# SOME EVIDENCE ON THE FUNCTIONAL ORGANIZATION OF THE BRAIN

by

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"With health, the assertion is that each person's normal thought and conduct are, or signify, survivals of the fittest states of what we may call the topmost "layers". Now suppose that from disease the normal highest level of evolution (the topmost layer) is rendered functionless. This is the dissolution . . . I contend that his mental symptoms are survivals on the lower, but then highest, level of evolution" (remaining in function).

So wrote HUGHLINGS JACKSON in 1884[1]. One type of evidence for such an evolutionary concept involving a hierarchy of levels is observed by studying behaviour following a series of surgical sections of the brain. A transection below the medulla gives rise to the spinal animal[2], a decapitated preparation kept alive by artificial respiration but still responding to stimulation with primitive though appropriate muscular actions. A painful stimulus applied to the foot pad, for example, evokes flexion of that leg, a movement that makes for survival as the leg is withdrawn from harm.

The decerebrate animal produced by cutting through a higher level[2], namely the lower portion of the midbrain and therefore retaining the medulla reveals a release of the antigravity muscles permitting an abnormal sort of erect standing called decerebrate rigidity. The decorticate animal with extirpation of the highest portion of his brain only, expresses sham rage, a release of emotional patterns from cortical control[3]. Both decerebrate rigidity and sham rage may appear spontaneously or may be evoked. These three sections of the neuraxis reveal patterns of behaviour which are functional in the intact organism but are modified by anatomically higher areas, of later development which facilitate more delicate sensory perception and finer execution of movement. For the organism to take advantage of these improved capacities the behaviour of the lower portions of the brain must be subjected to the inhibition as well as the reinforcement of the higher planes and when their influence is removed we see a release of function in the lower areas, a result of loss of restraint. Strong support for the observation that inhibition is a function of the brain has been afforded by the physiological experiments of DUSSER DE BARENNE AND MCCULLOCH[4] who demonstrated that stimulation of one cerebral area suppresses activity in another.

For another type of evidence we must turn to an examination of man for an opportunity is afforded to study the human brain when sections are made in a functional manner. An example is observed during hypoglycemia when a temporary "dissolution" of the brain is a result of excessive insulin[5]. The behavioural phenomena observed may be allocated to certain cerebral areas. In fact, the signs exhibited are those that might

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be expected if successive surgical sections were made at different levels of the brain.

In order to explain the changes observed in hypoglycemia it must be recalled that glucose is no longer available to the brain. Since glucose is the chief foodstuff of the brain[6, 7, 8] the metabolic fires falter because of the decrease in the coal to be burned[9]. A decrease to 52 %[10] and 40 %[11] respectively of the normal rate have been reported in hypoglycemia. With the most profound metabolic depression (*i.e.*, in the 5th phase, see below) cerebral metabolic rate may be reduced to 25 % of the normal[11]. But not all parts of the brain are effected to an equal degree. Though the brain possesses a high rate of metabolism, the rate is not the same in all regions but in general exhibits a quantitative gradient along the neuraxis, most intense anteriorally and superiorally in the cerebral hemispheres and less so posteriorally and inferiorally until it reaches its lowest level in the medulla oblongata. This conception is borne out by the observation of excised cerebral tissues which show a decreasing rate of oxygen intake as the neuraxis is descended[12, 13]. The oxygen consumption of various parts in the human brain *in vivo* will not be considered at this time because of conflicting results[14, 15]. Pending the solution of this discrepancy we may point to another bit of evidence of a hierarchy in metabolic rate. In order to combat hypoglycemic coma carbohydrate must be administered and it has been observed that a larger amount of glucose is required to restore the functions of the cerebral hemispheres than for the subcortical areas[16]. Presumably a greater amount of foodstuff is necessary to support a higher rate of metabolism.

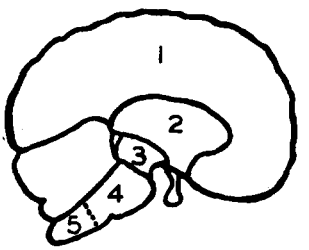


Fig. 1. Representation (transverse section) of the brain disclosing the five phyletic areas: 1. cerebral cortex; 2. subcorticodiencephalon; 3. midbrain; 4. pons and upper medulla; 5. medullary centers

If we accept the concept of dissimilar metabolic rates it must follow that all parts of the brain will not be equally affected by hypoglycemia but that those regions with fastest rates would succumb first and those with the slowest, for example the medulla, last. Then in accord with HUGHLINGS JACKSON'S idea[1] that the brain is so constructed that the higher anatomic and newer phyletic portions contain areas which regulate and control the lower anatomic and older phyletic regions we might expect a series of release phenomena as each area in turn succumbs to an increasingly severe degree of carbohydrate deprivation[17]. Such a series is seen in the insulin hypoglycemia repeatedly produced in the pharmacologic treatment of schizophrenia[18].

Following the injection of insulin the first phase involves the depression of the cerebral cortex (area 1, Fig. 1). Sensations become dull and abnormal, understanding is impaired and motor activity poor in execution. Contact with the environment is gradually lost as the patient becomes unconscious, the beginning of the second stage. The second group of signs proves to be due to a release of the functions in area 2, the subcorticodiencephalon. Three types of phenomena are observed in this stage. First are changes in motility reminiscent of those seen in a newborn baby with motor restlessness and primitive movements of many types such as involuntary sucking and involuntary grasping. Second there is increased sensitivity so that responses to stimuli become intense, excessive and at the same time lose direction. Finally, alterations in the autonomic system are seen with sympathetic predominance indicated by dilatation of the pupils, bulging of the eyeballs from their sockets, acceleration of the heart rate and rise of blood

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pressure. This stage is not unlike that of sham rage exhibited by the decorticate animal. The third constellation (area 3) represents functions allocated to the midbrain. For example the body is seized by violent (tonic) spasms during which the legs become rigidly extended, the trunk is arched while the arms are thrust forward, bent at the elbows. The fourth group of manifestations, referable to the pons and upper portion of the medulla (area 4), begins when the arms are no longer held in front of the body but are slowly forced back over the head (extensor spasm). The back however is arched the legs are extended as in the third stage and the entire picture is similar to that of a decerebrate animal. Finally in the fifth stage (area 5) the cold, gray, clammy skin, the slow and feeble heart, the greatly depressed respiration, the muscular flaccidity, and the contracted pupils all give evidence that the metabolic depression is now affecting the vital medullary centers.

Soon after the fifth group of signs appear it is necessary to give the patient sugar. The blood glucose values rapidly rise and the brain once more obtains adequate supplies. The alterations in behaviour during recovery conform to the same plan as those seen during their development but this time their order is reversed.

It is well to make comparisons with the results of metabolic depression other than those produced by hypoglycemia. If the signs are due to a metabolic deficit then the same or at least a similar series of signs should be produced irrespective of the manner by which the metabolic deficit is created. As an example let us consider anoxia, a condition in which oxygen is no longer available to the brain in common with the other organs.

It is true that energy may be provided in the absence of oxygen, an anaerobic mechanism of great biological importance, for example, in sudden muscular activity. In the brain however, though not without significance[19, 20, 21], the anaerobic release of energy is strictly limited for most of the energy usually available in the carbohydrate foodstuff of the brain, glucose, cannot be realized. For that reason the brain is highly sensitive to oxygen lack and when thus bereft of energy, can no longer support its own functions.

Whereas the signs of hypoglycemia may be observed over a period of 5 hours those of acute anoxia are more fleeting and must be limited to a period of as many minutes. Nevertheless the changes in behaviour follow the same general path of those of hypoglycemia and indicate a downward progression during anoxia and the reversed direction on recovery. These signs were demonstrated in a series of psychotic patients who respired undiluted nitrogen administered by means of a mask[22]. Early is seen a brief period during which consciousness becomes impaired as the cerebral hemispheres are the first to suffer from the decrease in available energy (area 1, Fig. 1). The first phase ends as environmental contact is lost. With the loss of consciousness a series of dramatic neuromuscular reactions occurs beginning with a period of aimless motor restlessness which ensues after the subcorticodiencephalon acquires freedom from cortical restraint (area 2). Next come strong muscular contractions like those described in the third phase of hypoglycemic coma (tonic spasms) as the midbrain is freed from higher control (area 3). Finally emprosthotonos, flexion of the body, or opisthotonos, extreme extension, are seen in the fourth stage (area 4). These signs are release phenomena and indicate a decerebration of functional origin. At this point the inhalation of nitrogen is stopped to prevent involvement of the medullary centers. With the subsequent administration of air or oxygen the normal cerebral integrations are rapidly restored.

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Supporting data for such a sequence of changes during hypoglycemia[23] or acute anoxia[24] is afforded by electroencephalographic tracings which reveal that the cortical rhythm vanishes before the subcortical. Conversely the administration of glucose or oxygen restores the subcortical waves before those of the cortex, additional evidence that the cerebral cortex workes at a higher rate of activity and has greater demands for energy than the subcortex.

Turning to the problem of pentothal anesthesia, we find that pentothal, like the

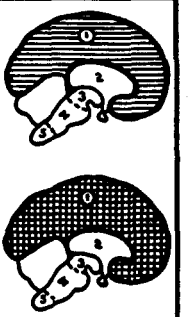
| Stage | Anesthesia | Characteristics | Site of depression | Brain |
|---|---|---|---|---|
| I | Clouding | Euphoria loss of discrimination to impairment of environmental contact | Slight depression of cortex to moderate depression of cortex |  |
| II | Hyper sensitivity | Loss of consciousness | Predominant control by subcortex |  |
| III Plane I | Light surgical | Hypoactivity to painful stimulus | Moderate depression of subcortex |  |
| Plane II | Moderate surgical | Loss of somatic response to pain | Predominant control by midbrain |  |
| Plane III | Deep surgical | Loss of visceral response to pain | Moderate depression of midbrain |  |
| IV | Impending failure | Fall in pulse pressure | Moderate depression of pons |  |

Fig. 2. A correlation between the stages of pentothal anesthesia and the outstanding clinical signs and their neuro-anatomic allocations

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other barbiturates, exerts a metabolic inhibition which is most marked in the brain and relatively unimportant in other organs[25]. Measurements of brain metabolism made on human beings in the second and third stages of pentothal anesthesia disclose a decrease of approximately one-third[15].

The barbiturates not only employ metabolic deprivation but also act on nerve function[26]. The latter action may be described as an elevation of the synaptic threshold[27] due perhaps to impeded recovery after impulse propagation[28]. Despite these diverse influences it is feasible to follow the events caused by metabolic depression.

In this brief exposition it is impossible to review the signs of pentothal anesthesia. Instead an explanatory diagram is inserted (Fig. 2). The figure is taken from a paper[29] in which it is suggested that the metabolic inhibition is the cause for certain similarities between barbiturate anesthesia and hypoglycemia or anoxia and especially so for the march of signs down the neuraxis with deepening anethesia. On the other hand the distinguishing characteristics of the anesthesia are attributed to the special effects which the barbiturate exert upon nerve functions.

Since the progression of the changes in behaviour observed following surgical or pharmacologic intervention seem to depend upon the hierarchy of metabolic rates in the various parts of the brain it is worth while to examine that phenomenon further. A clue as to its origin may be offered by a study of the changes in oxygen intake of the various parts of the brain during early growth. Animals which are born in an immature state, resembling man in that way, are appropriate material for a study of postnatal metabolic changes. The newborn rat, blind, poikilothermic and without righting reflexes, essentially a bulbospinal animal, can be followed through early growth while the later developed portions of the brain take on their due functions. The birth process marks the passage from intrauterine life to individual independence but does not necessarily represent a definite change in the fundamental patterns of growth and energy production.

Numerous *in vitro* studies of oxygen intake reveal a higher rate of metabolism in the adult than in the infant. This was first observed in infant rat brain[30], and later confirmed on the dog[13]. These results indicate a rapid rise of cerebral metabolism in early life. The metabolic changes are the resultants of the distinctive rates in the discrete parts of the brain. It has been experimentally established that the metabolic rates are not equally affected by growth, but that each area possesses its own pattern of development. In experiments on the rat[31] and the dog[13] (Fig. 3) it was found that the lower parts of the brain are relatively more active than the higher ones at birth, and as development continues, the wave of metabolism presses forward so that the lower portions of the central nervous system are surpassed by the anatomically higher and phyletically more recently developed regions. The increasing rate of metabolism of the brain as a whole must therefore be attributed chiefly to the increasing rate in the newer parts of the brain during early life.

Additional evidence for this phyletic sequence can be observed by a study of the anaerobic metabolism. The short period of survival in anoxia observed in the mammal is made possible by the anaerobic production of energy which includes the splitting of carbohydrate to form lactic acid. The cerebral glycolytic rates are slowest in the newborn and increase to a maximum in early life[32, 33]. In order to determine the contribution of each area in the brain making for this changing rate of glycolysis both dogs and cats were employed[34] and in several age groups: newborns to one week, three to seven weeks, three months, and adult. In general, the results of the experiments on dogs and cats

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were similar. At birth the medulla oblongata revealed the highest glycolysis. In the adult, however, it is the cortex that shares the most rapid metabolic rate with the caudate nucleus.

The developmental progression observed in oxidation and glycolysis has also been found in the distribution of cerebral glycogen. Chemical determinations demonstrate that glycogen concentrations of the cerebral cortex and caudate nucleus increase with age. The percentage of glycogen in the lower parts, however, the cerebellum, medulla and spinal cord diminish progressively and are least in the adult[35].

The quantitative analyses presented above show that both aerobic and anaerobic mechanisms are accelerated after birth. It seems probable that the more rapid rates are an expression of an increased concentration of enzymes. Such an increase can be accounted for by the growing capacities of phosphorylase, phosphoglucomutase[36], adenosine triphosphatase[38] and the cytochrome-cytochrome oxidase system[37, 38] occurring in the brain during the early postnatal growth of the rat. Carbonic anhydrase though not found in the fetal rat is present in the adult where it is more plentiful in the functionally dominant cerebral areas than in the cord[39]. A study of fetal sheep proved that the enzyme cholinesterase is present in greater concentration in the spinal cord than the brain during early gestation. This relationship however is reversed in the last weeks before birth as the cholinesterase activities of the cord diminish while those of the brain far outstrip it[40]. This enzymatic evolution which appears earlier in the sheep than in the rat is not to be attributed solely to a difference in the enzyme studied in these two species but it must also be remembered that the sheep is further advanced in the development of behavioural patterns at the time of birth.

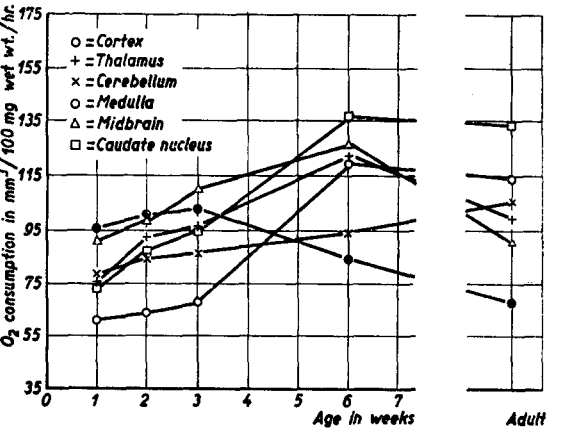


Fig. 3. Oxygen consumption vs. Age Dog Brain Parts. In the first week of life the highest rate of metabolism in the puppy's brain is found in the medulla; during the third week the midbrain assumes the highest oxygen consumption. From the fifth to the seventh week, the respiratory metabolism of all parts, with the exception of the medulla, is higher than the corresponding values for the first week of life and the caudate nucleus has advanced to the greatest oxygen intake up to this time. In the adult dog the latter still retains its prime position, while the cerebral cortex ascends to second place. The cerebellum, thalamus, midbrain and medulla follow in descending order.

To summarize, the increase in metabolic intensity does not occur in all parts of the brain simultaneously, but appears in the various portions at different times. The order of appearance is not a haphazard one but develops first in the posterior portions of the neuraxis and then progresses in an anterior direction. Such a stepwise passage advancing from the older to the newer parts of the brain recapitulates its phyletic development. Since many of the metabolic studies reviewed were made on newborns. It would seem that HAECKEL's dictum that ontogeny recapitulates phylogeny[41] should be broadened, in the case of the brain, and the time extended to include early postnatal growth with prenatal development.

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To climb the phyletic ladder from our remotest ancestors through the fish, amphibia, reptiles and mammals, would entail a tremendous volume of description, which is not the point of this contribution. The general trend of this process of cephalization, or concentration of neural functions in the oral end of the animal, may be described briefly: as far back as the fish, brain is divided into five portions as it is in man, but in the fish and amphibia the chief site of integration for sensory and motor impulses lies in the midbrain. In these species the highest portion of the brain consists chiefly of the olfactory bulb, and the cerebral cortex which becomes all-important in man, is represented only by a thin layer of cells. On further ascending the phyletic scale to reptiles and birds as well as mammals, the subcortical structures immediately anterior to the midbrain become more prominent, as the organism achieves greater coordinating control. Lastly, the cerebral cortex, though getting off to a late start, gradually attains more complexity of structure and diversity of function until in the lower mammals it surpasses all other regions, and in the primates, especially in man, forms the largest and most complex part of the cerebral tissue. As this process of phylogeny is carried on from one species to another, no part of the neuraxis is scrapped, but each older part, in turn, comes under the influence of a later developed portion, which not only possesses finer discrimination and analysers but also plays a rôle in determining the motor expression of the older areas.

Though the brain of man as we see it today looks like a static structure, when it is examined more closely in the light of the phyletic conception, we see that it has come to its present construction as a result of a long series of accretions, beginning with the spinal cord and medulla oblongata and spreading in a cephalad direction, layer upon layer, until the cerebral hemispheres form the greatest mass of the brain. It is not to be supposed that each level is independent of its predecessors, but rather that it exists with a specific relation, both anatomically and physiologically, to the phyletically older portions[42]. Owing to this relation, the central nervous system may function as a unit, but a unity which is brought to a higher plane of integration with each successive step. The human brain is undoubtedly the latest arrangement of the central nervous system, but not necessarily the final one.

Sir CHARLES SHERRINGTON[43] has expressed vividly HUGHLINGS JACKSON'S conception. "That leading end, the head, has receiving stations signalling from things at a distance, things which the animal in its forward movement will next meet. A shell of its immediate future surrounds the animal's head. The nerve-nets in the head are therefore busy with signals from a shell of the outside world which the animal is about to enter and experience. The brain has thus arisen where signalling is busiest and is fraught most with the germ of futurity. Small wonder then that the brain plays a great rôle in the motor management of the muscle. Nerve management of muscle resolves itself largely into management of nerve by nerve, especially by brain, more and more so as evolution proceeds. With no greater equipment of muscle the superimposed amount of nerve becomes greater and greater; each new nerve-growth seems to entail further nerve-growth. Fresh organization roofs over prior organization. Brain is an example. 'So on our heels a fresh perfection treads'. But were it a government office we might be suspicious. This brain of ours is a perfect excrescence although our endowment of muscle remains but moderate".

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Received April 8th, 1949