

## COMMENTARY

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### **Towards a Cellular Understanding of Motivation: Structural Reorganization and Biochemical Switching as Key Mechanisms of Behavioral Plasticity**

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#### **What is ‘Motivation’?**

When new students arrived at the Max Planck Institute for Behavioral Physiology in Seewiesen, one of the first lessons Konrad Lorenz taught was that an ethologist could be a good ethologist only if he knew his animals extremely well. In fact, said Lorenz, the observer should be able to write down a behavioral protocol some seconds in advance, which means that he should be able to predict what an animal was going to do.

Some obvious factors which allow an animal’s behavior to be predicted originate from the environment in the form of stimuli. Different stimuli typically elicit different behaviors, as different intensities of a stimulus may elicit different frequencies, durations, or intensities of a behavioral pattern. Very often, however, this input/output relationship is not fixed. The variation in the animal’s response, even under identical stimulation regimes, has led to the assumption that variable internal causal factors exist which modify the relationship between external stimuli and resulting behaviors. The influence of such internal factors on the neural control of the respective behavioral pattern is referred to as ‘mood’ or ‘motivation’. Motivational factors are, thus, endogenous, or internalized exogenous, factors that

affect the probability of occurrence of a behavioral pattern through internal neural or neuroendocrine mechanisms. Structures within the central nervous system from which a modulatory influence originates may be regarded as 'motivational' components of the neural network involved in the generation of the behavior. Note that this model does not make any predictions where the modulatory influence exerts its effect within the neural chain connecting the sites of sensory perception with those which initiate motor action. In particular, the existence of a single central structure devoted to exclusive control of the level of motivation ('motivation center') is not required. In a given instance, the only effect of motivational factors could, for example, be to modulate the perception and processing of sensory stimuli. Central structures controlling the motor output may then modify their response solely on the basis of altered sensory information relayed to them, rather than due to a direct influence of motivational factors.

### **Approaches to Understanding Motivation**

In principle, there are two possible approaches to understanding motivational factors underlying behavior. One, the black-box approach, aims at a 'software' explanation of motivation. First, the animal is observed in order to find regularities at the behavioral level, for example correlations between the frequencies of different behaviors. Then, parsimonious hypotheses are made about the internal variables and their relationships within the individual such that, by employing this model, the output corresponds to the behavioral observations. The classical textbook example is the use of the term 'thirst' (cf. Miller 1959; Hinde 1970). This intervening variable is a parsimonious construct which depicts the various relationships found between certain causal factors and behavioral measures. The introduction of such an intervening variable may drastically reduce the number of relationships in the system compared to the original number of relationships between causal factors and behavioral output.

Although this approach simplifies the explanation of causal relationships, it also increases the likelihood that possible differences in the details of the relationships will be lost during the reduction procedure. Typical examples of this approach are statistical methods, such as principle component analysis and factor analysis, which aim at extracting independent intervening variables from a set of correlations. They produce general intervening variables such as 'aggressiveness', 'sexual arousal' and 'readiness to flee'. Instead of dealing with varying frequencies of individual behaviors believed to be 'aggressive', such as attack, frontal display and lateral display, this method provides factor scores of a principle component for the measurement of 'aggressiveness'.

There are at least two major problems involved in this statistical approach: First, one may be led to believe in independent motivational systems such as 'aggression', 'flight' or 'sleep', and thus to disregard the fact that the factors often change in number and explanatory properties with the marginal eigenvalue, which is arbitrarily set for the respective model. Also, different algorithms for factor rotation commonly generate different results. Thus, it is not surprising that different

behaviors are not necessarily based upon different dedicated neuronal networks. Rather, neurobiological studies are in favor of the idea of overlapping neuronal networks for, for example, the aggressive system and the sexual system (Koolhaas et al. 1997).

A second danger lies in the conclusion that the number of independent causal factors or axes found is a genuine property of the organism studied. As can be shown easily, the number of competing behavioral commands that can be identified in the behavior of an animal is crucially dependent on the relationship between the animal and its environment. In an animal which is well adapted to a given environment, we may be able to distinguish as many independent behavioral commands as there are independent outcomes of the animal's behavior (McFarland & Sibly 1972). For example, if we provide a rat with only one standard type of food, we may measure different levels of hunger depending on how much or how fast the rat eats. If, however, we give the rat three different kinds of food, we may find three different types of hunger, which compete with each other for the so-called 'behavioral final common path' (McFarland & Sibly 1975).

Software explanations can, at best, constitute hypotheses about the functional structure within the black box, and – if sufficiently specific – may allow simulation of the behavioral output under different motivational conditions. This output can then be compared with the actual behavior of the animal. Similarly to computer programs, however, there are always many different models that can account for the outcome of the experiment. How can we find the more realistic of two equally potent models?

Often parsimony is recommended as a criterion. But how is parsimony judged? Is a model with fewer variables or one with fewer connections between the individual variables more parsimonious? Also, despite the fact that more parsimonious models are easier to test, parsimony is by no means a warranty for biological realism. Rather, simple models are probably unrealistic, as they lack many of the links to other motivational systems which certainly exist in the intact animal. Furthermore, biological solutions have not been designed from scratch; rather, they have developed on the basis of pre-existing structures. Thus, biological solutions, as we encounter them in today's animals, often may not be the most elegant ones but those which could most easily emerge through modifications of other capabilities of the animal. A biologically relevant reduction of the various software explanations towards more realistic models can therefore only be achieved by incorporation of details known about the hardware and obtained through neurobiological research. After years of stagnation at the software level, studies using this approach suggest common principles in the neural substrates underlying motivation in a large variety of systems.

### **Toward a Cellular Understanding of Motivation**

The central dogma of the physiological approach is that motivational changes in behavior are possible only if the neural network underlying this behavior exhibits the potential for neural plasticity. This is not the case in the 'ideal' reflex, and

therefore the behavioral response is solely determined by the type and intensity of the stimulus. In contrast, plastic neural networks can, even under identical stimulation regimes, produce different behavioral outputs.

Examination of a variety of different systems suggests that at least two major types of mechanism generate the required changes in the properties of the neural network. These mechanisms can be subsumed under the terms 'structural reorganization' and 'biochemical switching'. We shall illustrate the principles emerging mainly by referring to one well-examined behavioral paradigm, the 'chirping' of weakly electric gymnotiform fish (for review, see Zupanc & Maler 1997).

### Structural Reorganization

Structural modifications in neural networks underlying behavior include generation of new neurons and glial cells, elimination of older cells, changes in dendritic structure of neurons, and retraction or outgrowth of axons. Growing evidence demonstrates that such dynamic processes are not restricted to embryonic or perinatal stages of development (where drastic changes in behavioral output also take place), but may occur throughout adulthood. Recently, it has been demonstrated that postnatal neurogenesis even occurs in the aging brain of man (Eriksson et al. 1998). In the gymnotiform fish *Apteronotus leptorhynchus*, details of this continued neurogenesis during adulthood have been revealed by quantitative analysis (for review, see Zupanc 1999). Day after day, an extremely large number of brain cells undergo mitosis (Zupanc & Horschke 1995). This production leads to a continuous addition of new cells to the population of already existing cells. While, in the process of differentiation, many of the newborn cells die through programmed cell death (Soutschek & Zupanc 1995, 1996), a significant portion become integrated in pre-existing neural networks, where they remain for the rest of the fish's life (Zupanc & Zupanc 1992; Zupanc et al. 1996; Ott et al. 1997). Such persistence of neurogenesis into adulthood, also observed in various regions of the central nervous system of other fish, as well as in those of amphibians, reptiles, birds, and mammals including man (for review, see Alvarez-Buylla & Lois 1995), could provide the means for a restructuring of neural networks, and thus for drastic changes in their properties. Interestingly, adult mice living in an enriched environment exhibit significantly more new neurons in the dentate gyrus of the hippocampus than controls (Kempermann et al. 1997, 1998). This is due to a survival-promoting effect of environmental stimulation on the progeny of neuronal precursor cells rather than to an influence on proliferative activity. It has been hypothesized that the greater number of neurons in the dentate gyrus may be directly related to enhanced behavioral performance, as environmental enrichment is sufficient to induce behavioral improvement in spatial learning tasks assessed through performance in the Morris water maze (Kempermann et al. 1997).

In *Eigenmannia* sp., a weakly electric gymnotiform related to *Apteronotus leptorhynchus*, alterations in dendritic morphology of motoneurons have been hypothesized to be causally linked to seasonally induced changes in the propensity to execute a social behavioral pattern. This behavior, the so-called 'chirping',

consists of transient frequency modulations of the otherwise extremely constant electric organ discharge (Larimer & MacDonald 1968; Bullock 1969; Hopkins 1974). While fish kept under breeding conditions chirp heavily either spontaneously or when confronted with a conspecific, this behavior is almost completely absent outside the breeding season. Chirping is controlled by a few dozen neurons within the central posterior/prepacemaker nucleus in the dorsal thalamus (Kawasaki et al. 1988; Zupanc & Heiligenberg 1992). Retraction of dendrites of these motoneurons in one specific territory of the dendritic arbor – a process occurring after the end of the breeding season – leads to an interruption of the neural connection with sensory neurons (Zupanc & Heiligenberg 1989). As a result, the balance between excitatory and inhibitory input is shifted toward a higher degree of inhibition, since the input received by dendrites is predominantly excitatory, whereas somatic regions are distinguished by a high density of inhibitory chemical synapses (Zupanc 1991). The ‘veto’ exerted in these somatic regions appears to be the cause of the suppression of electrical activity in the chirp-controlling neurons outside the breeding season, thus resulting in cessation of chirping behavior. Similar changes in dendritic morphology have been observed in motoneurons controlling penile muscles in white-footed mice (*Peromyscus leucopus*), a seasonal breeder that exhibits marked fluctuations in reproductive behavior (Forger & Breedlove 1987).

Changes in neuronal excitation may be caused not only by changes in the number or the morphology of neurons, but also by alterations in the organization of the network provided by glial cells. In the magnocellular hypothalamo-neurohypophysial system of mammals, for example, magnocellular neuronal somata are almost completely separated from their neighbors by fine astrocytic processes, so that only approximately 1% of the total neural membrane is in direct apposition without intervening glial processes. In response to changes in the animal’s physiological state, for example during periods of water deprivation or lactation, the astrocytes rapidly retract, resulting in a tremendous increase in the number of neuronal elements directly juxtaposed (for review, see Hatton 1997). This glial withdrawal leads to an enhancement of neuronal excitability which is believed to be directly linked to the observed behavioral changes.

The strategy to produce motivational changes by modifying the structure of either neurons or glial cells, or both, and thus the properties of the associated neural network, appears to be especially applicable in the following cases: (1) the changes in the readiness to execute this behavior are rather slow; (2) the alterations at the behavioral level are drastic; (3) a new motivational status becomes manifest for rather long periods of time. All three phenomena are found in seasonally breeding animals. A corollary of our hypothesis is therefore that structural reorganization may be a mechanism frequently used to accommodate seasonal alterations in behavior, although it does not have to be the only strategy employed.

### **Biochemical Switching**

A second frequently encountered neural mechanism to accommodate motivational changes in behavior is biochemical switching (Swanson 1988/89). This

involves biochemical modulation of synaptic transmission within anatomically fixed circuitry through use of 'neuromodulators'. A common principle of neural networks displaying this strategy appears to be that sensory, motor and motivational components are segregated. Such segregation has been strikingly demonstrated in *Aplysia*, where a single neuron, the cerebral-pedal regulator, may evoke a central motivational state representing the neuronal correlate of feeding behavior (Teyke et al. 1990). In weakly electric fish of the genera *Eigenmannia* and *Apteronotus*, such a modulatory influence on the neural control of chirping behavior appears to be exerted by structures located in the hypothalamus and the preoptic area. A similar function of these subdivisions of the brain has been proposed for other systems in a variety of vertebrate species.

Interestingly, in gymnotiform fish, the nucleus electrosensorius, a sensory processing station, projects not only to the prepacemaker nucleus, where it provides direct sensory input to the motoneurons controlling chirping behavior, but also to hypothalamic regions (Keller et al. 1990). The nucleus electrosensorius contains neurons that respond specifically to chirps of neighboring fish. Thus, the projection to the hypothalamus may provide the substrate for another phenomenon well known in ethology: repeated broadcasting of a stereotyped social signal not only elicits direct behavioral responses, but also exerts a tonic and motivational effect upon the receiver (Schleidt 1973; Heiligenberg 1977). In *Eigenmannia* and *Apteronotus*, the extended bouts of chirping of mating males may bring about the physiological readiness of a female to spawn (Hagedorn & Heiligenberg 1985).

Modulators commonly found to mediate motivational influence include neuropeptides, catecholamines and serotonin. In gymnotiform fish, the prepacemaker nucleus receives input mediated by each of these three classes of neuroactive substances. In addition to the catecholamines noradrenaline and dopamine (Sas et al. 1990), the following other neuromodulators have been identified: serotonin (Johnston et al. 1990), as well as the neuropeptides somatostatin (Sas & Maler 1991; Zupanc et al. 1991a,b), including its receptors (Zupanc et al. 1994), galanin (Yamamoto et al. 1992), substance P (Weld & Maler 1992), met-enkephalin (Richards & Maler 1996) and corticotropin releasing factor (Zupanc et al. 1999). The density of somatostatin immunoreactivity (Zupanc et al. 1991a) and that of substance P (Dulka & Maler 1994; Dulka et al. 1995) change with the degree of sexual maturity and with the level of testosterone, respectively.

Steroid hormones may affect the level of expression of different neuropeptides differentially, leading to an alteration in the ratio of neuropeptides released (Swanson et al. 1986; Swanson & Simmons 1989). As a result, an enormous number of different combinations of neuroactive 'cocktails', probably with different behavioral effects, are possible.

The properties of catecholamines and neuropeptides make them well suited to mediate motivational influences within the central nervous system. Neuropeptides and catecholamines are frequently released in a non-synaptic fashion rather than at synaptic specializations, as is typical for 'classical' transmitters such as glutamate and GABA (for review, see Zupanc 1996). Such a non-synaptic function has been implicated for the neuropeptide somatostatin in the central

posterior/prepacemaker nucleus (Stroh & Zupanc 1995; Zupanc et al. 1997). Furthermore, there is often no focal relationship between the site of release and the location of the respective receptors ('peptide-peptide receptor mismatch'; for review, see Herkenham 1987). Both properties lead to a 'diffuse' effect, as the respective endogenous ligand may interact with receptors at more than just one site in the central nervous system. These sites may be involved in the control of several behaviors. Such a notion is, again, in agreement with behavioral observations: factors which affect the occurrence of one type of behavior tend to influence the probability of other behavioral patterns as well.

At the cellular level, the effects of catecholamines, serotonin, and neuropeptides are frequently exerted not by initiating behaviors, but rather by influencing ongoing neural activity. This is often achieved by modulating the synaptic transmission of classical transmitters at the pre-synaptic and/or post-synaptic level (for review, see Zupanc 1996). Intraventricular injection of serotonin, for example, greatly depresses spontaneous and evoked chirping in *Apteronotus leptorhynchus* (Maler & Ellis 1987).

Serotonin is believed to be of crucial importance in neural control of aggressive motivation. Investigations examining the effect of this amine have benefited, in particular, from the establishment of crayfish as an ethological model system to study aggression. These crustaceans readily engage in aggressive encounters when placed together in an aquarium. The fights, which can be quantified easily, escalate in a probabilistic manner until one of the opponents retreats (Huber & Kravitz 1995). While, under normal circumstances, animals faced with much larger opponents quickly withdraw from the encounter, administration of serotonin into the hemolymph of freely moving individuals leads to an alteration of their decision to retreat and behave as subordinates. As a consequence, fights last considerably longer compared to controls (Huber et al. 1997; Huber & Delago 1998). Thus, serotonin injected into subordinate animals appears to change the aggressive motivation of the crayfish toward higher levels. At present, the central sites responsible for this effect are unknown.

An exciting new research direction for examining the action of neuromodulators has recently been taken in studies which were also conducted in crayfish (Yeh et al. 1997). These investigations have demonstrated that the modulatory effect of serotonin on the lateral giant interneuron, a command neuron controlling escape, is itself modulated by the social status and the social history of the animal. In dominant crayfish, the response of the lateral giant interneurons triggered by serotonin is transiently increased, whereas in subordinates it is transiently inhibited. These slow but reversible modulatory alterations appear to result from changes in the population of serotonin receptors.

Biochemical switching is likely to allow faster motivational changes in behavior than structural reorganization does. This strategy appears to be the mechanism of choice where 'all-or-none' alterations are not desired, but where fine gradual differences within a broad range of possibilities must be accommodated. It is, therefore, not surprising that biochemical switching has been found in circuitries associated with ingestive and reproductive behaviors (for review, see Swanson 1988/89).

### **A Role for the Ethologist?**

The above two concepts open new vistas in motivational research, although certainly they do not provide exclusive mechanistic explanations for changes in the propensity to execute specific behaviors. The merit of neurobiology is to have revealed many of the structural and physiological details involved in neuronal plasticity – although the relevance of these findings for a cellular understanding of motivation has too often not been realized. But what will be the role of the ethologist in these new developments? That of a neutral spectator? Or is there room, possibly even the need, for his/her active participation? In our opinion, ethologists could make a significant contribution especially to the following two aspects of this research.

**1** Neurobiologists deal with very simple, often reflex-like, behaviors, if behavioral patterns are included in their research at all. In contrast, ethologists are predominantly interested in complex behavioral patterns. Such patterns are often believed to be inaccessible to detailed neurobiological examination. Results of studies on seasonally induced changes in chirping behavior of weakly electric gymnotiform fish (for review, see Zupanc & Maler 1997), however, disprove the general validity of this assumption. In this area of research, one current major problem is a lack of ethological information on, for example, the behavioral factors that lead to changes in chirping behavior, the various types of chirps generated under different behavioral conditions, and the functional significance of this social behavioral pattern. Such pieces of information can only be provided through rigid ethological analysis.

**2** Use of behavioral aspects in neurobiological paradigms requires robust and well-defined behaviors that can also be elicited under laboratory conditions. This is clearly today's biggest deficit preventing further progress in motivational research. One of the very few exceptions is, again, the chirping behavior of gymnotiform fish. Although this electrical behavior is far from simple, it can readily be evoked simply by presenting an isolated fish with an electrical sine wave in the range of the frequency of its own electric organ discharge (Dye 1987; Maler & Ellis 1987). This stimulation regime, thus, simulates the presence of a neighboring fish. By employing this behavioral assay, even during the performance of neurophysiological experiments, chirping can be elicited in a highly reproducible manner (Zupanc & Maler 1993). There are many behavioral assays available which can readily be used in the laboratory. However, only a very few of them are also usable by the physiologist who, ideally, would like to be able to evoke and record a behavior, with a high degree of reproducibility, also from a physiological preparation of the animal. In addition, the neuronal network underlying the behavior should, at least in principle, be known and accessible to physiological manipulation. The physiologist can, then, specifically change individual neuronal or neuroendocrinological factors within this network and directly assess the effect of this experimental manipulation on the behavioral output. To develop such behavioral assays, or refine existing assays to meet the requirements of the physiologist, will certainly be a challenge, but also a great opportunity, for ethologists.

Joint applications of ethological and neurobiological techniques and concepts will enable us to develop novel models to explain motivational influences on behavior. By incorporation of structural and physiological data, these models will be closer to reality than the previous pure software explanations.

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