old infant rhesus macaques under both light and dark conditions. Our data show that the 5–7 Hz frequency band responds reliably to changes in illumination. As well, we found EEG in higher frequencies (12–20 Hz) that significantly increase between dark and light conditions similar to the increase in the beta band of humans during cognitive tasks. These findings demonstrate similarities between infant human and infant monkey EEG and suggest approaches for future translational research in developmental psychobiology.

1. Introduction

Rhesus macaques have been an invaluable model for understanding the development of human cognitive and social behaviors and there has been increased interest in comprehending such changes in relation to the maturation of the non-human primate brain [1]. Evidence from a recent imagining study of typically developing rhesus macaques from birth through 4 years of age has shown remarkable similarities to the order and timing of human brain maturation [2]. While MRI provides important structural information, requiring the sedation of the animals, it precludes its application for understanding functional neural activity. The electroencephalogram (EEG) has been a powerful tool for understanding functional neural development in humans [3] and has significant promise for use in non-human primates.

Prior reports on the characteristics and development of the electroencephalogram (EEG) in rhesus macaques suggested remarkable similarities with the patterns of EEG in humans. In both human and rhesus adults, the dominant frequency in the EEG is around 10 Hz and typically ranges from between 8 and 12 Hz [4–7]. Moreover, humans and rhesus macaques share similar developmental trajectories, with the dominant frequency beginning around 4 Hz in infancy and increasing to 10 Hz in adults [8–12]. These early studies in human infants referred to this slow frequency activity in the EEG as "alpha" because of its resemblance to the classic adult alpha. However, in humans, the presence of a dominant "alpha" frequency has not been identified at birth, and some studies suggest that it only begins to emerge around 3 months of age [4,5,13].

EEG oscillations in the first week of life have been investigated in infant rhesus macaques. In the first developmental study of EEG in rhesus macaques, Kennard and Nims [11] measured EEG over the first 2 years, starting in the first week of life. During all of the testing sessions the infants were swaddled and their eyes were bandaged shut. Recordings were made once the infant had calmed after a period of struggling. They noted that in the first week the dominant frequencies in the EEG were slow wave activity ranging from 3 to 5 Hz, that those frequencies steadily increased over the first year, and that there was almost no activity in higher frequencies.

In contrast to the findings of Kennard and Nims [11], Robert de Ramirez de Arellano [12] measured rhesus macaque EEG activity from birth to 2.5 years. She noted that in the first week of life the EEG of awake infants was characterized by activity in the 5 to 10 Hz range superimposed on irregular slow waves ranging in the 1 to 3 Hz band. The methods used were nearly identical to those of Kennard and Nims [11]: infants were restrained in a chair and blindfolded, but in contrast to the previous study, the state of each monkey was noted during recordings. When the infants became drowsy during EEG acquisition, an increase in the amplitude of the 2 to 3 Hz band was observed [12]. This finding may partially explain why the dominant activity described by Kennard and Nims [11] was lower than the frequencies previously reported.

The two studies discussed above are the extent of the literature examining EEG in the first week of life in rhesus macaques. The descriptive nature of these studies and the lack of methodological information

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limit the interpretation of the findings and the potential comparison with human developmental studies. Furthermore, during data acquisition in both of these studies, the eyes of the monkeys were blindfolded, and there was no examination of the EEG while the infants sat quietly with their eyes open. In human infants in the second half of the first year of life and in children, the “eyes closed” condition causes an enhancement in the amplitude of the EEG frequency band thought to reflect alpha that is suppressed when the eyes are opened [4,14]. More recently, Stroganova, Orekhova, and Posikera [15] found in human infants that the enhancement of this frequency band could be achieved by placing infants in complete darkness. They examined the EEG of 8- and 11-month-old infants under light and dark conditions and showed a significant enhancement in the 5 to 7 Hz band for 8-month-olds and 6 to 8 Hz band in 11-month-olds. This effect was maximal over the occipital electrodes but was observed over parietal and precentral (FC3 and FC4) scalp locations as well. Marshall, Bar-Haim, and Fox [3] extended these results to 5-month-old infants. They found that the peak frequency in these young infants ranged from 4 to 7 Hz and could be identified across the scalp.

We recently examined the EEG activity of one-week-old infant rhesus macaques while observing biologically meaningful visual stimuli [16]. We identified activity in the 5 to 6 Hz band in the anterior electrodes that responded similarly to visual stimulation of facial gestures that were presented in front of the infant monkeys. The results of this study suggested that in newborn monkeys the sensorimotor mu rhythm is present at birth and within the range of the rhythms described by Robert de Ramirez de Arellano [12].

The goal of this study was to fill in the gaps in our understanding of the EEG during the first week of life in infant rhesus macaques. Due to the fact that previous research on EEG in monkeys relied on visual examination without relating it to changes in the infant's state or environment [6,11,12], it was unclear under what conditions changes in EEG frequencies would be present in the first stages of postnatal development. Recent studies using computational methods to quantify EEG have suggested that there is functional EEG activity in frequencies around 5 to 6 Hz and investigated the responsiveness of this frequency band by examining the EEG under conditions of both light and darkness.

2. Methods

2.1. Subjects

Subjects were 39 infant rhesus macaques who were involved in ongoing experimental protocols that required separating the infants from their mother on day 1 post-partum. Ten infants were excluded from analyses due either to incomplete data ($N = 5$) or statistical outliers ($N = 5$). Of the remaining 29 infants, 7 provided data on all 4 testing days, 13 from 3 testing days, 8 from 2 testing days, and only 1 provided data from 1 testing day.

Animals were housed individually in plastic cages ($51 \times 38 \times 43$ cm) that contain an inanimate “surrogate mother,” made of a polypropylene cylinder wrapped in a heating-pad and covered with fleece fabric. The incubator was maintained at a temperature of ~27 °C and at 50%–55% humidity. Lights were on from 07:00 to 21:00. Infants could see and hear, but not physically contact, other infants. All animals were provided with a 50:50 mixture of Similac (Ross Laboratories, Columbus, Ohio, United States) and Rimilac (Bio-Serv, Frenchtown, New Jersey, United States) formulas. They were hand-fed until they were old enough to feed independently, usually by day 4. Formula was administered ad libitum until 4 months of age.

2.2. Procedure

Subjects were tested on days 1–2, 3–4, 5–6, and 7–8 post-partum. During each testing period the infant was presented with three conditions of an imitation paradigm whilst EEG data were being collected (described by Ferrari et al. [16]) presented in random order. Following the imitation paradigm, 1 minute of EEG was collected while the lights were turned off. This “dark” condition was similar to the procedure described by Stroganova and colleagues [15]. The 40-second baseline period while the monkey was observing an inanimate object (a disk; for details see Ref. [16]) was used as a visual stimulation control condition. Video and EEG were recorded simultaneously while the infant had its eyes open. A video camera (Sony Digital Video Camcorder ZR600) was positioned 0.5 m behind the disk so that the infant's behavior could be easily identified. The start and end times of epochs where the infant was still and observing the disk were subsequently identified during behavioral analysis (frame-by-frame coding). These start and end times were then combined with the EEG analysis software and only epochs with artifact-free EEG were included in the analyses.

2.3. EEG acquisition and analysis

A custom lycra cap was made and fitted with 6 tin electrodes with their placement based on x-rays made of a typical infant rhesus macaques and a plaster mold of an infant skull. Two posterior electrodes were placed on scalp locations above the parietal–occipital lobes and two anterior electrodes over the frontal lobes (Fig. 1). The zenith served as reference, and an electrode placed above the forehead served as ground. Each infant's head was shaved and a mild abrading gel was applied to clean the scalp and improve impedances. Impedances were measured and kept below 20 kΩ. Prior to recording EEG, a 50 μV 10 Hz signal was collected for calibration purposes. EEG was band pass filtered (0.1 to 100 Hz), digitized with a 16bit A/D converter (± 5 V input range) and sampled at 1000 Hz. Signals exceeding $\pm$ 250 μV were removed. Epochs of clean EEG identified by the behavioral coding were submitted to a fast Fourier transform (FFT) using a 1 second Hanning window with 50% overlap, and spectral power (μV^2) was computed for single hertz bins from 2 to 20 Hz. All data processing was performed using EEG Analysis System software, James Long Company.

Preliminary analyses showed no effects of day on any of the spectral power values so, for each infant, spectral power was averaged in each single hertz bin across all available testing days. The distribution of EEG spectral power is generally skewed left [17,18], so the natural log of each single hertz bin was computed to better approximate a Gaussian distribution. We then computed the difference between dark and light conditions averaged across hemispheres. Fig. 2 presents the difference in power between light and dark in the anterior and posterior electrodes. Based on visual inspection of the most sensitive frequencies and the previous literature, we created five bands: 2–4 Hz, 5–7 Hz, 8–11 Hz, 12–16 Hz, and 17–20 Hz by taking the natural log of the summed power in each single-hertz bin.

For the analyses of the frequency bands, relative power was computed for each electrode by dividing the absolute power in each band by the total power and multiplying by 100. Relative power has been used in a number of developmental EEG studies and has shown to have the greatest sensitivity to frequency composition [3,18–20]. For the band analyses we employed a 2 Condition (dark vs. light) $\times$ 2 Region (anterior vs. posterior) $\times$ 2 Hemisphere (left vs. right) repeated measures ANOVA.

3. Results

3.1. 2–4 Hz

The results of the 2–4 Hz band analyses revealed a significant Condition $\times$ Region interaction ($F(1, 28) = 4.409$, $p = .045$). Post hoc analyses of the interaction revealed that there were no differences in relative power in the 2–4 Hz band between dark and light conditions in the posterior region ($t(27) = .254$, *ns*), but there was greater power in the dark compared to the light in the anterior region ($t(27) = 2.122$, $p = .043$).