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Neurophysiological Correlates of Information Transaction
and Storage in Brain Tissue

W. R. Adey

Brain Research Institute, Center for the Health Sciences
University of California, Los Angeles

Please send proofs to: Dr. W. R. Adey
Brain Research Institute
Center for the Health Sciences
University of California
Los Angeles, California, 90024

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Study of functions of the brain on a behavioristic basis, divorced in greater or lesser degree from associated activity in brain systems, has afforded the physiological psychologist a broad field of endeavor in the past decade, as he has manipulated schedules of reinforcement dependent on both peripheral and central stimuli. While it has been claimed for these studies that they have yielded information about brain organization in perception and learning, with disclosure, for example, of specific brain regions that constitute "centers," this notion itself has little place in the physiologist's current scheme of cerebral functions. For whatever may be the apparent dominance of one brain region in the behavioral expression of a particular function, our enthusiasm must be tempered by knowledge of profoundly influential, wide ranging and substantially reciprocal pathways involving such centers; of continuous activity in neuronal firing patterns related complexly and in stochastic ways to sensory stimuli; and of brain substance organized in a series of tissue compartments, each contributing functionally to the whole, and carrying with them the keys to that most unique function of brain tissue, the storage of information.

As though by a flanking movement, the physiologist, the biochemist and even the mathematician and engineer, have come to involve themselves in the past decade directly in studies of behavior, bringing with them the intricate knowledge and techniques of their specialties to directly confront critical problems of brain and behavior. The physiologist has proved himself adept at recording electrical activity of the brain in freely performing individuals. He has learned to record activity of single cells in unanesthetized brains during perception and learning. He has benefited from his engineering colleagues experience in data acquisition systems, and in computer analysis

of neurophysiological data.

It may be argued that there persists a gulf that deepens and widens between physiological activity of any recordable kind and mental activity in perception and learning. There can be little dispute with such a view, insofar as the physiologist discerns processes which have varying degrees of correlation with mental activity. At this stage, the physiologist has barely begun evaluation of these correlates, and it is in the elucidation of their progressively finer patterns that he will concern himself for some time to come. The hierarchical nature of these correlates, however, as they have already been disclosed from the level of the single cell to cerebral system interrelations in man, invite consideration of the possibility of causal significance in at least some of these physiological events.

Essentially, we face the problem of what constitutes information at the input of cerebral systems, what are its transforms in transactional processes, and what are the bases of storage and recall. We have tended to assume that at each stage of these presumably sequential events, the electrical activity of the brain might provide the sole, or at least an adequate measure of the state of tissue in which any or all of these processes might simultaneously occur. Yet, as will be discussed elsewhere, we do not yet know to which of a variety of electrical processes that occur simultaneously within cerebral nerve cells, and in certain respects are apparently unique to cerebral neurons, we may attach special significance in initiation of storage, as opposed to transaction, of information in brain tissue. Moreover, it is quite conceivable that the changing states of brain tissue deriving from storage of information may not be reflected in electrophysiological records, except during information retrieval. A gamut of new techniques quite unrelated

to classical electrophysiological recording methods may thus be necessary to detect such changes.

Let us embark, then, upon a journey wherein fact and speculation may sometimes go hand in hand, to the baffling complexity of the mosaic that forms the tiny cosmos of the neuronal membrane, and to the narrow clefts that mark off each neuron from adjacent neurons and neuroglial cells. Let us look in broader view at the summed activity of neuronal populations during a variety of behavioral performances, and ways in which these aggregated populations reflect in their patterns of activity a repertoire of behavioral performances. At the outset, we may discuss a structural scheme of cerebral organization on which our functional evaluation will largely rest.

1. Salient features of cellular organization in cerebral structures: a tricompartamental model.

New knowledge of the relations between cellular elements in brain tissue has come from electron microscopy studies which have revealed a series of intimate interrelations between cells of neuronal and non-neuronal systems. These findings have invited a reappraisal of structural organization within organized populations of neurons in a domain of cerebral tissue.

Nerve cells in mammalian cerebral cortex are arranged in a pattern characteristically described as laminar. The degree of orderliness in this layering varies from one cortical region to another, and, indeed, with the eye of the beholder (Sholl, 1956). It may be noted, however, that a unique and characteristic feature of cerebral cortex, and also of cerebral ganglia of many invertebrates, is the great overlap of the dendritic branches, or "tree," of one neuron, with those of adjacent neurons. Moreover, there appears to be a progressive enlargement of the size of the dendritic

apparatus in the higher mammal, so that the neuronal packing density appears to progressively decrease as one ascends the phyletic scale. The electron micrographs show that, in some instances, these contacts between dendrites of different neurons are as close as in synaptic junctions, or about 100 \AA° (van der Loos, 1962). Possible functional interactions which might be initiated in this way are unknown, as are the numbers and locations of such contacts on any particular neuron. Nevertheless, it is necessary that we take account of such structural relations at this stage, since they may determine the degree of "coupling" between a neuron and others in its vicinity, in their mutual interaction in certain slow wave processes to be discussed below.

Neuroglial cells have long been known to intervene between nerve cells and the vascular apparatus, so that they may exercise a regulatory function on neuronal metabolism. Some authors have described the neuroglial envelope as essentially complete around individual neurons, while others have noted a more restricted distribution, with a "packeting" of glial elements around synaptic terminals and with relatively bare intervening areas (Peters and Palay, 1964). It is now possible to combine cytochemical techniques with electron microscopy, and thus, to display distribution of a variety of enzymes in the interfaces between these cellular elements. These enzymes lie at adjacent membranes where neuronal and neuroglial cells are in contact, and similarly, where neuroglial elements are in contact, but are not seen where neuronal elements adjoin one another. Enzyme concentrations are also high in the basement membranes outside the vascular endothelium of capillaries, and in the "sucker feet" of astrocytes attached to these membranes, although endothelial cells themselves show little enzyme activity (Barnett, 1963). Perhaps herein is a structural basis for the "blood brain barrier," since

transport of blood-borne substances across the capillary wall may depend in varying degrees on the presence of appropriate enzyme systems.

So far, we have considered two compartments, neuronal and neuroglial, in a tricompartamental cerebral system. A third compartment, ^{the extra cellular} traditionally given scant attention in most histological descriptions, may well rank equally with the other two in functional significance. While it would be easy to dismiss it as a mere bucket of saline, if our notions of cerebral organization required it merely to contribute sodium ions, in accordance with certain popular neuronal models, attention has recently been focused on its content of mucopolysaccharide material (Barker et al, 1962). The evidence suggests that it may exhibit considerable organization in its content of these large molecules, which are capable of modulating and controlling rates of ion movements through this compartment. Since it lies between the neuronal and neuroglial elements, its role in delimiting metabolic exchange with nerve cells may be of the utmost importance. These mucopolysaccharides have been shown to be chemically disordered in the types and location of their sugar molecules in mental disorders, such as infantile amaurotic idiocy. Their presence in the "ground substance" of brain tissue was recognized many years ago, but their functional significance, and that of the extracellular compartment generally, has received little attention.

The size of the extracellular compartment has been hotly debated. Traditional methods of fixation of tissue for electron microscopy with osmic acid have indicated quite small values, between about 1 and 4 per cent. Van Harreveld (1965) has shown that very rapid cooling of brain tissue to a low temperature (-207°C) against a metal plate produces an electron micrograph with as much as 24 per cent extracellular space. Failure to cool rapidly, and particularly, allowing an interval of 90 seconds or more to pass

after circulatory arrest and before fixation leads to obliteration of the extracellular space and transfer of fluid to an intraglial location. Chemical estimates of the extracellular space (Reed, Woodbury and Holtzer, 1964) have indicated about 14 per cent of cerebral volume, so that the figure derived from osmium fixed electron micrographs may be too small.

At all events, these recent studies have emphasized the peculiar nature of cerebral cellular organization, with emphasis on a dendritic tree of substantially greater volume than the cell body, a tree that overlaps and may be physically contiguous with those of neighboring neurons; a neuroglial compartment intimately involved in neural metabolic exchanges; and an extracellular compartment disposed between neuronal and neuroglial elements and characterized by a macromolecular "glue."

2. Neuroelectric activity in brain tissue: the genesis of waves and their relation to unit firing.

Ever since Berger (1929) recorded the electroencephalogram across large volumes of cerebral tissue, attention has been directed to its correlates with states of consciousness, and with abnormalities of cerebral functions. In turn, other studies have examined the possible relationship of these waves to neuronal activity (Li, McLennan and Jasper, 1957; Green, Maxwell and Petsche, 1961). Despite intense efforts, both lines of research have been frustrated in attempts to disclose simple relationships. The early hopes that the phenomenon of alpha blocking, or similarly obvious EEG changes from sleep to wakefulness, might have their counterparts during finer perceptual and learned performances, for example, have not borne fruit. Instead, it has been necessary to seek subtle aspects of patterning in wave trains that appear stochastically organized, as discussed below. Unit firing patterns recorded

simultaneously with wave activity in the same tissue have failed to disclose constant phase relations between the waves recorded grossly and the unit firing, even in the very regular waves of hippocampal theta trains, thus giving no support to the notion that the waves arise as the envelope of the firing of many neurons in a population.

The search has therefore turned to possible origins in slow processes generated by individual neurons. In extracellular records, Elul (1962) noted that paired microelectrodes separated by only 30 μ m recorded a spontaneous EEG of apparently normal form and amplitude. Moreover, no similarity could be found between monopolar and differential derivations of both spikes and slow waves recorded simultaneously with such small tip separations. These findings thus emphasized the limited dimensions of cortical dipoles in the genesis of the EEG to distances of cellular magnitude. In more recent studies, Elul (1964) has pursued these findings with intracellular recording.

In approach to the membrane of the single neuron with a fine, liquid-filled micropipette with recording sensitivities in the low millivolt range, no EEG wave activity was found until actual penetration of the neuronal membrane. Immediately after penetration, however, large rhythmic waves were seen in unanesthetized cortical neurons, superimposed on the resting membrane potential (Elul, 1965). These intracellular waves are large, with an amplitude of 5 to 15 millivolts, thus involving a major portion of the membrane potential of 70 to 90 millivolts, and are hundreds of times larger than the EEG recorded in adjacent extracellular tissue, or on the cortical surface. Essentially similar findings have been reported also by Creutzfeldt, Fuster, Lux and Nacimiento (1964) and Jasper and Stefanis (1965). Large waves have been recorded intracellularly also in the hippocampus during typical theta

wave trains in larger volumes of tissue by Fujita and Sato (1964).

There is a strong general relationship between frequencies in these intracellular waves and the EEG recorded grossly from the same region. In sleep with large, regular slow waves, similar patterns characterize intracellular records. Conversely, the rapid surface EEG in the aroused state is accompanied by comparably increased frequencies in intracellular waves (Elul, 1965). Elul has considered ways in which such intraneuronal generators might jointly produce the EEG recorded grossly. The ratio of the high resistance of neuronal membrane to the lower resistance of the enclosing extraneuronal medium will determine the magnitude of the EMF appearing in the extraneuronal medium through transmembrane flow of current from intracellular generators as related to the magnitude of the intracellular potential. Available data supports the view that this ratio would be at least 100:1, so that the observed amplitude of 50 to 200 mV at cortical surface is compatible with such an origin.

There remains a more substantial consideration in establishing a causal relationship between individual neuronal generators and the EEG. This concerns statistical operation of a population of generators, and ways in which individual generators may contribute to the configuration of the EEG. Elul has applied the central limit theorem of statistics (Cramer, 1962) to an evaluation of this problem, and considers that cortical neuronal generators meet the theorem requirements of individual amplitude distributions, which are not linearly related, and possess a mean, and a finite standard deviation (Loève, 1955). He concludes that the EEG may be accounted for as the normal distribution ensuing from combination of activity of non-linearly related neuronal generators.

In such a scheme, it would be anticipated that the frequency

characteristics of individual generators would relate strongly to the gross EEG, but that phase relations would be lost in the process of summation. And thus we come to yet another frontier, where once again the baffling complexity of cerebral organization requires that we pause and take stock of the adequacy of our observations to proceed further. We must concern ourselves with such phenomena as regional differences, and indeed, regional specificities, in rhythmic processes, such as the 40 cycles/sec rhythms of the amygdala, or the 6 cycles/sec theta trains of the hippocampus, or the characteristic frequencies of the alpha band. If such rhythms arise in summed activity of neuronal generators, it is also necessary that we consider ways in which individual generators may be coupled in constantly varying degrees to other generators in the system. None of these questions can now be answered, nor do we know precisely the mechanisms by which these waves arise within the cell, whether it be by synaptic potentials, or in intrinsic activity in "dendritic" potentials.

Let us consider briefly, however, certain findings about the relationship of intracellular waves to firing of the neuron. Firing of the neuron occurs near, but not necessarily at, the peaks of the depolarizing phase of the intracellular wave. However, it has been our consistent observation that the level of depolarization reached on the depolarizing peaks of these waves is not a critical determinant of the initiation of firing. In many instances, depolarizing peaks exceeded those on which firing occurred without initiation of a spike, suggesting that the relationship between intracellular waves and the spike output may not always be a linear one (Elul and Adey, 1965). If we accept the notion that initiation of the spike discharge normally occurs from restricted zones in the vicinity of the axon hillock, these findings suggest that internal organization of the neuron may involve selective internal

current paths to the spike triggering zone. There may be different abilities in various parts of the neuronal membrane to influence current flow through the membrane of the axon hillock, and thereby, to determine the onset of a propagated impulse. Interrelations between intracellular records and unit firing have been studied by Jasper and Stefanis (1965).

The firing of the neuron in relation to either evoked potentials or induced trains of waves recorded in the same tissue domain appears complex, as is the simultaneously recorded activity of neurons in a single region after a stimulus (Amassian, et al., 1961; Verzeano and Negishi, 1960). Fox and O'Brien (1965) have recently averaged the discharge rate of a single cortical unit in response to repeated peripheral stimuli, and found that variations in firing rate follow a contour similar to the evoked potential in the same region, but only after as many as several thousand repetitions of the stimulus. These findings appear to support the view that there is at best only a statistical relationship between the firing pattern of the individual neuron and the behavior of the integrated neuronal population, as indicated by the contour of the evoked potential. This interrelation will be discussed further below.

3. Unit firing patterns in response to conditional stimuli.

In the light of the foregoing discussion of neuronal activity in both slow processes and simultaneous pulse coded firing, we may now consider evidence on the development of conditional firing patterns in cerebral neurons. Polymodal input to individual cells in brainstem and diencephalic and reticular structures (Moruzzi, 1954; Scheibel, et al., 1955) has encouraged the notion that "temporary connections" may well be established via these cells. In cortical structures, meaningful patterns have also been detected, despite the great variability of response at this level of analysis (Jasper, et al., 1960;

Yoshii and Ogura, 1960; Morrell, 1960; Olds and Olds, 1961).

The importance of reticular structures in conditioning has been established in both recording and lesion experiments (Chow, et al., 1959; Doty, et al., 1950). Olds and Olds (1961) emphasized the relative ease of establishment of conditional behavior in paleocortical and subcortical units, by comparison with cortical units. Gastaut (1958) has pointed to the thalamic reticular formation as the locus of "closure" in his well known theory of conditioning. More recent studies (Kamikawa, et al., 1964) have indicated that medial thalamic units can be repeatedly extinguished and retrained during classical conditioning.

The behavior of these medial thalamic units during repeated conditioning and extinction emphasizes the plasticity of responsiveness of single cells in such a paradigm, with the gradual development of firing patterns which might be the converse of those initially elicited. Extinction tests following each conditioning also exhibited progressive rebound phenomena, so that over a period of several hours, it was possible to see here also a series of gradual changes that increased in magnitude, as well as showing qualitative differences from those in the first extinction trial.

The "training" situation used by Kamikawa, et al. (1964) involved pairing of a light flash as a conditional stimulus with an unconditional shock train to the sciatic nerve. The CS-US interval ranged from 300 to 800 msec. Tests with intervals shorter than 300 msec failed to elicit a conditional response. Training trials were given once every 10 sec. A change in firing in the CS-US interval characteristic of a conditional response required a minimum of about 50 trials, presented over a period of about 20 minutes. These findings offer a tiny chink in the door to our understanding of the processes that might

underlie the lasting structural changes associated with a memory trace.

The requirement for a minimal CS-US interval of the order of 300 msec suggests a time scale comparable with electrophysiological events at the neuronal membrane, such as the prolonged inhibitory postsynaptic potentials seen in cortical neurons (Andersen, et al., 1963), lasting up to several hundred milliseconds, and without an equivalently persistent counterpart in spinal motoneurons; or the wave processes in cortical neurons described above (Elul and Adey, 1965), which at this time are less definitely related to synaptic potentials. On the other hand, the requirement that training trials have a time course of 20 minutes to generate a conditional response suggests a much slower process, perhaps the synthesis of a macromolecule, protein in nature, and located at the neuronal membrane, where it might influence directly the excitability of the cell by synaptic volleys.

Further evidence about the development of a conditional response in medial thalamic neurons, and particularly its fragility, came from extinction trials. Usually 10 to 20 unreinforced trials were required to extinguish a conditional response in the early extinction periods. Following a pattern familiar to experimental psychologists, repeated sequences of unpaired trials extinguished the conditional response more rapidly, until less than 5 trials abolished it. This pattern was less clear after prolonged training, with "spontaneous recovery" of an extinguished conditioned response not uncommon. Two types of rebound were noted in these extinction trials. The first occurred on the first trial of any set of extinction trials, and resembles the familiar postinhibitory acceleration. It is presumably a property of individual nerve cells, and masked by the unconditioned response during training trials. The second occurred after several extinction trials as a more complex phenomenon,

possibly related to a conditioned synaptic input which is both excitatory and inhibitory, with the latter extinguishing more rapidly than the former. These observations have suggested an intriguing hypothesis that the rebound activity is one aspect of a dynamic process by which the brain actively suppresses functions associated with the conditioned state. This possibility has been discussed by Roitbak (1960) in terms of an inhibitory role for non-specific thalamic nuclei.

Although no general statement can be made about the incidence of "conditionable" cells in any one nuclear group, most cells in the non-specific thalamic nuclei that ultimately displayed such a response required approximately the same number of trials to be conditioned, suggesting that they participated in comparable phases of the conditioning process. Yet once conditioned, its subsequent behavior was often markedly different from that of other cells. Certain general correlations between conditioning and more gross EEG activity of the brain have been noted in widely differing experimental situations. A previously habituated conditional stimulus generally elicits behavioral arousal, and its electrical concomitants, after a few pairings with a meaningful stimulus (Beck, et al., 1958; Lissak and Grastyan, 1960). This prompt appearance of behavioral and electrophysiological arousal parallels the early occurrence of conditioned activity in the mesencephalic reticular formation (Yoshii and Ogura, 1960). By contrast, conditioned activity in medial thalamic units rarely appeared before the 50th training trial, so that it does not appear that these units are involved in the early generalized arousal phase of a developing conditioned response.

In summary, these studies in single thalamic units are compatible with much other evidence that 75 to 100 training trials are required to establish

consistent conditioned leg flexion in cats (Beck and Doty, 1957; Beck, et al., 1958; Majkowski, 1958), with occasional and irregular responses appearing earlier (McAdam, 1962; McAdam, et al., 1962). On the other hand, crude avoidance movements, gamma motor neuron activity and pupillary responses may be conditioned in less than 10 trials (Buchwald and Eldred, 1961, 1962; Galambos and Sheatz, 1962), suggesting that conditioned unit activity in the non-specific thalamic nuclei develops at some point during the transition from generalized orienting responses to integrated, adaptive behavior (Kamikawa, et al., 1964).

Our further insight into the role of single neurons in the conditioning process must await future studies evaluating the behavior of single cells as members of a neuronal population, and in relation to both overt behavior and concurrent electroencephalographic wave phenomena in the same tissue. It is to these wave phenomena that we may now turn in consideration of their patterns in conditional responses.

4. Electroencephalographic correlates of conditional responses; their relationships to EEG wave trains, and to evoked responses as "tracer" signals.

The ceaseless EEG activity of the brain in wakefulness and sleep, persisting after removal of major aspects of peripheral sensory influxes (Bremer, 1935), and the inherent complexity of these seemingly intrinsic and spontaneous patterns, have disappointed those seeking simple relations between a developing conditional response and induced EEG wave trains. Where consistent induced changes have been noted, lack of means until recently for quantified assessment of subtle but important differences between records accompanying a repertoire of behavioral performances (Galambos, 1961;

John, 1961) has led to the inference that the EEG activity accompanying these behavioral performances represents a stereotype (Sokolov, 1963). It would thereby be precluded from further consideration as the basis for information transaction in cerebral tissue, being merely a noise without causal relations to transactional processes; even, perhaps, "full of sound and fury, signifying nothing." It would be unfortunate if our curiosity were so easily satisfied. The power of such mathematical techniques as spectral analysis (Blackman and Tukey, 1959; Tukey, 1965) to reveal strong patterning within and between a series of EEG records challenges us to follow the long and difficult road that leads at first to delineation of those interrelations that are primarily linear (Walter, 1963; Walter and Adey, 1963) and thence to more subtle but no less informationally significant non-linear patterns (Walter and Brown, 1963; Walter & Adey, 1965a). Girt about with such an armor, the neurophysiologist no longer faces bewilderment and defeat in the avalanche of exceedingly complex records that have for so long defied specification of pattern by visual inspection.

We may examine as indices of learning alterations in spontaneous rhythms, including induction of "activated" EEG patterns and those characterized by rhythmic slow waves; or alterations in evoked potentials following either single stimuli or trains of repetitive stimuli. These topics have been admirably reviewed by Morrell (1961) and John (1961), and will be discussed here in summary only. We may ask at the outset whether these procedures may rank equivalently in our attempts to unravel the electrical signal patterns correlated with learning.

Spontaneous rhythms and the changes induced in them in the course of conditioning may be presumed to relate in varying degree to the processing

of information arriving in an essentially continuous fashion from environmental stimuli. On the other hand, environmental stimuli to which conditioning occurs do not typically possess rhythmic characters, nor is the environment normally perceived as a series of tachistoscopic impressions. In the frame of a communication system, these brief, iterative signals constitute transients in a system already occupied in varying degree with processing of information on a continuous basis. The arrival of these transients in a "signal space" so occupied might reflect in evoked potential configurations only residual availability of "space" not occupied in the primary processing of information essential to the conditional process. The use of such "tracer" signals is further obscured in two ways.

The triggering of an evoked potential is indicative in its primary deflections of immediate postsynaptic responses to an afferent volley, but in later deflections this relationship may well be lost, so that there is no easy means of distinguishing from "local" processes those deflections arising in continuing trans-synaptic activation by afferent volleys. The latter may have been initially triggered by a single or iterative train of stimuli, but may continue thereafter as locally sustained rhythmic processes having only a fortuitous frequency relationship to that of the stimulus train. The distinction is obviously important, and emphasizes the second area of difficulty in interpretation, in that "spontaneous" rhythms in the frequency bands of the "tracer" signals commonly used characterize many cortical and subcortical regions. With this caveat, that evoked potential changes in the course of conditioning may indicate residual responsiveness of a neuronal population concurrently engaged in essential information processing on a quite different basis, we may nevertheless admire the ingenuity of experimental design and

and extensive extrapolations made with this technique.

a. Characteristics of spontaneous rhythm changes in classical conditioning.

Any sudden stimulus arrests or "blocks" the alpha rhythm in the scalp electroencephalogram of man, as part of a general orienting response, which may include eye turning toward the stimulus, momentary cessation of respiration, galvanic skin response and increased muscular tone. The low voltage fast EEG activity which replaces the alpha rhythm was first described as an "activation" pattern by Rheinberger and Jasper (1937). Repeated stimulus presentation is associated with gradual disappearance of both the orienting response and its EEG concomitants. Moreover, the cortical distribution of the response may be selective, depending on the degree of arousal induced. The activation may be restricted to the cortical zone enclosing the primary projection area for the particular sensory modality (Adrian, 1947). The first manipulation of the alpha block in a conditioning experiment was by Durup and Fessard (1935), where a click stimulus as the CS came to evoke an alpha block initially elicited in pairing with light as the US. Jasper and Shagass (1941) later demonstrated many aspects of Pavlovian conditioning in similar experiments, including simple, differential, delayed, cyclic, trace and backward responses. Gastaut, et al. (1957) made similar studies of motor responses to light stimuli in the concomitant effects on the rhythm in central scalp areas (rythme en arceau) which blocks to limb movement rather than to light.

Historically, these findings led Gastaut (1958) and Yoshii (1957) to emphasize the role of the reticular formation of the brainstem in conditioning mechanisms, and that herein would be found the basis for the "temporary connections" underlying cortical activation and the conditional response.

More recent studies have emphasized the role of the cortex (Gastaut and Roger, 1960) and the participation of limbic structures (Lissak and Grastyan, 1960). Galambos (1958) has proposed a more elaborate scheme in which specific sensory pathways are modulated by corticifugal volleys to delimit environmental inputs. Arousal and alerting functions would require complex interrelated activity in reticular and limbic structures. These interrelations will be considered further below in discussions of instrumental conditioning.

A variety of manipulations, such as by lesions combined with EEG recording, or by electrical stimulation of cortical and subcortical structures, have been used to evaluate systems participating in the conditioning process (Morrell, 1961). Lesion experiments in reticular tissue have emphasized the tremendous recuperative powers and redundancy of integrative capacity in cortico-subcortical interrelations (Adamez, 1959, Doty, et al., 1959). Electrical stimulation of the midbrain reticular formation can clearly improve the speed of discriminative performance (Fuster, 1958), but the effects are obscure, since others have reported amnesia for an immediately preceding experience (Glickman, 1959) from reticular stimulation, and defective maze performance in rats where each run was followed by intralaminar thalamic stimulation (Mahut, 1957). Similarly, the elegant studies by Olds and his colleagues (1958) with brain self stimulation remain difficult to interpret in a frame of reward or punishment, despite the unexceptionable evidence of topographic organization of reinforcing systems in subcortical structures.

These studies of the activated EEG in classical conditioning have contributed to the view that the desynchronizing response represents a stereotype that can scarcely be pursued further in finer analysis of correlates with behavioral responsiveness and conditioning. Yet, it has long been

recognized (Iwama, 1950) that certain manipulations of a classical conditioning procedure leads to trains of synchronous slow waves. This was observed where the CS-US interval was prolonged, or in cortical areas surrounding a focal activated response. Gastaut (1957) attributed this phenomenon to "internal inhibition" in the Pavlovian sense. He construed the internal inhibitor as a measure of conditioning, whereas external inhibition from a novel environmental stimulus produced a low voltage fast or activated EEG. Interest in these synchronous discharges led to the use of flickering light at low frequencies as the US in rabbits, cats and monkeys (Morrell, 1958; Yoshii and Hockaday, 1958), to test the possibility that such a stimulus might act as a "tracer" in brain systems (Livanov and Poliakov, 1945; John and Killam, 1959). Difficulties in analyses of such records are discussed above, and by Morrell (1961), who emphasizes that there is no good reason for assuming that the code used for inscription is the frequency itself. The coding may, however, underlie the wave trains occurring "spontaneously" during a learned performance, and be detectable in finer degree than in analysis of an imposed "tracer" rhythm.

The foregoing account has considered the development of our knowledge of EEG changes accompanying classical conditioning. The recognition that a synchronous, rather than activated, pattern of cortical activity accompanies certain aspects of classical conditioning, has led to a finer analysis of distribution of wave activity in cortical and subcortical structures regularly occurring in certain operant performances, and to extensive computer analysis of their patterns (Adey, et al., 1960; 1961; Adey and Walter, 1963; Walter and Adey, 1963).

b. Characteristics of EEG activity in visual discriminative performances.

It would be easy to assume, as has, indeed, been commonly done over the past fifty years, that there is an essential equipotentiality between cortical regions in the processes of storage of information. Much has been written, and many studies performed, in support of the theme that, with the exception of the primary receiving areas, the cortical mantle functions as a whole in processes of information storage, and that performance defects ensuing upon regional ablations relate essentially to the volume of cortex removed, rather than to its location on the cortical mantle (Lashley, 1926).

Slowly evidence has accumulated that there may be at least two major cortical zones having a special relationship to the laying down of the memory trace, or, at least, to the recall of the information under appropriate circumstances. Lesions in prefrontal cortex have been shown to interfere with tasks involving recent memory, but the possible relationship of the defective performance to modifications in mechanisms of sensory discrimination, rather than to a specific defect in memory function, has been emphasized by Rosvold and Mishkin (1961). The dramatic memory defects resulting from interference with temporal lobe structures, as first described in the monkey by Klüver and Bucy (1939), have been comprehensively reviewed by Drachman and Ommaya (1964), who conclude that medial temporal lobe damage is associated with loss of retention and impairment of acquisition, rather than with impaired short-term memory.

Attention has been focused on the allocortical structures of the amygdaloid and especially the hippocampal systems in the laying down of the memory trace (Baldwin and Bailey, 1958; Adey, 1959; Gastaut and Lammers, 1961; Alajouanine, 1961). The great antiquity of the hippocampal system in the

evolution of the brain, and the essential stability of its basic structure in the face of immense evolutionary changes in the remainder of the cerebral mantle, are in themselves a challenge to seek a fundamental comprehension of its functional role. If our understanding of the homologies between the avian and mammalian brain is accurate, it would appear that damage to the hippocampal cortex in the new born chick leads to defective imprinting behavior (Hess, 1959). Despite this and other strikingly suggestive evidence for participation by the hippocampal system in essential processes of memory even in simple brains, many persisting difficulties in such an easy interpretation have demanded a cautious attitude. For example, the memory trace may be laid down outside the hippocampal system (Penfield, 1958), but integrity of its interrelations with these seemingly unrelated cortical and subcortical regions may be vital to the appropriate recall of previously learned discriminative habits (Adey, et al., 1962c).

Very importantly, not all learning requires the integrity of this system, and many classical conditioned reflexes involving the cardiovascular and respiratory systems persist after large diencephalic lesions disrupting major connections between the cerebrum and more caudal levels of the brainstem (Doty, et al., 1959). A variety of partial lesions in the hippocampal system of the rat (Kaada, et al., 1961), the cat (Hunt and Diamond, 1959), monkey (Orbach, et al., 1960) and baboon (Adey, 1957) have produced varying decrements in ability to achieve new learning, but often with a high retention of old learned habits, including those involving discriminative tasks. As noted above, in considering these sometimes incompatible and even contradictory findings, Drachman and Ommaya (1964) have concluded that the essential defects involve impairment of acquisition and loss of retention, rather than impaired

short-term memory.

In broader perspective, it may be asked whether a careful examination of the hippocampal system in the course of learning a discriminative task would reveal changes in patterns of electrophysiological activity closely correlated with acquisition of a learned task, and more fundamentally, whether such changes in electrical patterns might suggest anything about the essential nature of the processes by which information is stored in cerebral tissue. Findings in these studies (Adey, et al., 1960; Adey, et al., 1961, 1962a; Adey and Walter, 1963; Walter and Adey, 1963; Radulovački and Adey, 1965) appear to provide supporting evidence for the basic importance of the wave process in handling of information in cerebral systems. The neuron may be considered in terms of its ability to sense complex spatio-temporal patterns of waves induced at its surface. Such a frame of functional organization would assist in defining the possible uniqueness of integrative processes in cortical systems, characterized by dendritic overlap in a palisade arrangement of cells as described above, and with wave phenomena, not seen in intracellular records in other parts of the central nervous system, such as the spinal cord (Gasteiger, 1959), as a concomitant of electrotonic processes, which, as indicated above, appear to arise in large measure in dendritic structures.

The patterning of EEG activity in the course of acquisition of a visual discriminative performance has been extensively studied in the cat. The following account of EEG correlates is based on training in a modified T-maze, with approach to a concealed food reward on the basis of a visual cue. An initial direct approach to the illuminated side of the T-maze was a requirement for the food reward (Adey, et al., 1960; Adey and Walter, 1963).

It was repeatedly observed that adult animals, on their first exposure

in the test box, showed an extremely wide distribution of regular rhythmic trains of slow waves in the hippocampus (Adey, Dunlop and Hendrix, 1960; Porter, et al., 1964), a point considered further below in relation to the orienting response. This alerted behavior was accompanied by a wide spectrum of activity at 4 to 7 cycles/sec, but predominantly at 4 cycles/sec. Characteristic rhythmic wave processes appeared in the course of discriminative approach to food. The period of the discriminative performance was characterized by a very regular burst of "theta" waves at an essentially single frequency around 5.5 cycles/sec in the dorsal hippocampus, and in the entorhinal area of the pyriform cortex. At the same time, less regular and less constant rhythmic processes frequently appeared in subcortical structures, including the midbrain reticular formation and subthalamus. We may next consider changes in the hippocampal components of these slow wave trains during discrimination at increasing performance levels.

i) Changes in computed averages of hippocampal EEG wave trains during performance acquisition. Beginning at a time when discriminative capability remained around chance level, but a relatively stable response pattern and approach latency were already established, computed averages of 30 or 40 daily trials showed some rhythmicity at 5 cycles/sec. This rhythmicity was apparent in the averages on many days as separate trains appearing immediately after the doors opened, and again as the approach to food was completed. These averaged waves were not as regular, nor of such high amplitude as those appearing toward the end of training.

In the course of subsequent training, the rhythmicity at 5 cycles/sec became less obvious in the computed average at performance levels between 80 and 90 per cent, but with attainment of a behavioral performance in the

vicinity of 100 per cent, a greater degree of regularity was noted than at any previous stage of training. This transient decline in rhythmicity in no way reflected a decline in regularity of the 5 cycles/sec burst in the individual records. It thus appears to have resulted from either a loss of locking of these bursts in a phase-related fashion to the onset of the situational presentation at mid-training level, or, perhaps, to the appearance of significant degrees of frequency modulation on the 5 cycles/sec bursts, as detected by sensitive digital filtering techniques (Adey and Walter, 1963).

At high performance levels, the duration of the regular burst in the averaged hippocampal EEG was often abbreviated, but the persisting regular components sustained into substantial degrees of overtraining, by contrast with the findings discussed below in subcortical structures, such as the midbrain reticular formation.

ii) Effects of cue reversal on EEG and performance. If, after attainment of a high level of performance to a light cue, a switch was made from a light cue to food rewards on the unlit side of the T-box, performance fell to chance levels, or below. Striking changes were observed in computed averages, and in concomitant impedance measurements in cerebral structures, as will be discussed below. On the first day after cue reversal, averages of hippocampal activity were extremely regular at 5.5 cycles/sec, higher in amplitude than before cue reversal, and sustaining throughout the approach epoch. Since no increase in amplitude of the 5 cycles/sec wave trains in the individual EEG records was noted at this time, the increase in averaged output apparently resulted from diminished scatter in phase patterns in consecutive performances (Adey and Walter, 1963; Porter, et al., 1964). In ensuing training days, with performances ranging from 50 to 75 per cent, there was a progressive

decline in the amplitude and regularity of the computed average. However, the rhythmicity persisted in greater degree during this retraining period than in the comparable levels of initial training. There was a certain "fly-wheeling" in the persistence of stable wave patterns established at the end of the initial training paradigm into the early days of the new situation. On attainment of a performance level around 90 per cent in the new paradigm, a highly rhythmic average again appeared.

In hippocampal structures, repeated cue reversals with retraining to high performance levels, or substantial overtraining in a particular paradigm, led only to shortening of the length of the regular average during approach in the retrained animal. In subcortical structures, such as the midbrain reticular formation, however, each cue reversal and retraining was at first accompanied by decline and then gradual reestablishment of a regular average at high performance levels, as described above in the hippocampus. Beyond the fifth or sixth cue reversal over a six month period, a sophistication in the situation appeared, with a rapid rise in performance in the first few training days after cue reversal. Reticular records did not regain a rhythmicity comparable with that in earlier tests, even at performance levels over 95 per cent. Speculatively, it may be surmised that information essential for discriminative performances may have reached minimal proportions, and that appropriate behavioral performance may occur with little more than fleeting attention to behavioral cues. A high scatter might once again appear in phase patterns of successive records, but with subtle differences from the irregular patterns in early training. These less regular patterns may still contain key aspects of information represented in a "shorthand." It is noteworthy that averages following the first cue reversal do not revert

to the degree of irregularity seen in initial training at any time during retraining.

iii) Comparison of EEG patterns in orienting and discriminative behavior.

In the mammal, the response to a sudden stimulus runs a gamut from the "startle response," with arrest of ongoing behavior, through various investigative reactions, to an almost infinite variety of complex coordinated motor patterns, constituting "fight or flight" responses (Cannon, 1929).

It is in the second category that we may group the behavioral components of the orienting reflex. Pavlov (1947) first characterized it as an immediate response in man and animals, in which "they immediately orient their appropriate receptor organ in accordance with the perceptible quality in the agent bringing about the change, making full investigation of it." The uniqueness of the orienting reflex rests on certain "principles" in the intimate behavior of its component reflexes, including their non-specificity with respect to both quality and intensity of the stimulus, and the selectivity of extinction of various properties of the stimulus with repeated presentation (Sokolov, 1963; Vinogradova, 1961).

Attempts to find electrophysiological correlates of the orienting reflex led Grastyan and his colleagues (Grastyan, 1959; Grastyan, et al., 1959) to postulate a specific relationship between hippocampal theta wave trains and orienting behavior. However, the exquisite plasticity of hippocampal theta rhythms in changing behavioral states, including the appearance of bursts of waves in a narrow spectral range during performance of a visual discriminative task, have suggested more subtle and specific relations to discriminative functions and judgment capability (Adey, 1964; Adey, et al., 1960, 1962a and c; Radulovački and Adey, 1965).

Radulovački and Adey (1965) found it possible to distinguish hippocampal EEG activity in three basic states in the cat; in alert but non-performing animals, in the course of discriminative performance, and during orienting behavior. Alert but non-performing animals exhibited a wide spectrum of "theta" waves in the range 3 to 7 cycles/sec on first introduction into the test situation, without overt aspects of orienting behavior. This activity persisted in EEG epochs between discriminative and orienting trials throughout many months of training. During T-box discriminative performance, theta waves regularized at 6 cycles/sec, as described above. Computed averages in orienting trials, given in the same numbers on each test day and randomly interspersed with the discriminative trials, showed slower and less regular averages at 4 to 5 cycles/sec.

Single doses of LSD-25 were followed by prolonged disinhibition of inhibited orienting behavior, and by the gradual appearance of a regular EEG average during orientations 5 to 10 days after the drug, and declining after 15 to 20 days, concurrently with the decline of orienting behavior. A similar but accelerated series of behavioral and EEG changes was induced by a psychotomimetic cyclohexamine, CL-400. In his review of the orienting reflex, Sokolov (1963) emphasized non-specificity of EEG responses accompanying a wide repertoire of specific reflexes in different species. The studies of Radulovački and Adey, however, indicate that in the cat, at least, it is necessary to take account of hippocampal wave trains with characteristic features that relate in clear and specifiable ways to the performance of a discriminative task, and in different, but equally recognizable patterns, to aspects of orienting behavior.

This exquisite sensitivity of neuroelectric processes in the hippocampus

to subtle shifts in cerebral states, and indications that hippocampal theta activity during discrimination has the characteristics of a "pacemaker," with fragmentary and less regular rhythms in midbrain reticular formation, subthalamus and primary sensory cortical areas, have suggested that deposition of a "memory trace" in extrahippocampal systems may depend on such wave trains, and subsequent recall on the stochastic reestablishment of similar wave patterns (Adey and Walter, 1963). These hypotheses will be considered further below.

iv) Characteristics of hippocampal EEG patterns during correct and incorrect decision making. Although no causal relationships can be established at this time between the decision making process and a particular EEG pattern, the detection of such patterns would serve to support the view that the wave process has the characteristics of an information processing system. At such fine levels of behavioral performance, correlates of this kind can at least be construed as relating to the establishment of a particular behavioral "set," even if the causal relationship to decision making remains uncertain.

In our studies, we initially used correlation analysis in seeking differences in hippocampal wave trains accompanying correct and incorrect decisions (Adey, et al., 1961). Cross correlograms prepared between the dorsal hippocampus, ventral hippocampus and entorhinal cortex in the fully trained cat indicated consistent phase patterns in a series of six different correct T-box responses, taken from two different test days. Similar analyses of two of the infrequent incorrect responses taken from the same two training days indicated phase patterns, consistent with each other, but entirely the converse of those in the correct responses, as measured between dorsal hippocampal and entorhinal area, and between ventral hippocampus and

entorhinal area, and between ventral hippocampus and entorhinal area. Within both groups of responses, the phase patterns were unaffected by approach to rewards on either left or right sides of the T-box.

Extension of these analyses by cross-spectral techniques confirmed the substantially different patterns of EEG activity between correct and incorrect responses. Shared amplitudes were lower during incorrect responses. Phase angles reversed at 5 cycles/sec in contrast to the sustained phase angles across a wide spectrum during correct responses. Moreover, coherence, or linear predictability between hippocampal records (Walter and Adey, 1963; Walter, 1963) dropped sharply to insignificant levels in the theta frequencies, where they had been high in correct responses. Comparison of probability bounds in cross-spectral analysis, with a polar coordinate display, have also indicated major differences in phase relations between correct and incorrect responses in certain circumstances, with consistency in different examinations.

These findings have emphasized the strong possibility of a stochastic mode of operation in the handling of information on the basis of a wave process. Such a scheme would envisage the excitability of the individual neuron as depending not only on its previous experience of complex spatio-temporal patterns of waves, but additionally, would suggest that the effectiveness of any subsequent wave pattern in eliciting neuronal firing might depend on its multivariate relationship to an "optimal" wave pattern, capable of inducing firing of that neuron at its lowest threshold.

c. Use of iterative stimuli and evoked potentials in studies of conditional processes.

This technique will be discussed only briefly here, and has already been touched on above, and reviewed in detail by Morrell (1961). Responses to

rhythmic, repetitive stimuli in the frequency range of dominant cerebral rhythms have been used as a means of identifying cerebral systems activated by a conditional stimulus. These iterative trains have been delivered both as peripheral (John and Killam, 1959) and central stimuli (John, et al., In press).

With these methods, John et al. have detected a marked increase in similarity of responses in different brain regions as the conditioned response is established. Differences between correct and incorrect responses have also been detected, with decomposition of relations in a widespread system during incorrect responses. They point out the difficulties in interpreting their results on the basis of elaboration of simple new connections between sensory and motor regions, with memory of the learned response arising in facilitatory processes which stabilize these new pathways. In agreement with the thesis developed above in studies of wave patterns, they conclude that learning may involve development of interacting patterns of activity in extensive neural regions.

5. Electrical impedance characteristics of cortical and subcortical structures.

a. Cerebral impedance measurements during acquisition of a learned discriminative habit.

The disclosure of a variety of patterns in slow wave processes in cerebral tissue having highly consistent relations to the performance of a behavioral discriminative task suggested the possible importance of monitoring concurrent changes in functional state in the cerebral tissue from which these wave processes were recorded. The possibility was considered that changes in conductance characteristics, for example, measured in restricted volumes of tissue in hippocampus, septum, amygdala and reticular formation, might

provide a series of correlates with states of tissue excitability, and might show changes related to acquisition of learned behavior (Adey, et al., 1962b).

Changes in the state of cerebral tissue relating to storage of information may not manifest themselves as clearly in aspects of on-going electrophysiological activity presumably involved in transactional mechanisms, as in other more subtle measures capable of revealing long lasting changes in the functional state of the tissue relating to the storage of information. In particular, it would seem important to pursue the possibility that these storage mechanisms may not lie exclusively within the neuronal compartment, but that such structures as the neuroglial cells may be importantly concerned by reason of their profound metabolic interrelations with the neuronal compartment which they enclose, and on which they may exercise a modulating influence (Adey, et al., 1963; Adey, et al., 1965; Galambos, 1961; Hydén and Pigon, 1960).

Using microvolt signals at 1000 cycles/sec applied through chronically implanted coaxial electrodes in volumes of cerebral tissue about 1.0 cmm, with a current density of the order of 10^{-13} Amperes/square micron, current changes of the order of 10^{-15} Amperes/square micron can be detected. We have observed three types of responses; brief evoked transient changes in hippocampal septal and reticular impedance, following peripheral stimuli in visual, auditory, somatic and olfactory modalities, as well as induced rhythmic changes, and long lasting shifts in baseline impedance values during sleep, and under the influence of psychotomimetic drugs, and in barbiturate anesthesia (Adey, et al., 1962b).

In applications of this impedance recording technique to possible changes during discriminative T-box performance (Adey, et al., 1963), it was found that at chance levels of performance, separate computed averages of

Impedance records from the hippocampus during correct and incorrect responses showed only irregular deviations around the baseline. At intermediate performance levels, a deep transient fall of 2.0 to 6.0 per cent of the baseline value immediately followed presentation of the test situation, and persisted beyond completion of the task. It was followed by a slow rise, exceeding 8.0 per cent of baseline impedance in some cases, with slow return to the pre-approach level after 6 to 8 seconds. This "evoked" impedance change persisted undiminished with considerable overtraining. Extinction of the learned habit abolished these responses, which reappeared with retraining. No baseline impedance shifts were seen in these hippocampal impedance records during acquisition or extinction of the discrimination.

Regional differences were noted in time of first appearance of hippocampal impedance changes in the course of training. With improving behavioral performance, concomitant changes in averaged hippocampal impedance occurred more slowly on one side than in an essentially symmetric hippocampal placement in the opposite hemisphere. However, at the 100 per cent performance level, the magnitude of the fall in impedance during discrimination was similar on the two sides, supporting the notion of a temporal sequence of brain changes characterizing the learning process.

We have recently examined effects of repeated cue reversal on the impedance changes in the hippocampus, amygdala and midbrain reticular formation accompanying the behavioral performance. The behavioral paradigm allowed separation of orienting responses from the discriminative performance (Adey, 1965; McIlwain and Adey, in preparation). Immediately following the cue reversal, hippocampal impedance responses during discrimination were markedly augmented, a finding inviting comparison with the exaggerated regularity of

the computed hippocampal EEG averages occurring at this time (see above). With retraining, the hippocampal impedance responses then disappeared until performance rose above chance levels, at which stage a new response was detected, persisting into overtraining. By contrast, impedance responses during discrimination in the midbrain reticular formation remained ill-defined throughout, but marked responses were detected in the orienting epochs prior to discrimination. No consistent responses in either orientation or discrimination were detected in the amygdala.

b. The nature of cerebral impedance responses and their manipulation by hypercapnea and hypothermia.

Although these impedance measurements have revealed empirically both brief and enduring modifications in the conductance characteristics of cerebral tissue, their nature and exact locations within the complexly interrelated tissue compartments described above has remained obscure. It is unlikely that, in the gamut of shifting cerebral functions from altered attention to terminal asphyxia and death, a single simple mechanism, such as ionic redistribution between tissue compartments, would necessarily explain all observed changes. Establishment of the essential independence of the more rapid physiologically induced impedance transients from such factors as blood pressure and blood flow, for example, would not necessarily preclude these factors as partially or indirectly causal in certain long term impedance changes (Adey, et al., 1965b).

The evidence suggests that impedance responses reflect changes in intrinsic characteristics of cerebral tissue, rather than relating in a direct fashion to cerebral blood flow or blood pressure. The effects of hypothermia in the range 28-21°C on cerebral impedance, carbon dioxide excretion and

blood pressure were studied by Adey, et al. (1965a). The excursions of resistive and reactive impedance components induced by hypothermia showed no primary relationship to systemic blood pressure, which remained unaltered during their development, and which could also vary substantially without modifying the course or direction of impedance shifts. Temporary cardiac arrest in hypothermia was without effect on impedance for approximately two minutes, and was then associated with impedance shifts an order of magnitude larger than those in physiological manipulations. On the other hand, impedance shifts followed the general contour of falling temperature, and closely paralleled the carbon dioxide excretion, both in the phase of falling temperature, and in the recovery phase, when carbon dioxide excretion continued to drop below control levels.

In the frame of the tricompartamental system discussed above, with neuronal, neuroglial and extracellular divisions, carbon dioxide metabolically produced in neurons may undergo conversion to carbonic acid in the presence of carbonic anhydrase, and not diffuse directly into the blood as molecular carbon dioxide (Tschirgi, 1958). Intervention of the neuroglial cells between neuronal elements and the vascular capillaries has suggested to Tschirgi that this reaction might take place within the neuroglial compartment, with selective exchange of hydrogen and bicarbonate ions so formed with sodium and chloride ions drawn from the plasma.

Nevertheless, these ionic shifts may be controlled by other, more complex factors. The notion that carbon dioxide, for example, may be the ultimate arbiter of these effects should be treated cautiously. Although large impedance responses occur to sensory stimuli, they are accompanied by only minor shifts in endtidal carbon dioxide levels, and inhaled carbon

dioxide is relatively inefficient in promoting comparable impedance responses (Adey, et al., 1965a). It thus appears that tissue compartments which underlie the impedance response, presumably neuroglial and extracellular, have an inherent capacity to isolate the neuron from the immediate impact of circulatory metabolites, and are only indirectly influenced in their conductance characteristics by such mechanical factors as blood pressure.

Of the three tissue compartments, neuronal elements offer the highest resistance to an applied current, with a membrane resistance in excess of 1000 ohms/cm^2 , whereas neuroglial cells may have a membrane resistance of 3 to 10 ohms/cm^2 (Hild and Tasaki, 1962). Higher values for neuroglia noted in perfused preparations in the absence of a controlled carbon dioxide environment may require further assessment (Kuffler and Potter, 1964; Nicholls and Kuffler, 1964). The preferred current pathways would thus lie in low resistance shunt paths in the extracellular space and in neuroglia, rather than through neurons, and suggest that the impedance responses noted in our studies, including those related to learned performance, occur in non-neuronal compartments, including the neuroglia. As described above, the neuroglial compartment, essentially enclosing the neurons in many areas, may be regarded as intervening between the neuron and the blood vascular system in metabolic exchanges, and as forming a micrometabolic module of neuronal and neuroglial elements (Barnett, 1963; Hydén and Pigon, 1960; Hydén and Egyhazi, 1962). Evidence has been cited for the presence of organized macromolecules in the extracellular compartment (Barker et al., 1962).

c. Relationships of impedance changes to EEG characteristics in the same tissue domain.

If these impedance changes during functional activity occur in

perineuronal compartments, it may be asked in what way such impedance changes may relate to electrophysiological activity in neurons. The physical proximity to adjacent tissue elements of dendritic structures initiating electrotonic processes, both dendritic and neuroglial, raises the question of the role of these adjacent elements as impedance loads to the electrotonic phenomena (Adey, et al., 1963). The lower membrane resistance of neuroglial cells and evidence for long-lasting changes in their membrane characteristics after electrical stimulation (Hild and Tasaki, 1962; Tasaki and Chang, 1958) suggests that they may exercise a modulating role on electrotonic dendritic processes, determining aspects of both rate and regularity in their rhythmicity (Adey, et al., 1963). This impedance loading may have non-linear characteristics.

6. Aspects of a model of cerebral organization in learning.

This study has emphasized the structural characteristics of cortical tissue that might underlie mechanisms of information storage; the palisade of cells in close proximity to one another; and the dendritic tree of one cell substantially overlapping that of one or more adjacent neurons. Concomitantly, wave-like electrical activity characterizes this tissue, and has its origins in an intracellular wave process, many millivolts in amplitude, and apparently arising in the dendritic tree as an electrotonic process. This wave process has not been detected in neurons in other parts of the central nervous system such as the spinal cord. At least through the window of a microelectrode within the body of the cortical neuron, firing to produce a propagated spike is not a regular concomitant of the depolarizing phase of the intracellular waves, even where this exceeds the threshold level for firing in some cases. The intracellular wave and initiation of a propagated impulse thus appear to involve processes that may occur in parallel in individual neurons, and may

bear non-linear interrelations to one another.

With the establishment by computer analysis of patterns in wave activity that relate to orientation, acquisition of discriminative habits, cue reversal with extinction and retraining, and to correct and incorrect decisions in discriminative situations, it is necessary to consider ways in which these wave patterns in larger domains of tissue may relate to individual neuronal generators, and perhaps, to the storage of information in neurons and its subsequent recall. The individual generators have been shown to probably meet the requirements of the statistical theorem of central limits, behaving essentially independently, and with the gross EEG arising in the normal distribution ensuing from combination of many such independent or non-linearly related neuronal generators.

Our computed analyses of these EEG wave processes have indicated the possibility of a stochastic mode of operation in the sensitivity of cortical neurons to recurrent similar, but not necessarily identical, patterns of waves. This hypothesis of a probabilistic mode of operation would infer that the excitability of the cortical neuron would depend on the relation of the spatiotemporal pattern of wave phenomena at the cell surface to an "optimal" pattern of waves for which its firing threshold would be lowest. This "optimal" pattern of waves would be determined by the previous experience of the cell, with the wave phenomena intimately concerned in the physicochemical changes associated with the deposition of the memory trace.

This proposed model of the cerebral system would therefore exhibit non-linear and stochastic characteristics as local phenomena within a particular cortical domain. Recent studies have indicated that such non-linear interrelations may occur between different cortical regions, in systems that

operate in great degree on a substrate of linear processes (Walter and Adey, 1965a, b). In broader perspective, generator analysis of these wave processes from widely dispersed points in a cerebral system has emphasized the ubiquitous and protean character of wave processes that could relate to storage information. Such schemes are far removed from simple connectivity concepts of facilitated connections as the basis of learned behavior.

Finally, we have come to recognize the critical difference between the sensing of physiological processes that relate to transmission and transaction of information, as opposed to its storage. Future developments in such areas as impedance measuring techniques may enhance knowledge of those delicate processes underlying storage, and establish the basis of structural and functional organization which endow brain tissue with a uniqueness not found in "non-learning" neural systems of admittedly great complexity, such as the human spinal cord. At least, these studies have raised questions as to whether perineuronal tissue, including the neuroglia, may not only be the site of impedance changes, but also whether the interface between glial and neuronal tissue may be a region of special significance in the storage of information.

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Fig. 1. Typical examples of cortical surface (top trace) and intracellular (lower trace) records in the same domain of tissue. The much smaller surface record bears a close resemblance to the intracellular record in its frequency characteristics, but is rarely coherent with it. Initiation of action potentials in the intracellular records occurs on the depolarizing phase of the concurrent wave process, but not necessarily on the largest waves. Records A and B during sleep show slow waves in both extracellular and intracellular traces, whereas the alerted record (C) is faster in both. (From Elul, 1965).

Fig. 2. Development of an inhibitory conditional response in an habenular unit. Each dot represents a unit discharge and each horizontal row of dots, a single trial. Trials are grouped according to stimulus conditions A: sciatic nerve stimulation only vs. control; B: flash only (CS) control; C: flash and sciatic (first sequence of training trials, etc. Left vertical line (marked flash) indicates time of CS presentation. Vertical line marked sciatic indicates time of onset of US. (From Kamikawa, McIlwain and Adey, 1964).

Fig. 3. Typical EEG records during approach to food reward with a visual cue. Approach commences at L end of time marker bar. Regular theta burst at 5-6 cycles per second appears in dorsal hippocampus (RDH) and entorhinal cortex (RENT). Similar but less regular trains appear simultaneously in midbrain reticular formation (LMBRF) and visual cortex (L.OOC).

Fig. 4. Representative EEG records with computed averages from 20 pairs of hippocampal traces at mid-training after first cue reversal (left). Note irregular character of averages. Later in training, regular average appeared (right) and sustained into over training. (From Adey and Walter, 1963).

Fig. 5. Averages of EEG from midbrain reticular formation in successive reversals of training cues, first to light (A), then successively to dark (B), light (C) and dark (D). From Adey and Walter, 1963).

Fig. 6. Effects of introduction of orienting trials (daily $n = 40$) into training schedules of a cat already at a high level in discriminative task performance. Computed averages during discrimination (A) showed high amplitude waves at 6 cycles per second. Randomly interspersed orienting trials (B) exhibited a lower amplitude 4 to 5 cycles per second rhythm in later parts of analysis epoch. (From Radulovacki and Adey, 1965).

Fig. 7. Simultaneous impedance and EEG records during various physiological stimuli. Top left: impedance record from left dorsal hippocampus (L. Dorsal HIPP.), and EEG record from R. visual cortex (R. VIS. CORTEX). Top right impedance record from L. septum and simultaneous EEG records from left and right dorsal hippocampi. Bottom: Septal impedance record and EEG tracings from R. amygdala (R. AMYG) and L. dorsal hippocampus (L. DORSAL HIPP). In the top left record, the animal made orienting movements of the head, in the top right record the stimulus was sexual, and in the lower traces olfactory. In each case there was a transient drop in impedance, as indicated by the calibrations.

Fig. 8. Development of regularity in brain wave trains and appearance of impedance responses in hippocampus during acquisition of the T-box discriminative task. Computed averages of brain wave records (A) at chance levels of performance were essentially irregular; showed some at 80 per cent correct; and sustained regularity at 100 per cent. Impedance records at the same levels of training (B) initially showed only irregular perturbations; at 80 per cent a small fall at the start of the performance followed by a rise; and at 100 per cent a profound fall out lasting the performance. In its full configuration (C), the response is biphasic and lasts about 5 seconds. The animal takes about 1.5 seconds to reach the food reward. (From Adey and Kado, *Scientific American*, in press).

Fig. 9. Changes in blood pressure in cat with cervical cord transection during hypothermia, plotted concurrently with core temperature and resistive and reactive impedance factors. No relationship was noted between blood pressure and typical impedance changes (From Adey, Kado and Walter, 1965).