Electrocardiographic Notching in Rats Deficient in Essential Fatty Acids

Abstract. *A notch has been seen in the electrocardiograms of rats who were fed diets deficient in essential fatty acids. This notching occurs consistently at a point 37 percent through the* QRS-*complex. It can be prevented by the addition of small amounts of linoleate, linolenate, or arachidonate to the diet of these rats.*

An interest in the relationship between heart disease and essential fatty acid (EFA) nutrition led to this study of the changes in the electrocardiogram of rats maintained on EFA-free diets.

In one of our experiments, 75 male rats who weighed from 35 to 50 grams each, were fed a fat-free diet for 10 weeks. The diet contained 18 percent casein, 74 percent sucrose, 4 percent cellulose (Alfacell), 4 percent Wesson Salt Mixture, and a complete vitamin mixture (*1*). As a control, 10 other rats were placed on a similar diet which contained 5 percent corn oil in place of an equal weight of sucrose. By the end of eight weeks, rats on the fat-free diet had developed a dermatitis of the paws, tail, and coat [total dermatitis score = 3 to 5 (*2*)] and they weighed an average 230 grams as compared with 290 grams for the controls.

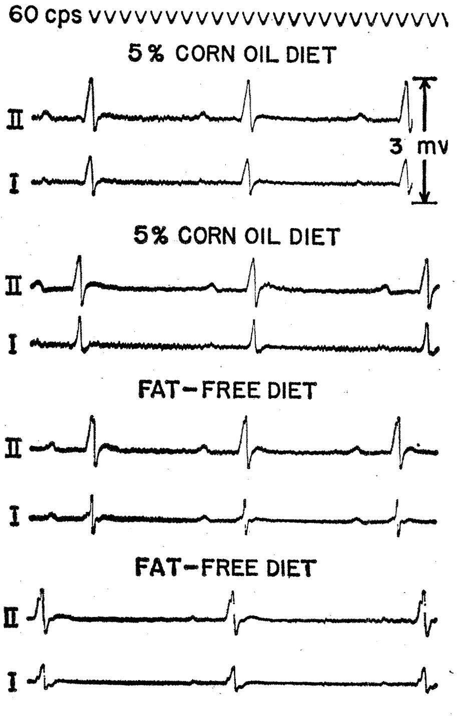

Fig. 1. Typical electrocardiograms of two normal and two EFA-deficient rats.

Each 3 weeks during the depletion period electrocardiograms were recorded on all animals. For this, each rat was anesthetized with an intraperitoneal dose of 40 mg of Nembutal per kilogram of body weight. Ether was not used since it is highly toxic to EFA-deficient animals. Electrocardiograms were recorded with a Honeywell Visicorder with a T-1500 galvanometer (response essentially flat to 900 cy/second) which was driven by a Tektronix (type 122) preamplifier and a transistorized power amplifier which was designed to provide an essentially flat frequency response from 0.2 cy/second to the upper frequency limit of the galvanometer.

Figure 1 shows a typical electrocardiogram for both the normal and the EFA-deficient rat. The time tracing, which marks each one-sixtieth of a second, was taken from the power line. The tracings marked I and II represent lead I (between right and left forelimbs) and lead II (right upper forelimb to left hind limb) as used previously (*3*).

This same experiment, with slight variations, has been repeated so that over one hundred EFA-deficient animals have been observed and their electrocardiograms have been studied. The one consistent change noted in the electrocardiogram of every one of the EFA-deficient animals was a notching in the *QRS*-complex. Similar notching has not been seen in the record of any control animal (*4*) either in this experiment or in previous work (*5*).

As measured from the start of the *Q*-wave, the notch appears typically at 37 percent (S.D. = 5 percent) of the horizontal distance (time) through the *QRS*-complex and it may have an amplitude of as much as 10 percent of the vertical distance from *R* to *S*. The horizontal position of the notch is highly consistent, but the amplitude of the notch in any single lead varies. This makes quantitation of the degree of notching difficult.

In general, this *QRS*-notching, which points to an alternation in ventricular conduction, appeared before the rats developed dermatitis, and it disappeared more rapidly when linoleate was administered than when other substances were used. In 30 to 60 percent of the rats, administration of a single dose of 200 mg of linoleate, 100 mg of linolenate, or 50 mg of arachidonate returned the electrocardiogram to normal within four days. *QRS*-notching thus provides a sensitive indicator of essential fatty acid deficiency in the rat (*6*).

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4. In one control rat (5 percent corn oil), notching was seen at a point 59 percent of the way through the *QRS*-complex. Since this point was more than 4 standard deviations away from the position in the *QRS*-complex described in this report, the record was excluded.
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Psychophysics of Perceived Intensity: A Theoretical Basis for Fechner's and Stevens' Laws

Abstract. *A "matching-response" model of psychophysical judgment is proposed, in terms of which power-law relationships would be expected between perceived intensity and stimulus strength, even though receptors had logarithmic response characteristics. On this model, observed differences in exponent for various modalities would reflect differences in coupling coefficients, rather than in transducer mechanisms.*

Fechner's famous contention (*1*), that the "strength of sensation" is logarithmically related to the stimulus intensity, has recently been challenged by Stevens (*2–4*), who adduces convincing experimental evidence for a "power law" of the general form

$$\psi = a(I - I_0)^\beta \quad (1)$$

Here ψ is the perceived intensity, I the physical intensity, and a, I_0, and β are constants.

Some authors have regarded Fechner's law as a reflection of the logarithmic relation between the frequency of nerve impulses from sensory receptors and the intensity of stimulation. With the advent of Stevens' law (Eq. 1), the question is then raised whether a closer look at receptor firing-frequencies might

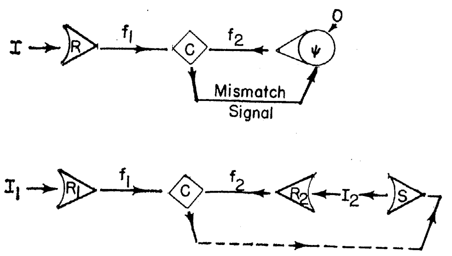

Fig. 1. (Top) "Matching-response" skeleton model for perception of stimulus intensity. (Bottom) "Matching-response" skeleton model for cross-modal matching of perceived intensities, I_1, I_2, of two stimuli. The source S of intensity I_2 is supposed adjustable by the subject to meet the matching criterion (Eq. 4) of comparator C.

not reveal a power-law relation to stimulus intensity, or, if not, how the nervous system succeeds in putting them through the transformation supposed necessary to square with the power law of perceived intensity. Thus Marimont (*5*) suggests that an "exponentiating" device at some point could enable the visual receptors to retain their traditional logarithmic response without embarrassing Stevens' law. No satisfactory neurophysiological basis for such a transformation, however, is as yet known.

The object of this report is to present a simple theory of perceived intensity that requires nothing but approximately logarithmic or linear transformations to take place at receptors or at any point within the nervous system, yet leads directly both to a prediction of Stevens' power law and to an explanation of the approximate proportionality of the just noticeable difference (jnd) to intensity, which led to Fechner's classic postulate. In the process it suggests a direct functional interpretation of Stevens' exponent β, and of its wide variability from one sense modality to another.

The hypothesis here advanced stems from a theoretical model (*6*) in which perception is regarded as an internal, outwardly directed, adaptive or "matching" response to stimulation, generated within the organizing system that determines the current "state of readiness" of the organism. On this view the perceived intensity of a stimulus should reflect, not the frequency of impulses from the receptor organ, but the magnitude of internal "organizing activity" evoked to match, or in some other sense "counterbalance," that frequency.

The information-flow model thus suggested is outlined in Fig. 1 (top). The receptor R emits a frequency of f_1 in response to intensity I, according to the law

$$f_1 = k_1 \log (I - I_0) + a_1 \tag{2}$$

where I_0, k_1, and a_1 are constants. In the estimation of perceived intensity as described by Stevens, we now postulate that an internal "organizer" or "effort-generator" O produces a "matching" frequency

$$f_2 = k_2 \log (\psi - \psi_0) + a_2 \tag{3}$$

where ψ_0, k_2, and a_2 are constants, and ψ is the internal activity which is sufficient to make f_1 match f_2 according to the criteria of the comparator C.

Suppose that equilibrium is attained when

$$f_1 = bf_2 + k_3 \tag{4}$$

where b is a factor representing the relative "weight" given by C to the output from O compared to that from R, and k_3 is the "zero bias" of C. Then

$$k_1 \log (I - I_0) = bk_2 \log (\psi - \psi_0) + k_3 - a_1 + ba_2$$

or, in the notation of Eq. 1,

$$\psi - \psi_0 = a\,(I - I_0)^{\beta} \tag{5}$$

where

$$\log a = (a_1 - ba_2 - k_3)/bk_2 \tag{6}$$

and

$$\beta = k_1/bk_2 \tag{7}$$

Stevens' power law, on this model, is thus the natural consequence of the existence of logarithmic or near-logarithmic transfer functions in the elements of the system.

As well as predicting the power law, Eqs. 4 to 7 offer a direct interpretation of Stevens' constants a and β in quasi-neurological terms. According to Eq. 6, a reflects essentially the "zero bias" of the transducers and the postulated comparison process, weighted according to the effective strength of coupling between the internal "effort generator" O and the comparator C. The exponent β invites interpretation as measuring the relative extent to which stimulus and matching response respectively are attenuated before comparison (in logarithmic form). A value of β greater than 1 means that the coupling between effort-generator and comparator is relatively the weaker; a value less than 1 means the opposite.

With this in mind it is interesting to glance at the values of β obtained by Stevens for various modalities. His table shows a range from 0.33 to 3.5, where the perceived intensity was estimated by the subject on a numerical scale (*3*, pp. 1–34). Intermodal comparisons (brightness matched against loudness, for example) are stated to be consistent with the figures so obtained for each modality separately (*3*, p. 17 ff.; it may be noted that in the form in which Stevens presents his results, $\psi_0 = 0$).

The presupposition behind Stevens' discussion of his results is that differences in exponent β reflect "basic differences in the transducer systems involved. . . . The exponents for taste are generally about twice as large as the exponents for smell. Does this difference . . . mean that two wholly different mechanisms underlie the transduction processes in taste and smell?" (*3*, p. 30).

Our present model (Fig. 1, bottom) would suggest that this conclusion, though admissible, is by no means nec-

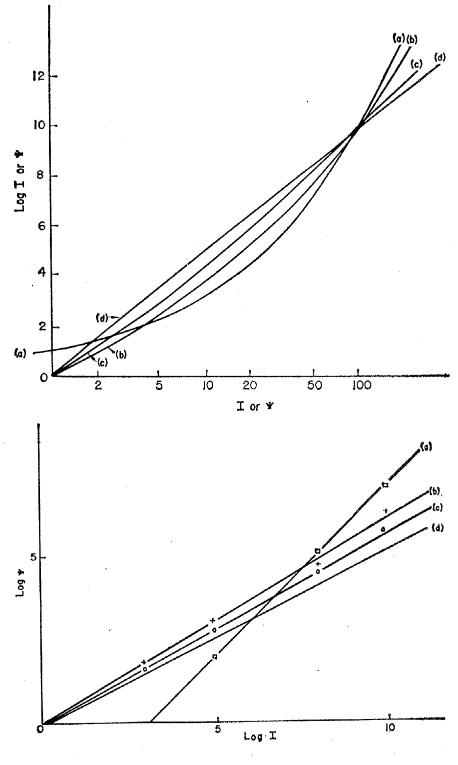

Fig. 2. (Top) Log-linear graphs of hypothetical receptor characteristics. *a*, power-law; *b* and *c*, successive approximations to log-law; *d*, log-law. (Bottom) Log-log graphs of resulting "psychophysical laws" according to the model of Fig. 1. Note that a wide range of receptor and matching generator characteristics give rise to "power laws" of perceived intensity, to a good approximation.

essary. On the face of it, all that need be implied is that the receptive input for taste is more weakly coupled to our hypothetical comparator than that for smell. Both transducers could well be logarithmic. Similarly, our "matching" hypothesis would interpret the disparity between the exponents β for a 5° visual target and a point source, or for different states of adaptation (*4*), not as a sign of different input transfer functions, but simply as an indication that the action of other stimulated receptors around a given point, or the changes in dark adaptation, alter the effective coupling between its output and the comparator (or, of course, that between O and C). (Note that this is quite different in effect from an attenuation of the *input* to the receptor by a constant factor, which would not affect the exponent β.) Area for area, a small stimulated region gets relatively more impulses through to the comparator per log unit of brightness; but the responses of both can still be logarithmic, and indeed should be (approximately) so on the simplest form of the present theory.

How important is it, for this model, that R and O should follow a logarithmic law? The easiest and most practical test of tolerance would seem to be to try some samples of alternatives to the logarithmic law, and show graphically the extent to which the resulting psychophysical curves would depart from a power law. Figure 2 presents some results. The first of these (curve *a*) shows that if we assume an absence of zero bias ($k_3 = 0$ in Eq. 4), then with a *power law* instead of a logarithmic law in R and O the model would still predict a power law of perceived intensity. This is easily seen analytically, since if

$$f_1 = k_1 (I - I_0)^{\alpha_1} \tag{2a}$$

and

$$f_2 = k_2 (\psi - \psi_0)^{\alpha_2} \tag{3a}$$

then if

$$f_1 = b f_2 \tag{4a}$$

it follows at once that

$$\psi - \psi_0 = a(I - I_0)^{\beta} \tag{5a}$$

where

$$a = (k_1/bk_2)^{1/\alpha_2} \tag{6a}$$

and

$$\beta = \alpha_1/\alpha_2 \tag{7a}$$

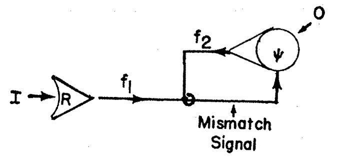

Fig. 3. Simplified skeleton model in which "comparison" is performed by way of retroactive inhibition of the input to O.

Note, however, that in this case β should no longer depend on the relative strength of the couplings between R and C and between O and C. This makes an operational difference that should in principle be detectable.

The second general point to be noted is that if the exponent β is not too far from unity, almost any monotonic transfer function for both R and O could yield a passable fit to a power law of perceived intensity. This is illustrated by curves *b* and *c* in Fig. 2, for two arbitrarily chosen but plausible departures from log-linearity in the transfer functions of R and O.

The moral of this exercise is that unless rather specific experimental tests are made, no firm inference to the transfer function of the sensory channel can be drawn from demonstrations that the curve of perceived intensity is best fitted by a power function. If the present model is valid in its simplest form it is a mistake to suppose that *any* stage or chain of stages performs a power-law transformation; but in any case it is clear that no stage or chain *need* do so in order to produce Stevens' results.

What, then, of the dependence of jnd on intensity, and Fechner's "law"? On the present model they also invite a simple interpretation, fully in harmony with the power law.

Suppose that in the system of Fig. 1 the effort generator O has "matched" the output from R, so that the net input to C (the "mis-match") has fallen below some effective threshold of significance, Δf. This means that unless the net input rises or falls by Δf, the internal "setting" that determines the activity of O is not significantly altered. (Whether Δf is defined for the "method of constant stimuli," or for the addition of ΔI to a background I, the point of the present argument is unaffected.)

Clearly, if the transfer-function of R is near-logarithmic, the change ΔI required to produce a mismatch Δf will be nearly proportional to I (more strictly, to $I - I_0$). Thus, on the present model, Fechner's "law" is exactly what one would expect if the subject is in fact here reporting, not the strength of the "internal activity" in O, but the occurrence of significant disturbance of the "setting" of O. Starting with a low intensity of stimulation (I), and adding up the number of significant disturbances as I is increased, we should, of course, obtain a near-logarithmic curve relating the total number to the intensity I, if Δf were constant.

What, then, was Fechner measuring? Certainly not, on our model, the perceived intensity of the stimulus; but this does not mean that his total had no significance. On the contrary, if we are on the right lines, Fechner's method is precisely what would be needed if we wanted to derive the form of the transfer function of R, assuming that Δf was constant. The "threshold" in Fechner's procedure is being used simply as a movable "yardstick of frequency," laid end-over-end, so to say, against the output of R, in exactly the way that a literal yardstick is employed to measure large distances.

It would follow that, by comparing the Fechnerian curve for a given sensory channel with the physiologically ascertained transfer function, we should be able to study *changes* in the threshold Δf as a function of the input to the comparator; but it must be remembered that this assumes that the whole sensory channel concerned, and not merely the receptor organ, has been identified and characterized physiologically.

It may be well to point out some of the refinements to which the present theory is open at the neurological level.

The basic function of a comparator is, of course, found in the mechanism of simple neural inhibition. It is quite common to find the net firing frequency f_3 of a cell or pool of cells related to the frequencies f_1 and f_2 of excitatory and inhibitory input according to a law of the form

$$f_3 = \phi(f_1 - bf_2) \tag{8}$$

where ϕ is some monotonic function, and b represents the relative effectiveness of inhibitory as against excitatory input.

Such a system is well-suited to operate as a comparator according to Eq. 4, provided that the cells obeying Eq. 8 are "backed up" by a complementary population of cells that fire when bf_2

$> f_1$. In some cases it might even be sufficient to have a single cell system with a high enough resting frequency to cope with negative as well as positive values of $(f_1 - bf_2)$.

In any case, it is important to note that, as in all "servo" comparators, the linearity or the exact form of the response-function ϕ (Eq. 8) is of little consequence for the overall performance, provided that the sensitivity of O is high enough: that is, in technical jargon, "loop gain" large compared with unity. Moreover, it is totally unnecessary for ϕ to be "exponentiating" in form. It could quite well be linear, as in analog operational amplifiers (*7*). Only if the interaction of f_1 and f_2 were not linearly subtractive would serious departures from a power law be likely on our present model.

By the same token, there is no reason why the process we have called "comparison" should not take place in more than one stage or even in a continuously distributed interaction between efferents from O and afferents reaching O from R. Although the functional distinction between C and O is useful in Fig. 1, the neurological correlate might well be reduced in principle to something like Fig. 3, where the subtractive process is shown as occurring on the way in to the active system that organizes response. In this case, however, the requirement of high loop gain demands that O generates a high (aggregate) frequency f_2 in response to a low-frequency mismatch signal.

Histological and physiological evidence of this kind of self-inhibitory action abounds in the central nervous system (*8*). The problem of greatest interest, if the model of Fig. 3 were at all correct, would be to identify the "activity" that gives rise to the matching frequency in this case. Since we postulate a logarithmic relation between activity ψ and firing rate f_2, there is little attraction in the idea that the activity is itself linearly represented by some other neural firing rate. More plausible would seem the identification of this activity (and so, in turn, of perceived intensity) with the intensity of some metabolic or other physical disturbance known to be logarithmically related to firing frequency, in the kind of way that stimulus intensity is related to receptor firing frequency (*9*). I am aware this comes close to suggesting a heretical doubt that all conscious experience is tied directly to patterns of nerve impulses; but the task of intelligibly linking conscious perception with brain action seems neither more nor less perplexing if we fasten it upon the physicochemical "effort" of the cell or its environment, rather than upon the impulses it emits. If anything, the first would seem a little easier to square with the unity and continuity of perceived experience.

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9. A brief note may be in order regarding the "naturalness" of the logarithmic transformation (or something near to it) as a basic operation in a neurophysiological model. One might well ask: why logarithmic, rather than linear or power-law? There are in fact two reasons, one functional, the other structural. First, receptor organs, especially of mobile organisms, have to function over wide ranges of intensity. Moreover, the significant information conveyed by most sense organs depends on spatial and/or temporal patterns (for example, of surface brightness) which are specified by the *ratios* between various received intensities, regardless of overall level. Thus, for example, if the ambient daylight on an object waxes or wanes, it is obviously desirable that the contrast between signals representing different parts of its optical image should be preserved from significant change. A logarithmic transfer function would ensure this in the simplest possible way, since it would leave the differences between firing-frequencies unaffected by changes in intensity of illumination. Second, logarithmic laws arise naturally in the kinetics of self-equilibrant chemical reactions, and can therefore be postulated with the minimum of *ad hoc* assumptions in the context of neural activity. They imply simply that the "gain" or incremental sensitivity of the transducer in question is automatically reduced in proportion to the intensity of input.

2 January 1963

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Reversible Section of the Brain by a Wall of Cold

Abstract. *A fork made up of hollow tubing may be chronically implanted in the cat's brain. When cooling fluid is pumped through this fork a reversible plane lesion is formed. This technique permits analysis of functional parts of the nervous system in unanesthetized animals.*

Cooling may be used to block conduction reversibly in nerves. This phenomenon has been used in the study of the peripheral nervous system (*1*) and in the study and treatment of diseases of the central nervous system (*2*).

Local extravascular cooling is one subdivision of a recently published classification of hypothermia (*3*). We feel that it is useful to further classify cooling techniques by purpose, method, and geometrical dimensions of the source and cooled area. The cooled area must, of course, be three-dimensional, regardless of the nominal dimension of the source. The region of complete conduction block, however, may be adjusted to be a good approximation of zero, one, two, or three dimensions by varying the temperature of the thermodes.

Local cooling has been used for study of temperature-sensitive receptors (*4*), for reversible block of conduction (*5*), and for permanent surgical lesions. The heat-sink requirements of thermodes for each of these purposes are quite different and so have lent themselves to different techniques of refrigeration. As one would expect, lower temperatures require more involved systems.

The geometric dimensions of the heat sink (thermodes) may be defined as follows: 0: point, or zero-dimensional thermodes for cooling small masses of tissue on the surface of or in the depths of the brain; 1: line, or one-dimensional thermodes for cooling cylinders of tissue (the area of interest may be only at the tip of the thermode and thus be zero-dimensional); 2: plane, or two-dimensional thermodes for cooling the surface of the brain; 2-D: planar cooling thermodes which are not full planes but provide a planar thermal field in the depths of the brain; 3: solid, or three-dimensional thermodes which may be either special configurations of one-dimensional heat sinks or multiple one-dimensional heat sinks arranged to form an even thermal field in a large mass of tissue. The configuration of only the heat-sink portion of the thermode is of importance because this defines the area which will be cooled.

Zero-, one-, and three-dimensional cooling are now being used in surgery and physiology. This report describes a technique for two-dimensional cooling