Neuroscience Vol. 74, No. 3, pp. 625–651, 1996

Printed in Great Britain
0306–4522/96 $15.00+0.00

Pergamon

PII: S0306-4522(96)00163-7

COMMENTARY

GLOBAL AND SERIAL NEURONS FORM A HIERARCHICALLY ARRANGED INTERFACE PROPOSED TO UNDERLIE MEMORY AND COGNITION

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Abstract—It is hypothesized that the cholinergic and monoaminergic neurons of the brain form a global network. What is meant by a global network is that these neurons operate as a unified whole, generating widespread patterns of activity in concert with particular electroencephalographic states, moods and cognitive gestalts. Apart from cholinergic and monoaminergic global systems, most other mammalian neurons relay sensory information about the external and internal milieu to serially ordered loci. These ''serial'' neurons are neurochemically distinct from global neurons and commonly use small molecule amino acid neurotransmitters such as glutamate or aspartate.

Viewing the circuitry of the mammalian brain within the global–serial dichotomy leads to a number of novel interpretations and predictions. Global systems seem to be capable of transforming incoming sensory data into cognitive-related activity patterns. A comparative examination of global and serial systems anatomy, development and physiology reveals how global systems might turn sensation into mentation. An important step in this process is the permanent encoding of memory. Global neurons are particularly plastic, as are the neurons receiving global inputs. Global afferents appear to be capable of reorganizing synapses on recipient serial cells, thus leading to enhanced responding to a signal, in a particular context and state of arousal. Copyright © 1996 IBRO. Published by Elsevier Science Ltd.

Key words: acetylcholine, glutamate, monoamines, neural plasticity, memory encoding, learning.

Abbreviations: BDNF, brain-derived neurotrophic factor; bFGF, basic fibroblast growth factor; ChAT, choline acetyltransferase; EEG, electroencephalogram; LTD, long-term depression; LTP, long-term potentiation; MAP-2, microtubule-associated protein 2; NGF, nerve growth factor; NMDA, *N*-methyl-D-aspartate; PKC, protein kinase C.

Table 1. Serial or global characterization of central neurons

	Serial systems*	Global systems†
Brain regions:	Primary sensory neurons, sensory relays, cerebellum, thalamus, hypothalamus, hippocampus, cortex	Motor neurons, raphe nuclei, locus coeruleus, mesopontine tegmentum, substantia nigra, neostriatum, basal forebrain
Neurotransmitters:	Glutamate, aspartate, GABA	Acetylcholine, serotonin, norepinephrine, dopamine
Embryological origin:	Alar plate derivatives	Basal plate derivatives
Axonal plasticity:	Central axons largely lack regenerative capacity in adult	Central axons exhibit robust plasticity in adult
Neurotrophism:	Adult central neurons decrease sensitivity to NGF, BDNF, neurotrophin-3 and bFGF	Adult neurons maintain or increase sensitivity to NGF, BDNF, neurotrophin-3, bFGF and insulin-like growth factors
Physiological response pattern:	Isolated circuits are electrically silent unless stimulated directly	Isolated cells continue to fire spontaneously in rhythmic patterns
Specialized functions:	Relay data from external and internal milieu; repository for neural representations encoded by reorganization of global afferents	Control overt behavior; regulate EEG; focus attention; modulate potentiation or depression; enhance signal-to-noise ratio of responses in retrieval and recognition

*Neurons arranged in ordered series which participate in the relay of information ultimately derived from a sensory receptor to ascending centers, generally preserving some degree of modality and receptive field specificity.
†Constellations of neurons which are highly interconnected and physiologically interactive, and which determine the pattern of activity in their targets.

1. INTRODUCTION

The profound complexity of neuroanatomical circuitry in the mammalian brain makes it particularly challenging to elucidate the neurobiological underpinnings of higher cognitive functions. One thing lacking is a general scheme for categorizing neural systems. This would simplify neural modeling of cognition. The current treatise postulates a basic scheme that classifies neurons into two categories. Arguments are made that the mammalian brain consists of two chemically, anatomically and physiologically distinct types of neural systems that are presently termed ''serial'' for neurons that use small amino acid neurotransmitters or ''global'' for neurons that use acetylcholine or monoamine neurotransmitters (Table 1; also see Refs 11 and 267).

1.1. *Chemical neuroanatomy of global and serial neurons*

Serial processing typifies the numerous circuits relaying inputs from a number of sensory receptive fields, systems in which the majority of neurons use the small molecule amino acid neurotransmitters, glutamate, aspartate, GABA or glycine.[67,118,187] These serial pathways account for most of the neurons in the brain. All serial neurons convey sensory information of a specific modality from some exteroceptive or interoceptive field to successively higher brain levels. Through ascending levels of the cortex, serial neurons continue to relay parallel streams of sensory information in a step-by-step fashion.[62,190] Even in association cortex, some aspect of sensory information is topographically encoded.[172] Learned responses are superimposed on these topographical maps (e.g., face cells[285]). Experience modifies response characteristics as basic as receptive field properties, indicating that they are partly learned.[13]

It is presently argued that these learned responses are due to changes in global afferents to serial neurons. Firstly, serial neurons need to send information in a constant manner, otherwise basic sensations would be highly variable and learning would be impossible. (For example, we know that repeated exposure to constant stimulus parameters is necessary for learning. We can further assume that those sensory parameters need to be relayed to the learning locus in a constant fashion.) Second, learning is context and state dependent.[199] If learning changed the way messages were sent in serial circuits, sensory relay of information would be altered, non-selectively, in every context, mood and state of arousal. For these and other reasons, it seems appropriate to hypothesize the separateness of serial relays from analytical systems, such as the global networks.

Populations of global neurons look very different from serial neurons. Even without the aid of specific neurochemical markers, the reticular appearance of the so-called ''isodendritic core'' distinguishes its global neurons from the serial neurons in the brain.[54] Cholinergic and monoaminergic somata are not regularly localized to specific nuclei, as are serial neurons. They invade fiber bundles and are frequently ectopically located within nuclei of serial cells.[267]

To handle context and state dependency, highly interlinked neural systems with widespread influence

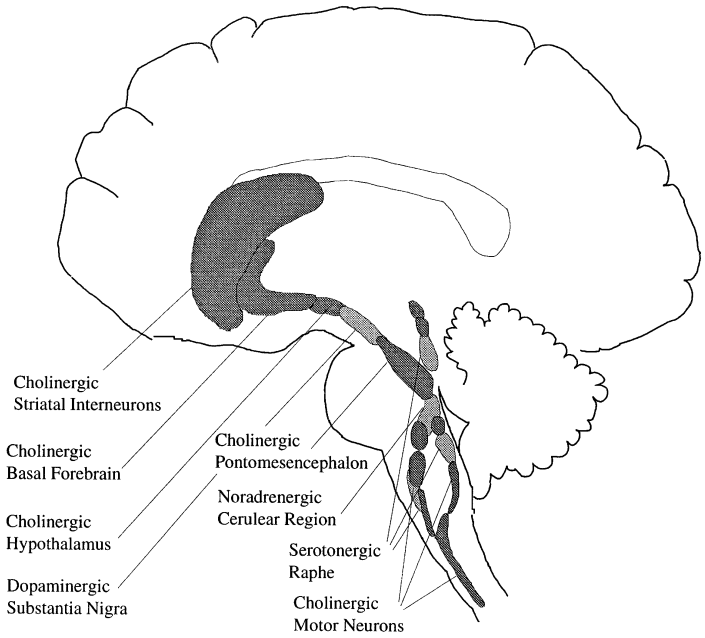

Fig. 1. A schematic diagram of the cholinergic and monoaminergic neuronal somata in the CNS. Note that these global system neurons are organized in a continuum that extends from the spinal cord to the basal telencephalon. Projections deriving from these relatively few neurons innervate the entire CNS and all peripheral muscles, organs and glands. See text for further details.

are mandated. Although cholinergic and monoaminergic global neurons are relatively few, their extensive dendritic and axonal arbors reach virtually every part of the CNS.[24,239,267,274,275] This diffuse nature contrasts with the labeled line specificity of serial connections.

A previously overlooked characteristic of global neurons is that they form an uninterrupted chain. Cholinergic and monoaminergic neurons form a continuous neural network extending from the basal ganglia and basal forebrain of the telencephalon to the ventral horn of the caudalmost region of the spinal cord (Fig. 1). The dendritic arbors of these cholinergic neurons commonly aggregate into closely adherent bundles.[23,267] Ectopically placed cells provide continuity between global systems.

Intrinsically organized cholinergic cells in the ventralmost aspect of the putamen, for example, overlap with cholinergic basal forebrain cells having cortical projections.[267,270] Individual cholinergic neurons of the basal forebrain have extensively overlapping dendrites, and neighboring neurons often project to very different cortical areas.[23,267] The stream of ectopically placed cholinergic neurons in the hypothalamus mingle with basal forebrain cholinergic neurons rostrally and with dopaminergic cells of the substantia nigra caudally.[247,267] The dopaminergic cells of the compact part of the substantia nigra form a continuous sheet that extends through the basal midbrain tegmentum.[50] At the mesopontine juncture, the mesopontine cholinergic neurons merge with the caudalmost aspect of the substantia nigra,[271] and a few cholinergic somata are found within the substantia nigra.[78]

The chain continues. The mesopontine cholinergic neurons extend caudally to the rostral extent of the locus coeruleus.[271] Cholinergic and noradrenergic neurons overlap extensively in and around the locus coeruleus and subcoerulear area.[115] The more medially placed serotonergic raphe neurons intermingle with the cholinergic and noradrenergic neurons mentioned above, as well as with the cholinergic motor neurons of the cranial nerve nuclei.[36] Additionally, individual motor neurons within the spinal cord and medulla are interlinked to one another by cell bridges and extensive overlapping dendritic matrices.[221,267] Dendritic bundles link motor neurons at the correct positions to act as repositories for central pattern generation of motor programs.[221]

Dendritic bundles suggest, but of course they do not prove, that junctions exist between global neurons. Traditional synapses provide proof of contacts between global neurons. Small numbers of axodendritic contacts link adjacent global cells in many brain regions. Both cholinergic motor neurons and basal forebrain cells exhibit axonal arbors near their somata and dendrites.[220,226] Cholinergic synapses provide modest input to other cholinergic neurons throughout the CNS.[22,43,161] There also appear to be reciprocal connections between cholinergic and monoaminergic cell groups, and both contain high levels of acetylcholinesterase.[36,267,272]

Whether bundled dendrites or local synapses provide contact, integrated physiological activity occurs throughout the global network. Neighboring cells in the medial septal nucleus, for example, fire synchronously while producing hippocampal rhythms.[198] These clusters of synchronously firing cells measure less than 1 mm in the vertical direction.[198] Various cholinergic and monoaminergic cell groups work together to mediate many rhythmic activities, such as locomotion, respiration, mastication and sleep–wakefulness.[74] Locomotion, for example, involves the activation of particular motor neurons in particular temporal sequences.

The scarceness of contacts between global neurons has always raised doubt about the functional importance of these links. Weak links, however, may be critical for the rapid coupling and uncoupling of firing patterns. Global neurons can enter and exit phasic firing patterns with other neighboring or distant global neurons. Cross-correlograms of diaphragmatic and gastrocnemius muscle activities, for example, reveal coupling between the respiratory and locomotor firing rhythms when animals step in certain patterns, but not while walking slowly.[120]

Why might a continuous chain of linkages be important? Could distant global neurons entrain each other's firing rates through a cascade of interconnections? This does seem to happen, for example, during slow wave sleep. Phasic relationships exist between the slowing of the respiratory rhythm and the electroencephalogram (EEG) rhythm. Rhythmic patterns in the EEG are mediated by global neurons of the cholinergic basal forebrain and serotonergic raphe nuclei,[26,243,255] whereas the respiratory rhythm is expressed by motor neurons innervating the diaphragm.[120] Thus, a large number of global systems using different neurotransmitters show phasic relationships in this example.

Because of their anatomy, global neurons are well suited to analyse, integrate and possibly create patterns across independent channels of information gathered by the serial systems. Moreover, the state-dependent global neurons can incorporate the level of arousal into their actions.[265] The high degree of interdigitation between global neurons with one another may permit these systems to operate as a unified whole, integrating together the activities of individual neurons in space and time. Conversely, the serial pathways are perfectly arranged to relay different sensations independently, largely unaffected by previous sensory activity, and in an unbiased manner.

It could be argued that since global afferents affect serial neuron response, it is impossible to dissociate the two systems. The neurotransmitters associated with global cells do modulate the serial processing of sensory information.[8,64,121,162,209,231] However, as described more fully in Section 1.4, global modulators affect cortical cognitive potentials that continue long after responses to sensory stimuli are relayed to the cerebral cortex.

1.2. *Embryological origins and capacities for plasticity in the mature animal*

Neurotransmitter phenotype plasticity expressed by developing and adult neurons indicates that epigenetic, as well as genetic, influences govern which neurotransmitter is ultimately expressed by a neuron.[114] Thus, whether a neuron synthesizes a global or serial neurotransmitter partly depends on factors in the local environment. Serial and global systems are derived from two separable neural pools. Early in development the neural tube has two compartments, an alar and a basal plate, separated by the sulcus limitans.[137] Neural regions deriving from the alar plate include the sensory relay nuclei, thalamus, hypothalamus, cerebral cortex and hippocampus,[137] corresponding to the same regions in which a majority of neurons use small molecule amino acid neurotransmitters.[67,187] Neural regions containing cholinergic and monoaminergic neurons, such as the ventral horn of the spinal cord, mesopontine tegmentum, substantia nigra, neostriatum and basal forebrain, develop from the basal plate or from basally located neuroepithelial cells in the telencephalon.[90,134,137] When the cholinergic medial septal nucleus is separated from the hippocampus early in embryological development, cholinergic synthetic enzymes fail to appear in the hippocampus,[208] suggesting that there is a complete separateness between global and serial neurons at this early stage.

Dramatic axonal restructuring occurs in serial systems during the critical period of postnatal development.[143,280] Even at this early stage, plasticity depends on cholinergic and noradrenergic cortical afferents.[16,119] After development is complete, the capacity for plasticity decreases abruptly for serial neurons. Although some exceptions exist, there is a lifelong disparity between the plasticity exhibited by global axons and the majority of serial axons.

Cholinergic and monoaminergic neurons remain plastic and respond with dramatic axonal reorganization following injury in the adult brain.[25,69,149] Experimentally severed cholinergic axons are able to reinnervate denervated cortex and even restore normal laminar patterns.[69] Since global neurons comprise only a small percentage of all central neurons, their capacity for reinnervation does not contradict the long-standing observation that regeneration occurs infrequently in the mature CNS.[39]

Axons originating from serial neurons in the mature brain do not generally demonstrate the robust plasticity exhibited by global axons. Dorsal root ganglion cells, for example, have peripherally and centrally directed axons that use glutamate or other small molecule amino acid neurotransmitters.[15,217] The centrally directed axons normally are not plastic unless the glial environment of the CNS is altered.[55,84] Other central sensory pathways lack connectional plasticity in the adult as well.[143,280] Axons

originating from cortical pyramidal cells, which have been shown to be glutamatergic,[284] do not regenerate in response to axotomy.[252] These corticofugal neurons also do not show increased regeneration-associated growth-associated protein 43 when injured.[206]

Glutamatergic axons do not reorganize robustly in transplant studies either. Grafts composed largely of glutamatergic neurons extend processes only a short distance into host tissue, whereas grafts containing cholinergic and monoaminergic neurons fully innervate the host tissue.[180] Extensive reinnervation to grafted tissue occurs from host nuclei containing cholinergic and monoaminergic neurons, in contrast to minimal reinnervation from glutamatergic-rich cortical and thalamic sources of the host.[104]

Axonal regeneration is mediated by neurotrophic factors, such as nerve growth factor (NGF). Global neurons retain or increase neurotrophic factor sensitivity in the adult, in marked contrast to the majority of serial neurons, which generally decrease their sensitivity to neurotrophic factors in the adult CNS (see Table 1). Cholinergic neurons in the basal forebrain and striatum, for example, are among the few central populations that demonstrate receptors for NGF in the adult.[218,276] NGF induces morphological alterations in injured basal forebrain cells and in uninjured striatal cells.[68,86,94] Developmental studies have shown that NGF receptor mRNA increases in basal forebrain cells during postnatal maturation.[32,147] Developing, as well as mature, basal forebrain neurons also respond to basic fibroblast growth factor (bFGF) and insulin-like growth factors.[7,125,189]

Serial neurons, such as those in the primary sensory ganglia, express their highest levels of NGF receptor during fetal and early postnatal development. After the developmental period, these sensory neurons decrease or lose their sensitivity to NGF or brain-derived neurotrophic factor (BDNF).[32,112,147,210,282] Serial neurons in the cortex show a similar profile. Neurotrophin-3 and bFGF, for example, regulate early neurogenesis of cortical neurons but do not affect their survival after that stage of development under normal conditions.[76]

NGF, BDNF and neurotrophin-3 stimulate cholinergic basal forebrain neurons while having no effects on GABAergic neurons.[127] This selectivity is perhaps less in the mesencephalon, where BDNF, neurotrophin-3 and neurotrophin-4/5 have greater effects on dopaminergic cells, but also affect GABAergic cells.[102] However, the cells in the latter study were derived from embryonic tissue containing the substantia nigra, so they may have been too immature to show dramatic differences.

Perhaps the most striking difference is that, unlike serial axons in the adult, mature axons deriving from global neurons can regenerate or sprout under the influence of neurotrophic molecules like NGF, BDNF or neurotrophin-3.[68,256] This suggests that global neurons could reorganize their presynaptic elements as a function of experience or learning. Thus, rather than merely strengthening or weakening pre-existing synapses according to an early proposal by Tanzi[248], the capacity of global afferent axons to rearrange their synaptic ensembles could produce more dramatic synaptic reorganization, as suggested by many modern memory theorists.[80,236]

1.3. *Activity dependence of global neurons*

Electrical activation of cholinergic and monoaminergic cells is required for the synthesis of choline acetyltransferase (ChAT), tyrosine hydroxylase and dopamine-β-hydroxylase.[31,250] The synthesis of ChAT in cells cultured from the spinal cord depends on electrical activity, which enables the uptake of the necessary neurotrophic factors.[31] Target cell activity is an important variable. The activity of target neurons controls the levels of NGF and BDNF available to cholinergic septal neurons.[286] Afferent contacts are also important. Cell membrane contacts must be present on cholinergic cells before they will begin to manufacture ChAT.[2] Global neurons appear to provide each other with the necessary pattern of activation. The expression of ChAT in basal forebrain neurons, for example, is markedly decreased following the interruption of cholinergic innervation from mesopontine cholinergic cells.[183]

Dependence on sustained activation to maintain protein synthesis and neural survival seems to be uniquely exhibited by global neurons. In contrast to cholinergic cells, GABAergic neurons in the same tissue culture conditions do not degenerate or decrease their synthesis of glutamate decarboxylase in the absence of activation.[31] Mature serial sensory pathways do not appear to be activity dependent, because cortical function eventually recovers following the removal of sensory inputs in adults. Recovery in the visual cortex is not dependent on reorganization in the thalamus or in the thalamocortical pathway; however, lateral sprouting of cortical interneurons has been suggested.[53] Cholinergic afferents are possible participants in functional recovery. Receptive fields in the auditory cortex, for example, are altered by experience and this process is modulated by cholinergic afferents.[8,13,162]

Neurotrophic dependence exhibited by global cells seems to mandate their continuous activation throughout life. Accordingly, global neurons fire regularly and appear to activate one another to fill voids in incoming activity. This autonomous ability to balance activity is defined here as the ''balance principle''.

The balance principle is a key characteristic of all global systems and is illustrated by firing pattern changes during stages of sleep and wakefulness. For example, cholinergic basal forebrain neurons fire at

low to moderate rates during slow wave sleep.[245,246] During wakefulness and dream sleep, however, some cholinergic basal forebrain neurons increase their firing rates while others are inhibited.[245,246] Thus, the total amount of activity generated by the system does not vary much across states. What varies is the distribution of that activity.

According to the balance principle, global cells must transform incoming patterns of serial information into distributed activity that falls within the permissible limits. Whenever heightened arousal increases firing in one part of the system, another part of the system must be inhibited. As a result, singular gestalts are created that incorporate the context, mood state and level of general arousal. The brain's capacity to restructure global axons further provides a mechanism to permanently encode these integrated relationships.

1.4. *Neurophysiological computational styles of serial and global neurons*

There are special physiological characteristics of global cells that accompany their activity dependence. To unequivocally assess the unique physiological properties of global and serial neurons, these neural types need to be completely separated from each other. Completely isolated serial structures, such as the cerebral cortex, hippocampus or olfactory bulb, exhibit a period of afterdischarges and then go silent in the absence of global inputs.[34,72,128] It has been proposed that the thalamus is the pacemaker of the cortex, but thalamic neurons seem to lack intrinsic pacemaker qualities.[37]

In contrast, cholinergic and monoaminergic cells demonstrate rhythmic pacemaker-like activity when isolated from their afferents, such as *in vitro* or in tissue slice preparations.[33,82,142,153,171,264] Cholinomimetics reinstate rhythmic and pacemaker firing patterns abolished in isolated hippocampal slices.[128] Similarly, the application of norepinephrine or serotonin elicits rhythmic firing of deafferented neurons in the spinal cord.[140,283] Cholinergic or noradrenergic stimulation also interrupts slow cortical rhythms and replaces them with fast activity.[241] Thus, fast activity and slow rhythms depend on these global modulators.

Among the mechanisms proposed that enable cholinergic and monoaminergic cells to produce spontaneous rhythmic activity, a Ca^{2+}-activated Na^{+} current triggered by a long-lasting afterhyperpolarization has been suggested.[142] Mesopontine cholinergic neurons and dorsal raphe serotonergic neurons demonstrate a low-threshold Ca^{2+} conductance that produces firing in repetitive bursts.[33,264] The summation of weak, but widespread, cross-connections between global cells,[267] along with additional afferent input from multiple unrelated sensory modalities,[10,19,222] may collectively contribute to the pacemaker-like activity exhibited by global cells *in vivo* (see Ref. 225).

If both fast and slow cortical activities depend on global modulators, how can we assess the separate contributions of serial and global pathways in whole brain responses? One way is to take advantage of the fact that serial pathway neurotransmitters such as glutamate and aspartate act more quickly than global neurotransmitters such as acetylcholine and the monoamines.[35] Evoked potentials show that sensory information is relayed through serial circuits earlier than global processing of that same information. Auditory information reaches the feline thalamus within 5–10 ms following stimulus presentation. However, as reflected in the P1 wave, activation of mesopontine cholinergic neurons occurs substantially later, in the 17–25 ms range.[93,277]

Similarly, the P3 event-related potential does not occur until 200–600 ms after stimulus presentation, whereas the same stimulus activates the cortex within approximately 25 ms. The P3 potential is associated with information processing, sensory discrimination and short-term memory.[63,238] This evoked potential critically depends on the cholinergic septohippocampal pathway.[92] Synaptic activation by acetylcholine occurs much earlier than 200–600 ms, so the time course of P3 may correspond to the time it takes for activity to cycle through multiply interlinked global neurons.

The time interval of the P3 cognitive potential is roughly equivalent to the burst cycles of global cells. Basal forebrain and mesopontine cholinergic cells exhibit basic firing cycles of 200–700 ms and a wide range of firing frequencies (0.3–18 Hz) which reflect complex sleep–wakefulness states.[61,66,135,136,198,242,246] Monoaminergic cells also exhibit regular firing patterns of about 1–7 Hz that fluctuate with sleep–wakefulness, but demonstrate less variability in firing rates within each state.[9,129,229]

Stimulation from various sensory pathways alters the firing rates of global cells.[10,19,129,222] Within each burst cycle, there is summation of activity across multiple sensory channels. Since the firing rate reflects the inputs over the burst interval, a global cell inherently exhibits a kind of memory that lasts for the length of the burst cycle. This is a possible basis for the transient sensory memory. When visual information is scanned very quickly, subjects can later recall information limited to the 200–500 ms following stimulus presentation.[205] Subjects remember little, if any, of this information a short time later.[234] The time interval of this visual sensory or ''iconic'' memory matches that of the burst cycles of global neurons. Thus, in iconic memory, the global neuron's memory may be reduced to its bare essence due to inattention, distraction or other causes. Echoic memory is slightly

longer (approximately 2 s), suggesting that it may last for more than one burst cycle or that the cycle length can be extended to digest more complex information. That global neurons sometimes fire at 0.3 Hz suggests that cycles may occasionally last up to 3 s.

The next question that arises is whether the aggregate of global neurons can utilize this basic property, expand on it and apply it to other types of memory. The following section presents a hypothetical model addressing this question.

2. THE HYPOTHESIS: NEURAL REPRESENTATIONS ARE FORMED BY GLOBAL AFFERENT REORGANIZATION ON SERIAL NEURON ENSEMBLES

I present here three neural mechanisms—potentiation, degradation and rigidification—postulated to permanently encode memory in the form of enhanced signal-to-noise ratios of response (Fig. 2). After augmenting memory encoding, the global systems are ready to participate in retrieval processes. The precise mechanisms described here are offered as one scenario of how global and serial neurons might interact. The diverse CNS probably uses any number of mechanisms. The present hypothesis is presented in steps that might be compared to the progression from working to reference memory.

2.1. *The first step in memory encoding: global afferents potentiate serial neuron responses*

It is generally agreed that altered synaptic efficiency is one potential memory mechanism. Facilitation or inhibition occurs when global neurotransmitters are released or applied with serial neurotransmitters or with sensory input. The iontophoretic application of both acetylcholine and an *N*-methyl-D-aspartate (NMDA) glutamate agonist, for example, potentiates responses in hippocampal cells.[152] Iontophoretic application of glutamate paired with stimulation of the cholinergic basal forebrain enhances responses in cortical cells.[253] Cholinergic actions dramatically facilitate or suppress sensory stimulus-evoked responses in many types of cortex.[64,163,175,230] All these modulatory actions only occur when acetylcholine or cholinomimetics are applied at the same time as the sensory inputs are stimulated. Since stimulus-specific information is relayed by thalamocortical inputs using the neurotransmitter glutamate,[118,188] interactions between cholinergic and glutamatergic mechanisms are involved.

Long-lasting changes in electrophysiological responses, such as long-term potentiation (LTP) and long-term depression (LTD), are models of short-term or working memory.[186,235,249] LTP was initially discovered following the artificial stimulation of whole afferent fiber bundles, which caused widespread and synchronous activation of hippocampal neurons.[27] These kinds of long-lasting response patterns are induced by global systems. A significant portion of cortical neurons shows long-lasting (5 min) potentiation by the co-application of acetylcholine and glutamate, and occasionally this potentiation lasts as long as 1 h.[165] Cholinergic stimulation regulates population spike amplitudes according to their endogenous oscillatory cycles, and thereby produces LTP.[101] Not only acetylcholine, but also the 5-Hz oscillatory cycles produced by cholinergic simulation modulate LTP.[101,138] Norepinephrine also selectively induces LTP and LTD in hippocampal slice preparations.[48] Rather than actually producing potentiation, global afferents seem to coordinate the electrical activity across an expanse of cortical circuitry, thereby enabling sustained responses such as LTP and LTD.

The viability of LTP and LTD as memory models is partially supported by the occurrence of potentiated population spike amplitudes of dentate gyrus cells following several types of training.[213,233,262] Enhanced and suppressed firing rates of cortical cells accompany the slow potentials recorded during conditioning, and these effects critically rely on cholinergic afferents.[201] Thus, synchronously firing global neurons produce population spike amplitude alterations during actual learning.

A number of intercellular molecules appear to underlie both LTP and learning. Protein kinase C (PKC) is a prominent example. LTP induced in hippocampal slices depends on the translocation of PKC to the membrane and its subsequent activation.[3,145] During LTP, PKC enhances NMDA currents.[20] Classical conditioning also increases PKC activity in the hippocampus of intact animals.[185] The γ isoform of PKC is preferentially found in cholinoceptive cells,[259] and it may mediate the potentiated cortical responses that rely on cholinergic inputs in intact learning organisms.

Let us consider the hypothetical situation where interactions between the stimulus, the context and the mental state increase acetylcholine release. A concomitant increase in glutamate release is anticipated through the modulation of sensory relays. As schematically diagrammed in Fig. 2A, coordinate increases in glutamate receptor activity and muscarinic cholinoceptors could lead to potentiation. Since glutamate activates both NMDA and non-NMDA glutamate receptors,[116] there are a number of ways glutamate might increase a signal transduction molecule such as PKC. There are direct effects[5] and effects caused by inward Ca^{2+} currents.[151] The muscarinic receptor G-protein complex also activates PKC.[179]

PKC-induced potentiation is correlated with structural alterations of the postsynaptic density.[29,30] The postsynaptic site contains microtubule-associated protein 2 (MAP-2),[168] which is dephosphorylated by NMDA activation,[88] leaving it free to bind with actin and tubulin in the post-

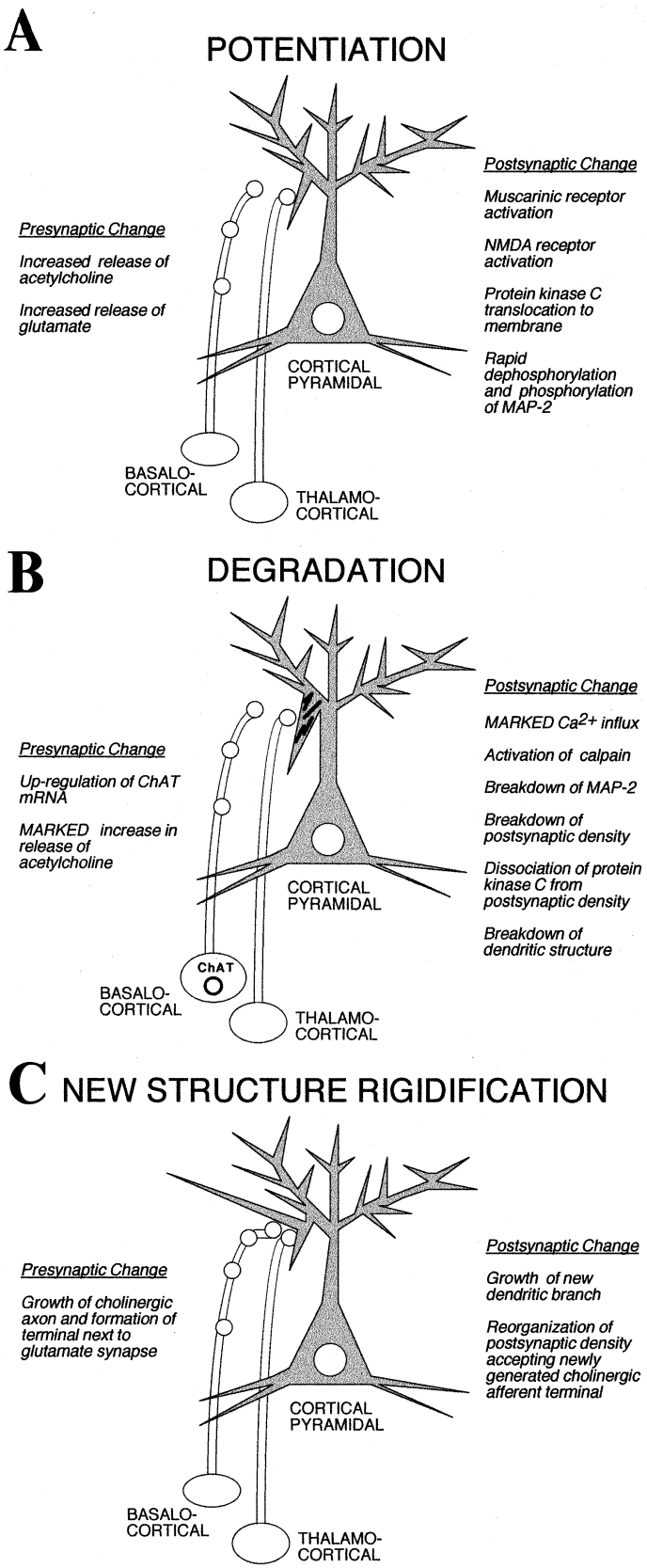

Fig. 2. Potentiation, degradation, new growth and rigidification are proposed to occur sequentially during memory encoding, as exemplified in the cerebral cortex. See text for details.

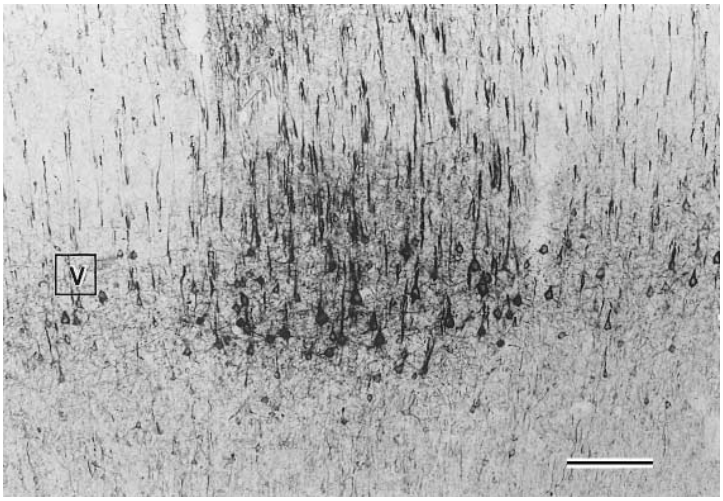

Fig. 3. Immunohistochemistry for MAP-2 in and around layer V in a module of the parietal cortex is enhanced above that detected in flanking adjacent modules. Scale bar = 100 μm. Enhanced staining for MAP-2 of this type, along with increased proteolytic products of the intact protein, occurs in the temporal cortex following Pavlovian conditioning to tone.[279]

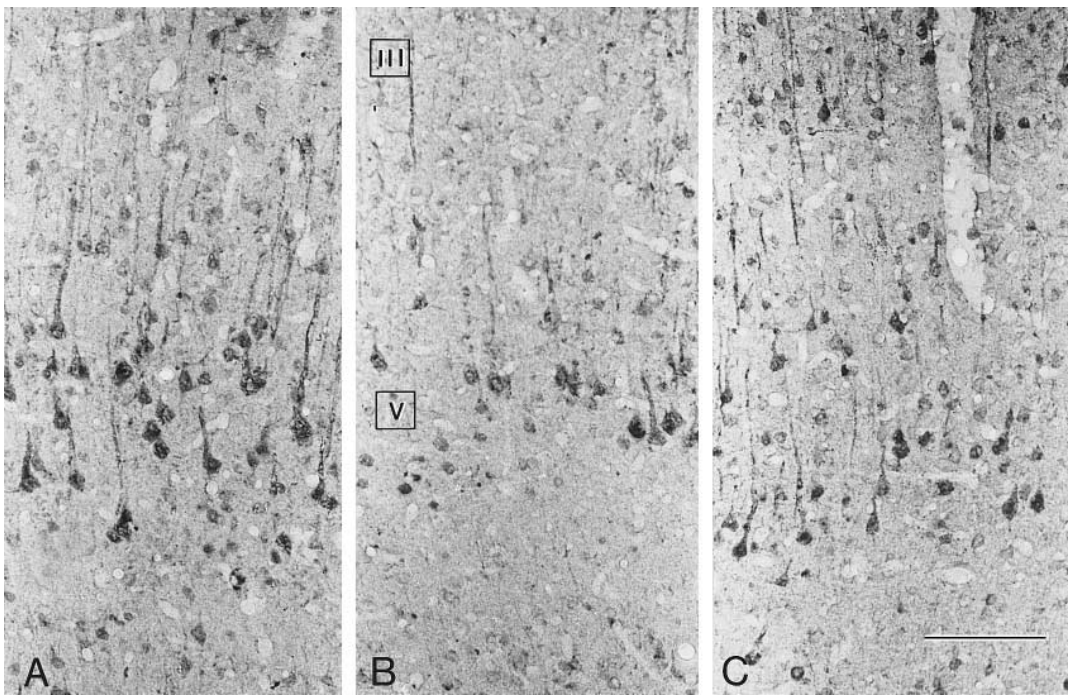

Fig. 4. Immunoreactivity for the γ isoform of PKC is selectively increased in the auditory cortex (Te3) with training.[278] (A) Rats were trained to a 2-kHz tone followed immediately by a 1-s, 1-mA foot shock. (B) Animals received the same tone and foot shock unpaired. (C) Animals received only tone. Scale bar = 100 μm.

synaptic density, potentially stabilizing any structural changes.[109,168] Neural–cell adhesion molecule and amyloid precursor protein, which are increased by LTP, may also be critical to morphological modifications in learning.[70]

PKC and other Ca^{2+}-dependent kinases also phosphorylate MAP-2.[109,223] Cholinoceptive cells in the cerebral cortex and hippocampus selectively possess a somatodendritic enrichment of cytoskeletal proteins,[269] especially MAP-2 (see Fig. 3). PKC is found in the same cortical cells (see Fig. 4), and it is also altered with Pavlovian conditioning.[278]

Phosphorylation of MAP-2 decreases its ability to stabilize structural proteins.[281] Kinase-mediated phosphorylation of MAP-2 would counteract NMDA-activated dephosphorylation, thereby limiting structural modifications of the postsynaptic density. PKC also inactivates the muscarinic acetyl-

choline receptor,[144] possibly limiting the participation of the postsynaptic cholinoceptor in LTP or population spike amplification.

2.2. *The second step in memory encoding: degradation of the existing structure*

Although LTP and LTD are relatively long-lasting, permanent memory storage arguably requires more extensive structural changes than those limited to the postsynaptic density. Degradation of the existing structure, however, is necessary for more dramatic structural change. Moreover, degradation *in vivo* probably halts kinase-mediated potentiation, suggesting that potentiation and degradation are two separate steps. Increased immunostaining for PKC (see Fig. 4) may be a sign of learning-related breakdown. Breakdown of PKC and its translocation away from the postsynaptic density would interrupt potentiation.

Structural degradation appears to be essential for memory encoding, as memory is disrupted by inhibitors of the Ca^{2+}-activated protease, calpain.[148] Calpain degrades cytoskeletal proteins, being especially effective on MAP-2.[110,111] MAP-2 is of particular interest, because we have shown that Pavlovian conditioning is correlated with its degradation.[279]

As indicated by increased MAP-2 immunohistochemical staining and proteolytic products, signs of structural change are evident in all cholinoceptive cells throughout an affected cortical module.[269,279] These altered modules measure 1–2 mm^2, indicating a correspondence with the extents of cholinergic afferent fiber terminations.[23] Based on this correspondence, could presynaptic changes in cholinergic afferents serve as a catalyst for postsynaptic change? Possibly, they could under some circumstances. Cholinergic afferents appear to regulate alterations in MAP-2.[269] Moreover, MAP-2 is changed in the hippocampus according to a spatial and temporal pattern which corresponds with that of cholinergic terminal sprouting.[133,149] These simultaneous occurrences of cholinergic sprouting and possible postsynaptic density reorganization in response to injury may reflect the pattern of cholinergic synapse reorganization that occurs during learning.

What might be the trigger for degradation? If cholinergic afferents do play a role, then one possibility is that prolonged and elevated acetylcholine release amplifies Ca^{2+} influx and that activates calpain. Long-term increases in acetylcholine are produced by the up-regulation of ChAT mRNA regulated through neurotrophic factors.[215] We have found ChAT mRNA increases in cholinergic cells projecting to the auditory cortex in tone conditioning at the same time that MAP-2 degradation occurs.[182]

An attractive aside of this postulated scenario is that degradation could be restricted to those dendritic segments containing potentiated synapses. Typically, Ca^{2+} influxes extend 1–2 μm along the dendritic segment or are localized to individual spines.[85,176] Cholinergic actions amplify these Ca^{2+} influxes.[177] This kind of amplification produced by acetylcholine could very possibly induce selective degradation at key contact sites (see Fig. 2B).

2.3. *The third step in memory encoding: new structure rigidification*

Excess MAP-2 is normally available throughout the dendritic cytoplasm, where it maintains polymerization of tubulin in microtubules and suppresses neurite side-branching.[154] Calpain-mediated degradation of MAP-2, along with degradation of other susceptible cytoskeletal proteins, disrupts the old dendritic structure. Following the breakdown of MAP-2 and its linkages with tubulin, *de novo* dendritic side-branching is facilitated (Fig. 2C). Spine elaboration is enabled after the breakdown of MAP-2 and its linkages with actin.

Whereas altered presynaptic neurotransmitter release may or may not participate in potentiation and degradation, it seems imperative that presynaptic reorganization occurs if whole dendritic branches are being formed or remodeled. It seems unlikely that these new postsynaptic structures would be devoid of inputs. Neurotrophic factors may play roles in new growth of both presynaptic and postsynaptic elements. Neurotrophic factors, as well as monoaminergic neurotransmitters, increase intercellular cyclic AMP and stimulate neurite extension.[75,83] Varicosities releasing acetylcholine, for example, increase in both denervated and non-denervated regions of the cerebral cortex under the influence of NGF.[68]

As the structural changes become rigidified, further degradation must be halted (Fig. 2C). Cyclic AMP-dependent kinase phosphorylates MAP-2 at sites that prevent its degradation by calpain,[108] thereby possibly contributing to rigidification. The morphological changes themselves might contribute to rigidification. Spine elongation, for example, isolates receptors located on spine heads further away from the dendritic shaft. MAP-2 is less susceptible to proteolysis by calpain when it is not bound to microtubules.[110] Thus, the mobilization of receptor ensembles away from the microtubules in the dendritic shaft might prevent further degradation.

The current treatise proposes that global afferents reorganize their presynaptic synapses or release sites and that the structure of the postsynaptic serial neuron ensemble is altered. The new structure is called a ''neural representation'' and it is defined by a number of major characteristics. (1) Synaptic changes may be few or many; however, it is mandated that key global synapses throughout the serial neuron ensemble occur, thereby changing its overall response. (2) These changes must effectively alter the signal-to-noise response to a particular stimulus with reference to the mood and EEG state of the subject during learning and to the context in which the

stimulus occurred. (3) The overall activity resulting from the key structural changes should also alter the likelihood of subsequent patterns of activity arising in other serial neuron ensembles.

Computer modeling of pyramidal cell responses due to spine change give some clues to what could be achieved by synaptic reorganization on pyramidal neurons (see Ref. 107). Spine elaboration generally diminishes the electrophysiological response of that synapse in the future. However, coincident activation of key spinous synapses dramatically enhances responses, due to the increased temporal summation afforded.[107] In other words, response is enhanced only to a precise set of inputs, otherwise it is unaffected or inhibited. This type of situation would enable serial ensemble responses sculpted by global afferents to become active only in the appropriate context and state. Theoretically, many neural representations may be stored in each module of cortex or subcortical locus.

2.4. *Events following encoding: retrieval from memory*

Following its construction, the activation of a neural representation by key global–serial synaptic ensembles produces a reasonable model for recognition and recall, the distinction between which may be attributable to control processes over essentially the same fundamental memory process.[12] (For alternative view, see Ref. 124.) Regardless of possible inherent differences, the participation of global systems is consistent with evidence that cholinergic basal forebrain neurons mediate attentional focusing.[65,174,261] An essential component of attentional focusing is that the enhancement or inhibition is selective and increases the signal-to-noise ratio of the response. Acetylcholine applied to the visual cortex increases the signal-to-noise ratio in response to visual stimuli.[230] Signal-to-noise ratio changes produced by cholinergic and monoaminergic neurons are useful models of signal detection and associative memory.[95,227]

Global systems can focus attention and ''bring to mind'' information stored in various cortical regions. Activation of the nucleus basalis causes cortical neurons to shift from phasic firing rates of 1–5 Hz to tonic firing rates of 20–40 Hz.[164] Cortical activity in the 40-Hz range corresponds with visual recognition and focused arousal.[79,228] Phase-locked oscillations near 40 Hz in different cortical areas may enable various perceptual features to ''come to mind'' simultaneously.[60,113] Because even distant global neurons rapidly couple and uncouple, cortical phase-locking mediated by these global systems should be flexible and the overview of phasic coupling should be storable in memory.

Would facilitated responses corresponding with recognition activate reverberating circuits? Probably they would not. Event-related potentials corresponding with recognition become larger with familiarization, finally culminating in cognitive closure.[87] In other words, once we recognize an object we stop analysing it. According to the balance principle, we would expect neural regions enhanced during recognition or retrieval to be countered with inhibition or depotentiation afterwards.

Serial cell discharges do dramatically shift the firing rates of global cells. For example, hippocampal cell discharge can turn septohippocampal cell firing from a theta-on to a theta-off mode.[42] In this manner, the hippocampus can uncouple the firing patterns of global neurons in the septum. In turn, the global cells of the septohippocampal pathway can attenuate LTP and facilitate LTD in the hippocampus.[192] Theta frequency stimulation of the hippocampus reverses LTP to a depotentiated state.[139]

A number of mechanisms exist to shut off highly activated global neurons. High rates of tonic firing increase the release of acetylcholine in the cortex as much as two- to four-fold.[204] Acetylcholine inhibits its own release by an autoinhibitory mechanism.[71] Other intracellular mechanisms provide short-term control over acetylcholine synthesis,[254] which could contribute to potentiation–depotentiation shifts.

2.5. *When memory encoding takes longer: extending the period of consolidation*

The time taken for consolidation of working memory into reference memory varies from seconds to days based on memory disruption induced by electroconvulsive shock.[235,237] In tissue slice preparations, LTP can last for hours or days, as can potentiated population spikes in variously trained animals.[249]

Eventually, the cellular mechanisms supporting potentiation become exhausted. As evidenced in the tissue slice preparation, a decreased ability to synthesize PKC occurs within three days.[159] If exhaustion occurs before degradation is triggered, then recurrent bouts of potentiation could extend short-term storage beyond the point of exhaustion. Since neurons throughout a serial ensemble will simultaneously reach the same level of exhaustion, recovery later should likewise be simultaneous. Cues such as the same mood, EEG state or the context affiliated with the stimulus would influence this recurrence. The recurrence of potentiation provides a plausible short-term memory devise that would enable behaving organisms to divert attention away from one learning situation to focus on another.

As originally proposed by Hebb,[97] consolidation of particular kinds of memory may occur following the passage of a certain amount of time, largely independent of intervening events. If, for example, a neural representation cannot be encoding initially, recurrent bouts of potentiation may gradually move synapses closer to the trigger for degradation. This process would be time dependent, and the time

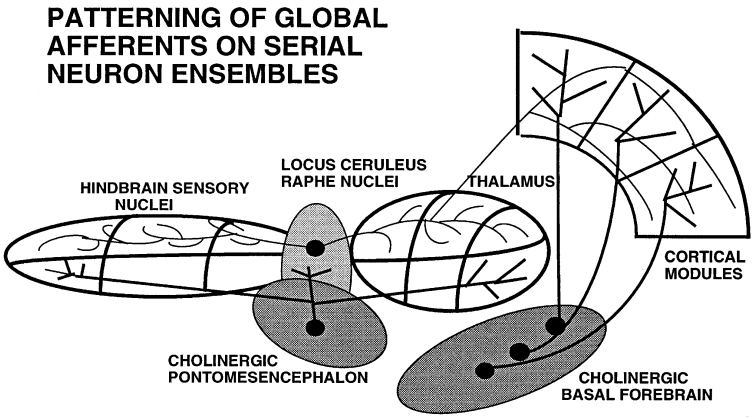

Fig. 5. Each set of global neurons has a distinct anatomical relationship with its serial targets. Monoaminergic neurons in the locus coeruleus and raphe nuclei project diffusely with single axons traversing multiple cortical and thalamic regions. Single monoaminergic neurons have descending and ascending collaterals. Mesopontine cholinergic neurons have slightly more restricted terminations, with collateral branching from individual cells limited to a few thalamic or hindbrain nuclei. Cholinergic basal forebrain neurons are the most selective; each neuron innervates a cortical expanse roughly equivalent to a module.

needed would depend on the initial distance between synapses.

Rehearsal provides a mechanism that sustains human memory for numbers or words beyond the suggested span for short-term memory of under 20 s.[178,197] Rehearsal is not practiced by experimental animals, however, and arguably is not essential for the consolidation of human memory. Interpreted within the present scheme, rehearsal most likely reflects a control mechanism,[12] in which subjects are invoking recurring bouts of potentiation.

Besides serving as a repository for ongoing working memory, recurring bouts of potentiation (or depotentiation) in global–serial circuits would also provide another source of autonomous activation for these activity-dependent global neurons. Serial inputs are erratic and do not provide a constant level of activation to each global cell. Lack of serial input can occur for a variety of reasons (e.g., sensory deprivation, sleep). The interlinkages between global cells seem capable of balancing activity regardless of serial input. Prompted by the balance principle (defined in Section 1.3), memory devises may have evolved to serve the more primary purpose of circulating adequate activity to ensure neurotrophic factor uptake and long-term cell survival.

3. CRITICAL EVALUATION OF THE HYPOTHETICAL MODEL AND ITS IMPLICATIONS FOR DIFFERENT TYPES OF LEARNING AND COGNITION

These last sections evaluate the present hypothesis in relation to experimental results in behaving animals and to neuropsychological studies of human subjects. The presently proposed mechanisms are evaluated in the context of the various contributions made by global afferents affecting serial neurons in different brain regions. As illustrated in Fig. 5, the global neurons orchestrate enhanced activation of serial neuron ensembles within the limits of their terminal field distributions. The following sections are presented in order of ascending CNS levels and the various functions performed in these structures.

3.1. *Global–serial interactions at subcortical sites*

3.1.1. *Integration of sensory stimuli with general arousal*. The basic functions of the brainstem include regulating sleep–wakefulness, general arousal, relaying sensory information and controlling vital functions. It is the mesopontine cholinergic cells, the serotonergic raphe nuclei and the noradrenergic locus coeruleus that mediate overall arousal and attention.[11,41,66,117,244] Sensory information bound for forebrain structures initially contacts global neurons in the brainstem. These global neurons sample multimodal information through long dendritic branches extended into different sensory pathways.[93,272] These diverse sensory inputs produce unitary responses lasting 50–500 ms. Global neurons show both augmented and suppressed responses.[19,129,229]

By these means, states of arousal, mood and context are all reflected in the activity of brainstem global neurons. Since brainstem global neurons mediate cortical activation as one of their primary functions, the level of arousal is inherently a part of all global cell operations. The many modalities of serial input are integrated with overall EEG activity.[11,19,129,150,229] Monoaminergic global neurons probably regulate mood, although this common assumption is based more on clinical responsiveness than on experimental studies. Also, the overall context is sensed through multimodal sensory input to brainstem global neurons. These primary assessments of the overall context are then relayed to forebrain global systems.

Attention is an important component of learning and what will receive attention is initially determined by brainstem global neurons. Brainstem global neuron responses reflect stimulus intensity and stimulus novelty (because of adaptation), as well as relationships with primary drive states encoded within visceral circuits in the brainstem. Since many of the effects of brainstem activity are seen at the cortical level, the projections involved are important. Mesopontine cholinergic neurons contribute to cortical activation partly through their effects on thalamocortical neurons.[241] Acetylcholine applied to the lateral geniculate nucleus enhances visual stimulus-specific responses.[231] Axon collaterals of mesopontine cholinergic neurons also terminate on the cholinergic basal forebrain in a topographical pattern,[271,277] and release acetylcholine in that forebrain structure.[44] By these dual paths, mesopontine cholinergic neurons affect the activity of the cortex. A third path is where mesopontine cells project on to sensory nuclei in the brainstem.[272] Attentional activation of the cochlear nucleus[98] is a probable example of these pathways in action.

We know that an active EEG typifies the alert awake state, whereas a less active EEG is the hallmark of slow wave sleep.[170] With an active EEG, some mesopontine and basal forebrain cholinergic neurons are markedly facilitated, while many others are inhibited.[66,245] The same is true of putative monoaminergic neurons.[9,229] Thus, a combination of activated and inhibited global neurons activates the cortex. Stimulation of the basal forebrain can also activate the EEG[18] and increase the release of acetylcholine in the cortex.[40] When the EEG is active, attention quickly shifts from item to item. The active cortex is like a chaotic attractor,[232] in which selective attention can focus on virtually any locus. Even though basal forebrain global neurons are ultimately responsible for selectively focused attention, we can conclude that the global neurons of the brainstem contribute to the overall degree to which attention can be focused.

3.1.2. *Modulation of motor programs and conditioned autonomic responses*. Many kinds of learning are a result of subcortical modifications. Global neurons involved in subcortical learning include the mesopontine cholinergic neurons innervating the brainstem, thalamus, basal ganglia and basal forebrain.[271,272] The serotonergic, noradrenergic and dopaminergic neurons innervating numerous subcortical regions are also involved.[49,239]

Behavioral responses depend on circuits between global neurons in the brainstem and the cerebellum or basal ganglia. The classically conditioned eyeblink response in rabbits is one such example. Acquisition of this conditioned response is not affected by decerebration but is abolished by lesions to the deep cerebellar nuclei.[155,157] The deep cerebellar nuclei receive a strong cholinergic projection from mesopontine cholinergic neurons,[272] and the deep cerebellar nuclei project directly on cholinergic neurons in the mesopontine region.[96] These cholinergic neurons may participate in the encoding of this learned response.

The learning of motor programs is clearly affected by global afferents from the dopaminergic cells of the substantia nigra.[123] Adaptive responses of striatal neurons are acquired and expressed in a context-dependent manner. Dopamine cells in the substantia nigra are essential to this process.

Modifying simple reflexes, such as the acoustic startle,[56] involves global neurons in the brainstem. Mesopontine cholinergic neurons, for example, show adaptation with the acoustic startle response when pre-exposed to a stimulus 100 ms prior to a conditioning stimulus.[126] The global neurotransmitter dopamine also modulates the startle response.[38] Cholinergic afferents to the locus coeruleus modulate the vestibulospinal reflex.[14] Norepinephrine is critical to the acquisition and expression of cardiac bradycardia.[91]

Many visceral reflexes alter hormonal release. Peripherally circulating hormones are also regulated by global neurotransmitters. For example, dense noradrenergic inputs to the hypothalamus[49] control autonomic responses and affect hormone release. Peripheral levels of epinephrine, in turn, modulate CNS cholinergic mechanisms contributing to memory storage.[158] These effects are mediated by an adrenergic activation of the locus coeruleus.[1]

The results reviewed here are compatible with the hypothesis presented in Section 2, although none of the studies address it directly. This could be because the hypothesis is based mainly on data from the neocortex. Critical comparisons at subcortical levels are important, however, as it is not possible to understand cortical function without an understanding of the actions of brainstem global neurons. Global neurons in the brainstem are profound in their ability to integrate arousal, mood and context with a particular stimulus.

3.2. *Global–serial interactions in the sensory cortex*

3.2.1. *Identification of the cells showing structural change*. Structural changes in cortical cells accompany many kinds of learning, in agreement with the current hypothetical proposal. Increased dendritic branching occurs with classical conditioning, maze learning, acquisition of sensorimotor function and, not surprisingly, with advanced education.[81,105,214,240] Apical dendrites of pyramidal cells (layers II/III and V) and basilar dendrites (pyramidal cells in layers II/III) change depending on the type of learning. Changes in spine density and spine shape also accompany learning.[194]

Many of the molecules underlying structural change selectively enrich cholinoceptive cortical cells.[269,273] Many of the cholinoceptive cells in the

cortex are pyramidal cells in layers II/III and V.[269] These are the same cell populations that show dendritic branch changes with learning.

The preferential consideration of cholinoceptive cortical cells also seems appropriate given the results of electrophysiological studies in behaving animals. Cortical conditional responses nearly always occur in cells that respond to acetylcholine.[160,207] Muscarinic receptor binding increases in particular cortical regions with discriminative learning.[260] Changes in cholinergic presynaptic elements also occur with learning. For example, maze learning following priming induces increases in acetylcholine synthesis.[193] Also, cells projecting to the auditory cortex show signs of increased ChAT synthesis with Pavlovian conditioning to tone.[182]

Conditional responses and receptive field properties in somatosensory cortices are manipulated by cholinergic transmission.[57,165] The same is true for cholinergic stimulation of the auditory cortex, and here cholinergic stimulation alters receptive field properties in a manner that depends on recent experience and the context of the stimulus.[8,163] Like many other global actions, these cholinergic effects are too complex and prolonged to be due to the synaptic action of acetylcholine alone, as the neurotransmitter is rapidly degraded by acetylcholinesterase.[46] Global neuron integrations, such as those hypothesized earlier, could account for these results.

Although the auditory cortex is not essential for acquiring conditional responses to tone stimuli,[211] it becomes essential if the animal is required to discriminate or identify the tone.[106] Since qualitative changes in auditory receptive field properties commonly occur with tone conditioning,[13] synaptic changes are likely to enhance responses to the signal and inhibit responses to competing stimuli. The synaptic changes proposed in this paper would do exactly that.

3.2.2. *The modular extent of structural change*. The cortical module was originally defined measuring approximately 1 mm^2 by Mountcastle[173]. The chemical neuroanatomy of the cortical module is fundamental to evaluating learning-related neural changes in cholinoceptive cells. Cholinergic afferent terminal fields not only match the modular dimension of learning-related change, they are also the only cortical fibers that match (see Fig. 5). Although many large pyramidal cells in the prefrontal cortex also receive dopaminergic input,[77] monoaminergic fibers are not confined to individual cortical areas. Individual axons releasing dopamine, norepinephrine or serotonin distribute terminals to large expanses of cortex or hippocampus,[24,203] overextending individual cortical modules capable of learning-induced change. The role that monoaminergic terminals in the cortex play in learning may be more general, for example, regulating the overall level of arousal.[11]

Vertically oriented circuits dominate cortical modules,[146] although horizontal connections also exist. The pyramidal and stellate cells primarily use the fast-acting neurotransmitter glutamate, and local inhibitory neurons use the neurotransmitter GABA.[45,67,118] Cholinoceptive cells comprise only 15% of neocortical cells, consisting of many layer V pyramidal cells, a number of pyramidal cells in layers II/III and occasional non-pyramidal cells in layers II–VI.[258,269] GABAergic interneurons and layer V pyramidal cells are frequently contacted by the same cholinergic axon. This dual cholinergic innervation induces temporally sequenced responses in the pyramidal cell, consisting of rapid inhibition followed by a prolonged facilitation.[156,175] The deep pyramidal cells from all parts of the cortex send axons through dendritic fields of the cholinergic basal forebrain.[141,216,267] Pyramidal cells in layers II/III typically supply glutamatergic corticocortical circuits.[45]

Each module contains several million cholinergic varicosities (based on Ref. 181). Virtually all of these varicosities contain synaptic vesicles that are potential release sites for acetylcholine. Only 10% make synaptic contact, 90% representing *en passant* varicosities.[100] Acetylcholine and monoamine neurotransmitters released from *en passant* varicosities probably act at nearby postsynaptic sites.[59,99] In the visual cortex, for example, cholinergic varicosities and presynaptic terminals are often next to glutamatergic terminals.[6] The vast majority of glutamatergic synapses form axospinous junctions, a synapse type that is securely held down by a dense meshwork of intersynaptic filaments.[195] *En passant* release sites are not tacked down by intersynaptic filaments, conceivably making them more adaptable to structural reconfiguration than synapses.

3.2.3. *Estimates of how key synapses are altered.* The manner in which cholinergic axons arborize in the cerebral cortex provides clues about how stimulus-specific information could be stored. In the rat, regions of either sensory or motor cortex are innervated by approximately 50 cholinergic basal forebrain cells, each of which arborizes profusely in every vertical, horizontal and oblique direction (Fig. 6A; also see Refs 23 and 130). All the branches from a single cholinergic axon densely fill the entire cortical region, making multiple contacts.

Results from developmental studies attest to the plausibility of the hypothetically proposed neural representations. Single cholinergic axon branches span across multiple pyramidal cells in the cortex, as shown in the four-week-old kitten. (At this age the kitten possesses only a few ChAT-positive axon branches, as shown in Fig. 6B.) In the visual cortex of developing kittens exposed only to stripes of one orientation, ChAT first appears in fibers traversing, rather than paralleling, the visuotopic map.[268] Basilar dendrites of pyramidal cells in the visual cortex preferentially develop in the same manner.[251] Thus,

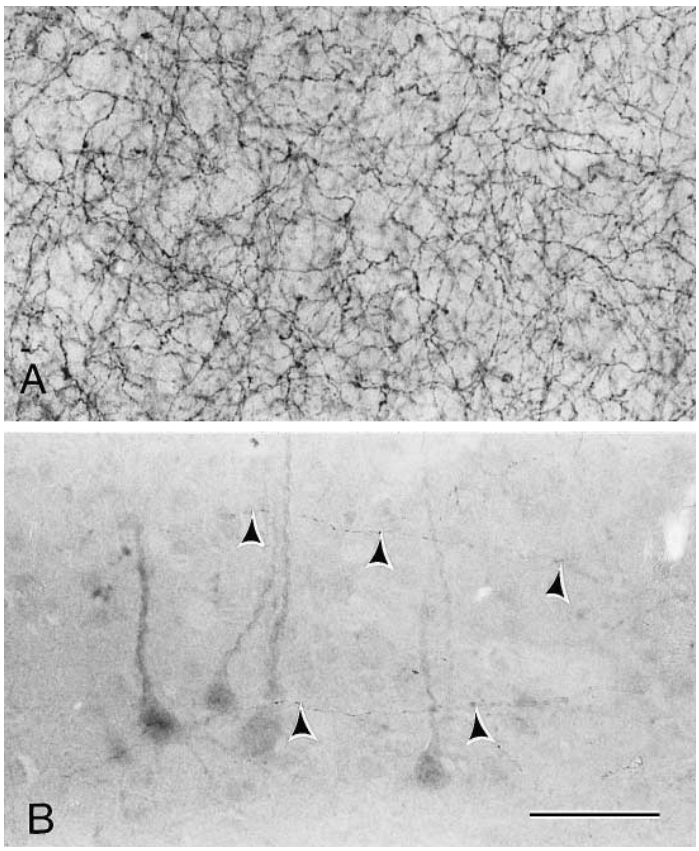

Fig. 6. (A) Cortical fibers immunoreactive for ChAT are found to evince every conceivable orientation, as exemplified in the ectosylvian gyrus of the adult cat. (B) In the four-week-old kitten, cortical fibers that begin to exhibit ChAT immunoreactivity (arrowheads) can be visualized spanning the apical dendrites of adjacent pyramidal cells in neocortical modules. Scale bar = 50 μm.

for any visuotopic or tonotopic comparison, a cholinergic axon branch undoubtedly exists that is capable of coming close to enhancing those vertical circuits corresponding with the conditioned stimulus, while inhibiting the circuits corresponding with dissimilar stimuli (see Fig. 7).

According to the present hypothetical model, the restructuring of a single cholinergic axon may encode a simple neural representation (e.g., see Fig. 7). A potential problem is that, despite a rough anatomical match, it is unlikely that cholinergic varicosities will always lie close enough to glutamatergic synapses to trigger degradation. This problem might not be insurmountable, however, as synaptic elements can be mobilized. Surrounding glia have actin side-arms, for example, that could guide the movements of *en passant* cholinergic varicosities.[47] Actin side-arms found on membrane-embedded muscarinic receptor molecules[28] might move cholinoceptors closer to glutamatergic receptors (Fig. 2C).

NMDA receptors might also move closer to muscarinic receptors. Locally recorded evoked currents are restricted to glutamate receptors located only at synaptic junctions.[17,116] Those NMDA receptors clustered at glutamatergic synapses are largely immobilized in dendritic spines, but sparser somatic and dendritic pools can be mobilized.[21] These sparser distributions of this receptor may not be related to glutamatergic transmission. Thus, NMDA receptors found scattered away from glutamatergic synapses may participate in plasticity and Ca^{2+} flux changes induced by neurotransmitters other than glutamate.

3.3. *Global–serial interactions in the association cortex and hippocampus*

Any model for encoding straightforward response changes in the sensory cortex must also work for more complex cognitive processes affiliated with the association cortex and hippocampus. The reason is that the entire neocortex is similarly organized into cortical modules. The hippocampus also has a modular organization into subfields. The neural representation idea presented here must be able to theoretically account for higher cognition or else be abandoned.

I have discussed Pavlovian conditioning involving tone and suggested that neural representations are formed in the auditory cortex that are capable of eliciting enhanced responses to that tone. In signal detection, the ratio between enhancement and inhibition is most important. Theoretically, synapse re-

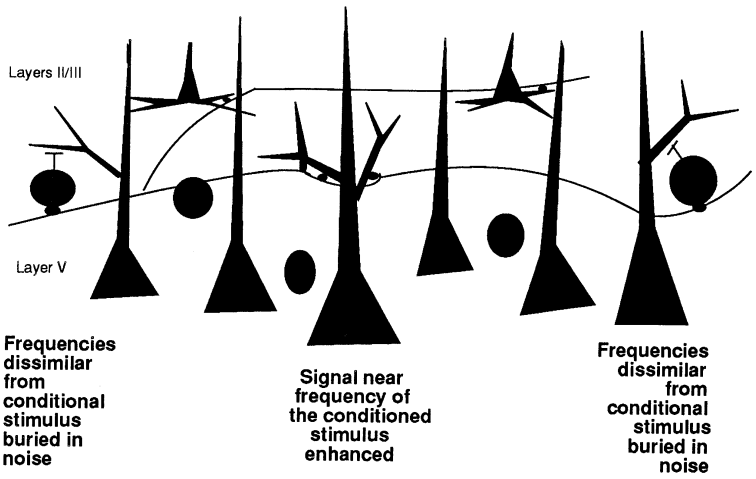

Fig. 7. A schematic drawing of the modified circuitry underlying a neural representation encoded in a module of the auditory cortex. Release sites of the global neurotransmitter acetylcholine are repositioned to produce enhanced activation of layer V pyramidal cells related to the conditioned stimulus, while release at other sites along the axon produces inhibition through interneurons connected to pyramidal cells related to frequencies dissimilar from that of the conditioned stimulus. A collateral of the same axon is shown to innervate the basilar dendrites of layer II/III pyramidal cells encoding intermodular relationships by altering corticocortical flow.

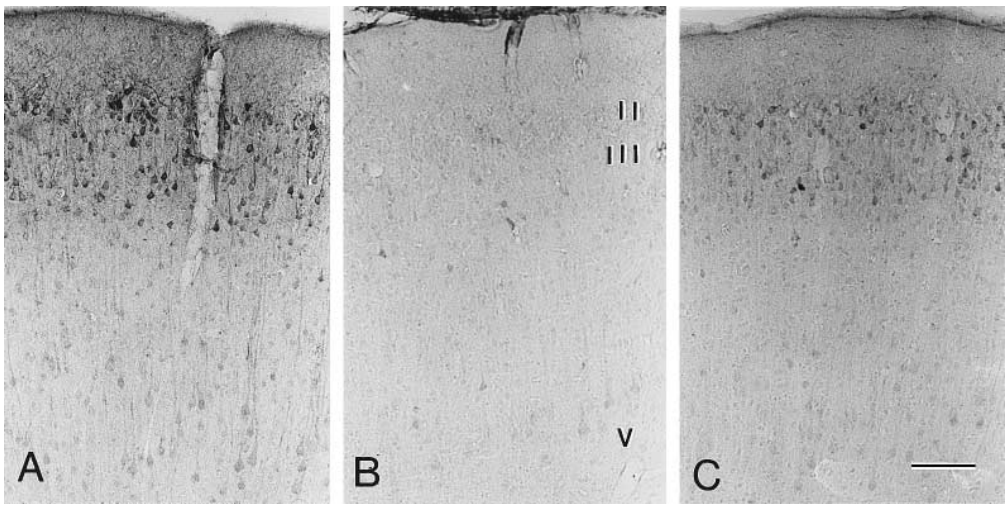

Fig. 8. Immunoreactivity for MAP-2 kinase is selectively increased in auditory cortex (TE3) layers II/III with training.[278] (A) Rats were trained to a 2-kHz tone stimulus followed immediately by a 1-s, 1-mA foot shock. (B) Animals received the same tone and foot shock unpaired. (C) Animals received only tone. Scale bar = 100 μm.

organization producing an enhanced response to the tone signal would occupy only a small part of that neural representation. The many vertical circuits in that module that are not similar to the conditioned stimulus would be unaffected or inhibited to varying degrees (see Fig. 7). Unaffected or inhibited circuits may have other important functions, however. Intermodular relationships might be stored in those unaffected or inhibited circuits. I will present new evidence suggesting that some of the reorganized synapses might alter the corticofugal flow of activity.

Data from this laboratory have shown MAP-2 kinase alterations in corticocortical neurons that may modulate intermodular flow of activity. As shown in Fig. 8, MAP-2 kinase is found preferentially in pyramidal cells of layers II/III and it is altered by Pavlovian conditioning.[278] A type of associative LTP that depends on corticocortical inputs occurs only in pyramidal cells of layers II/III.[103] Thus, intermodular relationships may be permanently encoded by a mechanism that selectively involves MAP-2 kinase and reconfiguration of global afferent modulation to corticocortical neurons affecting intracortical spread of activation.

The human forebrain contains several hundred thousand or more modules and approximately 500,000 cholinergic basal forebrain cells (derived from Ref. 263). Thus, the human brain is capable of

forming at least as many neural representations as there are cholinergic basal forebrain neurons. This is not a large enough storage capacity, suggesting that, as described in Section 3.2.3, each cholinergic axon branch makes a separate neural representation. Although the number of branches is large, this still may not be enough memory storage, suggesting that a multilayering of neural representations is needed to further increase their capabilities.

Cerebral functions are organized hierarchically, as indicated by the fact that lesions to increasingly higher serial levels of cortex (i.e. secondary sensory areas, association cortex, prefrontal cortex) cause increasingly more complex cognitive deficits.[58,73,287] Corticocortical pathways are ordered serially, but they are not necessarily arranged hierarchically. (Hierarchical infers an ascending ranking of function or importance.) The present hypothesis can account for the hierarchy of cortical function by assuming that higher-order neural representations store intermodular relationships rather than stimulus parameters. Accordingly, it is the neural representations that are arranged hierarchically. Thus, the hierarchy is based on multilayered interfaces between the global and serial neurons.

What happens during very long periods of consolidation of human memory? As new concepts are stored in the form of new neural representations, minor changes would be induced in the non-signal regions of older representations. According to the balance principle, intelligence would crystallize when the non-signal portions of older neural representations became incapable of further change. This might occur when further change would disrupt the signal-to-noise ratio or the even distribution of activity.

Intellect is a dynamic state, yet the global neurons exist in a state that is analogous to a closed economy. Differentials in the uptake of neurotrophic factors would be expected to introduce differentials in cellular requirements. As a result, some global neurons and their serial targets would expand, while others would retract their axonal and dendritic arbors. This would produce an increased diversity in response types and variability in coupling and uncoupling patterns between global neurons. Ultimately, large knowledge stores could be built in this manner, composed of unitarily interlinked neural representations.

3.3.1. *Spatial learning in rodents*. Many studies of spatial learning in rodents support the present hypothesis. Spatial or contextual learning in the rat depends on an intact cholinergic septohippocampal system.[224] The hippocampus may be the oldest form of higher association cortex.[191] As there are no equivalents to higher association regions of neocortex in the rat, neural representations formed in the rodent hippocampus may be the closest correlate to higher forms of human memory. Hippocampectomy in primates and humans is well known to cause anterograde amnesia, while generally sparing previously formed memories.[167,288] According to the current proposal, the same information stored as the signal in higher-order neural representations is embedded in the noisy non-signal portion of lower-order neural representations, resulting in dual storage. The higher-order neural representation may be initially necessary to crystallize the intermodular relationships embedded in the non-signal portions. After this process is complete, retrieval from either of the dual storage sites may accomplish the same goal. Accordingly, the hippocampus is no longer necessary.

Spatial or configural learning in the rat is more complex than elemental conditioning in that it involves an assimilation of multiple stimuli presented within a particular context to be represented as a unified configuration.[266] Configural learning appears later in postnatal development than does learning about a single elemental stimulus.[212] Consolidation of learned responses to a novel context also takes many more days than it takes to produce a neural representation about a single elemental cue.[122] Configural learning presumably takes more time because encoding the multiple elemental stimuli must be completed before an overall configural representation can be made.

Configural learning has advantages comparable to the savings in a multilayered analysis. Computation is slow in a single layer as compared to multilayered arrangements.[202,227] Encoding relationships between lower-order neural representations as unified configurations in higher levels of the association cortex increases computational efficiency. Combining higher-order configural neural representations to make even higher-ordered unified configurations achieves greater degrees of abstraction (i.e. the degree to which thoughts are removed from real stimuli).

There is evidence that PKC is altered in the hippocampus with a spatial discrimination task.[257] This suggests that some of the same molecules change with spatial memory encoding in the hippocampus as change with elemental learning in the sensory cortex.

3.3.2. *Human semantic memory*. As a comparison to spatial learning in rodents, let us consider a type of declarative memory in humans. Semantic or verbal memory is one type of declarative memory that depends on the association cortex and hippocampus. It represents an interesting example of a highly integrated cognitive system in which to test the viability of the current hypothesis.

There is evidence that the acquisition of language skills modifies cortical dendrites. Distal branches of cortical dendrites in speech areas, for example, are more organized in the left hemisphere as compared to the right hemisphere.[219] Speech development occurs at the time these distal branches are still growing, suggesting a structurofunctional correlation.

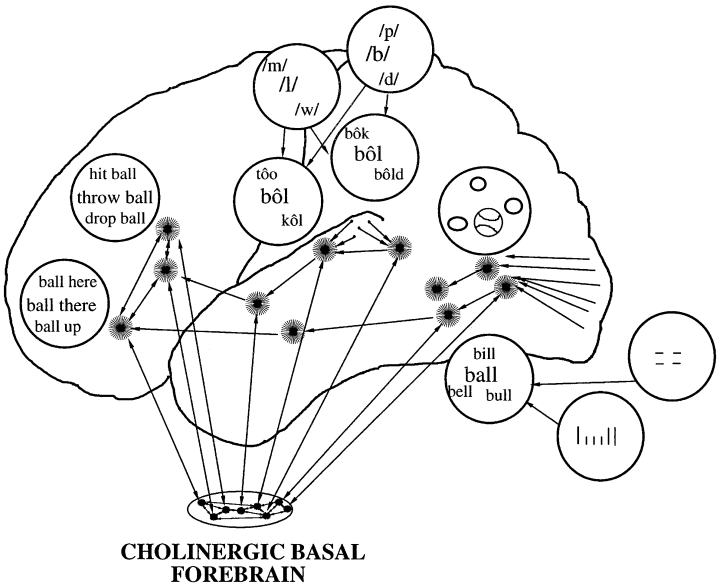

Fig. 9. Encoded relationships in lower- and higher-order neural representations affiliated with the word ''ball''. From orthographic cues, the dominant orientations of visual stimuli in the written word ''ball'' are vertical or horizontal bars. These would form neural representations in modules of the visual cortex. Similar neural representations based on phonological cues or visual perceptions would be constructed by the learning processes described in this paper. Neural representations in the prefrontal association cortex would encode previously learned word-pair orders. The illustrated clusters are positioned in cortical areas known to participate in language, as described in the text.

Studies of subcortical lesions suggest that cholinergic basal forebrain afferents participate in language tasks. Lesions to the posterior putamen and the external and internal capsules, for example, seriously impair verbal skills such as language comprehension.[4,51,166] These capsular regions contain the cholinergic fibers coming from the basal forebrain, as well as corticofugal fibers.[216,267] Amnesia and disruption of verbal memory also follow basal forebrain lesions.[52,169]

Language gestalts extracted out of hierarchies of orthographic, phonological and perceptual information could be encoded as neural representations, such as detailed in the current proposal. Higher-order neural representations in higher association cortices of the parietal, temporal, frontal and limbic lobes could serve as markers for these more abstract language configurations. Regions of the prefrontal cortex and paralimbic regions, for example, show increased blood flow when subjects generate uses for individual words.[196] Site stimulation studies show that, within language-specific areas, small subsections measuring less than 1–2 cm^2 are absolutely critical for naming.[184] (Although these subsections are larger than modules, we do not know how far the disruptive stimulation spreads in this kind of study.)

As illustrated in Fig. 9, interlinked global neurons could activate different neural representations in different orders as determined by learned intermodular relationships. For example, the neural representation for one monosyllabic sound could activate other monosyllabic sounds that commonly follow. Thus, even if the latter sound was only marginally audible, its representation might still be activated. Phasic couplings between cholinergic basal forebrain neurons could also link cortical modules that were not connected by any corticocortical fibers.

For each word in the lexicon, all the information assimilated at many levels of representation could be dually stored as a higher-order neural representation, probably located in a parietal or temporal association area. For semantic categories, groups of similar objects might be similarly represented. Syntactical rules governing the positioning of words could also be stored as higher-order neural representations. The prefrontal cortex is noted for prolonged responses elicited during the delay period of discrimination tasks.[73] Based on the ability of global neurons to summate inputs over a firing cycle, typically encountered word pairs and other syntactical arrangements could be stored as signals in neural representations located in modules of the prefrontal cortex.

Event-related potential studies support the notion that global systems mediate language functions such as word recognition and the temporal sequencing of words. Whole words are recognized within milliseconds, and the N4 and P3 potentials occur along with recognition.[132] The P3 potential also plays a role in linking one word to the next.[131] These late potentials depend on global neurotransmitters like acetylcholine and norepinephrine.[89,92,200]

4. CONCLUSION

A large number of studies support the present hypothetical model being applied to classical conditioning and higher cognition. Voids in the available data preclude proving the proposed model at this time. None the less, the specifics of the model are entirely amenable to empirical testing. The hypothesis that reorganized global afferents on serial neuron ensembles encode multilayered ''neural representations'' has potential heuristic value. It could guide new lines of investigation that aim to resolve basic neural mechanisms that apply to simple learning as well as to complex cognition.

The global–serial dichotomy may also provide new insights into the cognitive and motor impairments affiliated with neurological diseases showing preferential involvement of global neurons (i.e. Alzheimer's and Parkinson's diseases). In Alzheimer's disease, for example, both the global afferents and the cholinoceptive cells in the association cortex and hippocampus are compromised.[273] Functional plastic changes that occur with memory encoding may bear a strong relationship to the dysfunction and the neuropathological profiles that develop with that disorder.

Acknowledgements—I am especially grateful to Drs Arnold Scheibel and Vernon Mountcastle for their helpful comments on an earlier version of this paper. Some of the original research presented in this paper was supported by the Sigma Kappa Foundation and the UCLA Alzheimer's Disease Center Grant.

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(*Accepted* 12 *March* 1996)