tis, and reticularis tegmenti pontis were also selectively activated (Fig. 2). Nuclear components in the small medulla and spinal cord were too close to the threshold of the method to allow reliable assessment. Bilateral decreases were noted in cerebellar deep nuclei and substantia nigra. Intense uptake (4+) was present in bilaterally symmetrical patches of frontal and cingulate cortex, ventrolateral and anterior dorsalis nuclei of the thalamus, and the striatum, but high levels of deoxyglucose uptake in these regions were also found in freely moving control mice. Low activity (1+) was observed in both mutant and control mice in hippocampus, entorhinal or temporal cortex, septal nuclei, amygdala, and hypothalamic nuclei.

No morphological expression of the *tg* mutation has yet been recognized. Preliminary neuropathological studies at the light microscopic level revealed no lesions in the adult *tg*/*tg* cerebrum, cerebellum, spinal cord, dorsal-root ganglia, or sciatic nerves. Although adult *tg* mutants weighed an average of 7 g less than normal adults, brain weights were equal to those of normal littermates. It is worth noting that other alleles at the *tg* genetic locus (leaner, tg^{la}, and rolling mouse Nagoya, tg^{rol}) have been reported to show loss of Purkinje neurons, predominantly in the anterior lobe of the cerebellar cortex (*7*).

The abnormal patterns of cerebral activation during behavioral seizures in the tottering mouse are of considerable theoretical and practical significance with reference to human epilepsy. The murine spike-wave seizure disorder described here resembles in many, but not all, respects the electroencephalographic, clinical, and developmental characteristics of the recurrent centrencephalic absence seizures of human childhood (*8*). Heredity has long been thought important in the etiology of "genuine" or "essential" seizure disorders in man, but the genetic components of these clinical syndromes have been difficult to isolate and interpret. Our data show that a spontaneous, paroxysmal electrocorticographic disorder of the centrencephalic type accompanied by behavioral arrest and partial motor seizures can, in principle, be inherited as a simple autosomal recessive trait in mammals.

The evidence suggests that a presumably single gene mutation at the *tg* locus in the mouse alters specific central nervous system pathways at critical stages of maturation. The *tg*/*tg* mutant provides an opportunity to identify the nature of the defect in neuronal organization, its biochemical and electrophysiological features, and the pharmacological sensitivity of naturally occurring, spontaneous paroxysmal discharges in the brain. This genetically defined model of spike-wave epilepsy provides a rational basis for a search to identify a gene product at the molecular level that might be used in the detection and prophylaxis of this neurological disease at preclinical stages.

JEFFREY L. NOEBELS
RICHARD L. SIDMAN
*Department of Neuropathology,
Harvard Medical School, and
Department of Neuroscience,
Children's Hospital Medical Center,
Boston, Massachusetts 02115*

References and Notes

1. R. L. Sidman, M. C. Green, S. H. Appel, *Catalog of the Neurological Mutants of the Mouse* (Harvard Univ. Press, Cambridge, Mass., 1965); R. L. Sidman, in *The Cell Surface in Development* (Wiley, New York, 1974), pp. 221–253; V. S. Caviness and P. Rakic, *Annu. Rev. Neurosci.* **1**, 297 (1978); U. Drager, in *Function and Formation of Neural Systems* (Dahlem Konferenzen, Berlin, 1977), pp. 111–138.
2. W. G. Lennox, *J. Am. Med. Assoc.* **146**, 259 (1951); K. Metrakos and J. D. Metrakos, in *Handbook of Clinical Neurology* (American Elsevier, New York, 1974), vol. 15, pp. 429–439.
3. Genetic variations in the triggering threshold for artificially induced seizures exist in several species [K. F. Killam, R. Naquet, J. Bert, *Epilepsia* **7**, 215 (1966); R. L. Collins and J. L. Fuller, *Science* **162**, 1137 (1968); R. D. Crawford, *J. Hered.* **61**, 185 (1970)]. Most sensory-precipitated seizures induce generalized convulsions, often lethal, and are rare (< 1 percent) as a form of epilepsy in man [H. Gastaut and C. A. Tassanari, *Epilepsia* **7**, 85 (1966)].
4. M. C. Green and R. L. Sidman, *J. Hered.* **53**, 233 (1962). C57BL/6J-+/*tg* breeding pairs at the N13 cross generation were obtained from the Jackson Laboratory and maintained by brother-sister matings in the Children's Hospital breeding colony.
5. Carbon-14 labeled 2-deoxy-D-glucose (New England Nuclear, 0.2 μCi per gram of body weight) was injected into the dorsal tail vein. After 45 minutes the animal was killed by cervical dislocation and the brain was excised and frozen at − 70°C in isopentane. Serial frozen sections (20 μm) were exposed to Kodak SB5 x-ray film and developed according to the method of C. Kennedy, M. Des Rosiers, M. Reivich, F. Sharp, and L. Sokoloff [*Science* **187**, 850 (1975)]. Qualitative analyses of nuclear regions identified on corresponding stained histological sections were compared by using grain density over white matter (1+) as the lower, and vestibular nuclei (4+) as the upper limits of isotope uptake.
6. Ineffective stimuli include photic, auditory, somatosensory, and vestibular stimulation as well as hyperthermia and startle.
7. S. Tsuji and H. Meier, *Genet. Res.* **17**, 83 (1971); Y. Nishimura, *Saishin Igaku* **31**, 226 (1976).
8. W. Penfield and H. H. Jasper, *Epilepsy and the Functional Anatomy of the Human Brain* (Little, Brown, Boston, 1954); F. A. Gibbs and E. L. Gibbs, *Atlas of Electroencephalography* (Addison-Wesley, Reading, Mass., 1964); A. Matthes, in *The Physiopathogenesis of the Epilepsies* (Thomas, Springfield, Ill., 1966), pp. 26–30; R. Jung, *Epilepsia* **3**, 435 (1962).
9. R. L. Sidman, J. B. Angevine, Jr., E. T. Pierce, *Atlas of the Mouse Brain and Spinal Cord* (Harvard Univ. Press, Cambridge, Mass., 1971).
10. Supported by the William G. Lennox Trust (to J.L.N.) and research grant NS11237 (to R.L.S.) from the National Institutes of Health. We thank E. R. Grass of the Grass Instrument Company for the generous loan of an electroencephalograph.

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Perception of Echo Phase Information in Bat Sonar

Abstract. *Echolocating bats (*Eptesicus fuscus*) can detect changes as small as 500 nanoseconds in the arrival time of sonar echoes when these changes appear as jitter or alternations in arrival time from one echo to the next. The psychophysical function relating the bat's performance to the magnitude of the jitter corresponds to the half-wave rectified cross-correlation function between the emitted sonar signals and the echoes. The bat perceives the phase or period structure of the sounds, which cover the 25- to 100-kilohertz frequency range, as these are represented in the auditory system after peripheral transformation. The acoustic image of a sonar target is apparently derived from time-domain or periodicity information processing by the nervous system.*

The biological sonar of bats in the suborder Microchiroptera is currently under intense scientific study as a relatively well-defined example of a biological communication system (*1, 2*). Behavioral observations have established that echolocation enables bats to detect, identify, and track prey; to avoid obstacles; and to navigate the near environment. Psychophysical experiments have shown that bats can perceive a variety of different target features by extracting information from echoes (*1–5*), although only a few of these studies have revealed anything directly about how sonar signals are processed in the brain (*2, 4, 5*). Many aspects of the auditory and neural basis of orientation by echolocation have been explored physiologically (*6*), and neurons within the bat's auditory system respond in ways relevant to target perception by sonar. I now report new psychophysical data from bats on the perception of changes in target distance (or range), data that provide conceptual order to many diverse observations on echolocation and that identify the form of the acoustic image of a target to a bat.

Two echolocating bats (*Eptesicus fuscus*) were trained with food as a reward to choose between a simulated stationary target represented by echoes arriving 3.087 msec after the sonar transmission, corresponding to a target range of about

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5.3 cm, and a simulated target undergoing small step changes in range represented by echoes arriving $3.087 \pm \Delta t$ msec after the transmission. These step changes in arrival time were on the order of a few microseconds. The arrival time of these shifting echoes changed back and forth from the shorter to the longer delay on alternate sonar emissions that the bat directed at whichever of the two channels of the target simulator system was presenting the systematically "jittering" echo on that particular experimental trial. The simulated target was thus presented to the bat as alternating by a distance of a millimeter or so from one range to another. The data consist of the performance of bats at detecting which of the two simulated echoes was jittered as a function of the size of the jitter, $2\Delta t$.

The bats were initially trained to discriminate between two flat Plexiglas targets, one at a range of 45 cm and the other at a range of 50 cm; the two-choice procedures have been described (*5*). After learning this target range discrimination to a criterion of 90 percent correct responses, the bats were transferred to discriminating electronically produced echoes that simulated targets at 45 and 50 cm (echo delays of 2.6 and 2.9 msec, respectively). The simulated echoes were −34 dB at the bat's location with respect to the peak sound pressure emitted by the bat (100 to 110 dB sound-pressure level) measured 12 cm in front of the bat's mouth (Bruel and Kjaer model 4135 condenser microphones). The entire target simulator system for two-choice simultaneous presentation of stimuli has been described (*5*). The frequency response of the system was ± 5 dB from 25 to 80 kHz, and differences in response between the left and right channels at any given frequency were less than 1.5 dB.

After the bats learned to discriminate echo delays of 2.6 and 2.9 msec to criterion, this delay difference was reduced in 20-μsec stages while the closer "target" (earlier echo) was also jittered by ± 40 μsec. By a psychophysical fading procedure (*7*) the bats were brought to discriminate fixed echoes at 3.087 msec from echoes appearing on alternate bat sonar transmissions at delays of 3.047 and 3.127 msec. An electronic switching circuit changed the delay of these echoes from one value to the other 5 msec after the simulated echo had passed to the bat, when electronic switches in the left and right channels of the target simulator had attenuated all signals by at least 100 dB to suppress any possible switching transients from emerging as acoustic artifacts. The left and right channels were electrically and acoustically the same; both incorporated delay-jittering switches. The magnitude of jitter delay ranging from ± 40 μsec down to 0 μsec, which served as the positive stimulus, and the jitter magnitude of 0 μsec, which served as the negative stimulus, were alternated from the left to the right channel according to a pseudorandom schedule (*5*). After the bats learned to choose the ± 40-μsec jitter to criterion, data were collected for 50 trials at each echo jitter for jitters of ± 40 μsec down to 0 μsec in small steps. The data are in the form of percentage errors at each of these jitter values. Two bats completed the entire procedure.

One feature of the target simulator deserves mention. During discrimination trials the bat scanned back and forth while examining the targets being simulated. The bat typically emitted from 1 or 2 to 20 sonar signals at each channel before making a decision. These signals were produced at a repetition rate of 10 to 30 sounds per second and were 1 to 1.5 msec long, containing two or three harmonics of a fundamental sweep from 55 to 23 kHz (*5*). The microphone for the channel toward which the bat aimed its head received a louder signal than the other microphone as a result of the directional pattern of sound emission (*5*). A voltage comparator determined which of the two channels received the stronger signal and enabled only the channel at which the bat was aiming to return any echoes. The bat never received any simulated echoes simultaneously from the left and right but was presented with only one channel at a time. The bat scanned the channels during each data-collecting trial to determine which contained the jitter. Since the jitter was accomplished by alternating the echo delay on successive sonar transmissions, the bat received only one stimulus echo per transmission. Neither temporal overlap of jittered echoes nor overlap of echoes from the left and right channels occurred. The bat had to use memory to determine which channel contained the jitter. The other objects present, either close, such as the microphones at 12 cm, or far away, such as the loudspeakers at 88 cm, produced extraneous echoes that were more than 30 dB lower and occurred either earlier or later than the simulated echoes returned by the stimulus system. The bats used sonar sounds (*5*) 1 to 1.5 msec in duration, and these extended across 34 to 52 cm in space. The total path lengths between simulated targets and extraneous targets exceeded 75 cm. No temporal overlap between the extraneous echoes and the discrimination stimuli occurred. Furthermore, the bat's head movements produced changes in

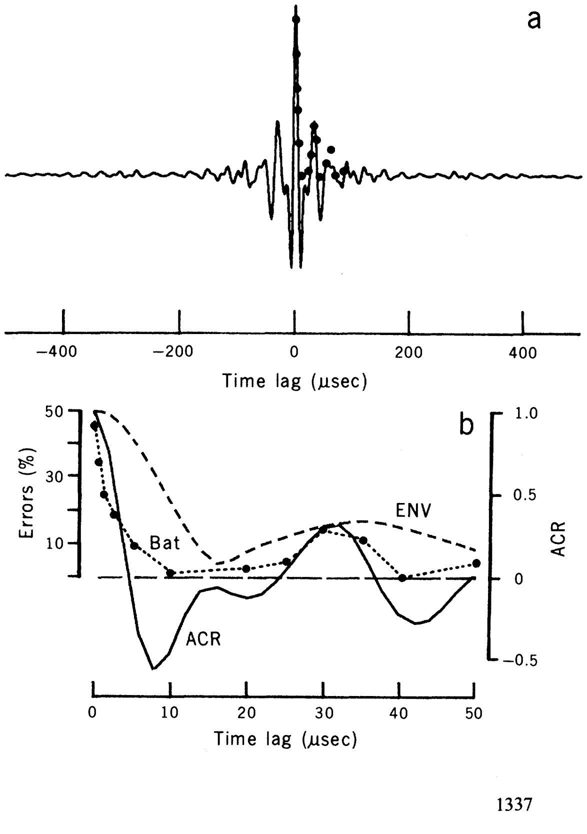

Fig. 1. Performance (percentage of errors) of one *Eptesicus fuscus* at detecting which of two simulated echoes is jittering compared with the autocorrelation function of the bat's sonar signals. The bat's performance is shown with data points [dotted lines in (b)], the autocorrelation function (*ACR*) is a solid line, and the envelope of the autocorrelation function (*ENV*) with minimal smoothing is a dashed line. (a) The entire ACR is shown with data points superimposed over a time span of ± 500 μsec. (b) The details of the data, the ACR, and the ENV are shown for an expanded span of + 50 μsec. The jitter is plotted as $2\Delta t$; thus, for a jitter of ± 15 μsec, the graphs show + 30 μsec. The relationships between vertical performance and autocorrelation axes are shown in (b). The vertical axes are the same in (a) and (b). The two bats performed similarly. The bat's performance corresponds to a half-wave rectified version of the ACR, not the full-wave rectified ENV.

the arrival times of these extraneous echoes that were much larger than the jitters in the stimulus signals. The stimuli were thus temporally isolated replicas of the bat's sonar transmissions and were presented individually.

The performance of each of the bats (percentage of errors) in the jitter-detection experiment was a cyclical, decaying function of the size of the jitter, which is shown as $2\,\Delta t$ or the total span of the jitter on the horizontal axis of Fig. 1. Two features of these data are especially significant. First, *Eptesicus* can detect very small changes in target distance (echo arrival time) on the order of 0.1 mm (0.5 μsec) (*8*). Since the bats emitted their echolocation signals at repetition rates of 10 to 30 sounds per second, the stepwise jittering echoes crudely simulate the fluttering of insect wings over surprisingly small distances. Bats using broadband echolocation with frequency-modulated (FM) signals can therefore detect insect fluttering motions as a consequence of highly acute acoustic imaging of target position. Bats using narrowband sonar with constant-frequency (CF) signals are known to detect fluttering motions from slight amplitude modulation and frequency modulation of CF echoes (*9*), thus accomplishing much the same perceptual task by a different strategy.

Previous experiments have shown that *Eptesicus* can detect small differences (6°) in the size of horizontal angles separating targets (*10*) and small differences (0.6 mm) in the depths of holes in targets (*11*). The data reported here suggest that information about echo arrival time could have served as cues for the bat in both of these studies, although additional cues cannot be ruled out. It may be that bats using broadband echolocation sounds use temporal information for most, if not all, perceptual tasks; the extreme acuity (Fig. 1) is provocative.

The second significant feature of the jitter-detection data involves a comparison of the bat's performance with the autocorrelation function of the sonar signals used for the task (Fig. 1). The bats performed as though they perceived a half-wave rectified version of the autocorrelation function of the echoes or the cross-correlation function of the transmissions and the echoes; the functions are identical for stationary targets that reflect well at all frequencies, such as the targets simulated here. [The autocorrelation function describes the period structure of a signal in much the same way the power spectrum describes the frequency content of a signal. One reads the autocorrelation function in Fig. 1 by noting that the time interval between peaks is the average period of the signal—in this instance about 30 μsec. As the heights of the peaks show, if one moves away from any given point in the bat's FM sonar sound by a time interval corresponding to more than three or four average cycles, the frequency sweep is sufficiently rapid and its bandwidth sufficiently broad that there is little correlation within the waveform across this interval. Because of the sound's harmonic structure, the average period in the autocorrelation function is not simply the reciprocal of the average frequency in the signal (*12*).]

The bats made more errors in determining which of the simulator channels carried the jittering echoes if the jitter was a small integral multiple of the signal's average period than if the jitter was either smaller or larger. For example, the bat in Fig. 1 made only 2 percent errors at 10 μsec and 6 percent errors at 50 μsec but 16 percent errors at 30 μsec (*8*). The bats achieved perfect performance for jitters not corresponding to a small number of average signal periods. These results demonstrate that *Eptesicus* perceives very small time intervals well enough to sense phase information in sonar signals and echoes and that *Eptesicus* experiences perceptual ambiguities for time intervals corresponding to average periods.

Fibers in the auditory nerves of mammals respond to sounds only on alternate half-cycles of the stimulus waveform. In cats and primates, however, phase locking and the associated half-wave rectification have been observed only for stimulus frequencies up to a few kilohertz (*13*). From the data presented here it is evident that, to preserve stimulus period information for perception, sufficient phase locking of discharges in peripheral auditory neurons must occur in bats over the range from 25 to 100 kHz. The registration by neural discharges of the time of occurrence of any particular frequency in the FM sweep of an echolocation sound is very precise in parts of the bat's auditory pathways (*14*). Some neurons respond selectively to sonar echoes at particular delays (*15*), and such "delay tuning" may be the neural equivalent of cross-correlation of transmissions and echoes.

If the time interval between a sonar signal and an echo is represented by interspike intervals between nerve-fiber discharges excited by the emission and by the echo (at each frequency across the range of frequencies contained in the FM sweeps of the sounds), a neural correlation-like system for extracting an encoding or displaying these interspike intervals would produce average interval histograms resembling the data in Fig. 1. Such a neural mechanism would extract intervals between sonar sounds and echoes with lengths varying by a small number of average periods of the sonar signals. A time-domain mechanism of this kind would arrive at period estimates for complex sounds based on the fundamental period or harmonic interval, even if the first harmonic itself were absent from the acoustic waveform.

JAMES A. SIMMONS

Departments of Psychology and Biology,
and Program in Neural Sciences,
Division of Biology and
Biomedical Sciences,
Washington University,
St. Louis, Missouri 63130

References and Notes

1. D. R. Griffin, *Listening in the Dark* (Yale Univ. Press, New Haven, Conn., 1958; reprinted by Dover, New York, 1974); A. Novick, in *Biology of Bats*, W. A. Wimsatt, Ed. (Academic Press, New York, 1977), vol. 3, p. 73; J. A. Simmons, M. B. Fenton, M. J. O'Farrell, *Science* **203**, 16 (1979).
2. J. A. Simmons, in *Recognition of Complex Acoustic Signals,* T. H. Bullock, Ed. (Dahlem Konferenzen, Berlin, 1977), p. 239.
3. E. Ajrapetjantz and A. I. Konstantinov, *Echolocation in Nature* (National Technical Information Service, Arlington, Va., ed. 2, 1974), report No. JPRS-63328.
4. J. A. Simmons, D. J. Howell, N. Suga, *Am. Sci.* **63**, 204 (1975).
5. J. A. Simmons, *J. Acoust. Soc. Am.* **54**, 157 (1973); _____ and J. A. Vernon, *J. Exp. Zool.* **176**, 315 (1971).
6. A. D. Grinnell, *J. Acoust. Soc. Am.* **54**, 147 (1973); O. W. Henson, Jr., in *Biology of Bats*, W. A. Wimsatt, Ed. (Academic Press, New York, 1970), vol. 2, p. 181; N. Suga, in *Basic Mechanisms in Hearing*, A. R. Moller, Ed. (Academic Press, New York, 1973), p. 675; *Fed. Proc. Fed. Am. Soc. Exp. Biol.* **37**, 2342 (1978).
7. W. C. Stebbins, *Animal Psychophysics* (Appleton-Century-Crofts, New York, 1970).
8. The data beyond 50 μsec in Fig. 1b are 60.0 μsec, 8 percent; 70.0 μsec, 0 percent; 80.0 μsec, 2 percent. For each bat (50 trials) the probability of obtaining 4 percent or fewer errors by chance is less than 10^{-7}, the probability of obtaining 16 percent or fewer errors is less than 10^{-5}, and the probability of obtaining 34 percent or fewer errors is less than 0.02 [I. L. Child, *Psychol. Bull.* **43**, 558 (1946); D. A. Grant, *ibid.*, p. 272].
9. H.-U. Schnitzler, *Verh. Dtsch. Zool. Ges.*, in press.
10. T. C. Peff and J. A. Simmons, *J. Acoust. Soc. Am.* **51**, 2063 (1972).
11. J. A. Simmons, W. A. Lavender, B. A. Lavender, C. A. Doroshow, S. W. Kiefer, R. Livingston, A. C. Scallet, D. E. Crowley, *Science* **186**, 1130 (1974).
12. J. A. Simmons and R. A. Stein, *J. Comp. Physiol.*, in press.
13. N. Y.-S. Kiang, D. K. Morest, D. A. Godfrey, J. J. Guinan, Jr., E. C. Kane, in *Basic Mechanisms in Hearing*, A. R. Moller, Ed. (Academic Press, New York, 1973), p. 455; J. E. Rose, J. F. Brugge, D. J. Anderson, J. E. Hind, *J. Neurophysiol.* **30**, 769 (1967).
14. G. D. Pollak, D. S. Marsh, R. Bodenhamer, A. Souther, *J. Neurophysiol.* **40**, 926 (1977); *Science* **196**, 675 (1977); N. Suga, *ibid.* **170**, 449 (1970).
15. A. S. Feng, J. A. Simmons, S. A. Kick, *Science* **202**, 645 (1978); W. E. O'Neill and N. Suga, *ibid.* **203**, 69 (1979); N. Suga, W. E. O'Neill, T. Manabe, *ibid.* **200**, 778 (1978).
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