

Research report

Timing in the baby brain

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Abstract

Ten-month-old infants and adults were tested in an auditory oddball paradigm in which 50-ms tones were separated by 1500 ms (standard interval) and occasionally 500 ms (deviant interval). Both infants and adults showed marked brain responses to the tone that followed a deviant inter-stimulus interval (ISI). Specifically, the timing-deviance event-related-potential (ERP) difference waves (deviant-ISI ERP minus standard-ISI ERP) yielded a significant, fronto-centrally distributed, mismatch negativity (MMN) in the latency range of 120–240 ms post-stimulus for infants and 110–210 ms for adults. A robust, longer latency, deviance-related positivity was also obtained for infants (330–520 ms), with a much smaller and later deviance-related positivity observed for adults (585–705 ms). These results suggest that the 10-month-old infant brain has already developed some of the same mechanisms as adults for detecting deviations in the timing of stimulus events.

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1. Introduction

Adult humans, non-human animals, and even young children have a precise ability to time events in their environment. All three populations have been tested in a variety of behavioral timing paradigms, including temporal generalization (e.g., Refs. [9,10]), the peak procedure [2,26], and the bisection procedure (e.g., Ref. [5]), to assess their capacity for representing temporal aspects of stimuli in the environment. An important conclusion from this research has been that non-human animals, adult humans, and young children all show the characteristic known as the scalar property, whereby the variability (standard deviation) in the remembered interval increases proportionally to the mean value of the interval (e.g., see reviews for animals [15]; adult humans [16]; children [9]).

Much less is known about the timing capacities of the human infant. A few studies have shown that infants produce conditioned responses to arbitrary periodicities. For example, Ref. [12] found that infants exhibited conditioned anticipatory pupillary constriction and dilation in response to regular changes in lighting (20-s intervals). Rivière [25] presented 4-month-old infants with a tactile screen where touching produced reinforcing video-clips of a cartoon at six different fixed-interval reinforcement schedules (FI 10, 20, 30, 40, 60, and 80 s) and found that the time between the infants' responses was systematically determined by the reward delay imposed by the schedule. Pouthas et al. [24] also showed that newborns and 2-month-old infants can learn to time the pauses between non-nutritive sucks. Furthermore, infants as young as 2 months of age can accurately discriminate linguistic or nonlinguistic sounds that differ by only a few hundred milliseconds in duration (e.g., Refs. [11,17]).

Other studies suggest that infants' heart rate responses are temporally sensitive. Clifton [6] conditioned newborns with a conditioned stimulus (CS) followed after 2 s by an unconditioned stimulus (US). After 30 trials, the US was

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omitted and infants showed heart rate deceleration at the time the US should have appeared. Recently, Ref. [7] measured 4-month-old infants' heart rate responses to an on–off stimulus pattern with an inter-stimulus interval of 3 s for one group of infants and 5 s for another group. On the ninth trial, the off period was set at 15 s rather than 3 or 5 s so that infants' heart rate response to an omitted stimulus could be measured. Colombo and Richman found that infants' heart rate decelerated within 500 ms of the time at which the omitted stimulus should have appeared.

Event-related potentials (ERPs) may provide a useful window into different aspects of timing because they provide a temporally precise window into the neural activity underlying time processing (e.g., Penney, this volume). Furthermore, this method is particularly well suited to working with infants because recording event-related potentials from the scalp is non-invasive and does not require a motor response [22]. However, one sticky issue with ERPs recorded from infants is that many components observed in adults are not observed in infants or have a very different morphology in infancy, which makes it more difficult to determine the function of ERP components in infancy [23].

An exception to this general rule appears to be the mismatch negativity (MMN) obtained in auditory oddball paradigms. The MMN is a negative deflection in the difference wave obtained by subtracting the ERP response to a frequent standard auditory stimulus from the ERP response to an infrequent deviant auditory stimulus [20,21]. Unlike many other ERP components, the MMN appears to be developmentally conservative in that it can be obtained in newborns and has a similar time course as in adults [3,8]. Although it has been shown that the amplitude of the MMN can be affected by attention [29,30], the MMN can be elicited in the absence of attention and when no response is required [19,27], and thus it is particularly well suited to studying the representation of time in infants.

The current study employed an unattended auditory oddball design in an attempt to elicit an MMN in 10-month-old infants and adults to a deviation in the timing of sounds. Infants and adults heard a stream of tones that were typically separated by an ISI of around 1500 ms but were occasionally separated by an ISI near 500 ms (e.g., Ref. [13]). Both infants and adults exhibited an MMN to the deviation in the ISI providing evidence that the 10-month-old infant brain is sensitive to small differences in temporal intervals.

2. Materials and methods

2.1. Subjects

The subjects were 23 infants with a mean age of 10 months 10 days (range=9 months 17 days–11 months 13 days) and 12 adults with a mean age of 20 years (S.D.=2.7

years). Eleven of the infants and five of the adults were female. Data from five additional infants were discarded due to fussiness ($n=2$), premature removal of the cap ($n=1$), or excessive artifacts ($n=2$). All infants and adults were healthy with apparently normal vision and hearing.

2.2. Stimuli and procedure

The experiment was conducted in a sound-attenuated electrically shielded room in The Center for Cognitive Neuroscience at Duke University. Adult participants and parents of the infant participants gave written informed consent to a protocol approved by Duke University Institutional Review Board. Infants sat on the lap of a parent approximately 60 cm away from a puppet stage. One experimenter conducted a silent visual puppet show to entertain the baby and keep the baby as still as possible. Infants were tested until they were unable to sit calmly on their parent's lap any longer (average 19.3 min). Adults sat approximately 60 cm away from a flat screen computer monitor and engaged in a visual target detection task with visual stimuli that were timed randomly relative to the auditory stimuli. Adults were tested for 45 min. The speakers through which the sounds were presented were located approximately 120 cm from the infants' heads. Adults wore earphones. For infants, stimuli were 50 ms, pure 1000-Hz tones presented at approximately 60 dBSL. For 6 of the 12 adults, the stimuli were 650-Hz tones; for the remaining 6 subjects the stimuli were 1000 Hz, identical to that heard by infants.¹

For both age groups, most of the tones (“standards”) followed ISIs that were on average 1500 ms; however, the actual ISI was jittered randomly between 1450 and 1550 ms in order to reduce triggered alpha and to facilitate our use of the Adjar procedure to eliminate overlap (see below). Fourteen percent of the tones occurred at the deviant ISI, which was on average 500 ms after the previous tone (jittered randomly between 450 and 550 ms). Deviants ISIs were always preceded and followed by standard ISIs.

2.3. Adjar

The Adjar technique [28] was used to remove the overlapping neural activity from the previous standard-tone stimulus that was distorting the ERP to the shortened-ISI deviant tone. In particular, this previous-response overlap was estimated by convolving the standard-tone ERP waveform with the temporal distribution of the previous event occurrences for the deviant-ISI stimuli. The result of that convolution was then subtracted from the ERP responses to the deviant-ISI tones.

¹ The use of the 650-Hz tones with half of the adult subjects was inadvertent. However, there were no significant differences between the two samples of adults.

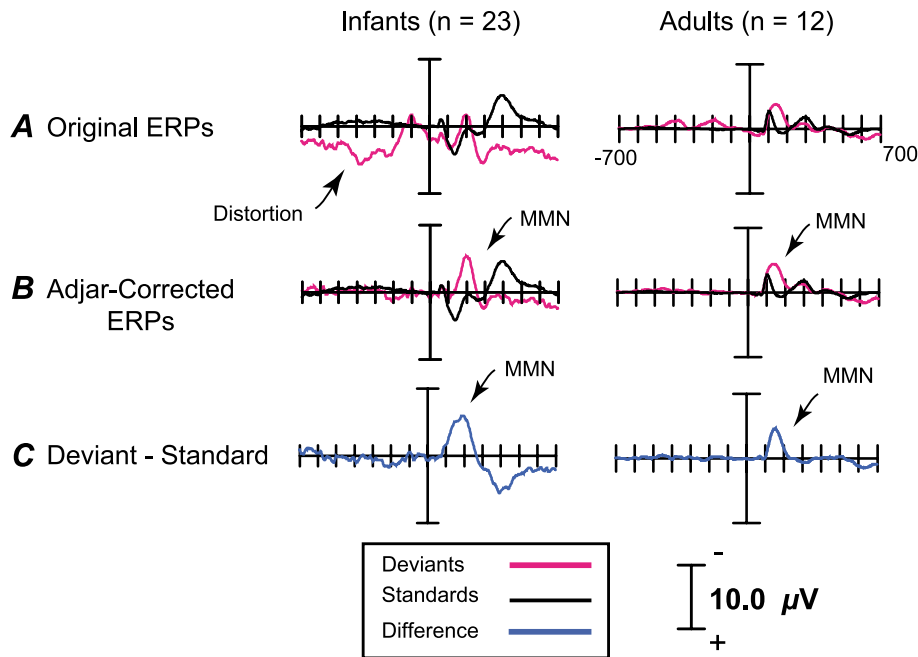


Fig. 1. Infants are plotted on the left and adults on the right. Data are from electrode Fz. Negative potentials are plotted upward. Each tick mark reflects 100 ms. (A) Responses to tones that followed the deviant (red) and standard (black) ISI for infants (left) and adults (right). Note the prestimulus distortion in the infant deviant waveform. (B) Deviant and Standard waveforms after Adjar correction. Note the relatively quiet prestimulus baseline. (C) Deviant-standard difference waveforms. The MMN is visible between 100 and 200 ms.

2.4. EEG/ERP acquisition and analysis methods

Brain electrical activity was recorded using tin electrodes placed according to the International 10–20 system using an elastic cap (Electrocap, Eaton, Ohio). Each infant also wore an elastic waistband, which was attached to the electrocap to help secure it in place. In addition, adhesive foam disks were used to secure the front of the electrocap on to the infant's forehead to help keep the cap in place. Nineteen channels were used for infants and 64 channels for adults. For the infants, one additional electrode was placed on the right cheek in order to help detect eye blinks and thereby aid in artifact rejection. For similar purposes, the 64-channels for the adults included four EOG electrodes below and lateral to the eyes. Impedances were maintained as low as possible, aiming for under 5 k Ω for adults and under 10 k Ω for infants. Simply filling each electrode with gel and eliminating air bubbles was generally sufficient to reduce impedance levels for infants, whereas some additional running was necessary with adults to get the gel to make a good connection with the scalp.

Recordings were referenced to the right mastoid during acquisition and later algebraically re-referenced to an average of the right and left mastoids. The EEG was amplified with a gain of 1000 for adults and 150 for infants; the gain was reduced for infants to accommodate the larger EEG compared with adults, presumably due to reduced resistance and thinner skulls for the infants. A recording bandpass of 0.05–100 Hz was used and the EEG was digitized continuously at a rate of 500 Hz/channel onto disk.

The recorded EEG was examined off-line (both visually and with computer algorithms) to reject those epochs with eye movements, blinks, motion, or other artifacts in any of the channels. After artifact rejection individual infants had an average of 86 deviant ISI trials (range = 35–137) and 534 standard ISI trials (range = 184–824), whereas adults had on average 190 deviant ISI trials (range = 117–266) and 1139 standard ISI trials (range = 622–1585). The data were selectively averaged for standards and deviants for each individual. Data were normalized using a standardization pulse of the system and filtered for activity at and above 60-Hz noise using a low-pass filter. EEG was high-pass filtered (>1 Hz) during averaging to remove low frequency noise and drift.

3. Results

The data for the adults tested with 650- and 1000-Hz tones were collapsed because an ANOVA comparing the difference waves for the two groups revealed no main effect ($F(1, 10) = 0.12, p > 0.5$). Fig. 1A shows the grand average ERPs for the standard and deviant ISI for lead Fz for both adults and infants. The Fz lead was chosen because the MMN was maximal at this site for adults and near maximal for infants,² consistent with previous reports that the MMN is

² In the infants, activity at site F3 located adjacent to Fz was of slightly higher amplitude than at Fz itself. However, it was judged more appropriate to use the same electrode site for infants and adults.

maximal at fronto-central sites [19]. The right side of Fig. 1A shows that, for adults, there is a clear enhanced negativity between 110 and 210 ms post-stimulus to the tone that occurred following a deviant ISI. In contrast, the left side of Fig. 1A shows that for infants the expected negativity to the deviant relative to the standard was not immediately apparent. However, examining the early part of the infant ERP, including before time zero, reveals that there was considerable distortion in the infant ERP from late-negative wave activity elicited by the previous standard that did not return to baseline within the 500 ms before the deviant occurred and therefore overlapped with the response to the deviant. Consequently, we used the Adjar technique [28] as described in Materials and methods to subtract out the overlapping response to the previous standard from the response to the deviant. Note that it was only necessary to apply the Adjar technique to the deviant waveform because there was no previous-response overlap for the tones that followed the standard ISI, which was considerably longer (1500 ms) and therefore allowed the neural activity to return to baseline. Fig. 1B shows the grand average ERPs after the Adjar technique was applied and illustrates that the baselines became fairly flat, reflecting the successful elimination of the overlap distortion. A negative deflection in the waveform to the deviant ISI is indeed clearly apparent in Fig. 1B for both infants and adults. Fig. 1C shows the corresponding ERP difference waveforms (deviant minus standard).

To determine the time window for which the standard and deviant waveforms differed significantly from each other, *t*-tests were conducted in 5-ms bins on the data (after the Adjar technique had removed the overlap distortion). The deviant and standard were statistically different between 120 and 240 ms for infants and 110 and 210 ms for adults, reflecting the MMN. In addition, there was a statistically significant difference between 330 and 520 ms post-stimulus in infants, and between 585 and 705 ms in adults reflecting a late deviance-related positivity.

Repeated-measures ANOVAs comparing the response to the standard-ISI and the deviant-ISI stimuli at the Fz electrode revealed a significant difference for infants between 120 and 240 ms ($F(1, 22) = 28.51, p < 0.0001$) and for adults between 120 and 210 ms ($F(1, 11) = 180.5, p < 0.0001$). Although Fig. 1 suggests that the MMN was larger for infants than for adults, this difference did not reach significance ($p > 0.5$). There were no significant laterality effects of the MMN.

Following the MMN, both infants and adults also exhibited a late anterior deviance-related positivity. Repeated-measures ANOVAs comparing the response to the standard-ISI and the deviant-ISI stimuli at the Fz electrode revealed a deviance-related positivity between 330 and 520 ms ($F(1, 22) = 18.97, p < 0.001$) in infants, and between 585 and 705 ms post-stimulus ($F(1, 11) = 14.66, p < 0.01$) in adults. When examining the waveforms elicited by the deviant and standard it can be seen that the deviance-related positivity in infants between 330 and 520 ms was apparently

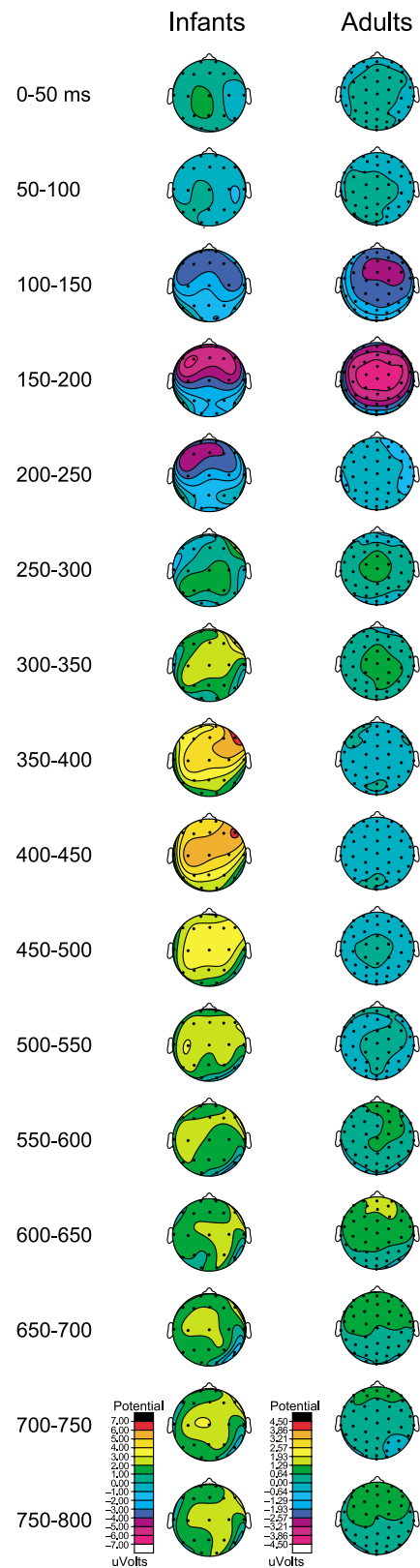


Fig. 2. Topographic distributions of the difference wave for infants and adults over 50-ms time periods. Note the difference in scale; -7.5 to $+7.5$ for infants and -4.5 to 4.5 for adults.

due to a large negativity for the standard and a correspondent positivity in the deviant waveform. In contrast, the deviance related positivity seen in adults was due to a small positivity in the deviant relative to the baseline and essentially no activity in the standard.

Fig. 2 shows topographic distributions of the difference waves for infants and adults over 50-ms time periods and allows a comparison of both the time scale and spatial distribution of the MMN and deviance-related positivity of the adults and infants. Fig. 3 provides a comparison of the time periods that showed a significant difference between standard and deviant waveforms and were therefore maximally sensitive to the timing deviation. The MMN in infants appeared to be slightly more prolonged and its distribution somewhat more anterior compared to the more fronto-central distribution in adults. In addition, the deviance-related positivity appeared more frontal in the adults than in the infants. However, it is entirely possible that the apparent differences in topographic distributions of brain activity in infants and adults was due to the large variability in infants' head shapes and sizes and the fit of the caps. In light of these considerations, and since the development of the precise spatial distribution of the MMN was not crucial to our question of whether the infant brain detects interval timing differences, we did not pursue these differences in topography with statistics.

Infants showed a slight right lateralization in the deviance-related positivity. A one-way repeated-measures ANOVA comparing the mean amplitude of the difference wave of electrodes F7 and F8 at 330–520 ms post-stimulus revealed a significant main effect of laterality ($F(1, 22) = 8.01, p < 0.01$).

4. Discussion

The present report shows that 10-month-old infants and adults show a similar brain response to a change in a temporal interval in a series of auditory tones. When a regular 1500-ms interval was replaced infrequently by a 500-ms interval, both infants and adults showed an early negative deflection (the MMN) and a later positivity in the ERP difference wave obtained by subtracting the brain's response to the tone that followed a standard interval from the brain's response to the tone that followed an infrequent deviant interval. However, there were some apparent differences in the timing, amplitude, and distribution of the MMN for infants and adults. The MMN started at approximately the same time in infants and adults but was statistically significant for about 30 ms longer in infants.

The MMN is thought to be generated by neural activity mainly in auditory cortex, with possibly some contribution from right frontal cortex [1,14]. This raises an interesting question as to whether the brain's response to temporal deviations reflects neural activity specific to timing in addition to the more general response to the detection of any auditory deviation. Presumably, neural networks specific to timing are recruited when infants and adults detect a temporal deviation. Future research could employ methods of source analyses to isolate the neural generators specific to temporal deviations and compare these to the generators implicated when infants or adults hear deviations in other dimensions such as pitch or amplitude.

We also found a deviance-related positivity in infants and adults; however it occurred much earlier for infants compared to adults (330–520 ms compared to 585–705 ms) and

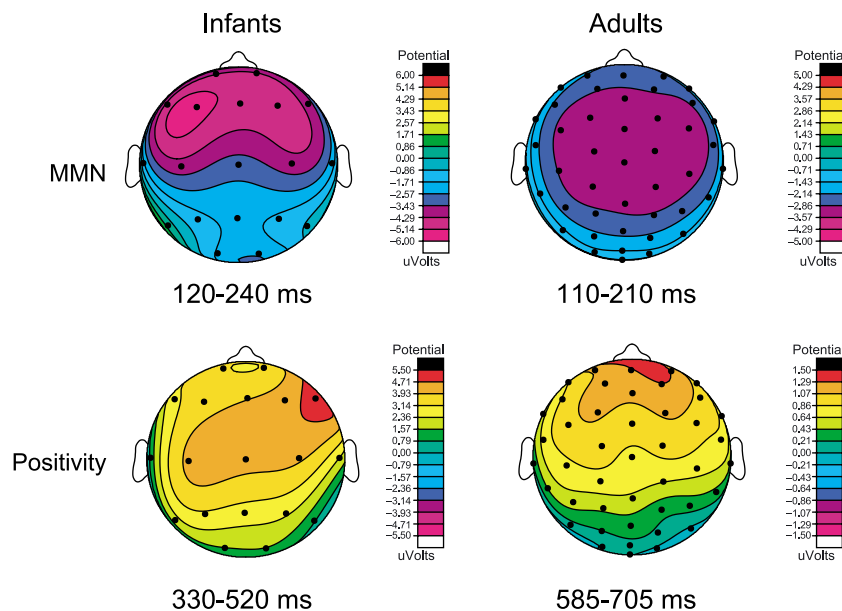


Fig. 3. A topographic distribution of the time-periods found to be maximally sensitive to the timing deviation. Note the differences in the amplitude scales between the four panels.

was of considerably greater amplitude for infants. The significance of the deviance-related positivity in infants and adults is unclear. Late components are generally thought to reflect more endogenous cognitive processing and may therefore indicate some awareness of the timing deviation. The deflection is fairly frontal and may therefore be related to the P3a, which is thought to occur when subjects detect changes in the environment (e.g., Ref. [18]). However, the observed deviance-related positivity in adults was small and late for a typical P3a. It is also unclear whether the late positivities observed in adults and infants are homologous. The large difference in the timing and the amplitude of the infant and adult deviance-related positivity may indicate that they reflect entirely different processes. For example, it is conceivable that the positivity observed in infants may have been due to increased refractoriness for the deviant response. More specifically, the large late negativity in the infant standard waveforms may have been reduced in their deviant waveforms due to the deviants occurring sooner after the previous stimulus and the response being more refractory. Alternatively, the visual target detection task used with adults may have produced a greater level of concentration than the puppet show performed for infants, and served to more thoroughly distract adults from the auditory stimuli. Since the MMN can be observed in sleeping infants [4], it would be of interest to test infants when sleeping and awake and determine whether the state of alertness alters the probability of obtaining a late positivity. If so this might suggest that the deviance-related positivity reflects some type of conscious detection process.

In summary, the present finding suggests that by 10 months of age the brain has a strikingly adult-like response to a 3-fold deviation in a temporal interval. These results lend credence to the idea that timing is a fundamental capacity that is built into the nervous system and suggest that in infancy humans are already capable of differentiating intervals that differ by a mere second.

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