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Precocious Cardiac Orienting in a Human Anencephalic Infant

Abstract. *An anencephalic infant, 3 to 6 weeks old, responded to acoustic stimulation with cardiac decelerations typical of the response pattern seen in normal, older infants. Such precocity implies unexpected competence of lower brain structures and suggests that, in the normal infant, feedback from immature higher centers may sometimes interfere with rather than modulate the functioning of lower centers.*

Slowing of heart rate following sensory stimulation presumably reflects attention or orienting to stimuli that carry information (*1, 2*). The slowing response is difficult to elicit during sleep (*3*) or from human infants less than about 2 months of age, but it is easily evoked from awake older infants (*4–6*). It is one of a number of qualitative changes in behavior which suggest that 2 months marks the period at which cortical-subcortical circuits become functional (*5, 7*).

Anencephalic infants would not, therefore, be expected to show the cardiac-orienting response. Although Brackbill (*8*) used the term "orienting reflex" to describe white noise–elicited behavioral changes observed in a 3-month-old anencephalic infant, the observed behaviors included startles and activity increases that are usually associated with cardiac acceleration. Recently, we studied a 4½-month-old hydr*an*encephalic infant and were surprised to find that acoustic stimuli evoked reliable cardiac slowing of characteristic latency, form, and duration which was frequently accompanied by behavioral quieting, eye widening, and sucking cessation. We could not verify morphological characteristics of the brain but tentatively assumed that basal ganglia and diencephalon might have developed at near-normal rates (*9*) and were capable of organizing the age-appropriate response.

Subsequently, we studied an anencephalic infant at ages 19, 20, 25, and 40 days. The infant died at 51 days, and autopsy showed a skull defect and a severely hypoplastic brain, weighing only 39 g. (The brain of a normal newborn weighs approximately 350 g.) Minute cerebral hemispheres with poorly developed lobation could be identified; but the diencephalon was absent, and cerebral microscopic as well as gross structure was so distorted as to preclude function. Molecular and neuronal layers varied irregularly in thickness, displaced gray matter was embedded in the white matter, and there were focal areas of calcification. The midbrain was also severely malformed; only lower levels of the brain, including medulla, pons, and cerebellum, were grossly normal though underdeveloped.

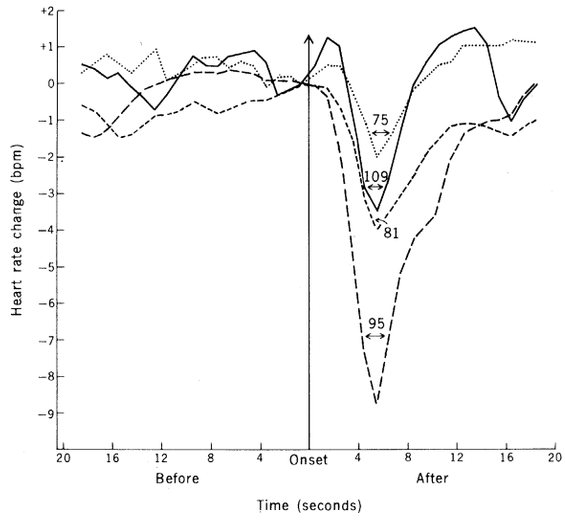

Fig. 1. Heart rate change for 19 seconds preceding and following the onset of acoustic stimuli of varying intensity (*14*).

Like the hydranencephalic infant, this infant also responded to acoustic stimulation with cardiac slowing. Tactile, olfactory, and mock stimuli did not produce reliable heart rate change, and visual stimuli were not tested. (Pupillary light reflexes were absent.) Over four 2- to 3-hour sessions, we presented 452 stimulations of which 330 were sounds with a 30-msec rise time, an intensity between 75 and 109 db (referred to a sound pressure of 20 micronewtons per square meter), and a duration of five or more seconds. The sounds included (i) continuous, constant-frequency sine waves at 250, 1000, 1800, and 6000 hertz; (ii) constant-frequency sine waves pulsed at various on : off ratios; (iii) frequency-modulated (FM) triangular waves sweeping at different rates to produce warbles or trills; (iv) trains of three-format, synthetic speech syllables, [ba] and [ga] (*6*); and (v) broadband white noise. The five classes of sound stimuli were presented in sets of varying numbers of trials, interspersed among tactile and olfactory sets. No successive sets were drawn from the same class of stimuli, and the order of sets was approximately balanced across sessions. Within sets, intertrial intervals averaged 36.4 seconds (standard deviation, 9.5 seconds). The interval between sets varied from 90 seconds to several minutes.

Testing was carried out in a sound-attenuated chamber with the infant reclining on a padded seat; stimulus-generating, calibrating, timing, and recording equipment were located outside the chamber (*6*). Chest electrodes detected cardiac R waves whose interbeat intervals were computer digitized and converted to heart rate (in beats per minute) for each second for 19 seconds preceding and 19 seconds following stimulus onset. Other activities recorded were respiration (via a mercury strain-gauge, session 4), electromyographic response of orbicularis oculi (not reported here), and sucking (which was too weak to provide satisfactory records). Sounds were delivered either through a midline speaker or through an earphone (modified Grason-Stadler TDH-49) held in place by a staff member. A pediatrician and a second staff member remained in the chamber to monitor the infant's condition and to rate behavior. Throughout, the infant

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remained in a state that approximated active sleep (*10*). The eyes were closed, but eye movements and lid twitching could be observed as well as small movements of head and mouth. Occasionally, gross body movement was observed. During prestimulation periods, respiration was irregular and averaged 40.2 cycles per minute, while the heart rate was relatively stable and low, declining over the four sessions from a mean of 118.4 ± 5.0 to 91.5 ± 4.0 beats per minute.

Despite the nonalert state, sound stimuli evoked heart-rate changes with form and latency resembling the changes seen in older awake infants (Fig. 1). The apparent response at 75 db was not reliable, but higher-intensity stimuli elicited changes during periods of 3 to 10 seconds that were significantly greater than changes during corresponding periods before onset (t tests, $P < .01$). Orthogonal components of trend over 10 seconds, the measure usually used with normal subjects (*4–6*), also differed for periods before and after the stimulus [F ratios for linear, quadratic, and cubic trends at 95 db and for linear and cubic trends at 81 and 109 db ranged from 11.25 to 55.52 ($P < .01$)]. Marked respiratory slowing was also seen. Thoracic respiration was apparently suspended for an average of 9.4 seconds during 12 of 36 scoreable poststimulus periods and for only 1 second during one prestimulus period.

The intensity effect (Fig. 1) is confounded with differences in the type of stimulus delivered at each intensity. However, analysis of the ten stimuli delivered at all four intensities (*14*) showed a similar and reliable nonmonotonic change (quadratic intensity by linear seconds, $F = 18.59$, $P < .01$). In theory, cardiac orienting is a nonmonotonic function of intensity because slowing should not increase with intensity beyond a level at which stimuli are sufficiently intense to elicit competing defensive or startle reactions of cardiac acceleration (*2, 11*).

The anencephalic infant also responded like normal subjects to other stimulus variations. White noise produces in adults an initial acceleration lacking in response to sine waves of equal sound pressure level (*12*), and it had a similar accelerating effect on the response of our subject. [For 109 db, sine wave versus noise: $t = 8.57$ at 4 seconds ($P < .01$), quadratic seconds $F = 12.86$ ($P < .01$).] Speech and pulsed tones have been especially effective in eliciting cardiac deceleration in normal infants (*6*); these

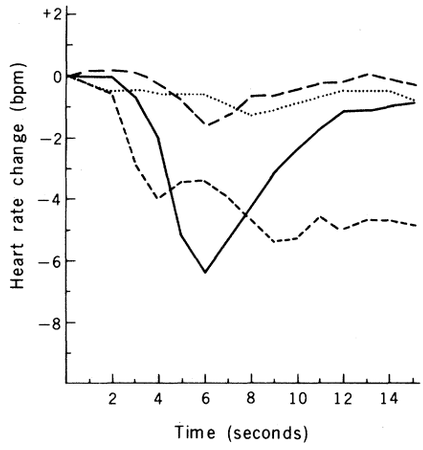

Fig. 2. Heart rate change in beats per minute (bpm) for 15 seconds following the onset of 81-db stimuli: continuous sine wave (. . . . .), FM triangular tone (– – –), speech syllable (_____), and pulsed sine wave (- - - - -).

stimuli also produced large decelerations in the anencephalic infant (Fig. 2). [For 81 db, 5-second speech versus continuous tone: $t = 7.95$ and 7.18 at seconds 6 and 7 ($P < .01$), cubic seconds $F = 10.09$ ($P < .01$); for speech versus FM tone: $t = 7.59$ and 7.89 at seconds 7 and 8 ($P < .01$), linear seconds $F = 7.97$ ($P < .01$); for the first 5 seconds of 20-second pulsed versus 5-second continuous tone: $t = 4.07$, 4.81, and 5.31 at seconds 3 through 5 ($P < .05$); for 20-second pulsed versus 5-second FM tone: $t = 5.62$ and 5.97 at seconds 3 and 4 ($P < .05$).]

Because we presented more speech than other stimuli, the speech response would be reduced disproportionately if repeated stimulation led to habituation. The data suggest that this may have occurred. Most of the 81-db speech, sine-wave, and FM sounds occurred in sets of six or eight repetitions of one stimulus followed by two repetitions in which there was a change of speech syllable ($N = 11$), of frequency ($N = 5$), or of modulation rate ($N = 4$). Both speech and nonspeech stimuli elicited less deceleration on trial 6 than on trial 1 or on the first change trial (Fig. 3). Over all 20 sets, habituation was significant (linear trials by quadratic seconds, $F = 4.73$, $P < .05$); over all sets and for speech sets, dishabituation was also significant (trial 6 versus change trial quadratic seconds, $F = 7.72$ and 5.15, respectively; $P < .05$).

We have described a response pattern typical of orienting behavior in normal subjects who are awake and more than 2 months old. The fact that this behavior occurred in a nonalert state in an anencephalic infant between 3 and 6 weeks of age makes it clear that lower brain structures not only can support cardiac orienting reflexes but can respond differentially to variations in stimulus characteristics. Recent animal studies have also emphasized unexpected competencies of lower brain structures when they are released by decerebration from descending influences (*13*). Our findings imply, in addition, that the traditional view of higher brain structures modulating (making more precise) the activities of lower centers may not be adequate to describe relationships in the developing brain. When higher brain structures are immature, their descending influence may interfere with or disrupt the activity of lower centers. If anencephaly re-

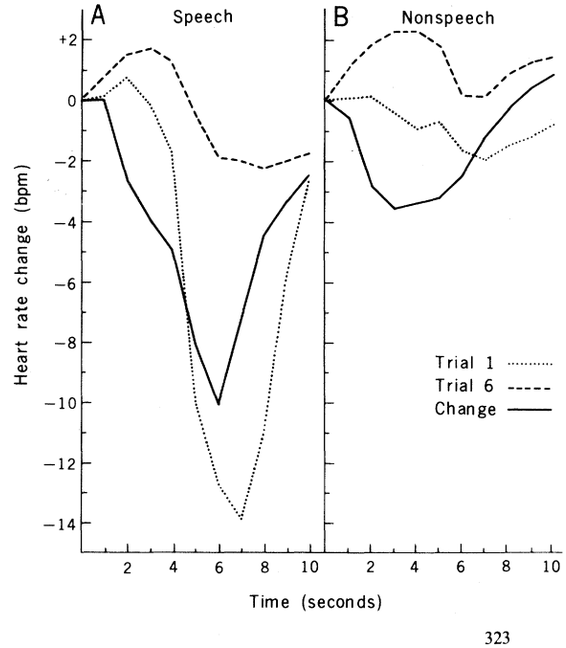

Fig. 3. Heart rate change for 10 seconds following the onset of 81-db stimulation on trial 1 (. . . . .), trial 6 (- - - -), and the first change trial (trial 7 or 9) (_____) of repeated stimulation sets. (A) Speech syllable sets. (B) Sets of continuous constant-frequency sine-wave and FM triangular tones.

moved only modulating influences, we should see behavior typical of an earlier rather than of a later developmental stage.

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4. The characteristic response during sleep and before 2 months of age is solely or primarily accelerative, as are the "defensive" and startle reflexes elicited by intense and sudden stimulation, respectively. In contrast, the cardiac orienting response to novel or informative stimuli shows monophasic deceleration beginning within the first or second cardiac cycle and lasting for several seconds, generally peaking between 3 and 7 seconds. The shift from an accelerative to a decelerative response during early development is not an all-or-none matter but a change in the probabilities that specific stimuli will elicit slowing. Under optimal conditions of state and stimulus characteristics, deceleration has been obtained even in the newborn. For reviews, see F. K. Graham and J. C. Jackson (*5*) and R. K. Clifton [in *Cardiovascular Psychophysiology*, P. Obrist, A. H. Black, J. Brener, L. DiCara, Eds. (Aldine, Chicago, 1974), p. 479]. See also W. K. Berg [*J. Exp. Child Psychol.* **17**, 303 (1974)], L. A. Leavitt *et al.* (*6*), and J. W. Brown, L. A. Leavitt, F. K. Graham [*Devel. Psychobiol.* **10**, 255 (1977)].
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14. The number and kind of stimulations given at each intensity.

db	Sine wave	FM triangular wave	Speech syllable	White noise
75	12	8	10	0
81	49	44	96	0
95	27	42	0	0
109	20	0	0	22

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Memory: Modification of Anisomycin-Induced Amnesia by Stimulants and Depressants

Abstract. *Mice were trained in a passive (foot shock) avoidance task. When administered after training, the stimulants caffeine or nicotine blocked amnesia for the task that had been produced by injections of the protein synthesis inhibitor anisomycin given prior to training. With foot shock at a higher intensity, anisomycin did not produce amnesia by itself, but the administration of the depressants chloral hydrate or sodium phenobarbital after training did cause amnesia. Stimulants and depressants did not have an appreciable influence on the overall degree of protein synthesis inhibition produced by anisomycin. The results support the hypothesis that arousal after training is an important factor in the conversion of short-term to long-term memory.*

To test the hypothesis that arousal facilitates memory consolidation, we determined whether excitant drugs could counteract the amnesic effects caused by inhibition of cerebral protein synthesis and whether depressant drugs could enhance the amnesia. Amphetamine administered after training can block the amnesia induced when cycloheximide or acetoxycycloheximide inhibit protein synthesis (*1*). We tested the generality of these findings by using the stimulants nicotine and caffeine and by using anisomycin to inhibit protein synthesis. We also extended the scope of such experiments by using depressants (chloral hydrate and sodium phenobarbital). Since the drugs producing arousal and depression produced significant effects on retention 7 days after training and drug administration, we tested whether the drugs affected the extent and duration of protein synthesis inhibition caused by anisomycin.

The subjects, CD-1 male albino mice 60 to 80 days of age (Charles River), were trained on a one-trial, step-through passive avoidance task (*2*). In brief, the avoidance apparatus consisted of a black compartment (start) joined to a white compartment (where shock was administered) by a partition containing a mousehole. Subjects were permitted to enter the white compartment through the mousehole where they received foot shock (0.32 ma) until they returned to the black compartment. The subjects were trained in a black-to-white situation because we found that this produced a considerably smaller variation in the time (latency) taken by the mice to enter the shock compartment than when subjects were trained in the opposite direction; typically, 80 percent of the mice enter in 2 seconds. To reduce and control the variability of the latencies to enter and escape the shock compartment, which control the degree of learning (*2*), only subjects with latencies of 1 to 3 seconds in entering and 1 to 4 seconds in escaping the shock compartment were used. On the retention test given 1 week after training, the mice were again placed into the black compartment and the time each mouse required to enter the white compartment was taken as a measure of retention. A latency-to-enter the white shock compartment on the test day of 20 seconds or less was defined as amnesia, since this represented the longest entry time for naive mice. Most trained nonamnesic mice did not enter the white compartment within 3 minutes. The percentage of mice entering within 20 seconds was defined as "percentage amnesia."

Anisomycin was dissolved in an approximately equal molar amount of 3*N* HCl, and the *p*H was finally adjusted to 6 to 7 with dilute HCl or NaOH as required. The final solution was 2.0 mg/ml in 0.9 percent saline. Mice received the first subcutaneous anisomycin injection (20 mg/kg) 15 minutes prior to training, the second 1.75 hours after training. When a third injection was used it was given 3.75 hours after training. Saline was administered subcutaneously to other groups as a control for the stress of the

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