Archives Italiennes de Biologie, 135: 5-14, 1997.

ONE OR MANY AROUSAL SYSTEMS? REFLECTIONS ON SOME OF GIUSEPPE MORUZZI'S FORESIGHTS AND INSIGHTS ABOUT THE INTRINSIC REGULATION OF BRAIN ACTIVITY

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INTRODUCTION

Outstanding among the many significant contributions of Giuseppe Moruzzi to the neurosciences is the discovery, jointly made with Magoun, of the EEG desynchronization produced by electrical stimulation of the brainstem reticular core (27). This discovery and its subsequent developments led to the hypothesis of a brainstem activating system, the arousal system, whose functioning was seen as the indispensable support for those activities of higher brain centers, especially the cerebral cortex, which underlie the waking state and the overall level of vigilance (17, 19, 24). In its original formulation, the concept ascribed sleep to the reduction or cessation of the activating influence of the brainstem arousal system on the cortex, but Moruzzi himself was one of the first to show that sleep, no less than waking, is an active state, or better a class of active states, the initiation and maintenance of which are also amenable to orderly modulatory influences of the brainstem on the cerebrum (25).

I. *The genesis of the concept of a single brainstem arousal system.*

In this paper I shall show that more than forty years ago Moruzzi was fully aware of a physiological problem which is still unsolved today, in spite of enormous advances in the understanding of the mechanisms of arousal. The question he asked then can be asked now: Is our knowledge of these mechanisms still compatible with the original concept of a single, homogeneous arousal system functioning as a whole, or does it demand the postulation of a multiplicity of arousal systems? The notion of the brainstem arousal system as a functional unit was challenged on several grounds already in the 1950s. Convinced that morphological differentiation means functional differentiation, Olszewski defined the reticular formation not as a morphological unit, but rather as a collection of nuclei of very different structure which, by implication, are likely to subserve different functions (28). Similarly, in speculating about the significance for behavioral motivation of the interactions between a nonspecific projection system (the arousal system) and the specific sensory inputs to the cortex (the cue systems), Hebb noted that the dissimilarities between different drives are not easy to fit into the notion of a single, homogeneous arousal system (12). As early as 1954, Moruzzi (23) called attention to the possibility that "for the lower intensity of sensory stimulation only some districts of the ascending reticular system might be activated, and therefore a more localized (or less diffuse) ascending discharge would contribute to the process of attention for the sensory modality involved". Four years later he reiterated the need for analyzing "the intermediate ranges of reticular activity" in order to assess the potential occurrence of "a fractional or selective activation of given provinces of the reticular system" (24). In accord with some aspects of Lindsley's activation theory (17) and with Hebb's postulate that effective behavior requires an optimal level of arousal, intermediate between the minimal and maximal degrees of physiological activation of the cortex (12), Moruzzi felt that the fusion of several reticular functions into one whole might occur solely in association with extreme emotional states during which the power of attention, discrimination and analysis is greatly diminished or lost altogether (24). The possible heterogeneity of the arousal system was suggested to Moruzzi by an analogy with the already ascertained heterogeneity of the descending or caudal activities of the reticular formation, including functions so disparate as the basic cardiovascular, respiratory and postural regulations.

II. *Accumulating evidence for the existence of multiple arousal systems.*

The evolution of new concepts about the intrinsic regulatory systems of the central nervous systems owes much to the so-called chemical neuroanatomy. Two major steps in this evolution were 1) the identification of different groups of neurons containing different catecholamines or acetylcholine within the brainstem reticular core, and 2) the precise mapping of the trajectories of the projections of these neuronal groups and their targets within different diencephalic and telencephalic regions. Before the discovery of the extensive innervation of the cortex by these chemically tagged projections, the fiber systems reaching the cortex were thought to originate solely from the thalamus, and the actions of the brainstem arousal system on the cortex were thought to be mediated exclusively by the thalamus and other subcortical centers projecting to the thalamus (8). Various anatomical and functional aspects of these chemically characterized ascending brainstem systems have been the topic of many extensive reviews (4, 8, 14, 15, 20, 21, 30, 32, 35, 36); the following is a very brief and incomplete summary.

Today we know that there are at least five anatomically and chemically identified ascending systems which project diffusely to most of the diencephalon and telencephalon, and especially to the cerebral cortex. These systems originate from relatively small nuclei lying mostly in the brainstem, but also partly in the hypothalamus and basal telencephalon; the enormous branching of the axons of their relatively few constituent neurons accounts for the widespread distribution of their projections within the neuraxis. 1) The noradrenergic system originates from a very small population of neurons constituting the locus coeruleus and projects to relay and intrinsic nuclei of the thalamus, as well as to most of the neocortex, where its fibers terminate with extensive arborizations in upper and lower cortical layers. Another population of noradrenergic neurons lies in the lateral tegmental area; these neurons are thought to project mainly or exclusively to the hypothalamus. 2) The brainstem cholinergic system originates from the pedunculopontine nucleus and the lateral dorsal tegmental nucleus whose projections supply widespread inputs to both relay and intrinsic thalamic nuclei as well as to the reticular nucleus of the thalamus. Like all layers of the neocortex, the latter nucleus receives cholinergic projections from the basal forebrain, including the medial septal nucleus, the diagonal band nuclei and the substantia innominata. The nucleus basalis, also constituted by cholinergic neurons, projects primarily or exclusively to the neocortex. 3) The dopaminergic system can be subdivided into two subsystems, the mesostriatal subsystem which projects from the pars compacta of the substantia nigra and the ventral tegmentum of the midbrain to several striatal areas and particularly to the neostriatum, and the mesolimbic-mesocortical subsystem which projects from the ventral midbrain tegmentum to several components of the the limbic system and to the the prefrontal neocortex. 4) The serotoninergic cephalic system originates from the dorsal and median raphe nuclei of the midbrain and upper pons. The dorsal raphe nuclei project predominantly to the striatum and frontal cortex; the median raphe nuclei project predominantly to septum and hippocampus. However, the serotoninergic projections are so diffuse that virtually all parts of neocortex receive them, their terminations being mostly restricted to the fourth layer. 5) Finally, the histaminergic system is not strictly a brainstem system, since it originates from the tubero-mammillary nucleus of the hypothalamus; it provides inputs mainly to the thalamus, but probably also to the neocortex, as shown by the heavy density of histaminergic terminals in most cortical layers.

The designation of these systems as "arousal systems" (20, 30) is justified by the fact that activation of each of them induces desynchronization of the EEG; all of them cooperate in some form to desynchronize the EEG during waking, while only the cholinergic system is responsible for EEG desynchronization during the phase of sleep with rapid eye movements (REM sleep). Their combined or single synaptic actions impact on a closed circuit formed by corticothalamic neurons, thalamocortical neurons and neurons of the reticular thalamic nucleus, which receives cortical projections and is reciprocally connected with all relay nuclei of the thalamus (21, 36). Noradrenergic neurons of the locus coeruleus are very active during waking and silent during sleep, particularly REM sleep; during waking, their firing rate is clearly modulated by environmental stimuli. Serotoninergic neurons display a very slow and regular discharge which is suggestive of being driven by an endogenous clock; this activity is highest during arousal and active waking, intermediate during quiet waking and non-REM sleep, and totally absent during REM sleep, and appears to be mostly unaffected by sensory stimuli and physiological stressors such as changes in body temperature and blood pressure. Some serotoninergic neurons, which perhaps constitute a separate anatomo-functional class, are activated during repetitive buccal-facial movements during feeding and grooming, and are inhibited during orientation (14). A correlation with the sleep-wake cycle similar to that for serotoninergic neurons has been described for histaminergic neurons; indeed arousal is the only physiological condition which is systematically accompanied by an increase in the firing rate of histaminergic neurons (32).

As a result, each of the five diffuse systems is capable of modulating the transfer of specific sensory information activity from the relay nuclei of the thalamus to the cortex. When they are active, their influences on the reticular nucleus of the thalamus as well as cortico-thalamo-cortical networks promote a switch from a bursting discharge mode to a single-spike discharge mode of thalamocortical neurons; only the latter type of activity is compatible with the faithful transmission of sensory information to the cortex (21, 36). The communication of specific sensory messages from thalamus to cortex during sleep with synchronized EEG is virtually impossible, as already suggested by an early study of Moruzzi with Maffei and Rizzolatti on the ability of the dorsal lateral geniculate nucleus to transfer visual information to the cortex during sleep and waking in the midpontine, pretrigeminal cat (18). Theoretically, the ascending brainstem systems may mediate selective attention by means of the action of the reticular nucleus of the thalamus on the relay thalamic nuclei (22), but this hypothesis is contradicted by the evidence that at least in the visual modality selective effects of attention arise in cortical areas beyond the primary receiving areas of the cortex (6, 7, 13). Direct projections of the brainstem systems to non-primary sensory areas of the cortex may subserve selective attention, possibly by being discretely activated by the cortex itself in a top-down fashion, but crucial evidence for this mechanism is still missing. The direct actions of acetylcholine and noradrenaline on cortical neurons have been described as increasing the signal/to/noise ratio of the response of these neurons to their specific stimuli. The effect on the signal/to/noise ratio by acetylcholine seems to be due to a signal enhancement relative to an unchanged noise, while that from noradrenaline seems to be due to a noise reduction relative to an unchanged signal (4, 30). The actions of acetylcholine and all the monoamines may of course vary considerably depending on the type of receptors to which these neurotransmitters bind (21).

III. *A behavioral investigation of the functional significance of four ascending arousal systems.*

A multitude of behavioral effects have been attributed to naturally occurring or experimentally induced changes in the activity of the chemically tagged brainsem systems, and it is impossible to review all of them here. The only investigations which will be described in some detail are those of Robbins, Everitt and their coworkers, since they have the merit of having tested the effects of the selective inactivation of each of four brainstem ascending systems on the same task in the same species under comparable experimental situations (see 30). On each trial of a visuospatial discrimination, one of five adjacent locations was cued with a brief luminous stimulus, and rats were trained to reach the cued location in order to get a food reward. There was a memory component to the task insofar as the cue went off before the rats could complete their response. While the cued location was varied randomly from trial to trial, cue presentation occurred systematically five seconds after the last reward. The performance of rats in which the ascending projections of the locus coeruleus were selectively destroyed by injecting the neurotoxin 6-hydroxydopamine into the dorsal noradrenergic bundle was unimpaired relative to intact rats, even when the difficulty of the task was increased by diminishing the luminosity of the stimuli. However, the performance of the same rats became significantly less accurate than that of normal rats if the temporal presentation of the stimuli was random rather than regular, or when the cuing visual stimuli were preceded by distracting bursts of noise. Reduction of cholinergic innervation of the cortex by the injection of excitotoxic aminoacids produced a quite different deficit: the performance of rats with such cholinergic depletion of the cortex, especially the frontal cortex, was much less accurate than normal. The deficit was not due to sensory, motor or motivational impairments, but rather to a decreased ability to detect and perhaps to remember the location of the positional cue. By contrast, the accuracy of performance of rats with dopamine depletion in the ventral striatum was found to be normal, but they were reluctant and slow in responding, as though the cue had partially lost its ability to activate behavior by way of its association with the reinforcement. Finally, rats with massive central serotonin depletion by intraventricular infusion of 5,7-dihydroxytryptamine showed only a significant increase in premature and impulsive responding. This complex pattern of results can be effectively, if somewhat simplistically, synthesized by assuming that each system contributed to high-level performance of the above task as follows: the noradrenergic, coeruleo-cortical system reduces the interfering effects of distracting stimuli; the cholinergic system improves accuracy of performance; the mesolimbic dopaminergic system improves speed of performance; and the serotoninergic system holds in check impulsive erroneous responding (30).

IV. *Unifying actions of the brainstem on the henispheres divided by a section of the corpus callosum.*

As originally conceived, the brainstem arousal system bore some clear resemblance to the "centrencephalic system" hypothesized by Penfield (29). Penfield identified the indispensable substratum of consciousness with a centrencephalic system containing the nervous mechanisms "which are prerequisite to the existence of intellectual activity and to the initiation of the patterned stream of efferent impulses that produce the planned action of the conscious man" (29). He thought that the functional areas of the cerebral cortex are employed in common integrated action by the coordinating action of those structures of the diencephalon, mesencephalon and at least part of the metencephalon which are connected by symmetrical projections to the cortex of both hemispheres. Penfield attributed little importance for overall cerebral organization to direct transcortical connections and believed that the most conspicuous of these connections, the corpus callosum, could be sectioned with astonishing little effect on the intellectual activity of man.

The results of subsequent studies are clearly at variance with some of Penfield's beliefs. First, the cortical projections of the brainstem noradrenergic, dopaminergic and cholinergic systems appear to exhibit bilateral asymmetries, in man and animals alike (10, 11, 20, 30), while the serotoninergic system does not (14). In man, the density of the noradrenergic projections seems to be greater in the right hemisphere, and that of dopaminergic and cholinergic projections seems to be greater in the left hemisphere (11, 20). These asymmetries may have a bearing on the organization of motor control, especially with respect to rotational behavior, as well as on the functional specializations of the right and left hemispheres in cognition, motivation and emotion (10, 11, 38).

Second, section of the corpus callosum does have profound effects on man's mentation: after this operation, each of the disconnected hemispheres can be shown to retain all or most of its functional abilities and specializations, but the specific contents of percepts and memories engendered in one hemisphere are generally excluded from the conscious awareness of the other hemisphere. "Split-brain" patients can be said to possess two largely separate and independent neural systems for cognition, one of which is specialized for linguistic, analytic and sequential processing and resides in the left hemisphere, whereas the other is specialized for non-verbal, holistic and parallel processing and dwells in the right hemisphere. The integrative action of the corpus callosum is indispensable for the unification of these specialized processes in the normal brain (33).

Yet, in accord with Penfield's ideas, there are many different aspects of brain activity which display a normal or near-normal interhemispheric coordination despite the absence of the corpus callosum, undoubtedly because of the integrative action of the undivided brainstem. This coordination goes well beyond the mere bilateral synchronization of the sleep-wake cycle: attentional, motivational, emotional and connotational components of cognitive processing are shared between the hemispheres with a high degree of efficiency. Sperry has argued that since these components constitute an eminently conscious property of cognitive processing, the fact that their interhemispheric sharing can occur at brainstem levels must be taken into account in the analysis of the structural basis of consciousness (33). Trevarthen (37) maintains that motor coordination, directed attention and emotional evaluation appear to rely upon an interhemispheric coordination which is far from eliminated by sectioning the corpus callosum, such that theories of perception and learning must pay heed to brainstem-based, intrinsically regulated programs that modulate the associative functions of the neocortex. Corballis (5) has recently reviewed much evidence which indicates how subcortical integration may ensure at least some degree of visual unity across the hemifields, thus allowing each of the disconnected hemispheres to have considerable awareness of the outside space on both sides of fixation. Gazzaniga's summary of many studies from his laboratory (9) points to the conclusion that split-brain patients appear to possess only one integrated spatial attention systems that remains intact following interhemispheric disconnection. When the hemispheres of a split-brain subject allocate attention voluntarily to different information processing tasks, the performance of each is impaired, suggesting that they call upon a common attentional resource system. A similar conclusion has been reached by Lewine *et al.* (16), who have interpreted their results from experiments in split-brain monkeys by suggesting that "in mnemonic processing the two divided hemispheres draw upon a unified, shared resource, probably allocated by the intact brainstem". Investigations of speeded bilateral symmetrical responses to visual inputs restricted to one hemisphere in normal subjects and patients with callosal defects have shown that there is an irreducible advantage in speed for the response emitted by the hemisphere which receives the visual stimulus (1,2). In normal subjects, this advantage is minimized by the corpus callosum which allows an efficient interhemispheric communication for the fast integration of the disadvantaged response. This syncronizing callosal influence is inferred from the increased asynchrony of bilateral hand responses which occurs in the absence of the corpus callosum, whether congenital or acquired (3). However, the persistence of strong temporal correlationsbetween bilateral hand responses to lateralized visual stimuli in acallosal patients suggests a not-negligible contribution of extracallosal mechanisms to the bilateral temporal coordination of the motor outputs from the two hemispheres (1-3). That the brainstem may make an essential contribution, perhaps under cerebellar control (34), to these extracallosal mechanisms for bilateral temporal coordination of hand responses is a very likely, though as yet unproven hypothesis. More information is available as to the mechanisms which ensure the bilateral synchronization of responses effected with axial and proximal arm muscles. Each hemisphere can control these responses on both sides of the body, so that the synchronization between the two sides is made possible by the shared origin of the motor commands and by the bilateral distribution of the cortico-reticulo-spinal pathways transmitting them (1-3).

IV. *Epilogue.*

All the above evidence is consistent with the view that the brainstem can exert unifying and coordinating influences on overall cerebral organization. At first sight the anatomical, chemical and functional parcellation of the brainstem systems which ascend to the diencephalon and telencephalon seems incompatible with the revival of the concept of a unitary arousal system. However the fundamental problem remains of how the simultaneous activities of these multiple ascending systems can be differentially modulated so that the parts are harmonized into a functionally meaningful whole. One possibility is that overall regulation comes about because each of the ascending systems possesses its own mechanisms of self-regulation, and the orchestration of their parallel functions would occur at their sites of termination through mutually reinforcing or antagonistic interactions between the effects of their transmitters on the target neurons. The alternative possibility is that the reticular formation itself contains local neuronal networks that by being superordinate to the chemically tagged, rostrally projecting systems are in a position to bring about an overall ascending discharge suitable for optimizing the behavioral and cognitive reactions to the current environmental circumstances. I don't know which of the two alternatives would have been more acceptable to Professor Moruzzi; I suspect that he would probably have cherished the second one. What I am sure of is that he would have said that only appropriate experiments can decide between these possibilities. The problem of understanding the coordination of multiple arousal systems is one of "the many problems (that) are uppermost in the minds of those of us who are concerned with how the integrated organism functions" (31). The entire scientific work of Moruzzi was inspired by this concern.

SUMMARY

Soon after the birth of the hypothesis of the ascending brainstem activating system, Giuseppe Moruzzi considered the possibility that a fractionated and differentiated arousing action of the reticular formation is required for effective behavior and cognition. Current knowledge about the chemically tagged brainstem systems which project diffusely to thalamus, neocortex and limbic structures has justified the assumption of the existence of multiple arousal systems. Combined changes in the activities of these systems are responsible for the sleep-wake cycle and the modulation of the reactivity of the brain to environmental inputs. There remains the physiological problem - one which has always been foremost in Moruzzi's thinking about the intrinsic regulation of brain activity - of how the separate actions of the different arousal systems are brought together into a functional whole. This problem still awaits experimental answers.

Acknowlegments. - Work by the author has been supported by the Ministero dell'Universita' e della Ricerca Scientifica e Tecnologica, the Consiglio Nazionale delle Ricerche, and the Human Frontier Science Organization Programme.

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