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Integration of brain activities: The roles of the diffusely projecting brainstem systems and the corpus callosum

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At the beginning of this century the great neurophysiologist Charles Sherrington [11] argued that a major function of the nervous system is that of integrating the activities of a collection of separate bodily organs into an individual endowed with physiological and behavioral solidarity. But successful integration of the activities of different somatic organs can only be achieved if components of the nervous system with different functions are themselves integrated into a coordinated whole. In considering the convergence of allied and antagonistic reflex pathways onto the same motoneurons, Sherrington noted that the output mechanisms of the nervous system are adapted to serve but one purpose, that is only one action, at a time. "The resultant singleness of action from moment to moment"—he wrote—"is a keystone in the construction of the individual whose unity it is the specific office of the nervous system to perfect" [11, p. 234]. On the mental side, this singleness of action is akin to the compelling subjective phenomenon of the unity of each span of conscious awareness. Of course singleness of action and unity of mental experience do not imply that the brain contains a single master center entrusted with the supreme responsibility of processing all kinds of available information and making all final decisions. Rather, the brain must be seen as an ensemble of several multiply interconnected neuronal systems, each with its own functional specialization, and integration must be seen as the process of interactive cooperation between these systems that allows efficient cognition and consistent behavioral control.

I would like to mention two pioneering experiments which in the mid-20th century have provided strong starting points for understanding at least some of the structures and mechanisms that integrate and unify different nervous functional activities. In 1949, Moruzzi and Magoun [8] showed that electrical stimulation of the brainstem reticular formation produced over the entire cerebral cortex and the thalamus an electroencephalographic reaction that was identical to the arousal reaction caused by natural sensory stimuli. This discovery and its subsequent developments led to the hypothesis that brainstem structures with diffuse projections can intrinsically modulate the activity of the entire nervous system, thus bringing about the major changes in vigilance that occur during the sleep-wake cycle, as well as subtler behavioral modifications that are usually attributed to attentional and motivational regulations. Originally, the ascending action of the reticular formation was thought to be the indispensable support for those activities of higher brain centers, particularly the cerebral cortex, that underlie the waking state and the overall level of vigilance. Accordingly, sleep was ascribed to the reduction or cessation of the activating reticular action on the cortex, but later it was shown 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 entire nervous system [7].

Recent developments have shown that in addition to the "classic" reticular ascending projections, which most probably use glutamate as their synaptic transmitter, other brainstem monoaminergic and cholinergic projections to the thalamus and cortex also exert controlling or modifying influences on the overall organization of the brain [5,9,15]. This concept has been and is presently applied to the interpretation of phenomena in various fields of medicine and the neurosciences, such as, among others, those related to vigilance, the orienting reaction, and the sleep-wake cycle in neurophysiology; to attention and motivation in psychology; to the action of hypnotic and anesthetic drugs, as well as of abuse substances, in pharmacology; to the pathogenesis of coma and sleep disorders in clinical neurology and neurosurgery; and to the investigation of the organic underpinnings of the major psychoses in psychiatry.

The other seminal experiment that gave birth to a very viable line of investigations concerns the integration of the activities of the two cerebral hemispheres. Neuroanatomic wisdom clearly suggests that interhemispheric integration should be carried out via the huge major connecting pathway that directly links cortical areas of the two sides, i.e., the corpus callosum. Nevertheless, during the first half of this century it was thought that no important function could be attributed to the corpus callosum, except perhaps the interhemispheric spread of epileptic discharges. The experiment that changed this paradoxical view was carried out by Myers and Sperry in 1953 (see [12]). In mammals with partially crossed optic pathways, like cats and monkeys, visual pattern discriminations learned with one eye transfer easily to the other eye. This successful interocular transfer is not disrupted by severing the crossed fibers in the optic chiasm, thus leaving each retina connected solely to the ipsilateral hemisphere. Split-chiasm animals must therefore utilize interhemispheric connections for transferring monocularly learned discriminations between the eyes. This was demonstrated by the finding that in split-chiasm cats with an additional section of

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the corpus callosum (split-brain cats) interocular transfer fails, and discriminations acquired though one eye have to be completely relearned through the other eye. Lack of interocular visual transfer was similarly found in nonhuman primates with section of the chiasm, corpus callosum, and anterior commissure. Additional experiments on interhemispheric transfer in other sensory modalities established beyond a doubt that after callosal section, information channeled into one hemisphere is generally not made available to the other hemisphere. The corpus callosum can thus be considered the main route for exchanging information between the hemispheres and for coordinating their activities [12], as also shown by direct recordings of callosal fiber activities in experimental animals [1,3].

This functional role was dramatically confirmed in epileptic human subjects who were submitted to a section of the corpus callosum in a last attempt to control drug-refractory seizures. After recovery from surgery, it was found that a sensory input experimentally restricted to a single hemisphere of these patients resulted in cognitive experience that was inaccessible to conscious experience of the other hemisphere. In the normal brain, all experiences and performances generated within one hemisphere are eventually shared with the other hemisphere via the corpus callosum, but each hemisphere of split brain patients seems to be restricted to experiencing its own private perceptions, thoughts, and memories. Unlike nonhuman mammals, the disconnected hemispheres of the human brain exhibit major differences in their cognitive abilities, the most conspicuous of which confirms the classical neurological notion that language abilities are largely mediated by the left hemisphere and largely absent in the right hemisphere. The right hemisphere may however prevail in nonverbal tasks, particularly in relation to space cognition [13,14].

This research has been crucial for supporting the concept that exchanges of information within the brain and the integration of brain activities are carried out largely if not exclusively via precise anatomical connections. In spite of its truistic character, this concept has been and is being periodically challenged by theories of brain organization which maintain that nervous integration occurs by means of mechanisms that do not require orthodox anatomical connections, such as electrical fields or neuronal modulations by diffusable chemical agents. In addition, split brain research has given impetus and provided special opportunities to the search for specific correlates between cognitive and emotional processes on one hand, and localized brain activities on the other, particularly in relation to hemispheric functional asymmetries. The initial claim that there are two entirely separate conscious minds and free wills under the cranial vault of a callosotomy patients is, however, now considered to be an exaggeration [2]. In everyday life, the behavior of split brain patients is wholly unitary and coherent with their preoperative personality, presumably due to the integrative activity of the regulatory brainstem systems that project diffusely to both hemispheres. Duplication of consciousness, if any, occurs only in the artificial conditions of the neuropsychological testing room, where sensory input and motor output can be restricted to a single hemisphere. Other suggestions that are still in need of confirmation are those that attribute cognitive disorders, ranging from dyslexia to certain schizophrenic symptoms, to disorders of interhemispheric communication. Finally, major mechanisms of brain reorganization and functional compensation are now being studied in subjects with callosal agenesis who do not exhibit the major symptoms of interhemispheric disconnection typical of split brain subjects (e.g., [4]).

Integration by the diffuse brainstem system and integration by the corpus callosum differ insofar as the first integration tends to affect the whole brain while the latter works to conjoin specific activities of select neural systems in the two hemispheres. The two types of integration may, however, depend on a common basic mechanism such as the formation of large-scale and small-scale neuronal cell assemblies by discharge synchronization [6,10]. This view of brain integration based on neuronal synchronization however is still in need of a crucial confirmation.

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