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2. Abbreviations: SV40 is simian virus 40; SSC is standard saline-citrate, 0.15*M* NaCl and 0.015*M* trisodium citrate; 4× SSC is quadruple-strength SSC; TES is *N*-tris(hydroxymethyl)methyl-2-aminoethanesulfonic acid; PM (Denhardt's "preincubation" mixture) contains 0.02 percent bovine serum albumin, 0.02 percent Ficoll, and 0.02 percent polyvinylpyrrolidone; SDS is sodium dodecyl sulfate.
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Number Coding in Association Cortex of the Cat

Abstract. *In electrophysiological investigations of single neurons in cortical association response areas of the cat, cells have been encountered that appear to code the property of number. In a sequence of stimulus presentations, these cells characteristically discharge to a particular numbered stimulus in the series. This effect is independent of stimulus modality, intensity, and interstimulus interval; thus, the cells seem to be responding to the number of stimulus presentations.*

Bertrand Russell, in his classic analysis of the concept of number, defined number as "anything which is the number of some class; the number of a class is the class of all those classes that are similar to it" (*1*). Number is a property of stimuli that is independent of all the particular properties of the stimuli and is determined solely by relational class. Results of number perception and memory studies in man suggest that number of objects can be estimated and recalled relatively accurately up to about seven "plus or minus two" (*2*). Animal studies of counting behavior indicate that primates can learn to respond to number of objects in simultaneous presentations (*3*) and that cats can learn to "count" successive stimuli (*4*).

Higher mammals thus appear able to abstract the number of stimuli, independent of the specific aspects of the stimuli; consequently, the brain must in some manner code the number of stimuli. To demonstrate that a neural response is, in fact, coding number, it is necessary to show that the response is at least to some degree independent of particular stimulus characteristics such as quality, intensity, and frequency of presentation. A logical possibility for the locus of this coding process would be higher regions of the brain, where responses to stimuli tend to be somewhat independent of specific stimulus parameters, an example being the polysensory association-response areas of the cerebral cortex (*5*). Several lines of evidence have implicated these regions in "attentive" aspects of behavior, where response is a function of the more abstract aspects of stimuli such as complexity, recency, and "significance" (*6*). Lindsley recently proposed that these areas may subserve the more complex aspects of behavioral alerting and attention (*7*). Counting number of stimuli would seem a relevant aspect of such behavior. In work on properties of polysensory cells in these regions of the cortex in the cat, we have encountered cells that do in fact appear to code number; they behave as though they are counters.

Animals were anesthetized with chloralose (70 mg/kg, intraperitoneally), and isolated single cell activity was recorded by standard techniques with glass-coated tungsten microelectrodes. Stimuli were free field click, binocular light flash, and single shock pulses (0.25 msec duration) to ipsilateral forepaw. The existence of counting cells is revealed when a sequence of stimuli is presented after a period of no stimulation. The cell typically responds to a particular stimulus in the sequence. Such cells also respond occasionally to other stimuli in the sequence, though with a much lower probability, and sometimes to more than one stimulus in the sequence. If the stimulus sequence is continued without interruption, counting cells tend to respond successively at each appropriate stimulus in the sequence, but the pattern is somewhat less clear.

An example of a "number 7" cell (a cell "coding" the concept of number 7) in the association cortex of the cat is shown in Fig. 1A, both in terms of probability of first discharge in the sequence and in terms of total proportion of discharges to each stimulus in the sequence. This discharge pattern differs significantly from a random distribution ($N = 23$, $D = 0.513$, $P < .01$; Kolmogorov-Smirnov one-sample test). Ten separate sequences of ten stimuli (here a trimodal, simultaneous click, flash, and shock) were given with a 2-second interstimulus interval and a 2-minute intersequence interval. The distribution of responses shown in Fig. 1A, particularly the proportion of total responses around the modal seventh stimulus, is strikingly similar to the distribution of behavioral responses in cats trained to respond to a particular stimulus (for example, sixth) in a sequence (*4*).

Responses of counting cells appear to be independent of stimulus modality. An example of a "number 6" cell in the association cortex of the cat is shown in Fig. 1B. In ten sequences of ten stimuli at an interstimulus interval of 1 second, the cell exhibits a clear modal response to the sixth stimulus for both auditory ($N = 14$, $D = 0.429$, $P < .01$) and visual ($N = 13$, $D = 0.423$, $P < .05$) stimulation. Effect of varying the interstimulus interval is also illustrated for this cell in Fig. 1B. The modal value remains the same for an interstimulus interval of 4 seconds and 1 second ($N = 16$, $D = 0.338$, $P < .05$) with an auditory stimulus. Responses of counting cells also appear to be independent of stimulus intensity, at least within certain limits. Although higher stimulus intensities occasionally result in increased overall discharge levels, the modal stimulus number does not shift.

To date we have observed five counting cells in the adult cat, which code the numbers 2, 5, 6 (two cells), and 7. With such a small sample, it is not possible to make a precise estimate of the proportion of cells in nonspecific association response areas of the cortex that "count." However, crude guesses based on the proportion of such cells that we have observed suggest that in the cat about 1 percent of the cells in association areas that respond to stimuli are counting cells (that is, five in a sample of about 500).

The data given above indicate that

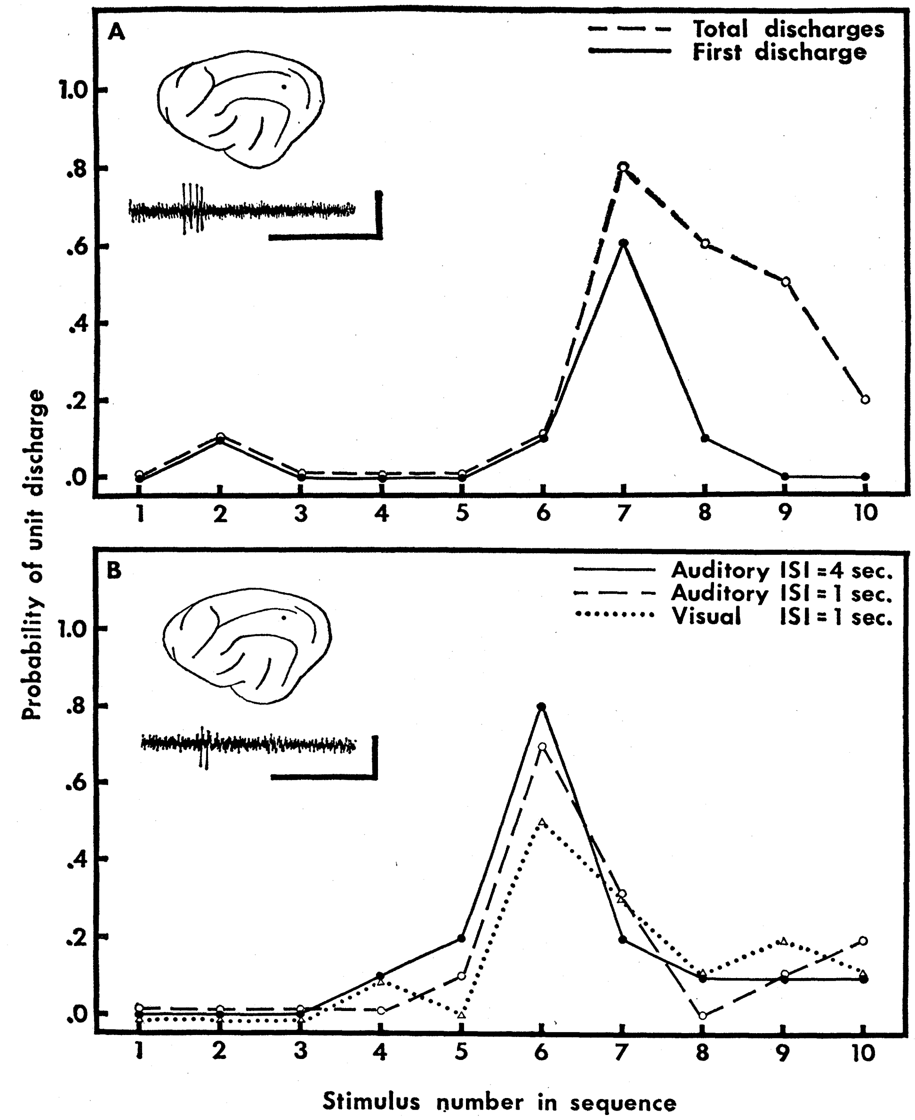

Fig. 1. Counting cells obtained in the association cortex of adult cats. Inserts show the area of cortex on a standard brain drawing where the unit was found and the characteristic unit discharge. (A) A "number 7" cell. The probability of total discharges and of first discharge is shown as a function of stimulus number in a series of ten stimuli (here, a simultaneous click, light flash, and footshock). Time mark, 50 msec; amplitude mark, 100 μv. (B) Probability of discharge of another neuron (a "number 6" cell) in the association cortex of the cat as a function of stimulus number in a sequence for visual stimuli and for auditory stimuli at interstimulus intervals of 4 seconds and 1 second. *ISI*, interstimulus interval; time mark, 50 msec; amplitude mark, 50 μv.

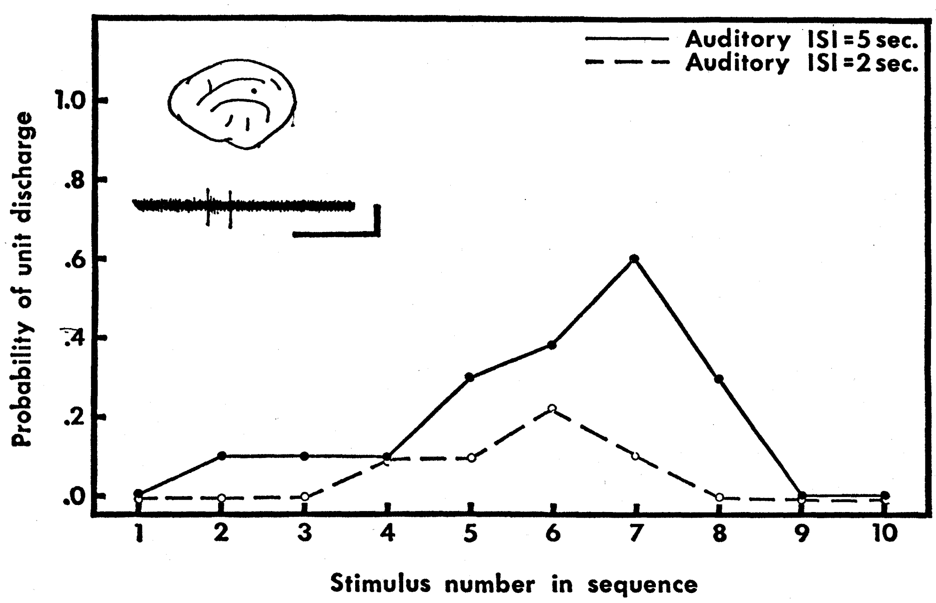

Fig. 2. Probability of discharge as a function of stimulus number in a series of stimuli for a neuron ("number 6 or 7" cell) from the association cortex of an 8-day-old kitten. Auditory stimuli at interstimulus intervals of 5 and 2 seconds were used. *ISI*, interstimulus interval; time mark, 200 msec; amplitude mark, 40 μv.

counting cells respond as a function of number of stimuli, independent of stimulus modality, intensity, and rate of presentation, at least over certain ranges. The independence of modality and intensity are not unexpected on the basis of previously known characteristics of cells in these association regions of the cortex (*8*). The independence of interstimulus interval is unexpected from past work but is, of course, crucial to the demonstration that the cells are behaving as counters. Temporal factors such as regular fluctuations in excitability are thus ruled out.

After Adrian's original definition of receptive field (*9*), studies have shown that the level of complexity of particular stimulus properties coded by single neurons is probably very great, particularly in sensory areas of the thalamus and cortex of higher mammals. Thus response to such relatively abstract aspects of visual stimuli as "angularity" has been found for cells in the visual cortex (*10*). However, as Konorski (*11*) notes, even this level of coding falls short of the apparent complexity of "perception," perhaps because these studies were concerned with coding that is essentially stimulus bound—that is, the cells respond only while the stimulus is being presented. Hebb observed that the coding of more abstract events may require "some sort of process that is not fully controlled by environmental stimulation yet co-operates closely with that stimulation" (*12*), and he proposed that complex stimulus attributes may be represented by complex phase sequences of interacting "cell assemblies." Konorski has recently developed an alternative view that the more abstract aspects of perception may be represented by single neurons, which he terms "gnostic" cells (*11*). We submit that the "counting" cells described here behave as though they code the abstract property of number and are by definition gnostic cells; however, it is entirely possible that the behavior of "counting" cells is the result of complex prior stimulus processing, perhaps by networks analogous to Hebb's cell assemblies.

The extent to which neural coding of stimuli develops as a result of experience is a fundamental problem, particularly for cells that code complex aspects of stimuli. Hebb (*12*) and Konorski (*11*) agree that complex coding, whether by cell assemblies or gnostic cells, is learned. At the other extreme, it has been suggested that even very complex attributes of stimuli may be coded by single neurons as a result of predetermined structural organization (*13*), as evidenced by Hubel and Wiesel's demonstration that complex coding of visual stimuli by cortical neurons is present in the very young kitten (*14*). Insofar as number coding is concerned, Miller, Galanter, and Pribram suggested that an innate stimulus-characteristic/brain-model comparison mechanism may form the basis of the abstract property of number (*15*). The data shown in Fig. 2 would seem to favor this general view. The cell, a "number 6 or 7" counter, was obtained in the association cortex of an 8-day-old kitten. The counting effect is perhaps less striking here than in the cells obtained in adult animals and does not reach statistical significance ($N = 24$, $D = 0.233$, $P < .2$). Although the modal value does not appear to be completely independent of interstimulus interval, the tendency is still clear.

Studies of concept learning in humans suggest that color, shape, and number may form an ordered series of increasingly complex concepts (*16*). It is perhaps relevant that differential neural coding of color appears to occur at or below the level of the visual thalamus (*17*), that neurons coding shape are found by the level of the visual cortex (*10*), and that number may be coded in association areas of the cortex. However, it must be emphasized that the data presented here merely show that, under the conditions of our experiments, certain cells in the association cortex fulfill the operational requirements necessary to code the concept of number. It remains to be demonstrated that these "counting" cells function to code number of stimulus events in the organism under conditions of normal behavior.

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Histochemical Abnormalities of Skeletal Muscle in Patients with Acute Psychoses

Abstract. *In 29 acutely psychotic patients (mostly schizophrenic), histochemical abnormalities of a myopathic type were demonstrated in skeletal muscle biopsies from 13 and were generally correlated with elevation of the "muscle" type isoenzymes of creatine phosphokinase in the patients' serum. The incidence was much higher than found in normal controls, hospitalized neurotic psychiatric patients, or parents of acutely psychotic patients. A diazo-coupling type of "alkaline phosphatase" reaction was particularly useful in identifying abnormal muscle fibers.*

A rise in the blood of the "muscle" type isozymes of creatine phosphokinase (CPK) associated with acute exacerbations of psychoses of various kinds has been reported (*1*). Histochemical abnormalities of a myopathic type have now been demonstrated in skeletal muscle biopsies from such patients.

Muscle biopsies were obtained from 29 patients with acute exacerbations of psychoses, 22 of whom were schizophrenic, the others having affective, paranoid, or involutional psychoses. They were compared with biopsies from two chronic schizophrenic patients, 11 hospitalized nonpsychotic psychiatric patients, four parents (one also an acute psychotic) of acutely psychotic patients, 45 nonpsychiatric normal control subjects, and 142 nonpsychiatric patients with various neuromuscular diseases. Biopsies averaging 8 by 8 by 12 mm were obtained from the gastrocnemius or vastus lateralis. No patient had any significant trauma, including that caused by needles, to the muscle prior to its being biopsied. The specimens were rapidly frozen within 5 minutes of removal (*2*), and kept well frozen until sections were cut from each specimen. Sections stained with the methods for modified trichrome (*3*), reduced nicotinamide adenine dinucleotide–tetrazolium reductase (NADH-TR) (*4*), myofibrillar adenosine triphosphatase at *p*H 9.4 (*5*), basophilia (thionine), and "alkaline