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“On” and “Off” Magnetic Auditory Evoked Responses in Early Infancy:

A Possible Marker of Brain Immaturity

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Abstract

Objective—To follow the development of the auditory evoked on- and off-responses in early infancy.

Methods—The subjects were healthy infants, studied at conceptional age (CA) 39–66 weeks. Serial auditory evoked responses (AERs) were recorded in 17 subjects in response to tones of frequency 1.5 kHz and duration 1.0 s in order to follow the development of the AERs. Two small substudies were performed to examine off-responses evoked by tones of varying duration. The first used 0.2, 0.3, 0.4, and 0.5 s tones; the second used 0.5, 1.0, and 2.0 s tones.

Results—For the 1.0 s tones, the on- and off-responses consisted of three components: P250m, P400m, and N750m. The on- and off-responses had similar amplitude, in contrast to adult AERs in which the on-responses are typically much larger. Prior to about CA 47 weeks, the on-responses were actually smaller on average than the off-responses, and in infants born prior to CA 38 weeks the AERs were dominated by the off-response. Off-responses were seen for tones as brief as 0.2 s; however, the P400m component was often absent in the off-responses for tone durations ≤ 0.5 s. An interaction was observed in which the N750m-On component was strongly suppressed when it overlapped the P250m-Off.

Conclusions—Off-responses are much more prominent in infant than in adult AERs, especially in pre-term infants and at early CAs. On- and off-responses also exhibit more complex behavior in infants than in adult; the individual components can interact and behave independently.

Significance—Measurement of auditory off-responses can improve the assessment of infant neurodevelopment, potentially providing a marker of brain immaturity.

Keywords

neonatal auditory evoked responses; off-responses; infant MEG

INTRODUCTION

The surface electric potentials and magnetic fields evoked by abrupt cessation of auditory stimulation (off-responses) are remarkably similar to those evoked by abrupt onset (on-

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responses). While the auditory evoked response (AER) literature is vast, the number of papers devoted to the off-response is exceedingly small.

Off-responses in the auditory evoked potential were demonstrated by Onishi and Davis in 1968 (Onishi and Davis 1968). Many of the EEG off-response studies in the literature were performed in the 1970s and focused on the question of whether or not on- and off-responses are physiologically independent. This was investigated by hypothesizing that if the responses were independent then the aggregate AER would be comprised of a simple superposition of the on- and off-responses. Although there is some data suggesting that they are independent (Johannsen et al. 1972), it is generally believed that they are not. The study of Hillyard and Picton (Hillyard and Picton 1978), for example, demonstrated convincing evidence of interactions between on- and off-responses, especially when they were separated by intervals of less than about 5 s. This finding supports the belief that on- and off-responses are manifestations of a common process that registers abrupt changes in the acoustic environment. A more thorough account of this topic is provided by Pantev and coworkers (1996).

Off-responses were subsequently studied with MEG. A primary aim of these investigations was to determine whether the on- and off-responses arose from the same location. Two studies found that the source locations did not differ significantly (Hari et al. 1987; Pantev et al. 1996) and a third study (Noda et al. 1998) found a small, but statistically significant, difference. The similar source locations of the on- and off-response were thought to be compatible with the view that the responses arise from closely related systems.

A third important line of investigation has been animal studies. Again, it is notable that there are far fewer studies of auditory off-neurons than on-neurons, perhaps because the proportion of off-neurons is much less in the auditory than in the visual system. While the significance of the cortical off-evoked response is not well understood, more recent animal studies provide evidence that off-neurons may facilitate specific functions. Toronchuk and co-workers (Toronchuk et al. 1992) suggest that on-neurons are important in detection of sound source movement, and Kuwada and Batra (Kuwada and Batra 1999) speculate that off-neurons in the superior olivary complex enable more precise temporal encoding of the envelope of a sound stimulus.

Lastly, we note that cortical off-responses can be recorded for other sensory modalities. They are seen in visual evoked responses (Crevits et al. 1982) and recently have been reported in somatosensory evoked responses (Spackman et al. 2006).

In this paper we investigate a new aspect of off-responses. The human studies cited above were all performed in adults; developmental aspects of off-responses have not been documented despite the fact that there is growing literature in fetal and neonatal MEG (Eswaran et al. 2002; Pihko et al. 2004), especially for the study of auditory evoked responses (Huutilainen et al. 2003; Lengle et al. 2001). In this paper we report on distinctly different behavior exhibited by on- and off-responses in neonates.

METHODS

The protocol was approved by our institutional human subjects committee and informed consent on behalf of the subjects was obtained from one or both of their parents.

The subjects were healthy neonates, born at conceptional age (CA) 35-42 weeks. They began participation in the study as soon as the mothers felt comfortable bringing them in for the study, and they returned for follow-up sessions at least once every four weeks up to age 6 months. To minimize movement artifact, the recordings were made during sleep. Each mother was asked to bring her baby after he/she was awake and fasting for several hours. Upon arriving in

the lab, she would feed her baby and the recordings commenced when he/she fell asleep. Subjects were eliminated from the study if during two consecutive sessions they did not sleep for at least 30 minutes.

The recordings were made in a magnetically-shielded room with a floor-standing 37-channel sensor (Magnes, 4D Neuroimaging, Inc.). The subject laid on his/her side with the head resting directly on the sensor, which was centered approximately below the auditory cortex of the right hemisphere. The MEG signals and a stimulus-trigger channel were band-limited using a 0.1-200 Hz analog filter and were digitized at 520.8 Hz. The baby's activity was visually monitored with a video camera that allowed us to observe the baby's face and to monitor upper body and upper limb movements.

In the main study, serial recordings were taken from 17 subjects over 95 sessions at CA 39-66 weeks (Table 1) in order to follow the development of the on- and off-responses. The stimuli consisted of tone bursts of frequency 1.5 kHz, intensity 70 dB SPL, and duration 1.0 s with 10 ms rise and fall times. The sound was generated by piezoelectric speakers placed just outside a small opening in the shielded room, approximately 2 m from the subject, and was delivered by air. The interstimulus interval (ISI) was pseudo-random with range 2.0-4.0 s and mean 3.0 s; 200-400 trials were recorded in each run. Probe position was recorded in 6 subjects in 11 sessions so that dipole fitting could be performed, but MR images were not obtained. A head-based coordinate system was defined as follows. The y-axis passed through the preauricular points with positive y in the left hemisphere, the x-axis passed through the nasion, perpendicular to the y-axis, and the z-axis was perpendicular to the x- and y-axes, forming a right-handed coordinate system.

A digital filter was applied to further band-limit the signals to 0.3-20 Hz. After performing artifact rejection, averaged on- and off-responses were computed for the entire run and for each sleep pattern. As in prior investigations (Lutter et al. 2006; Lutter et al. 2004), we found that the influence of MEG sleep pattern on the neonatal AER was small at CA < 48 weeks and was modest at greater CA. In some subjects, the off-responses were larger in the high-amplitude, slow (delta wave) sleep pattern than in the other patterns, but the differences were not significant when averaged across subjects. Thus, the AERs presented below were obtained by averaging over the entire recording, without regard to sleep pattern.

To assess developmental changes, the amplitudes and latencies of the AER components were measured and plotted as a function of CA. Linear regression was used to ascertain developmental trends, applying a zero-slope null hypothesis test.

Least square dipole fitting using a local sphere head model was performed over a 50 ms time interval, centered on the peak of the P250m component of the on-response and the off-response. The source location was taken to be the location of the dipole with the highest goodness-of-fit. The "on" and "off" dipole locations were compared using a two-tailed paired t-test.

Off-responses evoked by tones of varying duration were examined in two substudies involving a smaller number of subjects, most participating in one or two sessions. In the first substudy, AERs were recorded from 7 subjects, one of whom participated in the main study, at CA 40-52 weeks using brief tones durations—0.2, 0.3, 0.4, and 0.5 s—in order to determine the minimum tone duration required to elicit an off-response. The tones were presented 50 times each in pseudo-random sequence with pseudo-random ISI 1.5-3.0 s and mean 2.25 s. In the second substudy, AERs were recorded from 6 subjects, 4 of whom participated in the main study, at CA 40-46 weeks, using tone durations 0.5, 1.0 and 2.0 s, presented 100 times each in pseudo-random sequence. The time of stimulus presentation was varied to produce a pseudorandom 1.0-2.0 s interval from the end of one tone to the beginning of the next. This was done to shorten the ISI after the briefer tones in order to reduce the duration of the run.

RESULTS

AER Morphology

For the 1.0 s tones, the on- and the off-responses consisted of a 250 ms deflection associated with surface positivity, followed by a diffuse deflection of opposite polarity and nominal latency 750 ms (N750m; Fig. 1). Typically the 250 ms on-response deflection was broad and was comprised of two strongly overlapping components, one with nominal latency 250 ms (P250m) and a weaker, more variable component with nominal latency 400 ms (P400m), similar to AERs we have previously recorded at < CA 48 weeks, using 100 ms tones (Lutter et al. 2006).

Development of AER Amplitude and Latency

The development of the AERs obtained using 1.0 sec tones is summarized in Fig. 2, which shows scatter-plots of the amplitude and the latency vs. CA of the main AER components: P250m-On, N750m-On, P250m-Off, and N750m-Off. Data quality and quantity was limited by movement artifact, low signal amplitude, and the amount of time the babies slept. We discarded recordings in which the signal-to noise ratio was <1.5; the noise was computed in a 0.5 s prestimulus interval and was averaged across channels. Over 95 sessions, the number of amplitude and latency measurements that could be obtained was as follows: 50 (53%) for P250m-On, 47 (49%) for N750m-On, 62 (65%) for P250m-Off, and 47 (49%) for N750m-Off. The mean signal-to-noise ratios were 6.5 for P250m-On, 4.3 for N750m-On, 6.0 for P250m-Off, and 3.7 for N750m-Off.

An unexpected finding was that the on- and off-responses were similar in amplitude, in contrast to adult AERs in which the on-responses are typically much larger. Prior to about CA 47 weeks, the on-responses were actually smaller on average than the off-responses. This is exemplified in Fig. 1, which shows serial recordings from a full-term subject at CA 43-64 weeks. The foregoing results suggest that a low on-response-to-off-response ratio may be associated with brain immaturity. Further evidence for this suggestion comes from examination of data from infants born earlier than CA 38 weeks. Prior to 48 weeks, the AERs of these infants were dominated by the off-response (Fig. 3). An off-response was seen in all 8 sessions but an on-response was seen in only 4. In contrast, full-term infants showed similar detection rates for the off-response (19 of 20 sessions) and the on-response (17 of 20 sessions). After CA 48 weeks, the pre-term infants also showed similar amplitudes and detection rates for the on- and the off-response.

The P250m-On and N750m-On latencies clearly decreased with CA (Fig. 2). The off-response latencies showed similar, but weaker, trends that were statistically significant for the N750m, but not for the P250m. If the regression analysis was performed using only data for which both an on- and an off-response were obtained (45 sessions for P250m and 37 sessions for N750m), then neither of the off-response components showed statistically significant trends, whereas the on-response components still did. Although the AER amplitudes increased with CA, we did not perform linear regression on the amplitude data because the analysis was confounded by the substantial percentage of recordings discarded due to low signal-to-noise ratio.

Off-responses and Interactions at Short Tone Durations

For tone durations of several hundred ms or less, the presence of an off-response was often ambiguous due to overlap with the on-response. Detection of the P250m-Off, for example, was confounded by the presence of the P400m-On. Fig. 4, however, shows an example in which the on-response is narrow enough to allow resolution of off-responses. The P250m-Off is present for the 300 ms tone and seemingly even for the 200 ms tone.

Usually, the morphologies of the on- and off-responses were similar; however, an exception was noted in the substudy using 0.5, 1.0 and 2.0 s tones. The P400m-Off was evoked by the 1.0 and 2.0 s tones, but was not evoked by the 0.5 s tone in 5 of 7 sessions, all at CA<50 weeks. The absence of the P400m was conspicuous because it resulted in a narrow 250 ms off-response (Fig. 5), whereas for longer tones the on- and off-responses had similar widths or the on-responses were narrower, especially at later CAs. In addition, an interaction was seen between the N750m-On and the P250m-Off when they overlapped in time. Rather than superimposing, the N750m-On was virtually absent for the 0.5 s tone and was diminished for the 1.0 s tone, whereas the P250m-Off appeared to be unaffected (Fig. 5).

Source Locations

The source locations of the on- and off-responses were compatible with the auditory cortex. This was confirmed by overlaying the best-fit current-dipole location onto a scaled adult MR image (not shown). For the 1.0 s tones, the P250m-On equivalent current dipole had latency 261 ± 21 ms, goodness of fit 0.927 ± 0.04 , and location $x = 0.29 \pm 0.98$ cm, $y = -3.76 \pm 0.74$ cm, $z = 3.34 \pm 0.80$ cm. The P250m-Off equivalent current dipole had latency 1243 ± 17 ms, goodness of fit 0.933 ± 0.04 , and location $x = 0.19 \pm 0.75$ cm, $y = -3.93 \pm 0.61$ cm, $z = 3.61 \pm 0.84$ cm. Only the z-shift (approximately superior) was statistically significant ($p = 0.034$).

DISCUSSION

The most important findings of this study are the evidence suggesting that a low on-response-to-off-response ratio is a marker of brain immaturity. Several data support this suggestion. First, the on-response-to-off-response ratio seen here in neonates was much smaller than that seen typically in adults. The ratio in neonates was on the order of unity, whereas in adults it is typically three or more (Hillyard and Picton 1978; Pantev et al. 1996). Second, the on-response-to-off-response ratio was smallest at the earliest CAs and increased with CA. Third, in sessions prior to CA 48 weeks, the AERs of the subjects born prior to 38 weeks were dominated by the off-response, often showing little or no on-response, whereas the AERs of the term infants did not exhibit this disparity. These findings are unexpected based on single unit recording data in adult animals. In adult cats, for example, neurons producing on-responses are much more numerous and have a higher firing rate and a lower threshold than neurons producing the off-response (Abeles and Goldstein 1972). Apparently, neurons in the human infant brain show different behavior; however, our data cannot elucidate the specific causes. A practical implication of this study is that neurodevelopmental auditory investigations can benefit from the use of protocols that allow for recording of off-responses as well as on-responses. Measurement of off-responses can improve the AER detection rate in early infancy, when the signal amplitude of the on-response is quite low. More importantly, it has the potential to provide a simple marker of brain immaturity, which would be extremely useful for neurodevelopmental evaluations. There is no evidence, however, to suggest that a low on-response-to-off-response ratio reflects pathological brain immaturity.

In a prior study using 100 ms, 1.5 kHz tones, we found that the morphology of infant AERs showed little change until around CA 48 weeks and evolved rapidly after this time. In this study, we found that for infants born earlier than CA 38 weeks the on-responses were small or completely absent prior to CA 48 weeks, but were similar thereafter. These results suggest that CA 48 weeks marks the onset of a period of rapid development of audition for both full-term and pre-term infants.

A second notable finding of this study was that infant on- and off-responses can exhibit complex behaviors that generally are not present in adult AERs. These relate to several effects involving specific components of the infant AERs. The first concerns the P400m-Off component. Although the P250m off-response was observed for tone durations as brief as a few hundred

ms, the P400m off-response appeared to be refractory for tone durations less than about 0.5 s. This corroborates that the P400m, which is often obscured due to overlap with the dominant P250m, is a distinct component of the AER. In a prior study (Lutter et al. 2006) we identified the P400m as a distinct component based on its spatiotemporal characteristics. The second effect demonstrates an interaction of a different nature than those reported in adult studies. The N750m-On appeared to be suppressed by the P250m-Off when they overlapped in time. This suggests that the neural circuitry that generates these responses is shared and that the P250m-Off supersedes the N750m-On. Alternatively, the generators could be distinct, but the P250m-Off inhibits the N750m-On. In adults, it is well known that the P1 is present in the on-response but not the off-response (Hari et al. 1987;Pantev et al. 1996), but to our knowledge there have been no prior reports of interactions similar to those described here.

The off-responses also showed less developmental change than the on-responses, which exhibited a clear decrease in latency with CA. This is compatible with the expectation that the off-responses are a simpler, more automatic response, whereas the on-responses presumably manifest more complex processing dependent on the characteristics of the stimulus.

In this study we verified that infant AERs have source locations compatible with the auditory cortex, but we observed a small shift in the source location of the off-versus the on-response. In adults, Noda and coworkers (Noda et al. 1998) also reported a small source location shift; however, the off-response was anterior to the on-response, whereas we found that that it was superior. Recently, He (He 2001) showed that on-neuron clusters are segregated from off-neuron clusters in the auditory thalamus. It is therefore plausible that these neurons might project to distinct areas in the cortex.

Regarding the issue of physiological independence, the developmental differences and small shifts in the equivalent dipole locations of the on-response versus off-response imply that the underlying generators are physically and/or physiologically dissimilar. On the other hand, the strong interactions between specific on- and off-response components imply that they are not independent. These findings are compatible with the supposition that the on- and off-response generators are closely-connected and largely overlapping, though not identical.

Although the primary focus of this study was on developmental aspects, several inferences can be made regarding the dependence of infant AERs on tone duration: 1) As we found no evidence of off-responses in a prior study using 100 ms tones (Lutter et al. 2006), the observation here of off-responses for tone durations of 200-300 ms suggests that the minimum tone duration required to elicit an off-response is approximately 200 ms. 2) Whereas AERs evoked by 100 ms tones in our prior study exhibited marked developmental changes in morphology after about CA 48 weeks (Lutter et al. 2006), AERs evoked by 1.0 s tones in this study showed similar morphology throughout, dominated by the P250m and N750m. 3) The influence of tone duration on AER morphology can be complex due to interactions between AER components.

A limitation of this and most other neonatal MEG studies is the confounding factor of sleep state. Although we did not observe a significant sleep state dependence, it is likely that sleep state influences become more apparent with increasing CA, and might be observable in a larger study.

Lastly, we did not observe the auditory sustained field, implying that it is weak in early infancy. Whereas on- and off-responses are thought to register abrupt changes in the acoustic environment, it has been speculated that the sustained field relates to the encoding of new sensory information. This suggests that neonates exhibit relatively less brain activity associated with the latter. It should be noted, however, that our recordings were made with a 0.1 Hz high-pass filter, whereas ideally sustained fields are recorded without high-pass filtering. Also,

detection of the sustained field in neonates is made more difficult by the presence of AER components with long latencies, on the order of 1 s.

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Fig 1.

On- and off-response evoked by 1.0 s tones from the same subject at CA 43, 44.5, 46, 49, and 64 weeks. Tracings from all the channels have been superimposed; channels with a positive deflection at latency 250 ms are drawn in black and channels with a negative deflection are drawn in gray. The tone duration is indicated by the horizontal bar on the time scale of the bottom panel. A dashed vertical line is drawn approximately at the latency of the on-response; a decrease in latency with CA is evident. A second dashed vertical line is drawn shifted by an interval equal to the tone duration. The P400m is often indistinct and variable, as seen here. Notice that the off-responses are larger than the on-responses at the earliest CA, are about equal in amplitude at the intermediate CAs, and are smaller at later CA.

Fig 2.

Scatter plots of latency (left column) and amplitude (right column) of the main on- and off-response components, the P250m and N750m. Dashed lines are confidence intervals ($p=0.05$). Statistically significant correlations with CA are obtained for the latencies of the P250m-On ($p=0.00002$), N750m-On ($p=0.005$), and N750m-Off ($p=0.005$). A best-fit line is shown for the amplitude scatter plots, but linear regression was not performed.

Fig 3. Serial AERs taken from subjects 318, 381, and 292, born at CA 37.5, 35.5, and 35.5 weeks, respectively. Tracings from all the channels have been superimposed; channels with a positive deflection at latency 1250 ms are drawn in black and channels with a negative deflection are drawn in gray. The CA at the time of the recording session is indicated in each panel. Off-responses (coinciding with the dashed vertical lines) are present in all sessions, but on-responses (indicated by arrows) are present in only 4 sessions and generally are much smaller than the off-responses.

Fig 4. AERs evoked by 0.2, 0.3, 0.4, and 0.5 s tones from a subject at CA 46 weeks. Tracings from all the channels have been superimposed; channels with a positive deflection at latency 250 ms are drawn in black and channels with a negative deflection are drawn in gray. The tone duration is indicated by the horizontal bar at the bottom of each panel. A dashed vertical line is drawn at the approximate latency of the on-responses and a second line is drawn shifted by an interval equal to the tone duration to indicate the approximate latency of the off-response.

Substudy 2 (0.5, 1, and 2 s tone duration)

Fig 5.

On- and off-responses evoked by 0.5 (left column) and 1.0 s (right column) tones, taken from two different subjects at CA 41 weeks (top row) and 46 weeks (bottom row). Tracings from all the channels have been superimposed; channels with a positive deflection at latency 250 ms are drawn in black and channels with a negative deflection are drawn in gray. The tone duration is indicated by the horizontal bar at the bottom of each panel. For the 0.5 s tones, the 250 ms off-response consists of a single deflection (P250m-Off, slanted arrows). For the 1.0 s tones, the 250 ms off-response consists of two overlapping components due to the presence of the P400m-Off, as well as the P250m-Off (two downward-pointing arrows). In many subjects these components overlap strongly and appear as a single broad deflection. The N750m-Off is indicated by the upward-pointing arrows. Notice, however, that the N750m-On is not evident, except for the 1.0 s tone in the top row (thick arrow).

Table 1

Characteristics of subjects participating in the main study: subject number, number of sessions attended, number of sessions in which usable data were obtained, conceptional age at birth, and conceptional age range during participation in the study.

Subject	# Sessions	Used Sessions	CA at birth	CA Range
381	11	9	35.5	42.5-65.5
208	11	9	39	49.5-62
281	9	7	39.5	41.5-64
280	9	5	35.5	48.5-62
228	7	5	40.5	42.5-57
311	6	4	40.5	44-49
318	6	4	37.5	39.5-45
270	5	5	40.5	43.5-49.5
292	5	3	35.5	43-49
275	5	2	40	52.5-56.5
196	5	2	39	62-65.5
315	4	3	40	41-45
220	4	2	39	43-44
333	3	3	41.5	43.5-48.5
320	3	2	41	48-52
296	1	1	39	47.5
188	1	1	40	50