and cooling of the brain, suggest that the temperature changes are detected centrally in those animals. Under the same conditions as those for the experimental data shown in Fig. 1, we examined the time course of the change in brain temperature as a function of the temperature of the perfusing water. A thermocouple was implanted in the brain 2.5 mm from the midline and at the level of the posterior commissure. The changes in brain temperature lagged behind the perfusion temperature by 20 to 25 seconds; these have been added to Fig. 1, A and B, as a dashed line. Increased activity of both the warm- and cold-sensitive neurons therefore tended to be synchronous with a changing brain temperature, rather than the temperature step across the gills. This result is consistent with the interpretation that the sensory site is in the brain. Furthermore, preliminary experiments in which neural activity and brain temperature were monitored simultaneously indicate that activity does follow brain temperature (Table 1).

Although the initial constant brain temperature was different for each unit tested, it appears that the mean steady-state activity of different units can be quite variable. For example, during the initial phase of warming the brain, the temperature 11.5°C was common to the first four units in Table 1 but the mean steady-state activities were dissimilar. In addition, the temperature of the brain above which the activity increased with warming varied between units. The range of temperature sensitivities of +2 to +18 impulses sec^{-1} deg^{-1} for the trout is above the range of +0.09 to +1.0 for the warm-sensitive units in the lizard (*7*), but is within the range of +1 to +21 impulses sec^{-1} deg^{-1} for the dog (*8*). The variation in the temperature sensitivity of individual units, their steady-state frequency, and the temperature of the brain at which they switched on with warming, suggests that the brain might have a population of temperature-sensitive neurons consisting of individual units that function over a specific temperature range.

Cabanac *et al.* (*7*) have already noted the similarities between mammalian and reptilian brains with regard to temperature-sensitive units. Now, with identification of temperature-sensitive neurons in the fish it appears that the ability to centrally detect changes in temperature could be common to all vertebrates. Though one cannot necessarily infer a close association between the activity of these units in the brain and some behavioral thermoregulatory response of the fish, one might speculate that the beginnings of a central thermostat exist in the lowest class of vertebrates.

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References and Notes

1. H. T. Hammel, *Annu. Rev. Physiol.* **30**, 641 (1968).
2. T. K. Pitt, E. T. Garside, R. L. Hepburn, *Can. J. Zool.* **34**, 535 (1956); E. T. Garside and J. S. Tait, *ibid.* **36**, 565 (1958); C. M. Sullivan and K. C. Fisher, *J. Fish. Res. Board Can.* **10**, 187 (1953); D. M. Ogilvie and J. M. Anderson, *ibid.* **22**, 503 (1965); M. Y. Javaid and J. M. Anderson, *ibid.* **24**, 1507 (1967).
3. E. A. Lucas and W. A. Reynolds, *Physiol. Zool.* **40**, 159 (1967).
4. D. C. Wilhoft and J. D. Anderson, *Science* **131**, 610 (1960); C. B. DeWitt, *Physiol. Zool.* **40**, 49 (1967).
5. H. T. Hammel, F. T. Caldwell, Jr., R. M. Abrams, *Science* **156**, 1260 (1967).
6. H. T. Hammel, S. B. Strømme, K. Myhre, *ibid.* **165**, 83 (1969).
7. M. Cabanac, T. Hammel, J. D. Hardy, *ibid.* **158**, 1050 (1967).
8. J. D. Hardy, R. F. Hellon, K. Sutherland, *J. Physiol.* **175**, 242 (1964).
9. M. Cabanac, J. A. Stolwijk, J. D. Hardy, *J. Appl. Physiol.* **24**, 645 (1968).
10. D. J. Cunningham, J. A. Stolwijk, N. Murakami, J. D. Hardy, *Amer. J. Physiol.* **213**, 1570 (1967); T. Nakayama, J. S. Eisenman, J. D. Hardy, *Science* **134**, 560 (1961).
11. R. M. Dowben and J. E. Rose, *Science* **118**, 22 (1953).
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Auditory Frequency-Following Response: Neural or Artifact?

Abstract. *An electrical response which reproduces the waveform and frequency of the sound stimulus can be recorded from the central neural pathway for audition. Controversy has existed for some years over whether this frequency-following response (FFR) is neural or an artifact such as remote pickup of the cochlear microphonic or cross talk in the recording system. Two experiments resolve this issue by demonstrating that the frequency-following response depends upon functionally intact neural pathways. The frequency-following response, as well as auditory evoked potentials, is abolished by section of the eighth nerve; it is reversibly abolished by cooling of the cochlear nucleus.*

Some 40 years ago Wever and Bray (*1*) observed sound-evoked electrical activity in the eighth nerve, which reproduced the frequency and waveform of low-frequency sound stimuli. This response, which we have termed a frequency-following response (FFR), was observed at frequencies well beyond the limits of response of individual neural units. To account for this discrepancy, Wever proposed the "volley" concept of neural firing. Subsequently, FFR has been observed at higher levels of the auditory pathway (*2*).

Considerable controversy has existed over whether this response reflects neural activity, or some nonneural mechanism such as cross talk in the recording system, remote pickup of the cochlear microphonic (CM), or some artifact generated by such physical factors as acoustic vibration at the interface of brain and electrode. Evidence supporting a neural interpretation of FFR has been reported by a number of authors (*3*). The principal observations are: (i) FFR has latency appropriate to the neural level from which it is recorded; (ii) in contrast to the graded onset of the CM, FFR has an abrupt onset and a discrete threshold; (iii) FFR is so narrowly localized within the auditory pathway that it is not recorded at points a millimeter away; and (iv) under anoxia the disappearance of FFR is concurrent with that of known neural activity (for example, evoked potentials) whereas CM persists. Since the possible importance of FFR for processing of neural information and for theories of hearing depends upon an unequivocal demonstration of its neural basis, two experiments were undertaken to resolve this issue.

In the first experiment (Fig. 1), section of the eighth nerve abolished FFR at the cochlear nucleus, as well as the evoked potential, without affecting the CM recorded at the round window.

Since the functional integrity of the recording electrode in the cochlear nucleus is not demonstrable after transection of the eighth nerve, a second experiment was performed. Reversible blocking was produced by inserting a cryoprobe to cool the left cochlear nucleus. Both the evoked potential and

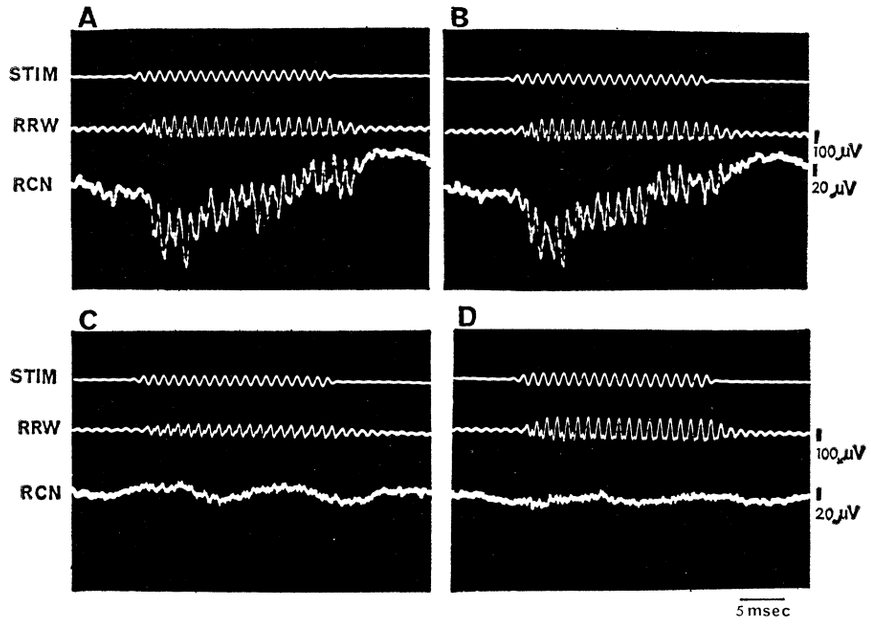

Fig. 1. Effects of transection of the eighth nerve on the cochlear microphonic (CM) and the frequency-following response (FFR). In each photo traces are: *STIM*, electrical signal to earphone produces a tone pulse with a frequency of 730 hz, duration of 25 msec, and an intensity of 100 db referred to .0002 μbar; *RRW*, cochlear microphonic recorded at the right round window; *RCN*, response recorded from right cochlear nucleus. The photos in the top row are (A) taken 5 minutes before, and (B) just before section of the eighth nerve. Photos in the lower row are (C) taken immediately after, and (D) 5 minutes after section of the eighth nerve. The CM response survives the section, whereas the FFR and the evoked potential from the cochlear nucleus are abolished.

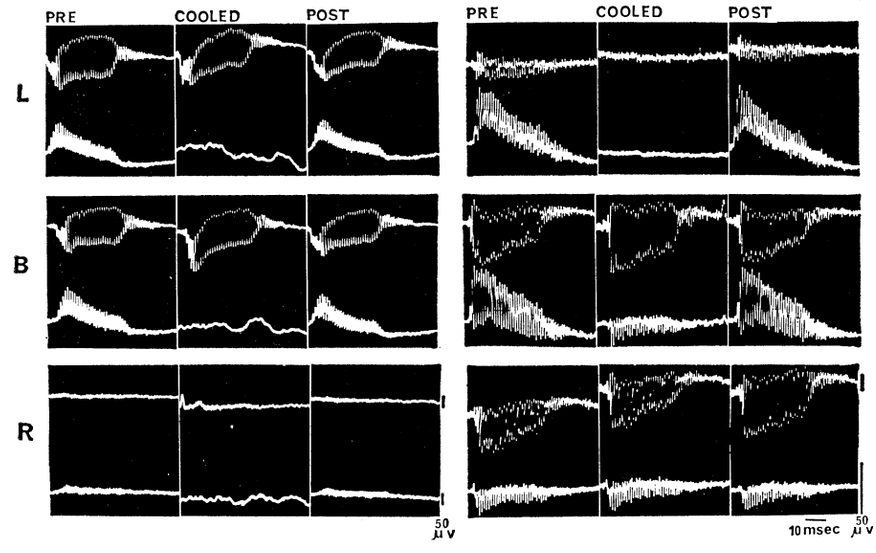

Fig. 2. Reversible interruption of neural conduction produced by cooling the cochlear nucleus with a cryoprobe. In the three left columns, the upper traces in all photos are CM responses recorded from the left round window. The lower traces show the evoked potential and FFR recorded from a recording tip on the cryoprobe. In the right-hand columns the upper and lower traces show the evoked potential and FFR recorded from, respectively, the left and right accessory nuclei of the superior olivary complex. The three rows of photos are: *L*, left monaural stimulation; *B*, binaural stimulation; *R*, right monaural stimulation. In all cases, the stimulus was a tone pulse with a frequency of 900 hz, duration of 20 msec, and intensity of 94 db. Each set of three pictures shows responses recorded before, during, and after cooling of the left cochlear nucleus. The cooling abolishes responses from the left cochlear nucleus without affecting the left CM recorded from the left round window. At the olivary level, responses are abolished to left monaural stimulation during cooling of the left cochlear nucleus. During cooling, olivary response to right monaural stimulation are not affected. Normally, the olivary response to binaural stimulation reflects an interaction between the effects of right and left monaural stimulation, whereas under cooling the response to binaural stimulation is the same as that to right monaural stimulation.

FFR recorded from the left cochlear nucleus at the tip of the cryoprobe were temporarily abolished by cooling (approximately 6°C drop at the cryoprobe tip); they were recovered completely when the temperature returned to normal. The CM response at the left round window was not affected by this cooling. At the accessory nucleus of the superior olive, FFR was evoked by sound stimuli to either ear, and cooling of the left cochlear nucleus abolished it for left monaural stimulation but not for right monaural stimulation.

That neural conduction was interrupted on the cooled side is further demonstrated by the polarity and amplitude of the olivary response to binaural stimulation during cooling. Before and after cooling the response to binaural stimulation reflects an interaction between the response to right and left monaural stimulation. In contrast, during cooling, the olivary response to binaural stimulation is identical to that of right monaural stimulation.

These results demonstrate that FFR is a neural response which, like the evoked potential, depends upon the functional integrity of the auditory pathway. It follows that further exploration of the significance of FFR should not be clouded by concern over whether or not it is in fact a neural response.

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References

1. E. G. Wever and C. W. Bray, *J. Exp. Psychol.* **13**, 373 (1930).
2. C. S. Hallpike and H. Hartridge, *Proc. Roy. Soc. London* **122**, 175 (1937); E. H. Kemp, G. E. Coppée, E. H. Robinson, *Amer. J. Physiol.* **120**, 304 (1937); J. C. Boudreau, *Nature* **208**, 1237 (1965); F. G. Worden and J. T. Marsh, *Electroenceph. Clin. Neurophysiol.* **25**, 42 (1968).
3. J. T. Marsh and F. G. Worden, *Laryngoscope* **78**, 1149 (1968); J. C. Boudreau, *J. Acoust. Soc. Amer.* **37**, 779 (1965); E. G. Wever and C. W. Bray, *Proc. Nat. Acad. Sci. U.S.* **16**, 344 (1930); A. J. Derbyshire and H. Davis, *Amer. J. Physiol.* **113**, 476 (1935); G. A. Moushegian, A. Rupert, M. A. Whitcomb, *J. Neurophysiol.* **27**, 1174 (1964); S. S. Stevens and H. Davis, *Hearing, Its Psychology and Physiology* (Wiley, New York, 1938).

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