

REVIEW

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Neuroethology has pregnant agendas

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Abstract Two of the many agendas of neuroethology are illustrated with examples. The first issue is what cells or assemblies of cells and what patterns of activity are sufficient to accomplish recognition of ethologically important stimulus configurations and initiation of behavioral action. The theme is the opportunities available in relatively neglected approaches to these objectives. As an example, the approach is developed of gentle microstimulation of loci in the brain where cells have been found to be responsive to complex, natural stimuli, under conditions conducive to the performance of tell-tale behavior. Other approaches include: (a) microinjection of modulatory substances into regions with such complex recognition cells, and (b) recording in efficient and informative ways, by using multiple electrode arrays, registering wideband activity, in behaving animals. The second issue is what brain and behavior differences has evolution produced between major taxa at distinct grades of complexity. Emphasized are our relative ignorance of basic aspects of connectivity, physiology and cognitive capacities in the major grades and the probability of surprises from new studies that employ comparison.

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I appreciate the honor of being selected from the crowd of founders – no doubt by reason of being chronologically gifted or having the least hair. There were going on for a hundred founders at that crucial ad hoc business

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meeting after Jörg-Peter Ewert's excellent symposium on lower vertebrate neuroethology in a lovely suburb of Kassel back in 1981, where we voted to perpetuate such good meetings and to broaden them to cover all animals and approaches. A goodly number of people had a strong hand in the founding, including Mark Konishi, Bob Capranica, David Ingle, Franz Huber and Jörg-Peter Ewert.

Now, while I appreciate the honor keenly, I am perfectly aware that the topic chosen for me is a polite way of saying "No data; this is not a platform to tout your latest findings or brag about your postdocs. What we want is some wild, after-dinner predictions that we can laugh at, both now and as they turn out to be wrong, one by one. That's what old geezers are good for!" So, I shall oblige, with some controversial predictions and questions that will not tax your already sated brain capacity. I have achieved the ultimate in weeding out slides – although it was hard not to pick one from each phylum. So, sit back and relax; I'll try to steer around the bumps.

Perhaps a good many modern neurobiology doctorates do not remember that neuroethology won the Nobel Prize for 1949. It went to Walter Rudolf Hess of Zurich for his studies of subcortical organization in the cat, with respect to the expression and apparent experience of emotion. He learned, for example, how to tell real rage from sham rage induced by stimulation through electrodes in the hypothalamus (Hess 1964). I would like to draw your attention to Hess's approach – a little-used form of *brain stimulation*. Another well known example is the report of Wilder Penfield (1956) who stimulated a spot on the conscious patient's cortex and elicited a vivid scene in memory. Strumwasser and Cade (1957) in my laboratory stimulated a falcon – a small hawk – through an electrode implanted somewhere in the hypothalamus and observed visual fixation behavior suggestive of the bird hallucinating an object of interest. Similar stimulation in a pocket mouse, *Reithrodontomys*, caused both forepaws to fly back and forth, stuffing invisible seeds into the mouth. Erich von

Holst and Ursula St. Paul (1960) stimulated the hypothalamus in an alert chicken and evoked various pieces of normal behavior. In the presence of a motionless, stuffed weasel which, by itself, caused no special reaction, electric current applied to the right place triggered conspicuous alarm and attack. Jose Delgado's taming of a Spanish fighting bull by stimulating the amygdala was featured in the New York Times. We heard a bit about the use of microstimulation from Randolph Menzel in honey-bees, and Franz Huber's use of this method in crickets in 1960 is well known (he learned the method during a period of work in the laboratory of Walter Hess).

These were all pregnant neuroethological observations that have received very little follow-up. I am starting, you observe, with a relatively neglected method that has much to offer and is unpopular today for reasons that are no longer very good.

One of the major questions facing neuroethology – in the category: “How do brains work?” – is: What spatiotemporal pattern of activity in cells of the brain is necessary or sufficient for a percept to be experienced; what spatiotemporal pattern for a sign stimulus to be recognized, what spatiotemporal pattern for an action to be initiated? Now, the relevance of the cases of Walter Hess and the others I mentioned is the following.

The prevailing view is that perception, recognition, motor initiation and other cognitive processes, for example expectation, generally come from *distributed constellations of large numbers of cells firing impulses in characteristic spatiotemporal patterns*. This view, which we may call the distributed spatiotemporal pattern theory of recognition is popular and, to many neuroscientists, the only plausible view. It has limitations: the fact that nothing clear is said about how the specific pattern is read and that it is difficult to demonstrate.

A contrasting view is not so fashionable. We may call it the *small set theory* but it is sometimes disparagingly called the “grandmother cell notion”. It says that cells, which may be unique or more commonly members of a smallish set, share the character trait that each one reads the large constellation of converging inputs carrying the features of its preferred class of objects or sign stimuli and, therefore, each one can make a decision, without requiring a pattern of them in space or time, perhaps only a threshold number of them.

The concept of grandmother cells or of smallish numbers of more or less equivalent recognition units has been around a long time. In a recent review Horace Barlow (1995) called it the cardinal cell idea, as opposed to a papal or single-cell idea and in contrast to the ensemble idea of encoding by large numbers of units. This cardinal cell or small set idea is based on empirical evidence. Several levels of so-called moving bug-sensitive and worm-selective cells in frogs and toads, face-selective and hand-selective cells in monkey cortex, song-selective cells in song birds, and other units that fire only when a rather complex stimulus is delivered, from near or far, or at different angles. Each one has a certain degree of specificity and at the same time a certain

degree of generalization over particular stimulus situations within a class. (A more complete statement of the alternatives and a selection of references is given in Bullock 1993.)

The common feature is that each is a relatively small population of similar but not identical cells, each of which requires a complex combinatorial stimulus. A specific spatiotemporal pattern is necessary but *only in the inputs* to these decision cells. The existence theorem for the small set idea is proved: such sets exist, but it has not yet been shown whether such cells actually mediate behavioral recognition. No one supposes it to be the only or the general principle for recognition of all kinds of objects or of stimulus situations (Bullock 1961, 1965, 1993; Barlow 1972, 1993), but perhaps it will be found to explain recognition of some classes of objects or stimulus situations. That's what I am suggesting in this first comment on the future of neuroethology – an example of a methodology capable of elucidating some very broad problems.

The next big step in the problem of recognition which seems to me ripe for a new approach, is to test for the behavioral relevance of these known complex cells. Are they either necessary or sufficient for the animal to experience the percept or to act as though the stimulus were recognized, consciously or not?

I inject note here to point out three leitmotifs of this talk which I want to underline with these and the other examples that I will use today. First is the wonder and awe we should feel when we contemplate what animals do, for instance in this sphere of recognition of sign stimuli. Just think of the examples you have heard about here – from Pat Kuhl's six-monthers discriminating language sounds that you and I cannot, to Baldomero Olivera's cone snail prey sniffing danger from one of its toxic predators. One of my favorites is the retina of a skate that “recognizes” when an expected flash of light is missing or 10 ms overdue. Second is the humility we should feel for the depth of our ignorance of the brain mechanisms mediating even simple information processing. We tend to be impressed by the overwhelming literature on advances and to forget how far we are from understanding. Third is the eagerness we should feel to do the next experiment, innovative and insightful.

The example of brain stimulation says that I expect some pleasant surprises if we experiment on each of the preparations just mentioned – monkey face selective cells, songbird song selective cells and others where cells of complex input requirement can be found, by applying microstimulation to them under conditions conducive to the performance of the tell-tale behavior. It seems likely that if the system funnels down to a small set of nearly equivalent cells that do not need to fire in any specific pattern, local microstimulation could trigger a normal percept and the consequent action, given the conditions that make the animal want to act. Microstimulation in a very local place which has already been found, by recording, to be responsive to a complex natural, ethologically important stimulus, *could* be a crucial

demonstration if it is sufficient to initiate the appropriate behavioral response. On the contrary, stimulation somewhere in a distributed pattern system is unlikely to elicit very normal examples of behavior reproducibly.

Some considerations, stipulations or conditions might be usefully made explicit while we are encouraging tricky but potentially crucial new experiments. Some of these thoughts are more subjective than others, so I invite your critical reactions.

In the first place, I do not expect the same results in all kinds of preparations. There are at least two distinct kinds of subsystems in the CNS, with respect to the degree of funneling. Posture, equilibrium reflexes, eye movements, the jamming avoidance response of wave-type electric fish and many other actions have in common a continuous form of control and a large population of cells, with relatively little funneling, at least in the vertebrates. They are probably outside of the domain I am speaking about today. Other behavioral acts are at least apparently more or less discontinuous – on or off, triggered with a threshold. A standing fly takes off; a jumping spider jumps; a toad flicks its tongue at a mealworm; I see my wife in a crowd or recognize the letter E. All of these have limited grey zones but rather sharp thresholds. This class of behaviors seems more suitable for the microstimulation experiments I am advocating and more likely to be associated with cells having complex input requirements, but that is only a guess.

In the second place, it would seem more heuristic to choose a preparation in which tell-tale behavior is triggered by a defined, natural stimulus and the identified cell fires selectively to this stimulus, rather than choosing a preparation like a startle response and its ostensible command cell. This consideration suggests a preparation such as a monkey trained to give a particular response to a face, or a particular face, with one or several electrodes recording face-selective units in the temporal lobe region. Then the idea is to deliver weak and tonic stimuli, going back to recording and repeating the cycle. Whereas primates would have to be carefully trained, a song-bird or a toad might respond sufficiently reliably to its own song or to a moving mealworm so that it could be tested by microstimulation through an electrode that had found a selective unit.

This test reminds us of two other stipulations. One is that it may be necessary and sufficient to provide some part of the natural situation – such as a nonmoving mealworm or a second, silent bird – like the stuffed weasel in von Holst and St Paul's experiment that greatly enhanced the reaction of their chicken to hypothalamic stimulation.

The other caveat is that failure of the experiment to cause the expected behavior will not mean much, since one excited cell may not be enough to convince a system that may normally use several or a small set excited together. The proposition being tested is not that a single recognition cell is responsible but that a smallish set of them are more or less equivalent and adequate to

make a decision at a certain hierarchical level after a large input set with a specific spatiotemporal pattern of firing. The adequate number of excited cells, among the presumed small set, might be a function of the ethological readiness or the general situation.

Brain stimulation was an important method in physiology long ago and then fell into disuse, as too crude, activating in unnatural synchrony a large population over a considerable time. In modern times, a number of workers have shown that this method can be useful, especially when applied with semimicroelectrodes at submaximal intensities and optimal frequencies. Sometimes it gives results when subthreshold current is injected over a longish time. It can also be applied in such a way as to suppress ongoing activity or excitability.

I will not develop the obvious possibilities in the related tool of chemical stimulation, modulation or block. A number of examples show that microinjection of transmitters or modulators or local “anesthetic” blockers can cause or alter natural behaviors, specific to a very small locus. An important advantage is that the effects are short-lived, so that they can be repeated in the same preparation and locus.

None of this is new. My message is that these tools have not yet been adequately applied to sites where prior recording has localized cells requiring particular afferent patterns or constellations. I wish I had realized this long ago, since it could, with luck, in one afternoon invalidate the hypothesis that normal recognition of natural stimuli has to culminate in distributed, large populations excited or inhibited in specific patterned constellations. It could validate the hypothesis that some decisions, in some situations, although they may require patterned constellations of *input* at intermediate levels, actually reach the threshold of decision by final common paths of small numbers of unpatterned “recognition” units. I do not propose that this mechanism is general but I am betting it exists in hierarchies of patterns and convergent funnels, for some as yet undefined classes of behaviors or decisions. A single experimentum crucis could provide an existence proof.

This is one of a long list of agenda items I see as deserving new attention. I chose this example for its high valence of staked out positions and logic of the “it stands to reason” variety, in the face of far too few facts. Neuroethology of this and many other sorts is here to stay and has plenty to do. With its peculiarly high demands for expertise in several disciplines, neuroethology is typically a tough challenge, but nothing beats it for satisfaction per square idea!

I turn to another dimension of our field, the *evolution of brain and behavior*. This time I have chosen a popular field – nevertheless, a dangerous one since everyone is a self-recognized expert.

I risk acceptance by saying that evolution is not all about who descended from whom. I am fascinated by the “what” questions: what has evolution wrought, especially in the brain and behavior? What brain traits have evolved in the reptilian pallium that differ from the

mantle of amphibian and fish forebrains? Are the few differences so far known adequate at all levels? Is the cerebellum really conservative in all respects? Do we adequately understand what it does and how it works in the several classes of vertebrates? What about the limbic system? Is it relatively more important or less, in reptiles than in mammals? What kinds of states and how many discriminable states result when it is activated or silenced in different vertebrate classes? Where are the spatial memory cells in tide pool fish that show good learned spatial memory but have no clear hippocampal differentiation? Are astrocytes, oligodendrocytes and microglia and their subclasses and functional roles just the same in fish and mammals? Is it true and adequate to say that the principal way muscle action is graded and controlled in amniotes is recruitment of motor units, whereas the older way was grading the contraction in each fiber?

Whatever subsystem or mechanism you are working on, have you wondered whether it differs in other classes and orders? Do you glibly assume every difference is an adaptation and accept the plausibility test of the explanation? Do you make a distinction between adaptations within the same general grade of complexity and macroevolutionary novelties in taxa of different grade, like reptiles and mammals? I do. It makes the following question much more interesting: what are the differences in functional organization and meaning between structures like the hypothalamus, hippocampus and cortex in the most advanced reptiles and mammals? Notice my emphasis on large taxa at clearly different grades of complexity!

How many distinguishable pallio-pallial connections are there in the most elaborate fish brains compared with the 758 connections linking 72 areas in the macaque cortex, which is 15% of that theoretically possible? How many of the connections are reciprocal – to compare with the 311 reciprocal pairs in the macaque – 82% of all the 758 cortico-cortical connections (Mountcastle 1995)? What about connections between diencephalon and telencephalon? What about the most endowed reptiles, compared with mammals? What classes and orders of vertebrates have good cortical minicolumns and macrolumens or other signs of modular organization?

Do brains of the most well differentiated teleosts, compared to those of amniotes, have motor and sensory areas, relatively less distinct or areas less specific to each sensory modality and submodality, or in contrast, less multimodal in representation, or less well mapped, for example with respect to retinotopy or somatotopy? Has the role and importance of inhibition in the pallium evolved differently in the classes of vertebrates? Is there any general difference among the classes in the highly structured population signs of activity, like the slow brain waves as part of the ongoing EEG or of the evoked or event-related potentials and in respect to their synchrony, their induced rhythms, their correlation with states or events we would call cognitive in ourselves? Can these objective signs help us to work out the evolution of levels of arousal, alertness and attention?

I am inhibited from developing examples of the great need for quantitative measures of *cognitive capacity* in each of a number of distinct aspects, including perhaps the most neglected – the measure of extent of *knowledge* or the number of learned items an organism is able to store and recall – because I am afraid to distract from the force of the more neuro-related, anatomical and physiological examples I have just been sampling. I have elsewhere elaborated on some two dozen practical measures which, if estimated in selected species, in quite distinct grades of neural complexity, would significantly expand our ability to compare behavior beyond the usual level of adaptive radiation within the same grade (Bullock 1986).

I referred previously to our profound ignorance about the specific operations performed by networks of brain cells. We have no real idea, for example, how much neural function depends on the known non-spike, non-synaptic, non-network activity! Here I want to underline our ignorance of even the basic anatomical and physiological phenomenology of the living representatives we have of major taxa. I feel culpably negligent when I can't teach even whether fish have relatively more or fewer than mammals of, say, intrinsic cells or neuromodulator or even neurotransmitter cell types or of distinct nuclei and subnuclei in this or that major brain region. I can say even less on functional traits like post-tetanic potentiation or augmentation or induced gamma waves or synchrony! We in comparative neurophysiology are so far behind the cardio-vascular and respiratory physiologists!

Quite emphatically, I am not saying the brain is too complex to figure out, but rather that it is still the richest reservoir of discoveries waiting to be made – far beyond all other organ systems. The main thing I am sure of, looking into the future of neuroethology, is that we are sure to turn up surprises.

My coworkers, Jim Prechtl and five others, from four countries, were surprised (perhaps each in his own degree) to find recently that the telencephalic pallium in a mormyrid fish has relatively distinct and hardly overlapping areas for evoked responses to visual, auditory, lateral line and electrosensory stimuli – the auditory being the best represented and most obviously differentiated (Prechtl et al. 1998).

The questions I have cited as examples are heavily weighted toward the vertebrates, only because I guess more of you are more familiar with them. I could as easily list questions about my first loves, the invertebrates, to whom we all owe a debt of gratitude. I mean basic questions, fundamental unknowns about the differences between major taxa, and their physiological and behavioral correlates. The bottom line and main theme of this part of my diatribe is comparison – the concern for major evolutionary steps, not only the specializations of different genera and families.

The ancient lament is still valid – the one that bothered Kees Wiersma, Ladd Prosser, Carl Pantin and successive editors of the *Journal of Comparative Neurology* – namely the typical hesitation, neglect or fear on the part of most authors of explicitly comparing

across major taxa. Authors end their discussions when they have cited references to other species or genera, sometimes families, and feel no obligation to readers to compare with other orders or classes.

Well, I have stuck my neck out far enough that even the dullest blade among you can chop it off – what with advocating specific items in an agenda including an old and forgotten methodology and an approach to evolution that is basically descriptive and does not shun the recognition of more advanced from less advanced or the quantitative estimation of complexity as distinct from adaptive specialization or the comparison of mental capacities in each of its many modalities. I humbly adjure you to think twice and beyond your reflex mode before you wield the blade! There just might be a germ there that you could cultivate.

Looking ahead, neuroethology has many fronts, plenty of exciting questions, new methods, unexplored taxa, collaborations with other disciplines like molecular neurobiology and comparative cognition. The agendas are pregnant; expect multiple births. I feel my crystal ball fading; but I believe neuroethology is in good hands – namely your hands.

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