Reports

Space-Time Relationships in Somesthetic Localization

It has been suggested recently that the representation of somesthetic space depends on temporal patterns of neuronal discharge in the parietal association areas of the cerebral cortex (*1*). This suggestion was based on the discovery that there are neurons in these areas which may be aroused from any of several points on the periphery, but with different latencies. It is likely therefore, that time and space should be interchangeable to some degree, and that increasing the temporal separation of two stimuli should decrease the spatial separation necessary for them to be judged as in different places. Such is actually the case for touch. It is well known that the two-point threshold (stimuli simultaneously presented) is considerably greater than the error of localization (stimuli successively presented) (*2*). But the temporal relationships have not been studied in detail, as is necessary if the neurophysiological and psychophysical data are to be correlated. The experiment reported here is a step in that direction (*3*).

The minimum separation of two stimuli to the skin which led them to be judged to be in different places was determined for each of several temporal intervals between them. The stimuli, electric square waves of 0.5-msec duration, were presented to the forearms of two subjects through silver-silver chloride wick electrodes. The stimuli were generated by a "two-shot" stimulator built in the department of physiology and biophysics, University of Washington. Intervals, from the end of pulse one to the beginning of pulse two, of 0.1, 1.0, 10.0, 100.0, and 1000.0 msec were used. Since the more distal of the two stimuli was always the second pulse, these intervals are about 2.1, 3.0, 12.0, 102.0, and 1001.0 msec when allowance is made for the extra conduction time. Four determinations of spatial separation were made for each interval on each subject at a single sitting, using the "up and down" method (*4*). Each subject had four sittings, with the different intervals given in balanced order, so that each threshold is based on 16 measurements. Considerable care was used to insure pure pressure stimualtion, painful spots being discarded, and the intensity of stimulation was adjusted each time an electrode was moved to maintain a moderately strong pressure sensation. Subjects' reports consisted either of "same place" or "different place," because at the longest intervals the duality of stimulation was evident. Apparent movement was sometimes observed but did not interfere with the judgments.

Table 1. Minimum separation, in centimeters, judged as "different place" by subjects F.N.J. and M.H.J.

Interval (msec)	F.N.J.		M.H.J.	
	Mean	S.D.	Mean	S.D.
2.1	11.0	1.4	11.8	1.2
3.0	10.6	.5	10.3	1.4
12.0	10.2	1.0	10.9	1.0
102.0	7.1	1.4	7.7	2.8
1001.0	4.5	.8	3.0	.9

The data are given in Table 1. If the shortest interval is taken to represent the two-point threshold and the longest is taken to approximate the error of localization, the data are in agreement with the older research. There is significant interaction of space and time, and increasing the interval reduces the separation necessary to produce the report of "different place."

The question now arises whether the psychophysical and neurophysiological data are consistent. If allowances are made for species differences and for the effects of anesthetics, the answer is in the affirmative. Amassian's "blocking" effects for the AAP (association-area positive response) extend over as many as 600 msec and are consistently noted below 150 msec. In the experiment reported here, the region of most rapid change in spatial threshold lay between 10 and 1000 msec, with only a slight change, if any, between 2 to 10 msec. The error of localization is approximated at about the interval necessary for blocking to be ineffective. The blocking could account for the lack of fine discrimination because the necessary information does not reach the parietal association areas.

There are possible alternative explanations of the psychophysical data. Some years ago Boring suggested that the difference between the two-point threshold and the error of localization could be due to the spread of excitation in the skin (he had mechanical stimulation in mind) (*5*). He did not have precise temporal data available, and the present data, because of the relatively large critical intervals, do not favor a peripheral explanation. The same spread-of-excitation argument could be extended to the relay nuclei and the primary sensory cortex, however. Isomorphic theories of space perception have been popular, and if two-point tactual discrimination is considered to be based on two regions of excitation in the primary cortex, it may also be that temporal separation permits better differentiation of these regions. This would imply that the "sharpening" process imputed to some sensory systems is improved by the delay of one afferent process, an implication that is not borne out by experimentation on vision (*6*). When it is considered in addition that lesions in the parietal association areas may lead to a severe deficit in somesthetic perception (*7*), the suggestion that space perception in the pressure sense arises from the translation of spatial patterns in the primary sensory cortex into temporal patterns in the association areas has both plausibility and appeal. If this suggestion should prove correct, it will be of considerable aid in clarifying the problem of the neurophysiological basis of perception.

F. Nowell Jones
Department of Psychology, University of Califorina, Los Angeles

References and Notes

1. V. E. Amassian, *J. Neurophysiol.* **17**, 39 (1954).
2. See, for example, E. G. Boring, *Sensation and Perception in the History of Psychology* (Appleton-Century, New York, 1942), pp. 484 ff.
3. This experiment was performed while I was spending a sabbatical year as research associate in physiology and biophysics at the University of Washington School of Medicine, Seattle.
4. J. P. Guilford, *Psychometric Methods* (McGraw-Hill, New York, ed. 2, 1954), p. 114.
5. E. G. Boring, *Am. J. Psychol.* **42**, 446 (1930).
6. Vision does not behave the same as somesthesis. M. Leyzorek, [*J. Exptl. Psychol.* **41**, 364 (1951)] found no time dependence for visual acuity up to 13 sec.
7. J. P. Evans, *Proc. Assoc. Research Nervous Mental Disease* **15**, 331 (1934).

2 July 1956

Enzymatic Deficiency in Primaquine-Sensitive Erythrocytes

Primaquine, 8-(4-amino-1-methylbutylamino)-6-methoxyquinoline, induces intravascular hemolysis in about 10 percent of Negroes, but rarely in Caucasians (*1*). This hemolysis is due to a defect of the red blood cells (*2*), is

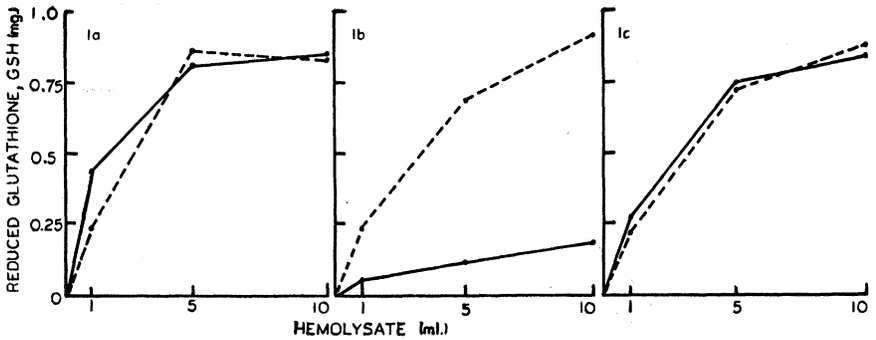

Fig. 1. Milligrams of reduced glutathione formed from oxidized glutathione as a function of milliliters of dialyzed hemolyzate. Solid curve, primaquine-sensitive subject; dashed curve, normal subject. (*a*) Assay of GSSG reductase, reaction 1; (*b*) assay of G-6-P dehydrogenase, reaction 2 + 1; (*c*) assay of 6-P-G dehydrogenase, reaction 3 + 1.

a function of cell age (*3*), and, therefore, is self limited (*4*). The red blood cells of susceptible individuals have a low glutathione level (*5*) and an increased tendency to form Heinz bodies (*6*). Hemolysis can also be induced by certain other aniline derivatives (*7*). In this preliminary report, we present evidence of an abnormality in glucose-6-phosphate dehydrogenase activity in hemolyzates of primaquine-sensitive erythrocytes.

The abnormality has been demonstrated by investigation of the following reactions in hemolyzates of red blood cells from primaquine-sensitive and normal subjects (*8*).

$$\mathrm{GSSG + TPNH + H^+} \xrightarrow[\text{reductase}]{\text{GSSG}} \mathrm{2\,GSH + TPN^+} \quad (1)$$

$$\mathrm{G\text{-}6\text{-}P + TPN^+} \xrightarrow[\text{dehydrogenase}]{\text{G-6-P}} \mathrm{6\text{-}P\text{-}G + TPNH + H^+} \quad (2)$$

$$\mathrm{6\text{-}P\text{-}G + TPN} \xrightarrow[\text{dehydrogenase}]{\text{6-P-G}} \mathrm{pentose\ phosphate + CO_2 + TPNH + H^+} \quad (3)$$

Rall and Lehninger have indicated that glutathione reductase is present in human red blood cells (*9*). Reduced triphosphopyridine nucleotide serves as coenzyme. Glucose-6-phosphate and 6-phosphogluconate are successive intermediates in the direct oxidation of glucose. Both substrates have been used to form a coupled system—by providing TPNH—for demonstration of glutathione reductase (*10*).

Heparinized blood from two normal men, one Caucasian and one Negro, was compared with blood from four sensitive Negroes. After the red blood cells had been centrifuged and washed with 0.145*M* NaCl, they were hemolyzed with 5 volumes of H_2O for 1 hour at 4°C. Each hemolyzate was cleared by centrifuging at 1400*g* for 90 minutes. (Stromata were not completely removed.) Maximum temperature during centrifugation was 37°C. Fifty milliliters of hemolyzate were dialyzed for 12 hours at 4°C in 2000 ml of 0.67*M* phosphate buffer at *p*H 7.4. Dialysis serves to remove glutathione and other subtrates and coenzymes from the hemolyzate.

To determine the presence, in dialyzed hemolyzate, of enzymatic activity capable of catalyzing each of the three reactions, we mixed aliquots of dialyzed hemolyzate with those constituents appropriate to each reaction. Final reaction mixtures contained 14 ml buffered to *p*H 7.4 in 0.036*M* tris(hydroxymethyl)-aminoethane and were incubated for 15 minutes at 22°C. The concentration of oxidized gluthathione was always $1 \times 10^{-4}M$. When used, the concentration of TPNH was $1.5 \times 10^{-4}M$; TPN, $1 \times 10^{-5}M$; G-6-P, $5 \times 10^{-4}M$; and 6-P-G, $2 \times 10^{-4}M$.

The reaction was stopped by adding 10 ml of 4.5-percent metaphosphoric acid. Reduced glutathione was determined by the method of Grunert and Phillips (*11*). Glutathione reductase activity was measured by the amount of oxidized glutathione converted to the reduced form. Appropriate controls were run.

Figure 1*a* shows results obtained for direct demonstration of glutathione reductase (reaction 1), expressed as milligrams of reduced glutathione formed versus milliliters of hemolyzate used. The curves show equal activities of glutathione reductase in hemolyzates of normal and primaquine-sensitive red cells.

Because glutathione reductase is TPNH-dependent, similar glutathione reduction should be demonstrable in coupled reactions 2 + 1 or 3 + 1, if the respective dehydrogenases are normally active. When glucose-6-phosphate and TPN were used as the sole source of TPNH for activation of glutathione reductase (reaction 2 + 1), hemolyzate from the sensitive subject showed a striking failure to reduce oxidized glutathione (Fig. 1*b*). This failure indicates that hemolyzate from the sensitive subject was deficient in glucose-6-phosphate dehydrogenase activity. Hemolyzates from three other primaquine-sensitive subjects showed virtually identical inabilities to reduce oxidized glutathione when glucose-6-phosphate was the substrate.

To determine whether the succeeding step in the direct oxidation of glucose was intact, 6-phosphogluconate was added instead of glucose-6-phosphate (reaction 3 + 1). The results (Fig. 1*c*) indicate equal 6-phosphogluconic dehydrogenase activity.

We interpret these data as demonstrating an abnormality in the direct oxidation of glucose in the red blood cells of primaquine-sensitive subjects. This abnormality affects glucose-6-phosphate dehydrogenase activity (*12*).

PAUL E. CARSON, C. LARKIN FLANAGAN, C. E. ICKES, ALF S. ALVING
University of Chicago–Army Malaria Research Project (Stateville Penitentiary), Department of Medicine, University of Chicago, Chicago, Illinois

References and Notes

1. R. S. Hockwald *et al.*, *J. Am. Med. Assoc.* 149, 1568 (1952).
2. R. J. Dern *et al.*, *J. Lab. Clin. Med.* 43, 303 (1954).
3. E. Beutler *et al.*, *ibid.* 44, 439 (1954).
4. R. J. Dern *et al.*, *ibid.* 44, 171 (1954).
5. E. Beutler *et al.*, *ibid.* 45, 286 (1955).
6. ———, *ibid.* 45, 40 (1955).
7. R. J. Dern *et al.*, *ibid.* 45, 30 (1955).
8. The following abbreviations are used: GSSG, oxidized glutathione; TPNH, reduced triphosphopyridine nucleotide; GSH, reduced glutathione; G-6-P, glucose-6-phosphate; TPN, oxidized triphosphopyridine nucleotide; 6-P-G, 6-phosphogluconate.
9. T. W. Rall and A. L. Lehninger, *J. Biol. Chem.* 194, 119 (1953).
10. B. Vennesland and E. E. Conn, in *Glutathione* (Academic, New York, 1954), p. 109.
11. R. R. Grunert and P. H. Phillips, *Arch. Biochem.* 30, 217 (1950).
12. This work was supported by the research and development division, Office of the Surgeon General, Department of the Army; by Winthrop Laboratories, Inc.; and by E. R. Squibb and Sons.
13. We wish to thank B. Vennesland and E. S. G. Barron for their advice and helpful criticism in this work.

28 May 1956

Ord Kangaroo Rat in Captivity

Methods recently developed in our faunal colony now make possible the rearing of kangaroo rats in the laboratory. These methods were evolved during the development of a program designed to provide laboratory-reared rodents native to the western Utah desert for use in laboratory studies (*1*). Several of the common species of the family Cricetidae