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# Consciousness: physiological dependence on rapid memory access

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## 1. ABSTRACT

Consciousness develops from birth during the early months as the senses and other nervous system functions mature sufficiently to receive, process and store information. Among these is the ascending reticular activating (arousal) system in the brain stem that is responsible for wakefulness and was proposed by Penfield and Jasper more than 50 years ago as the "controlling mechanism for states of *consciousness*". This concept has remained the most advanced physiological interpretation of consciousness although recent developments offer greater insights into its nature. The ascending arousal system is the source of activation of the thalamocortical and cortical mechanisms for sensory input and facilitates the rapid matching of sensory input and the binding of memory during cognitive processing. Nonetheless, it is proposed that memory is the critical element through which our connection with the world exists without which, despite a fully functional arousal system, consciousness as we know it could not exist. Evidence is presented in support of this concept in addition to the physiological difficulties that must be resolved if consciousness is to be understood.

## 2. INTRODUCTION

There are many interpretations of consciousness, some psychological from a mainly behavioral perspective, others philosophical, quantum mechanical, metaphysical or supernatural, but despite its great importance to life it has received remarkably little attention in either the basic or clinical neurosciences other than when impaired or absent

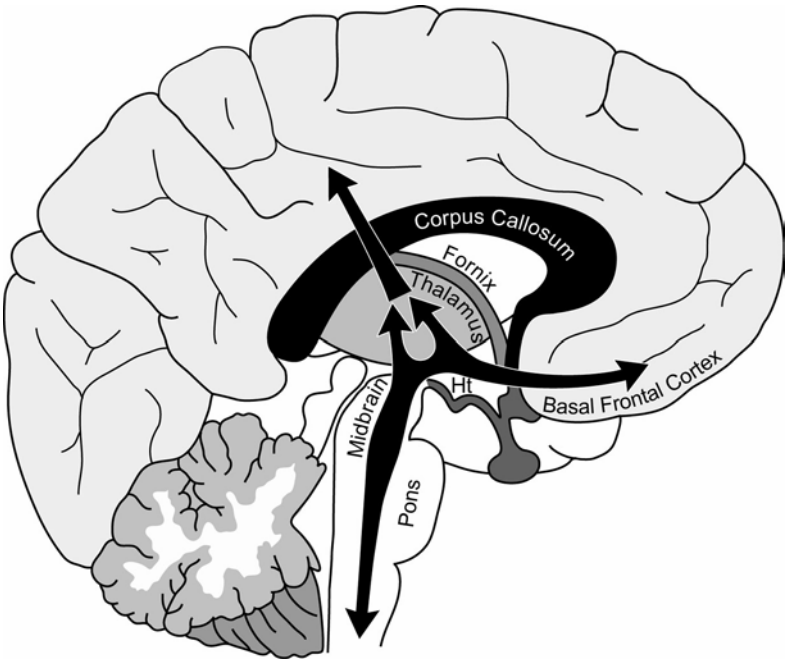


**Figure 1**. The ascending and descending reticular activating (arousal) system. The system, as displayed by the black arrows, represents the projections between the nuclei within the brain stem and hypothalamus (Ht) and to neurons in the thalamus, cerebral cortex and spinal cord, as first proposed by Magoun and his associates (10). The neurotransmitters of some of the nuclei and their functions are shown in Table 1 (102, 105).

(1-4). Nonetheless, the relationship of wakefulness to consciousness has long been a focus of interest and was stimulated by the description of the lesions in the posterior hypothalamus and midbrain in encephalitis lethargica by von Economo in 1930 (5). Five years later, Bremer (6) whose interest was in the mechanisms producing sleep, performed midbrain transections in the cat and induced a state of profound sleep. His and many other's belief at the time was that sleep is an outcome of functional deafferentation of the cerebral cortex. Accordingly, Bremer attributed the somnolence in the cat to his having severed ascending sensory pathways to the cerebrum (7). But in 1949 Moruzzi and Magoun (8) identified, by direct stimulation of the feline brain stem reticular formation, the source of sustained wakefulness and arousal. Its effects, they suggested, are exerted generally upon the cortex and may be mediated by the diffuse thalamic projection system. Transection of the midbrain tegmentum by Lindsley and associates (9) produced electroencephalographic (EEG) changes consisting of large recurring slow waves in the cortex typical of normal sleep which they attributed to blocking of the ascending influence of the brain stem reticular activating system. Indeed, when animals with chronic lesions of the midbrain tegmentum or posterior hypothalamus were bombarded by visual or auditory stimuli there was a very brief period of low voltage fast activity on EEG suggestive of arousal but, otherwise, behavioral responses were negligible (10). This indicated that the cortex responded to the sensory stimuli but in the absence of the reticular activating system it was unsustainable. Penfield and Jasper in 1954 (11). referring to the studies of Magoun and coauthors (10), concluded that "There can be little doubt, therefore, that it is the reticular system, with its diffuse and separate projections to the cortex, which is the central controlling mechanism for states of *consciousness*" and referred to the brain stem reticular system as a 'centrencephalic' locus for controlling consciousness. Thus, the reticular activating system having been identified with wakefulness, and since referred to as the 'ascending arousal system', also became identified with consciousness (Figure 1).

The reticular activating system is essential to the diurnal sleep/wake cycle and is clinically important in the diagnosis of patients with severe brain damage. Those who have sustained extensive damage to the brain, especially to the midbrain, are comatose and the sleep/wake cycle is absent (12). Some less severely injured patients who, nonetheless, display very limited mental and physical responses, are diagnosed as either in a 'persistent vegetative state' or a 'minimally conscious state' and in both the sleep/wake cycle, and accordingly the reticular activating system, are intact (13,14). The patients with the intact sleep/wake cycle generally have extensive cerebral cortical damage and show the influence the cortex has on consciousness. It is the extent of this loss, and not exclusively the role of the arousal system, that determines the state of consciousness.

As considered here, consciousness must be a mnemonic process if it is appreciated how we have had to learn and store in memory everything we know, such as our use of language and all that we experience and regularly hold in mind in the course of our daily activities. Without

memories dating from very early life all subsequent sensory input would be without meaning or effect. Indeed, the initial and most basic somatosensory and visceral stimuli may be personalized in memory and account for much of our sense of self. Accordingly, it is proposed that it is sensory input applied to memory as it is stored throughout the cerebral cortex, together with the driving force of the ascending arousal system, which forms a basis for consciousness. However, a difficulty with a physiological construct of consciousness that is based on memory has been in imagining the design of a neural mechanism that is capable of matching continuously shifting sensory inputs to memory, as when we visually scan our surroundings, within a mere fraction of a second. As a beginning, this requires an examination of the anatomical and physiological mechanisms that are designed to minimize delay in the transfer of information throughout the nervous system.

## 3. DENDRITIC INFORMATION PROCESSING

More than 30 years ago Schmitt and his colleagues (15) claimed that dendrites are far from being a "vast but passive receptor surface with integrative capabilities focused on the axon hillock for the transmission of the message to axon terminals". The concept they put forward reflected the need to identify "unifying conceptual principles capable of relating brain cell activities to psychological processes such as learning, memory, perception, consciousness, and other higher brain functions". Since then there has been an accumulation of anatomical and physiological evidence in support of Schmitt's view on how dendrites form synaptic and electrotonic networks for the transmission of information from one neuron to another at high levels of efficiency and speed (16-21). Localized dendritic networks of dendrodendritic neurotransmitter-gated (chemical) synapses and electrical (gap junction) synapses may be the principal means by which information is processed within the central nervous system whereas the axons, with their relatively low-sensitivity synapses, may be mainly responsible for integrating large groups of neurons in the processing of information (22).

There are temporal limitations to conduction in the neural apparatus irrespective of the location in the nervous system, but delays in the exchange of information between spatially separated locations or in the performance of intricately detailed tasks can be critically axonally time-dependent (23). Neurons have features that appear to have been designed with the purpose of reducing conduction delays such as the gap junctions connecting fast-spiking interneurons which synchronize spikes in dendritically coupled interneurons (24, 25). Dendrodendritic and dendrosomatic synapses also shorten the conduction time but by graded electrical potentials rather than dendritic spikes. The largely overlooked properties of the 'local circuit neuron', communicating through either gap junctions or dendrodendritic synapses, are especially well suited for rapid information processing.

### 3.1. Theta- and gamma-frequency oscillations

Because the brain is an electrical organ it is essential to understand what is known about the rhythmic activity being recorded from scalp or brain surface electrodes during EEG or from single neuron recordings and to apply this knowledge to brain functions. Rhythmical oscillations observed in the cerebral cortex during electroencephalography are due to electrical activities arising synchronously from very large numbers of neurons. They occur mainly at frequencies in the gamma (30-100 Hz) and theta (4-8 Hz) range during different high order mental states such as the encoding and retrieval of memory, in working memory and sensory processing (22, 26). Fries *et al.* (22) describe how networks of activated excitatory pyramidal neurons and inhibitory interneurons engage in a rhythmically synchronized and cyclical manner with the interneurons playing a key role in the generation of gamma range synchronization. In their model the activation of the interneuron networks is due to excitatory input from pyramidal cells and the interneuron networks respond to the pyramidal neurons by generating synchronized gamma wave activity regardless of whether the excitatory drive from the pyramidal cells is rhythmic. Indeed the "rhythmic synchronization of the interneurons imposes synchronized rhythmic inhibition onto the pyramidal cells and, therefore, their discharges also (become) engaged in rhythmic synchronization". As the authors describe, the timing of events is both complex and crucial such that "the resulting network inhibition terminates the firing of both the pyramidal cells and the interneurons" thereby abruptly ending the cycle. However, with the entire network inhibited the gamma cycle restarts anew and continues in a repetitive cyclical manner as long as the excitatory drive from the pyramidal cells persists.

Jensen *et al.* (27) proposed a model of the human brain wherein short-term and working memory involves sustained synchronized firing of neurons in the gamma frequency range and added that successful encoding and recall of long-term memory is also associated with gamma frequency synchronization. Osipova *et al.* (28) in a study of human subjects using magnetoencephalography and tests involving declarative memory concluded that theta oscillations facilitate memory encoding whereas gamma synchronization may reflect a higher order and a more widespread effect in the formation and retrieval of memories such as the binding of memories from different cortical regions (see also 29, 30). But as Klausberger and associates (31) found in a study of hippocampal interneurons, the frequency of the oscillations in neural networks depends on the type of interneuron (basket cells, axoaxonic cells, etc.) as these innervate distinct domains, i.e. synaptic release sites, on pyramidal neurons. Each type of interneuron responds in a distinctive manner to incoming oscillations as they arise during different states of animal behavior. Thus, by way of an overall perspective, both theta and gamma synchronization are required for the encoding and retrieval of memory but this depends on the type of interneuron each of which has a different and complex effect on the pyramidal cell.

### 3.2. Local circuit neuron (LCN)

A remarkable meeting of the Neurosciences Research Program (NRP) Work Session, attended by number of prominent neuroscientists, was held in June 1973. Its purpose was to seek agreement on a definition for a type of locally projecting neuron in the central nervous system known by many names but most commonly the Golgi type II cell or the short-axon interneuron (16). This neuron, in contrast to the Golgi type I or long-axon cell projecting to more distant sites in the nervous system, is exclusively a local circuit neuron. Ramón y Cajal (32, 33) who introduced the terms type I and type II cells (subsequently renamed Golgi type I and Golgi type II as a tribute to Golgi) commented that the functional superiority of the human brain is linked to the type II neurons (see 16, p. 301). The members of the work session renamed the Golgi type II cell with the more descriptive label of 'local circuit neuron' (LCN) and, moreover, described a local neuronal circuit as an "independent reverberation of impulses confined only to part of a cell membrane, to a single dendrite, or to several LCNs (16). More precisely the local circuit, as recorded by Rakic (see 16, p. 300) was defined as "*any portion of the neuron (or neurons) that, under given conditions, functions as an independent integrative unit*". Although the data is incomplete LCNs are almost entirely inhibitory (GABAergic) interneurons and conversely, all inhibitory interneurons are local synaptic neurons. They are, in effect, the interneurons of many varieties known by such descriptive names as chandelier cells, basket cells, double bouquet cells or dendrite targeting cells. The only known cerebral local excitatory (glutamatergic) synaptic interneuron is the stellate cell in the fourth layer of the cortex. These stellate cells carry a large number of dendritic spines and therefore interactions with other neurons are probably axodendritic rather than dendrodendritic as discussed below with the LCNs. Phylogenetically the LCN is most abundant in the human suggesting its association with high-order behavior (34).

Francis O. Schmitt (15), who was a participant in the NRP Work Session, expressed the belief that higher brain functions require "speed of processing, sensitivity, a high density of computational structures and potential for complex interactions". Toward achieving this, dendrites of LCNs form local networks and transmit information through gap junctions, dendrodendritic synapses and ephaptic transmission (electrical fields) by graded changes in electrical potential rather than spike action potentials. Schmitt and his collaborators noted how LCNs "may simultaneously be the site of many electrotonic (local) current pathways, involving components as small as dendritic membrane patches or individual dendrites". Conventional spike-mediated information is transmitted by axons locally to similar local networks and to more distant neurons by long-axon projections.

Most recently, in an expansion of the principle of the 'local circuit' Losonczy *et al.* (35) have shown how local dendritic spikes arising out of a "spatially clustered and temporally synchronous synaptic input" can selectively produce a form of dendritic plasticity. Local compartmental changes in dendritic ion channel function, referred to by the authors as 'branch strength potentiation' (a form of information storage), render the region uniquely responsive, by way of the same action potential output, to any subsequent arrival of an identical spatiotemporal synaptic input pattern. The significance of this could be, for example, in a holding in memory a primary idea while exploring other ideas during the process of reasoning.

To imagine a mere patch of a neuronal membrane being linked exclusively to comparable portions of other neurons and thereby, conjointly, constituting the components of an independent electronic circuit is a remarkable change from the conventional logic applied to neurocircuitry. With dendrites being assigned to a unique and more critical role than previously imagined a vast new dimension in electrotonic neural processing has been introduced.

### 3.3. Gap junctions

A gap junction (electrical synapse) is a channel formed by the fusion of two connexons, each composed of 6 protein connexin molecules in the cell surface membrane of contiguous cells that are mainly either astrocytes or the dendrites of interneurons (18). They allow cytoplasmic continuity and are in a constant dynamic state, intermittently opening or closing at either cytoplasmic end in response to the membrane potential and allowing a fast low resistance interchange of current (ions and small molecules) to flow from one cell to the other (36, 37). Dendritic gap junctions between interneurons in the hippocampus and neocortex have an important stabilizing and enhancing influence on the synchrony of underlying gamma oscillations during high order mental states as described above. As pointed out by Traub *et al.* (38) this should apply to any small computational units, such as the LCN networks.

Schmitz *et al.* (39) have offered evidence on behalf of there being gap junctions also between the axons of hippocampal pyramidal neurons which, they suggest, provide the means for the recruitment and engagement of pyramidal neurons in fast network oscillations during information transfer. Traub *et al.* (40), conjointly, in agreement with Schmitz and colleagues on the existence of axonal gap junctions between pyramidal neurons, added that axonal networks in the hippocampus may underlie very fast oscillations (greater than 70 Hz) between pyramidal neurons and the generation of gamma oscillations in the development of long-term memory in the cortex.

### 3.4. Dendrodentritic synapses

Presynaptic axons most familiarly converge on postsynaptic dendrites and somata or on axons but dendrites and somata can also act presynaptically by making dendrodendritic, dendrosomatic, somatodendritic chemical synaptic connections. As referred to earlier and shall be discussed further in the sections to follow dendrodendritic and dendrosomatic synapses have a unique functionally integrative importance that is distinct from the axodendritic and axosomatic synapse (41). Information can be exchanged by dendrodendritic synapses much more rapidly and efficiently as graded electrotonic potentials than is otherwise possible with axonal spikes (15, 16).

Dendrodendritic synapses have been described in the brain in a number of regions, notably in the cerebellar nuclei, superior colliculus, medial and lateral geniculate bodies, reticular nucleus of the thalamus and pons but, apart from an uncorroborated exception, not in the cerebral cortex (41-48). The dendrodendritic and dendrosomatic synapses, while frequent are largely limited in distribution to particular sensory structures such as the dorsal thalamic nuclei, geniculate bodies and reticular nucleus of the thalamus. Although dendrodendritic synapses may not normally be present in either the cerebral or cerebellar cortex Sotelo (49) described how x-irradiation to the whole head of newborn rats was followed by the appearance of LCNs making dendrodendritic and somatodendritic contacts with Purkinje cells in the cerebellar cortex. The findings were interpreted by author as a regenerative response by the local LCNs and demonstrated an otherwise normally repressed latent potential of these cells.

Synapses in the retina (and olfactory bulb not discussed here) are both conventional axodendritic and dendrodendritic and although predominantly the latter, axons and dendrites are largely indistinguishable and authors often refer to the projections of the neurons as merely 'processes' (neurites) (50-53). The types of synaptic arrangements in the retinal layers are extraordinarily complex (54, 55). In brief, there are two laterally inhibitory plexiform horizontal and amacrine cell layers in the retina and these are bridged by bipolar cells that extend vertically from the outermost photoreceptor cell layer of rods and cones to the innermost layer of ganglion cells whose axons project to the brain. The processes of the horizontal, amacrine and bipolar cells passively conduct electrical signals by graded changes in cell membrane potential similar to dendrites of central nervous system neurons which make dendrodendritic connections. Gap junctions are also present throughout the retina, including between rod cells and between the dendrites of ganglion cells, allowing voltage changes to spread rapidly from cell to cell (56, 57).

Lund (42) identified dendrites that were presynaptic to other neurons close to the surface of the superior colliculus of the rat and remarked how the synaptic patterns in this region resembled the patterns in the retina. Sterling (48) also described the dendrites in the superior colliculus of the cat making synaptic contact with one another and a postsynaptic dendrite was frequently seen to synapse, serially, with a third dendrite. Reciprocal synapses between dendrites (present in the retina wherein a postsynaptic dendrite is also presynaptic to the same 'donor' dendrite) were not seen. Auditory information from inner ear is sent by the afferent auditory pathway to the medial geniculate body of the thalamus and is there relayed to the auditory cortex. Morest (44) in a study of the medial geniculate body in the cat noted how dendritic synaptic endings of LCNs (referred to as Golgi type II neurons) made contacts with the dendrites on thalamocortical neurons. Serial dendrodendritic synaptic contacts were present but reciprocal contacts were not observed. The dendrodendritic terminals of the LCNs were considered by the author as having an inhibitory role as described for the synapses of the horizontal and amacrine cells in the retina.

Hamori and Mezey (41) found serial synapses in cerebellar nuclei, notably in the nucleus interpositus in the cerebellum of the cat, a structure in subprimate mammals and the monkey corresponding to the globose and emboliform nuclei in the ape and human (58). However, there was uncertainty as to whether the contacts were axodendritic or dendrodendritic although their serial character resembled the dendrodendritic synapses present in the thalamus and retina.

## 4. AXON CONDUCTION VELOCITY

The speed at which information in various parts of the nervous system is processed, especially through extensive areas of white matter, is subject to the conduction velocity of the axons and this is dependent on their diameter and whether they are myelinated. Impulse transmission in myelinated axons is saltatory between the nodes of Ranvier and, accordingly, myelinated fibers conduct impulses at far greater velocities than unmyelinated fibers (58). It has been calculated that the conduction velocity (CV) of the myelinated axon increases in proportion to the diameter of the axon minus its myelin. This ratio, termed the 'proportionality constant' (CV/mm/sec/axon diameter micrometres), has a value of 8.7 and while established only for myelinated axons in peripheral nerve trunks, it has been applied successfully to myelinated nerve fibers in the central nervous system (23, 59, 60). Thus, the time taken for an impulse to travel a specified length of an axon is inversely proportional to the axon diameter times the proportionality constant. With large fibers the delay is shorter but an impulse travels sometimes very long distances through the white matter and the delay can be considerable. As calculated by Ringo *et al.* (23) from studies undertaken on the macaque, the interhemispheric delay of impulse transmission in myelinated axons of average size interconnecting the temporal lobes in the human brain (about 1 μm in diameter in the anterior commissure and the anterior part of the corpus callosum) is about 50 msec. For nonmyelinated fibers conducting nerve impulses at 1 m/sec the interhemispheric delays are estimated to be in the range of 100 to 300 msec (61). Delays are compounded by the convoluted course of the axon through white matter such as around the ventricals or gyri. Accordingly, the distance and the duration of impulse transmission involves a major risk of significant conduction delays especially with time constraints on information transfer being generally very tight.

A number of authors have examined the diameter, proportion and topographical distribution of myelinated versus nonmyelinated axons in the corpus callosum and estimates have been made of interhemispheric conduction times (61-63). A consensus view is that a large number of the axons in the callosum are nonmyelinated and the average myelinated fiber size is less than 1 micrometre in diameter (23). The majority of the nonmyelinated axons have a diameter size of less than 0.25 micrometres (61). The proportions of nonmyelinated versus myelinated fibers in different parts of the corpus callosum as calculated in the adult rhesus monkey by Lamantia and

Rakic (63) varies with the largest proportion of nonmyelinated being approximately 30 per cent in the region of the corpus callosum carrying fibers from the association cortices and the smallest at approximately 6 per cent is found in the region carrying projections from the primary sensory cortices.

Because of the delays in information transfer and the temporal limitations imposed by the neural apparatus in the brain, Ringo at al. (23) propose that the performance of high resolution and time-critical tasks were gathered into one hemisphere to diminish hemispheric delays (64). In support of this it is estimated that only 2 to 3 per cent of all cortical neurons project to the opposite hemisphere (63). Hemispheric specialization especially includes such time-critical tasks as motor and auditory sensory speech being assigned to the left hemisphere, face and place recognition in the right fusiform gyrus and parahippocampal gyrus, respectively, and spatial skills in the right parietal lobe (65). This view has been supported by Sperry (66) who studied human subjects in whom the cerebral hemispheres had been separated by commisurotomy producing complete right and left hemispheric autonomy. Sperry concluded that "the two disconnected hemispheres appear to be actively, but separately, conscious in parallel, each working and contributing in its own way to the performance on which attention is focused".

## 5. AXONS AND FIELD EFFECTS

### 5.1. Mauthner and basket cells

That electrical fields generated by currents flowing across membranes of neurons can affect neighboring cells has been a subject of intense interest for more than 60 years (67). Early on Arvanitaki (68) coined the term "ephapse" (Greek - the act of touching) to "designate the locus of contact or close vicinity of two active functional surfaces" Any form of synaptic contact such as synapses or gap junctions is excluded. Accordingly, the term applies to both direct physical contact and field effects of currents through extracellular space but authors usually consider these individually. Apart from artificial or pathological states in which nerve fibers are in direct contact with one another causing 'cross talk' the only condition in which electrical information might normally be transferred ephaptically is a field effect. This was first demonstrated and referred to as an 'extracellular potential' producing a type of electrical inhibition by Furukawa and Furshpan (69) in the large bilateral Mauthner motor neuron (M-cell) in the medulla of bony fish (teleost). Its function is to flip the tail fin for a fast escape from predators (70, 71). The hallmark of the field effect in the M-cell is the encapsulation of the initial segment of the axon, isolating it within an electrically resistant extracellular space. The enclosure consists of a dense glial cover, referred to as an "axon cap", within which axon terminals of inhibitory interneurons are imbedded.

The Mauthner cell has not been observed in the mammalian nervous system but an architecturally similar structure to the axon cap employing the same ephaptic principle has been described by Korn and Axelrad (72) in the basket cells of the cerebellum. In the cerebellar cortex basket cells extend their axons along the Purkinje cell layer and each basket cell sends collateral branches to more than 150 Purkinje cells. When granule cells in the cerebellum excite both the Purkinje cells and basket cells there are *two* basket cell *inhibitory* responses (67, 70, 72). One inhibitory effect is by synaptic terminals on the Purkinje cell body surface and the other is by terminals in the basket-like structure that is similar to the axon cap of the M-cell around the initial segment of the Purkinje cell axon which does not make cell contact but creates instead a field of "passive hyperpolarizing potentials" (72). This inhibitory hyperpolarizing effect on the Purkinje cell initial segment, by preceding the action potential volley from the granule cell, briefly delays the Purkinje cell discharge at the initial segment. Presumably the delay enables the synchronization of the other Pukinje cells receiving input from the same basket cell. The origin and precise nature of the field potential remains unclear and since no other structure with a convincingly close resemblance to the M-cell and basket cell has been found in the nervous system it may be rare. Nonetheless, field effects may occur in different conditions such as 'population spikes' in the hippocampus.

### 5.2. Hippocampal population spikes

The pyramidal cell layer is the most prominent feature of the hippocampal formation and, in addition to pyramidal cells, there are LCNs and hippocampal basket cells (73). As described in the cerebellum, hippocampal basket cells form a dense basket-like plexus around pyramidal cell bodies (73, 74). Thus, there is the potential for gap junctions, dendrodendritic communication and also field effects as described by Korn and Axelrad (72). The most striking feature of the pyramidal cells in the hippocampus is their similar orientation in a single densely packed layer sharing the same electrical properties. The effect of active neurons on inactive cells, taking into account the anatomical arrangement of the pyramidal cells, was explored by Taylor and Dudek (75, 76). in the CA1 region pyramidal cells to determine "whether transient electrical fields, which occur during population spikes, can affect the excitability of adjacent inactive neurons". As proposed by the authors, an electrical field effect is produced by the large influx of sodium ions into the pyramidal cells during their activation creating a negative sink around the cell bodies where the space between adjacent neurons is minimal. A passive outward flow of current from the inactive region of the cell membrane near the cell body of the active pyramidal cell creates an electrical circuit back to the extracellular sink. Because the neurons are tightly packed with a very small space between their cell bodies the electrical resistance in this location is high compared to the pyramidal cell cytoplasm. Accordingly, the authors conclude, "the extracellular electrical field causes currents to flow passively across inactive pyramidal cell membranes, thus depolarizing their somata", triggering action potentials and a population spike.

Recently, Sylantyev *et al.* (77) observed a "speeding up" of synaptic responses due to the electrical fields inside synaptic clefts of CA1 pyramidal cells and

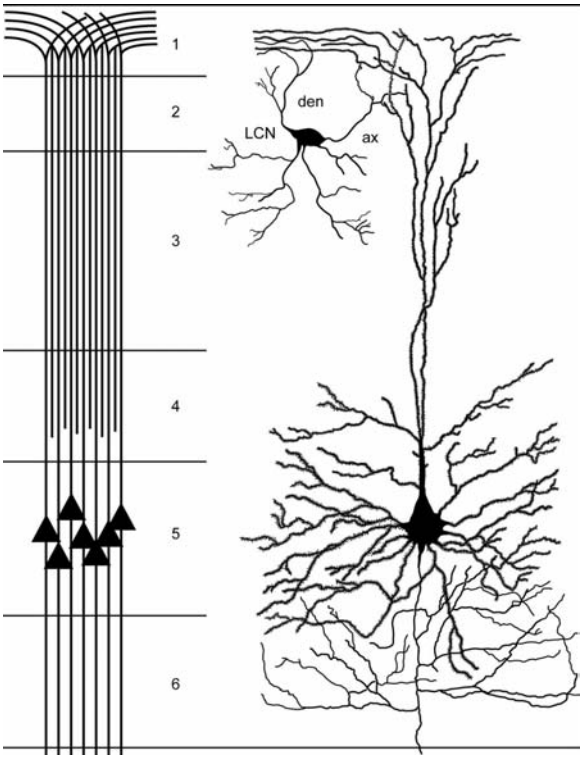


**Figure 2.** A dendritic bundle of cortical layer 5 pyramidal neurons and a local circuit neuron (LCN). A bundle of layer 5 pyramidal cell apical dendrites, schematically illustrated on the left, ascend through the upper layers of the cerebral cortex. From cortical layer 4 to layer 1 the ascending dendrites converge and produce an appearance of increased packing density as represented by the double layered vertical lines (19, 89). On the right a LCN (interneuron), showing dendrites (den) and an axon (ax), makes axonal synaptic contact with apical dendrites of a layer 5 pyramidal cell.

attributed this to "the electrophoretic interactions between AMPA receptor-mediated excitatory currents and negatively charged glutamate molecules (which) accelerate(s) the clearance of glutamate from the cleft".

## 6. MODULES, MINICOLUMNS AND DENDRITIC BUNDLES

### 6.1. Modules

Fifty years ago Mountcastle (78-80) described the columnar organization of the somatic sensory cortex using microelectrode recordings of single neurons responding to sensory input. All of the neurons in a 'Mountcastle's column', or macrocolumn and/or module as we often now refer to it, had similar properties inasmuch as these represented the sensory input from a particular region of the body. Crossing from one module to an adjacent area in the sensory cortex revealed a module containing neurons with distinctly different properties because it represented another part of the body surface (79). Modules are present throughout the neocortex and vary in size. Those in the sensory afferent areas are 300 to 750 micrometres in diameter whereas in the prefrontal cortex they are 200 to 400 micrometres across (81). The cortical module, thus identified, has since become familiar anatomically as being joined together to form stripes of generally 2 to 4 mm in length. As demonstrated by Hubel and Livingstone (82) in the visual area 2 (V2) receiving input from visual area 1 (V1), when V2 is stained for the enzyme cytochrome oxidase a pattern of dark and light stripes of different widths is seen. Stripes, depending on the properties of their modules, have independent functions and these relate to the particular region of the cortex where they are located.

The anatomical features of which modules are formed, such as minicolumns and dendritic bundles, are complex interconnected structures and although knowledge of these is at an elementary level and interconnections between them and with components in other modules are mainly hypothetical, there have been some significant recent developments offering fresh insight into how information in the cortex may be efficiently and rapidly processed (83, 84).

### 6.2. Minicolumns

The module (macrocolumn) in the human neocortex is composed of probably 40 to 80 minicolumns and these extend vertically from layer 2 to 6 with a diameter in the range of 40-50 micrometres and consist of about 80 to 100 neurons (80, 84-86). Lying roughly parallel to one another the minicolumns are separated by a small cell-sparse space of variable size throughout the cortex. The minicolumns in a module are 'bound together by short-range horizontal connections' (79, 84). No functions have been ascribed to the minicolumn and there is debate on whether it deserves recognition as having discrete functional identity but as discussed by Buxhoeveden and Casanova (84) it appears to be "the most basic and consistent template by which the neocortex organizes its neurons, pathways and intrinsic structure circuits". Indeed, the minicolumn contains a major very small-scale modularity in layers 1 and 2 of the cortex formed by dendritic bundles and a honeycomb-like structure (19, 20).

### 6.3. Dendritic bundles and honeycomb-like structure

There is an extensive literature on dendritic bundling throughout the central nervous system in mammals. Roney *et al.* (87), surveyed the literature on the experiments that have been undertaken on the cat or rodent and occasionally on the monkey and human. The number of dendrites forming a bundle in any particular region of the nervous system in different species varies but is usually between 5 and 30 and the distance between dendrites in a bundle averages 1 μm although there is direct contact between them (Figure 2). The number of bundles in any particular part of the central nervous system can be surprisingly large, between 60 to 80 per cent of the region such as in the ventral horn of the spinal cord or the brain stem reticular nucleus, but in the cerebral cortex the sites are more varied and selective in their location. Typically, the apical dendrites of cortical layer 5 pyramidal cells where they are vertically arranged as ascending bundles extending to layer 2, converge to form a bundle in layer 4 and remain maximally closely packed, making intermittent

physical contact with one another, until near the surface of the cortex in layer 1 (88, 89).

In 2002 Ichinohe and Rockland (19) and subsequently in 2003 Ichinohe *et al.*(20), in an extended study, identified bundled dendrites forming a unique structure in the upper layers of the neocortex that may provide new insight into how the cortex functions. The structure was seen by staining cortical nervous tissue for the calcium binding protein parvalbumin and histologically examining it in tangential sections. When tangential sections of the granular retrosplenial cortex of rats were stained for parvalbumin a honeycomb-like wall-and-hollow mosaic appeared in the lower half of cortical layer 1 (1b) and throughout layer 2. In scale the structure is less than 100 micrometres in diameter and does not invade layer 3. The *walls* of the 'honeycomb' were composed of merged dendritic bundles that were mainly the proximal dendrites and somata of layer 2 pyramidal neurons. Also in the wall were the synaptic terminals of parvalbumin stained GABAergic (inhibitory) interneurons and zinc-enriched corticocortical pyramidal neurons. Zinc ($Zn^{2+}$) in neurons is loosely bound to a protein transporter and is essential for transcription. As a cofactor for some glutamatergic synapses it contributes to neurotransmission, synaptic plasticity and long-term memory formation (90-92). Zinc-enriched terminals extend into layer 1b where, it is assumed, they make contact with the dendrites of layer 2 pyramidal neurons. The *hollows* of the honeycomb in contrast to the walls contained apical dendrites from, predominantly, layers 3 and 5 pyramidal neurons together with thalamocortical synaptic terminals. As yet, the precise microcircuitry in these structures is unclear. Gap junctions are abundant in the neocortex and are found predominantly between glial cells and between inhibitory interneurons of the same type, such as astrocytes and fast-spiking interneurons, as each has a specific role in the regulation of pyramidal cell activity (24, 31, 93). Although less frequent gap junctions connect neurons and glia of different types but gap junctions between interneurons and pyramidal cells are not recognized (94). Physical contact of bundled dendrites in the cortical layer 5 pyramidal neurons has been described by Skoglund *et al.* (89) but any synaptic contact with pyramidal cell dendrites would most likely be axodendritic and not dendrodendritic.

Schierhorn (87, 95) studied early neonatal development of bundling of the apical dendrites in layer 5 pyramidal neurons in the sensorimotor cortex of the rodent and found 'a loose bundle-like order' of dendrites by the 4$^{th}$ postnatal day, 3 dendrites in a bundle by 36 days and 6 dendrites per bundle by the 90$^{th}$ day. As discussed by Roney *et al.* (87) dendrites by this stage appear entangled allowing, perhaps, more contact between them.

Ichinohe and Rockland (21, 91) in their analysis of various areas of the macaque monkey cortex, using the same tissue staining techniques as applied in their studies of the visual cortex of the rodent, found basically the same 'wall and hollow honeycomb' features in the upper layers 1 and 2 of the cortex. However, the organization was not uniform and in some areas it was more difficult to identify, notably in the primary sensory cortex and the prefrontal areas 46 and 8 where zinc was not detectable. The $Zn^{2+}$ is distributed in the inferotemporal cortex of the monkey in a region associated with visual memory and the authors also found $Zn^{2+}$ enriched neurons in the CA1 pyramidal neurons of the hippocampus, several nuclei of the amygdala and the perirhinal region (91). The elevated levels of $Zn^{2+}$ in the perirhinal cortex originated from connections with pyramidal neurons in the CA1 region and amygdala and therefore the $Zn^{2+}$ in this region, the authors suggest, is probably related to cellular events associated with long-term memory formation.

## 7. RETICULAR ACTIVATING (AROUSAL) SYSTEM

Our knowledge of the physiological processes underlying consciousness and unconsciousness has been derived mainly from studies of wakefulness and sleep (96). Thus, to be awake is to be fully consciousness whereas to sleep is a suspension of consciousness from which the sleeper is normally aroused by the brain stem ascending reticular activating (arousal) system. There are two stages of sleep: rapid eye movement (REM) sleep and non-rapid eye movement (non-REM) sleep of which REM is the lighter more physiologically active form of the two and probably associated with most dreams. In the deeper non-REM sleep there are four levels of which the fourth is the most profound. A number of recent studies have shown that levels 3 and 4 of non-REM sleep are fundamental to the consolidation of newly-acquired memory and verbal memory retention and these correlate with the number of sleep spindles as recorded on electroencephalography (97-99). Sleep spindles have a rhythmic frequency of 7-14 Hz lasting for 1 to 3 sec and recurring at intervals of 3 to 10 sec (98, 100). As sleep deepens the frequency of the oscillations slows to 0.1 to 4 Hz, referred to as 'slow-wave sleep', and this is considered an important determinant to an overnight improvement of perceptual learning (101). By contrast REM sleep is characterized by a low voltage and mixed frequency pattern and in a normal relaxed conscious state the typical frequency is 10-14 Hz (96).

While wakefulness or 'arousal' is viewed as consciousness it is essential only as it serves to induce and sustain a state of consciousness. Both wakefulness and sleep are under the control of neurons in the reticular system of the brain stem that extends from the medulla oblongata forward through the pons and midbrain into the posterior hypothalamus (Figure 1) (8, 102). It has a netlike structure of cells and fibers in which groups of neurons, each with specific neurotransmitters, make contact with one another and more distal cells by both long ascending and descending axons and widely radiating dendrites (103-105). The neurons with *ascending* axonal projections are located in the upper pons and mesencephalon and terminate in the brain. The neurons with *descending* axons are mostly more caudally located in the pons and medulla and terminate on neurons in the dorsal horn, intermediate zone and ventral horn of the spinal cord. While the neurotransmitters in the ascending and descending pathways are largely the amino acids glutamate and gamma-aminobutyric acid (GABA), neuronal groups in the ascending arousal system also utilize acetylcholine, orexin and the biogenic amines (monoamines) dopamine, serotonin, norepinephrine and histamine (Table 1).

**Table 1.** The ascending and descending arousal system

| Brain Region | Nucleus | Neurotransmitter[1,2] | Main Function[2] |
|---|---|---|---|
| **Midpons** | locus coeruleus | norepinephrine | entire central nervous system activation |
| **Upper pons and lower midbrain** | pedunculopontine neurons | acetylcholine | facilitates wakefulness |
| | laterodorsal tegmentum | acetylcholine | facilitates wakefulness |
| **Midbrain** | dorsal & median raphé nuclei | 5-hydroxytriptamine (serotonin) | quiet awake state |
| | ventral tegmental area | dopamine | arousal |
| **Hypothalamus** | tubomammillary neurons | histamine | wakeful maintenance |
| | ventrolateral preoptic area | Galanin, GABA[3] | induces sleep[1] |
| | perifornical neurons | orexin (hypocretin) | maintains wakefulness |
| **Basal prefrontal cortex** | grey matter area | acetylcholine, GABA | promotes both sleep and wakefulness |

[1] 102, [2] 105, [3] gamma-aminobutyric acid

### 7.1. Dorsal thalamic and ventral hypothalamic pathways

Two pathways are involved in the ascending arousal system and each is formed by axons from nuclei containing cholinergic, aminergic and peptidergic neurotransmitters (102, 106). One, the cholinergic (acetylcholine) dorsal pathway innervates the thalamus which regulates the cerebral cortex via the internal capsule and the other, the aminergic ventral pathway (norepinephrine, serotonin and histamine), extends through the hypothalamus to project and extensively target neurons in the cortex. The neurons of the *dorsal thalamic pathway* and their neurotransmitters, as listed in Table 1, originate from the cholinergic pedunculopontine tegmental and laterodorsal tegmental nuclei in the posterior midbrain and anterior pons region. They project to multiple locations in the thalamus, including the intralaminar nuclei and thalamic relay nuclei, and the reticular nucleus of the thalamus. They are required for information, notably sensory input, received by thalamus being relayed via the thalamic reticular nucleus to the cortex (106). The *ventral hypothalamic pathway*, as it bypasses the thalamus and extends through the lateral hypothalamic area, is formed of fibers from the noradrenergic locus coeruleus in the pons and by fibers of the serotonergic dorsal and median raphé nuclei and the dopaminergic ventral tegmental area in the midbrain (Table 1) (102). These are joined in the hypothalamus by projections from a number of nuclei in the lateral hypothalamic area, especially the histaminergic tuberomammillary nucleus and the peptidergic orexin neurons, and by projections from the basal forebrain region inhibitory GABAergic neurons and cholinergic neurons to target neurons throughout the cortex.

As stated by Jones (104) the brain stem reticular formation provides through its widespread cortical projections "a tonic ascending activating influence to the cerebral cortex that is necessary for attention and wakefulness" (see also 105). It is the power source of the cerebral hemispheres upon which consciousness depends (96). However, inhibitory influences are also essential for sleep. The ventrolateral preoptic nucleus (VLPO) in the hypothalamus contains the inhibitory neurotransmitter GABA and its axons terminate on the ascending aminergic arousal neurons silencing them during sleep (107). Although evidence in support of the VLPO nucleus promoting sleep has also been demonstrated by lesions to the nucleus producing insomnia, neurotransmitters of the ascending arousal system can suppress the VLPO sleep-inducing function to evoke and sustain wakefulness (102, 108). A balance between wakefulness and sleep is regulated by the suprachiasmatic nucleus (SCN), the principal circadian pacemaker of the sleep/wake cycle in the hypothalamus, and is maintained by the stabilizing influence of orexin (see below). The VLPO nucleus receives input from the SCN and recently Saint-Mleux *et al.* (109) found that the SCN is capable, in addition to its usual modulating influence on the sleep/wake cycle, of independently inhibiting, and thereby diminishing, the sleep-inducing effect of the VLPO neurons.

### 7.2. Orexin nuclei

The number of factors involved in the control of sleep and wakefulness is remarkable. These include many nuclei, pathways and neurotransmitters (cholinergic, biogenic amines, amino acids) and to these the neuropeptide orexin has recently been added. Orexin, also known as hypocretin, is an excitatory peptide neurotransmitter released by neurons in the posterior lateral hypothalamic area (110, 111). The orexin neurons project rostrally to the cortex via the ventral hypothalamic pathway and caudally where contact is made with neurons in the ascending arousal system. The role of orexin is probably in the stabilization of wakefulness inasmuch as depletion of orexin results in narcolepsy, hypnagogic dreams, sleep paralysis and cataplexy in both the subprimate and human. As suggested by Chemelli *et al.* (112), narcolepsy and the other manifestations of orexin's absence probably represent a pathological intrusion of REM sleep into wakefulness. Lindsley *et al.* (10) described how the reticular activating system while directed to the brain also extends "caudally to facilitate motor activity, in maintaining a waking state" in the spinal cord. Sleep paralysis and cataplexy accompanying narcolepsy may be the effect of orexin depletion on the descending portion of reticular activating system and its influence on sustaining skeletal muscle tone.

Saper *et al.* (102) describe a 'flip-flop' model for switching from wakefulness to sleep and vice versa and how orexin, as a stabilizing force in the transition process, acts mainly on the nuclei of the ascending arousal systems. Orexin neurons project to the cholinergic and monoaminergic cells and are active during wakefulness whereas the sleep-inducing VLPO neurons do not express orexin receptors and are probably not directly inhibited. Instead, the VLPO neurons during the homeostatic drive to sleep, inhibit the aminergic cells and they, in turn, inhibit the orexin neurons, flipping a switch from a conscious to an unconscious state. However, as noted above, the VLPO

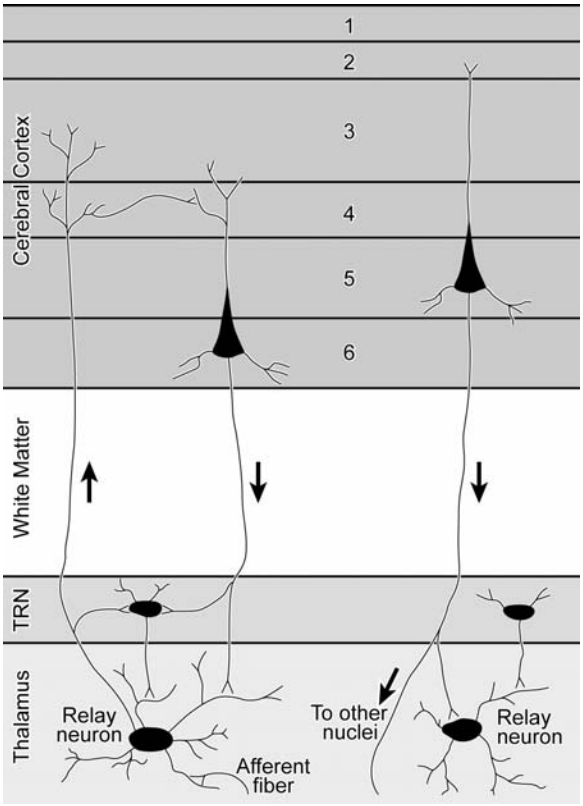


**Figure 3**. The thalamocorticothalamic relay system. Visual, auditory and somatosensory input received by the thalamus, as illustrated on the left, is sent to the cortex by thalamocortical relay neurons (118, 122). Layer 6 pyramidal neurons dendrites in the cortex receive input from thalamocortical relay collaterals and return information back to the thalamic relay neuron. Both pathways are excitatory and en route each sends a collateral branch to a thalamic reticular nucleus (TRN) neuron that produces inhibitory feed-back and feed-forward input to the relay neuron and sustains synchrony (122). On the right a layer 5 pyramidal neuron sends a branch to the thalamic relay neuron receiving layer 6 pyramidal cell input but does not send collateral input to the thalamic reticular neuron but projects to other nuclei.

neurons can be inhibited by the SCN, thereby restoring consciousness.

### 7.3. Suprachiasmatic nucleus (SCN) and the sleep/wake cycle

The 24-hour sleep/wake cyclical pattern as it is governed by homeostatic and circadian mechanisms ensures the maintenance of proportional periods of wakefulness and sleep and their restoration when the cycle is perturbed as, for example, by a prolonged period of forced wakefulness (102). The nature of the homeostatic mechanisms in mammals is obscure but clock genes and certain proteins have been found in a variety of tissues of lower life forms although these function in diverse ways and are not necessarily diurnal or even seasonal. Nonetheless, in mammals the SCN as the master circadian pacemaker mechanism in the hypothalamus, serves as a clock for many central nervous system functions that are matched to daily light and dark periods (113). It is connected to and guided by a novel type of photoreceptor ganglion cell in the retina that is not involved in visual photoreception but contains the photopigment melanopsin and responds to the diurnal solar cycle. The melanopsin-expressing retinal ganglion cells project to and regulate a number of light-driven mechanisms in the brain including, in addition to the sleep/wake cycle, the ocular pupillary light reflex and inhibition of melatonin secretion by the pineal gland (114, 115). Plasma melatonin levels are elevated at night and are diminished by light through connections with the SCN during the day (116). The elevation of melatonin nocturnally suppresses memory formation and, as suggested by Rawashdeh *et al.* (117), may inhibit memories being formed during the night.

## 8. THALAMOCORTICAL RELAYS AND THE THALAMIC RETICULAR NUCLEUS

The thalamus has long been viewed merely as a relay station sending incoming visual, auditory and somatosensory information to the cerebral cortex but it has remarkably intricate circuitry and a rich array of cell properties that are capable, facilitated by gap junctions and dendrodendritic synapses, of managing the rapid delivery of information to higher level functions of the brain (118-120). Afferent pathways from the special senses on arrival at the thalamus synapse with thalamocortical neurons in the dorsal thalamus where the received sensory input is relayed to the middle layers of the cortex (Figure 3). Messages are returned to the same thalamocortical nucleus by layer 6 small corticothalamic pyramidal neurons thereby forming a circuit. These two excitatory relay paths traverse a sector of the thalamic recticular nucleus overlying the lateral surface of the thalamus and during their transit each sends a collateral branch to a reticular neuron (73, 121, 122). The thalamic reticular neurons are inhibitory (GABAergic) and produce feed-back to the thalamocortical relay cells from which they have received collateral input (122). The returning corticothalamic neurons, by sending their collateral input to the thalamic reticular neurons, provide corresponding inhibitory feed-forward input to the thalamocortical relay cells. Thus, the recticular neurons in the 'thalamocorticothalamic' circuit afford bidirectional inhibitory influences on the relay cells. However, the control appears to rest with the cortex on how it receives and distributes the information that it has received from the outside world.

As pointed out by Jones (122) the predominant role of the cerebral cortex in the relay circuit is seen in a disproportionally large number of cortical axon terminals in both the thalamic relay nucleus and reticular nucleus as compared with other afferent terminals. The need for such control is in the matching and depositing of new sensory information into an already vast cortical network of imbedded sensory records. Indeed, the cerebral cortex has two independent and quite different corticothalamic mechanisms to meet its requirements one of which, the layer 6 pyramidal neurons referred to above, has a

restricted output while the other, layer 5 pyramidal cells, has very diverse connections in the brain (118). The cortical layer 6 pyramidal neurons are short with apical dendrites ending in the middle layers of the cortex where they receive monosynaptic input from the terminal endings of the ascending thalamocortical relay fibers and project back to the same thalamic neurons from which they received cortical input (Figure3) (122). The corticothalamic pyramidal neurons in layer 5 on the other hand make contact with relay neurons in the thalamus that receive input from layer 6 pyramidal neurons but, unlike the latter, they do not send collateral branches to the thalamic reticular nucleus. The layer 5 pyramidal neurons are large with apical dendrites extending into layer 1 with extensive axonal ramifications within the cortex and also the thalamus (122). They have horizontal collateral branches that extend considerable distances through cortical layers 3 and 5 and in the thalamus they also extend to other locations. The functions of the layer 5 and 6 pyramidal neurons in the thalamocorticothalamic network is unknown but as postulated by Sherman and Guillery (118) layer 6 neurons appear to have a direct and more elementary function than the layer 5 pyramidal cells. The latter cortical neurons have a more complex role such as linking assemblages of received information to their appropriate cortical regions.

## 9. NEURAL BASIIS OF MEMORY

Memory is such a familiar part of our being as to almost pass notice especially as it is intimately associated with consciousness and 'self'. But unlike consciousness memory can be linked to specific cortical areas, mainly the hippocampus and the adjacent medial temporal cortex and therefore more open to exploration. Associated with memory is its emotional content as contributed by the amygdala and by the prefrontal cortex for its role in executive control over both mnemonic and emotional expression (123). The close relationship between the hippocampus, amygdala and prefrontal cortex is manifested in the selective atrophy of dendrites in the hippocampus and medial prefrontal cortex, but enhanced dendritic arborization of pyramidal neurons in the amygdala, in conditions causing extreme emotional stress such as sleep deprivation, physical restraint, isolation and overcrowding (124-130). These studies were made on animals as part of enquires into the responses of the hypothalamic-pituitary-adrenal axis to stress but apply to humans as demonstrated in primates under similar or otherwise comparably severe conditions (124). Some of the damaging effects are from elevations of the plasma corticosteroid levels but the main effects are likely endogenous such as from stress-related decreases in the availability of neurotrophins upon which sustained synaptic growth and adaptability depend (125, 131). The anatomical and physiological literature on all three regions of the brain is extensive and the purpose here is to only briefly describe certain characteristics of each as they affect consciousness.

### 9.1. The hippocampus

The hippocampus is necessary for the storage of short- and long-term memory and also short-term memory retrieval. Long-term memory of weeks and months duration is consolidated in sensory association areas of the neocortex and its retrieval, while facilitated by the neural structures in the anterior and medial temporal region, may be independently accessible by way of processes within the neocortex as observed following the excision of the anterior and medial portions of the temporal lobes (132, 133). Resection of the medial temporal lobe bilaterally from the tip to include the hippocampus proper, dentate gyrus, subiculum, entorhinal cortex, parahippocampal gyrus, perirhinal cortex and amygdala bilaterally, as described by Scoville and Milner (134) in the classical case of H. M., produces profound anterograde amnesia with apparently full retention of prior memory apart from partial amnesia for the few years before surgery. Patients who have had selective bilateral destruction of only the hippocampal formation (hippocampus proper, dentate gyrus, subiculum and entorhinal cortex), memory for facts or events only are lost. As described by Vargha-Khadem *et al.* (135) selective loss of this kind, with the adjacent medial temporal cortices left effectively intact, neocortically-stored memories are retained with some capacity to learn and further retain ongoing memories such as language despite absence of the hippocampus.

A major advance in our understanding memory was made when Bliss and Lomo (136) in 1973 described long-term potentiation (LTP), a long-lasting increase in the sensitivity of synapses involved in the formation of memory. LTP as it normally develops in the hippocampal circuitry extends, as a generative process, by way of connections within the hippocampal formation and the adjacent limbic areas of the temporal lobe to the neocortex. Incoming sensory information received and processed within neurons for long-term memory involves structural alterations at the synaptic site. This change occurs initially in the recipient cell followed by an increase in the area of both pre- and post-synaptic active zones (137-139). Recently, Harvey and Svobova (140) described a reduction of the threshold for LTP at neighboring synapses at the level of the individual synapses on pyramidal cell dendritic spines. These local interactions between the synapses allow for a clustered synaptic response on dendrites as they undergo plasticity and permit "the binding of behaviorally linked information on the same dendritic branch" in association with learning and memory (141, 142).

### 9.2. The amygdala

The emotional content of memory is managed by the amygdala that responds to aversive stimuli with feelings of stress or fear. In a more commonplace sense the amygdala in association with the orbitofrontal cerebral cortex and hippocampus produces the feelings of uncertainty that accompany decision-making (143). It has a number of nuclei with extensive cortical connections, predominantly with the medial surface of the frontal lobe and posterior orbitofrontal cortex, the anterior portion of the cingulate cortex, the relatively advanced visual, auditory and somatosensory association areas in the anterior, inferior and superior temporal lobe and the insula (144-146). Amongst the heaviest projections of the amygdala are to the posterior orbitofrontal cortex and,

reciprocally, the prefrontal projections target amygdaloid nuclei but not necessarily those cells in the amygdala that were the source of orbitofrontal input (147).

The amygdala projects substantially to the subiculum and hippocampus although the dentate gyrus does not seem to have significant amygdaloid input (145). By contrast the output of the hippocampal formation to the amygdala is meager. As described by Ishikawa and Nakamura (146) both excitatory and inhibitory projections from the amygdala and hippocampus converge and interact within the medial and inferior areas of the prefrontal cortex. The authors suggest that simultaneous activation of the hippocampal and amygdalar neurons projecting to the same prefrontal neurons could significantly amplify prefrontal activity and "may be associated with better memory consolidation of matters or events accompanying emotional responses". As discussed below damage to the medial and orbitofrontal regions of the prefrontal cortex can have disruptive effects on moral judgments and decision making in emotional situations.

### 9.3. The prefrontal cortex

Different regions of the the prefrontal cortex have executive functions in the processing and selection of memory. A region for working memory in the dorsolateral prefrontal cortex selects and maintains behaviourally relevant information and is considered necessary for abstract reasoning, complex problem solving and future planning (148, 149). Goldman-Rakic *et al.* (150) found ample linkage between the dorsolateral prefrontal cortex and hippocampal formation and suggested that the prefrontal projections carry "highly specific information into the hippocampus and reciprocal projections may allow the retrieval by the prefrontal cortex of memories stored in the hippocampus". The prefrontal frontopolar cortex is viewed as forming the highest level of the executive system for decision-making by Koechlin and Hyafil. (151). The authors view this region as "protecting the execution of long-term mental plans" from interference by more immediate demands; in effect, holding in mind primary goals during decision-making while exploring newer more creatively rewarding goals.

The medial and orbitofrontal areas of the prefrontal cortex have connections with the subcortical nuclei notably, in addition to the amygdala discussed above, the thalamus, caudate nucleus, hypothalamus and autonomic brain stem nuclei. These subcortical nuclei have an important automated (reflexive) influence on the conscious state but are otherwise under prefrontal control. Damasio (152) found that ventral and medial prefrontal cortical injury produces "personal and social impairments of decision-making". Gehring and Willoughby (153) also assign to the medial-frontal cortex, and the anterior cingulate cortex, a role in decision-making as it involves monitoring behaviour and the detection of conflicting or erroneous actions. Focal bilateral lesions in the ventromedial prefrontal cortex can impair moral judgements. As demonstrated by Koenigs *et al.* (154) such patients who, when required to make decisions in potentially highly emotionally charged situations that affect the lives of others, showed 'utilitarian' judgements devoid of empathy, shame or guilt as to outcome (see also 155).

## 10. NEONATAL DEVELOPMENT OF CONSCIOUSNESS

Consciousness is dependent on the nervous system being equipped to receive, analyze and respond to information and at the end of gestation many regions of the neonatal nervous system are still undergoing change. Some regions of the brain develop quickly but others can take weeks, months or even years thereafter for completion. A novel technique for tracing very early pre- and postnatal development in the thalamus and cortex has been described by Richardson and others using the transient neonatal expression of acetylcholinesterase (AChE) activity (156-158). AChE degrades the neurotransmitter acetylcholine but, for reasons that are unclear, it is very active during the postnatal development of thalamocortical connections to the primary somatosensory, visual and auditory cortices. As studied in rats AChE peaks in various thalamic nuclei and the cortex during the first 10 to 12 postnatal days and then rapidly declines to adult levels. The cortical expression of AChE closely reflects thalamocortical innervation of cortical layers 1, 4 and 5. Sensory deprivation due to developmental failure or injury to sensory end organs or pathways in the infant within the first weeks of life can have a profoundly deleterious effect on the thalamocortical development in the primary sensory cortical areas.

### 10.1. Pre- and postnatal myelination of the brain

The neonatal brain is far from fully developed. As in the fetus it is grey and gelatinous throughout and separation into grey and white matter, i.e. the myelination of the axons in what will eventually be apparent as subcortical 'white matter', is grossly undeveloped (159). Also the cerebral cortex is still not fully formed at birth with the deeper strata showing a much higher level of development than the superficial layers (165). In the latter layer at birth the LCNs, especially, are still immature. As described by Polyakov (160) neurons in different areas of the cortex develop at different rates and "the earliest parts of the cortex to exhibit intensive growth and differentiation of neurons are those cortical areas which receive the most concentrated and powerfully developed projections of fibres from subcortical parts".

Estimates on the extent to which myelination occurs during early human life have been extensively explored. Poduslo and Yang (161) concluded that myelination of the major subcortical tracts of the brain are near completion by the end of the first year but certain pathways continue to myelinate for many months or even years afterward. For example, the reticular system in the brain stem and the corpus callosum are not entirely myelinated until the end of the first decade and myelination of the neuropil in the association areas of the cortex is still taking place during the third decade (162).

Paus *et al.* (163), using measurements of white matter density obtained from structural magnetic resonance imaging, described how age-related increases in density in

the white matter of some regions in the brain take until adolescence to complete. They ascribe increments in the white-matter density to increases in the diameter or myelination of axons that form fiber tracts. This was found especially in the internal capsule and left arcuate fasciculus, the latter fiber tract connecting the receptive and expressive speech areas in the left hemisphere. A similar late increase in density occurs in the frontotemporal pathway in the adolescent brain in the left hemisphere. As suggested by the authors these changes could be a response to the requirement for fast bidirectional speech-related information transfer between the auditory and motor cortical regions.

**10.2. Postnatal sensory development**

The newborn enters an unfamiliar world and the facility of the brain to acquire and store memories of the world within the first few years of life depends on the degree to which the systems for receiving, sorting and consolidating information in memory have matured. The stimulus afforded by sensory input from the environment into which the neonate is born is critical to the normal growth of the nervous system. In the human, as demonstrated in animals with eyes open at birth, the receptive-field properties of vision may appear fully mature but the peripheral visual system from the retina to the visual cortex at the time of birth is still incomplete. Indeed, the fovea of the eye is not fully formed nor is the optic nerve completely myelinated until at least one month postnatally (164, 165). Thus, the normal newborn may be effectively blind but if vision is unobstructed sight will develop.

Testing vision in the newborn is constrained by difficulty in obtaining adequate cooperation from the child, but quite accurate measurements of visual acuity from birth to age of six years have been obtained by novel means such as optokinetic nystagmus and visually evoked potentials. As summarized by Dobson and Teller (166) visual acuity in the newborn is between 20/1600 and 20/400 and thereafter this gradually improves to reach 20/20 by the age of six years (newborns are also normally hyperopic). Thus, vision in human infant develops very slowly from a state of almost complete sightlessness at birth.

**10.3. Sensory deprivation in the newborn**

Absence of visual, auditory or somatosensory input in the newborn has major anatomical and physiological effects on the early development of afferent subcortical nuclei and the primary sensory areas of the cortex.

**10.3.1. Blindness of ocular origin**

The visual cells in the striate visual cortex (area 19) which form the ocular dominance columns and receive input from the two eyes are not completely segregated into *monocular* input until the sixth week postpartum in the monkey (167, 168). Obstruction of vision by lid-suture of a single eye in a monkey at birth until 3 weeks of age was performed by LeVay *et al.* (168) and produced severe anatomical and physiological damage to the ocular dominance columns of the closed eye. The columns receiving afferents from the open eye expanded into the adjacent neural territory that was to receive afferent input for the sutured sightless eye. Remarkably, the same lid-suturing procedure performed later at 10 weeks of age yielded comparatively minor anatomical effects suggesting that basic maturation in the visual cortex by this time had neared completion. From studies on the monkey it is apparent that within the first few weeks of neonatal life development of the nervous system is very actively underway and the visual system is especially vulnerable to postnatal visual deprivation. Moreover, from the evidence of animal and human studies visual experience is essential to both the development of the visual cortex and the accession of visual skills. Children with monocular blindness due to cataract or corneal opacity arising from injury in very early life when treated surgically many years later are, with rare exception, left with high order visual deficits in the affected eye (169-171).

**10.3.2. Cochlear hearing loss**

Harrison *et al.* (172) induced cochlear hearing loss in the high frequency range in newborn cats using an ototoxic aminoglycoside that produced "a massive (bilateral) over-representation of neurons primarily responding to one stimulus frequency" in the auditory area of the cortex. This they described as similar to what might be expected with the long-term cochlear hearing loss in humans. Kral *et al.* (158), using cochlear implants, electrically stimulated the auditory system of deaf cats suffering from congenital dysplasia of the organ of Corti. They observed significant deficits in synaptic activity in the infragranular cortical layer of the auditory cortex which they ascribed to functional deficits of corticothalamic and corticocortical connections in the primary auditory cortex. Penhune *et al.* (173) using MRI measured the volume of tissue in the auditory region of the cortex (Heschl's gyrus and the planum temporale) in congenitally deaf human subjects and found it indistinguishable from normal subjects. This, the authors proposed, reflected a reorganization of the auditory cortex in the deaf subjects to other purpose, such as sign language. In agreement with this interpretation, Finney *et al.* (174), using fMRI, observed that visual stimuli are processed in the auditory cortex in early deafness which they ascribed to 'cross-modal plasticity' in deaf subjects due to absence of auditory input during early development. A similar effect occurs in blind individuals in whom auditory stimuli are processed in the visual cortex indicating the capacity of the brain during early development to reorganize and respond to sensory deprivation by yielding the deprived territory in the brain to certain other functions (174).

**10.3.3. Somatosensory deafferentation**

Sectioning of a peripheral nerve or amputation of a limb produces reorganization of the area the cortex representing the deafferented skin or limb (175). Following the amputation of one or two digits in the hand of monkeys, Merzenich *et al.* (176) described how, when the cortex was mapped 2-8 months later, "the representations of the adjacent digits and palmer surfaces (had) expanded topographically to occupy most or all of the cortical territories formerly representing the amputated digit(s)".

The authors suggested that because cortical skin surface maps are dynamically maintained by sensory input they may be potentially alterable by experience (continued use of the hand in the monkey).

Somatosensory deprivation, whether in the adult or newborn, generally produces a reorganization of the cortex (177, 178). Traumatic amputees, for example, who have both phantom limb and phantom pain display a major somatosensory cortical reorganization (179). However, by contrast, as described by Flor *et al.* (179), congenital (prenatal) upper limb amputees do not experience phantom limb sensation or phantom pain and the primary sensory cortex shows minimal reorganization. Surprisingly, patients with traumatic upper limb amputation who did not have phantom pain (but have phantom sensations) also show minimal reorganization of the primary somatosensory cortex suggesting that pain, in itself, may be a contributing factor in thalamocortical somatosensory reorganization.

## 11. MEMORY AND CONSCIOUSNESS CONSOLIDATION

We are aware of memory being a part of consciousness when, without deliberation, we recognize people and places around us or we are engaged in recalling past events (37). It is impressive how we can direct our thoughts to widely distributed cerebrocortically stored information and bind together bits of information and then extrapolate from these novel ideas in problem solving. Memory storage and retrieval in the neocortex depends not only on information received but also on its consolidation through experience. Much of our everyday life experiences which we recognize as familiar have been previously consolidated in memory. Tse *et al.* (180) described how memory of new information that is based on relevant past experience is quickly consolidated into existing neocortical memory. Without prior experience new memory is hippocampal-dependent and its consolidation in the neocortex is a gradual process but when based on previously created memory the subsequent experiences are hippocampal-independent and rapidly incorporated. A feature of memory of which we are unaware is the time that has elapsed, a hundred or more milliseconds, before sensory input from the outside world is matched to prior memory. This is due to the distance that incoming information must travel from the sensory receptors to the appropriate 'memory schemata' in the neocortex. Only on arrival at its cortical destination does the sensory event attain consciousness but due to the milliseconds delay it takes in reaching consciousness the information has become a past event and another event has taken place of which we are as yet unaware (181, 182). While the delay is imperceptible it nonetheless demonstrates our dependence on the perception of our being 'instantaneously' aware of what is taking place around us. In some diseases of the nervous system such as advanced parkinsonism or Alzheimer disease the delay may be much longer. In the normally aging brain the delay in searching in memory lengthens and items are often spontaneously recalled sometime later.

## 12. SUMMARY AND PRESPECTIVE

Consciousness has been widely perceived as an irresolvable problem because of the lack of substantive anatomical and physiological evidence as to its identity although the ascending reticular activating (arousal) system in the brain stem is considered essential for wakefulness and consciousness (11, 104). For sensory input to be received by the thalamus and the thalamic reticular network for delivery to the cortex it requires tonic activation by the ascending arousal system in the brain stem (122). The thalamocortical projections system was considered by Penfield and Jasper (11) as responsive to the "*centrencephalic reticular network* (their italics) located chiefly in the central core of the of the brain stem…". The actions of the thalamus by virtue of its topographical organization were, in these authors' view, restricted to more highly specialized local cortical functions. Thus, the source of consciousness as perceived by Penfield and Jasper resides in the mesencephalon. Nonetheless sensory input, facilitated by the ascending arousal system during wakefulness, is stored and/or matched to existing memory and, in the present author's view, it is memory rather than the arousal system which forms the basis of consciousness. A difficulty with this perspective is how in consciousness a continuously changing flow of sensory input upon its arrival at the level of the thalamus is almost immediately matched to memory stored in the cortex. Toward finding an explanation for this several mechanisms have herein been described, the most critical of which are as follows.

A number of neuroanatomical features contribute to reducing delay during the neural processing of information. The most familiar are saltatory impulse transmission in myelinated axons and the location of highly interdependent cortical functions in close proximity to one another (23, 64). For often used functions such as reading, there is a visual rapid and fluent letter and word recognition area in the fusiform gyrus of the left temporal lobe (183). A corresponding region for the rapid recognition of faces is present in the right fusiform gyrus close to an area for identifying places, such as houses, in the right parahippocampal gyrus (65, 184-186). Because of extracellular electrical fields and the ionic environments of neurons, or the proximity of dendrites (with axons) to one another in dendritic bundles, together with the densely packed superficial layers of the cerebral cortex, one is impressed with how remarkably efficient is the use of space within the cortex (20). This is especially manifest in the closely packed pyramidal cell layer of the hippocampus where field effects triggered by activated neurons fire inactive cells to produce population spikes (75, 76, 187). Field effects may also contribute to rhythmic electrical activity in the superficial layers of cerebral cortex where there is a large overlap of dendrites (15).

The neocortex is viewed by Letinic *et al.* (34) as having just two major forms of neurons to which they refer as projection (excitatory pyramidal neurons) and local circuit neurons (LCNs - inhibitory interneurons). The local circuit neurons have been especially recognized as forming large dendritic networks wherein information is

electrotonically processed by means of gap junctions and, in some locations subcortically, by dendrodendritic synapses (15, 16). Communication occurs passively by small graded changes in electrical potential between electrotonically coupled dendrites thereby reducing the time span as might otherwise involve comparatively 'low sensitivity' axodendritic synaptic transmission (15). The local circuit neurons are especially concentrated in the superficial layers of the neocortex, mostly in layers 3 and 4 but extending into layer 2, where the vertically arranged apical dendrites of cortical layer 5 pyramidal cells converge to form bundles (16, 188). A well-defined tangential honeycomb-like arrangement of dendrites and the cell bodies of neurons is present in layer 2 and 3 at least in certain areas of the cortex (19). The concentration of dendrites in the superficial cortical layers may be where much of the higher functions of the brain such as learning, memory and consciousness may be taking place (16, 189).

Memory is served by the hippocampal formation, the adjacent anterior and inferomedial (entorhinal and perirhinal) regions of the temporal lobe while the emotional content is provided by the amygdala and the executive control by the prefrontal cortex (109). Both the hippocampus and amygdala have extensive connections to the neocortex and especially the posterior orbitofrontal and medial regions of the prefrontal cortex where the processing and selection of memory and its emotional input via the amygdala (and cingulate cortex) are controlled (145, 146). Goldman-Rakic *et al.* (150) described the dorsolateral prefrontal cortex in the monkey - a region that is associated with working memory in the human for holding current information during ongoing cognitive tasks - as reciprocally well connected to the hippocampus via adjacent hippocampally-related cortices for memory retrieval. Koechlin and Hyafil (151) refer to the frontopolar prefrontal cortex as having a similar role in protecting the "execution of long-term plans" by holding in mind primary goals for ongoing cognitive tasks. Recently, Mongillo *et al.* (190) in a proposal applicable to both areas of the cortex, suggested that working memory, as such, is maintained during mental tasks in a state of short-term synaptic facilitation by an accumulation of calcium in presynaptic terminals - a process whereby a cognitive function can be suspended in a quiescent state of memory for many seconds and reactivated on recall (37, 191). Thus, a basis for creative thinking is ensconced in areas of the prefrontal cortex. As illustrated by Fusi (191) this enables us when driving a car to retain important information on heading to our destination while complying with the route and traffic requirements.

In conclusion, as proposed, an interdependent relationship exists between memory and consciousness and both mature together and become increasingly manifest during early life. The brain of the newborn is structurally incomplete and memoryless in terms of the world into which it is born but gradually over the ensuing months it matures and stores sufficient information gained through the senses to experience consciousness of its surroundings. As long-term memories accumulate, during the first year or two of life, the recall of past events and the performance of complex cognitive processing become possible. In the course of daily experience sensory input, facilitated by the ascending arousal system, is rapidly matched to memory and provides a state we recognize as consciousness. There are many mechanisms in the brain that diminish transmission delays in the matching of the outside world events to memory. However, understanding of how this is achieved will depend on our knowing how neurons interact in an extraordinarily short time at a computational level.

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**Key Words:** Consciousness, Memory, Reticular activating system, Sleep/wake cycle, Gap junctions, Dendrodendritic Synapses, Field effects, Thalamocortical relay system, Dendritic bundles, Electrotonic information processing, Sensory deprivation.

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