MEMORY

& CENTRAL NERVOUS ORGANIZATION

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ACRONYMS

ACh	Acetylcholine
AD	Alzheimer's disease
CAT	Choline acetyltransferase
COMT	Catecholamine-O-methyltransferase
CNS	Central nervous system
CR	Conditioned response
CS	Conditioned stimulus
CSF	Cerebrospinal fluid
DA	Dopamine
DOPAC	3,4-dihydroxyphenylacetic acid (DA metabolite)
DM	Thalamic dorsomedial nucleus
E	Epinephrine (adrenaline)
FD	Fascia dentata (Dentate gyrus)
GP	Globus pallidus
GAD	Glutamic acid decarboxylase
HD	Huntington's disease
5-HIAA	5-Hydroxy-indoleacetic acid (5-HT metabolite)
5-HT	Serotonin (5-hydroxytryptamine)
HVA	Homovanillic acid (dopamine metabolite)
IPN	Interpeduncular nucleus
LC	Locus coeruleus
LP	Thalamic lateralis posterior (association) nucleus
LTP	Long-term potentiation
MAO	Monoamine oxidase(s)
MFB	Medial forebrain bundle
MHPG	3-Methoxy-4-hydroxy-phenylethylene glycol (central NE metabolite)
NE	Norepinephrine (noradrenaline)

6-OH-DA	6-hydroxydopamine
PCPA	Para-chlorophenylalanine (5-HT synthesis inhibitor)
PNMT	Phenylethanolamine N-methyltransferase (Converts NE to E)
POMC	Pro-opiomelanocortin
RAS	Reticular activating system
REM	Rapid eye-movement sleep
RF	Reticular formation
SD	Sensory deprivation
SWS	Slow-wave sleep
Ss	Subjects
TBH	Tyrosine beta-hydroxylase
VL-VA	Thalamic ventralis lateralis and ventralis anterior (motor) nuclei

PREFACE

It is now over thirty years since the historic Henry Ford Hospital Symposium on the Reticular Formation of the Brain (held in Detroit, March, 1957). At that meeting, Nauta and Kuypers (1958) presented a landmark paper defining the principal structures of what is today known as the mesolimbic system.

Other papers—by the Scheibels on reticular fine structure; by Ward, on the beautifully organized motor patterns elicitable by stimulation of the reticulospinal projection system in the cat; by Eldred and Fujimori, on reticular facilitation of the gamma motor system; by Lindsley, on the reduction of response–time by precurrent alerting or central arousal; by Papez, updating his earlier (1937) fundamental work on motivational-affective functions of the limbic system; by Adey, on the behavioral effects of bilateral entorhinal ablation; by Mason, on the apparently inverse relation between hippocampal peak activity and diurnal maxima in 17-OH-corticosteroid levels—all marked that symposium as epochal.

(All of the foregoing were published in the same bound volume. See the reference to Nauta and Kuypers above.)

In the last paper presented, Sir Geoffrey Jefferson reported evidence of an "anterior critical point" evidently necessary to the maintenance of consciousness in man. It lay outside the mainstream of ascending reticular projections, in forebrain areas supplied by the anterior cerebral and anterior communicating arteries. He described this finding as "particularly disturbing," and indeed, its significance has only recently become clearer in light of the neuropathology of Alzheimer's disease.

This book has to do with questions relating to some of those raised at that Symposium. Specifically, it concerns the vertical organization of the central nervous system, and the way in which the reticular, limbic, and mesolimbic systems may act jointly to "steer" attentional processes, or to regulate the conditions making for memory formation in the neocortex.

The most speculative sections concern the possible organization of memory-functions in small cortical assemblies, or vertical columns, and the distributed organization of these functions on a larger (interareal) scale in neocortex.

Certain of the other ideas presented are, I believe, new, if not in principle, in the way they are developed. For example, the periodic alternance of

slow-wave and REM (rapid-eye-movement) stages of sleep is not ordinarily considered homeostatic, except in the crude sense that sleep corrects for fatigue.

The fact that selective deprivation of REM sleep can have extremely disturbing effects on human subjects, or on animals such as the cat, argues that this form of sleep has some unique stabilizing or corrective function. The transition from slow-wave (SWS) to REM sleep may indeed involve a "change in information processing mode" (Hobson, 1987); but why it occurs in higher vertebrates and what adaptive purpose it serves are still not understood.

What I have attempted to show is that slow-wave and REM sleep are, in a quite specific sense, functional complements. Each acts to reduce central nervous entropy, SWS at the intracellular level, by promoting metabolic recovery of neurons and glia, REM sleep at the intercellular level, by intervals of activation whose effect is to conserve acquired structure in the network. REM sleep has thus appeared relatively late in vertebrate evolution, *pari passu* as the CNS has come to include areas which are "open" (minimally preprogrammed; capable of memory-formation). These ideas and their implications are developed in detail, in chapter 5.

A second novelty, or novel shift in emphasis, has to do with the two types of learning which may be sequentially involved in the acquisition of conditioned responses. In many studies, the implication is that a transient sensitization, accompanying initial arousal or "orienting" responses, is responsible for subsequent primacy effects in serial recall. This initial sensitization may (as in lower organisms) have both short- and long-term forms, and in either case may figure in "contextually-cued recall" (Sara 1985). In mammals, it may coexist with learning of the more focal type, essentially because, under conditions in which focal learning is difficult or impossible, it provides an outlet into action. To the same extent, it may, under certain conditions, compete with learning of the more focal type.

As suggested in chapters 6 and 12, the distinction between sensitization and learning in the more usual sense may come down to the distinction between presynaptic learning, as modeled by Kandel and Schwartz (1985), and postsynaptic learning, as modeled by Lynch and Baudry (1985). More distantly, it may come down to the distinction currently made between "procedural" and "declarative" knowledge. (Squire 1986. Chapters 13 and 14, below.)

In the field of receptor types and their central nervous distribution, or of neuropeptide modulators, the current pace of discovery and the functional complexity suggested by some of the findings make interpretation difficult. However, in the reported properties of S1 and S2 serotonin receptors (Peroutka, Lebovitz and Snyder 1981), of alpha 1 and alpha 2 adrenergic receptors (Aghajanian and Rogawski 1984), of D1 and D2 dopamine receptors (Leff and Creese 1984), or of A and B GABA recep-

tors (Snyder 1985), we are perhaps starting to see paired and, in some respects, "opposite" functions, paralleling some of those known electrophysiologically.

Thus S1 serotonin receptors reportedly mediate inhibition and are regulated by guanine nucleotides, while S2 receptors are "less affected" by guanine nucleotides, and are excitatory. (Snyder 1985.) D1 and D2 dopaminergic receptors respectively enhance or decrease adenylate cyclase activity, are found in the parathyroid (D1) or in the anterior pituitary (D2), and differ markedly in their binding-characteristics. (Snyder 1985) See also Creese (1985) on guanine-nucleotide-binding protein as a membrane component with which receptors such as D-1 may "link up," resulting in transduction into adenylate cyclase activity. The involvement of S2 receptor systems in the animal "serotonin syndrome," and of D2 receptor systems in cocaine self-administration in animals (Goeders and Smith 1983), is discussed in the text.

Alpha 2 adrenoceptors, besides reacting more selectively than alpha 1 receptors to one of a pair of optical isomers (Ruffolo 1984), may have an inhibitory, mainly presynaptic mode of action, whereas the alpha 1 type is chiefly postsynaptic and excitatory. (Aghajanian and Rogawski 1984). However see Bousquet, Rouot and Schwartz (1984), who conclude that alpha 2 receptors may be mainly postsynaptic; and U'Pritchard (1984) who states that "thus far, presynaptic and postsynaptic alpha 2 receptors are pharmacologically indistinguishable," making it difficult to quantitate these populations.

Alpha 1 receptors reportedly mediate fast (phasic), and alpha 2, slow (tonic) pressor responses (McGrath 1984). Still other workers cite data suggesting that central alpha 2 receptors may mediate arterial hypotension, whereas "there is a population of a1 receptors which have the opposite function." (Bousquet, Rouot, and Schwartz 1984.)

Morley, Farley, and Javel (1984) report that "there is indirect evidence that there may be two ACh binding-sites in the brain," one of which is blocked by bungarotoxin. Kilbinger (1984) presents evidence that muscarinic agonists and antagonists respectively decrease or increase ACh output of cat cortical neurons, suggesting presynaptic inhibitory reuptake. He notes that this mechanism "bears a marked resemblance" to the modulation of the output of aminergic neurons "by release-inhibitory autoreceptors." (See also Birdsall and Hulme 1984, concerning M1 and M2 muscarinic receptors in the forebrain.)

GABA and 5-HT receptors, having the same function (inhibition), but distinguishable in that one (the 5-HT) is blocked by spiperone and the other not, may nevertheless modulate the same potassium channel. This was inferred from the fact that the increase in K^+ conductance did not appear to summate when generated by both. The result, in both cases, appears to have depended upon a pertussis toxin-sensitive GTP-binding

(G) protein acting as a second messenger system. (Andrade, Malenka, and Nicoll 1986. The units were pyramids in rat hippocampus.)

Finally, Bowery (1984) reviews evidence indicating that GABA B receptors are "confined to" the molecular layer in the cerebellum, the stratum containing the parallel fibers, apical Purkinje cell dendrites, and the (inhibitory) stellate cells. GABA A receptors, by contrast, "predominate" in the granule cell layer, internal to the Purkinje cells.

GABA A receptors are reported to be bicuculline-sensitive, postsynaptic to GABA neurons, and Ca^{2+} inhibited. GABA B receptors are bicuculline-resistant, found on GABA or other neuron terminals, and Ca^{2+} activated (Snyder 1985). That these receptor types should have such clearly differential distribution, in what is perhaps the most cytoarchitectonically stereotyped major subdivision of the central nervous system, is surely an interesting finding. The experiments cited in chapter 3 suggest a similar distribution for GABA A and B receptors in neocortex.

The biochemical relations disclosed by neuropharmacology, increasingly since the early or mid 1970's, have greatly complicated the models we use to conceptualize brain functions. In effect, they add further dimensions to problems still fundamentally unsolved—the modus operandi of the cerebellum being one of them. Not unexpectedly, however, some of the relations established by the older methods appear to be corroborated by the new.

An example, taken at random, might be the relation of neurotensin to feeding behavior in rats. It has been known for some years that stimulation of the far-lateral hypothalamus can initiate feeding, while stimulation of the medial hypothalamus (e.g. the ventromedial nucleus) can arrest it. (Anand et al. 1961. Morgane 1961. Krasne 1962.)

Stanley, Eppel, and Hoebel (1982) report that neurotensin is released into the bloodstream after a meal. They also find that feeding behavior, elicitable by intrahypothalamic injection of norepinephrine (into the paraventricular nucleus), is "significantly attenuated by neurotensin pretreatment." Neurotensin may thus be an important biochemical link in the circuitry of the hypothalamic "satiety" system described in the earlier literature. (Its relations to the limbic and mesolimbic dopaminergic systems are discussed in chapter 11.)

I should add, in conclusion, that the use of thermodynamic concepts in chapter 5, as a way of accounting for the basic properties of slow-wave and REM sleep, is not without precedent in pharmacology. Creese (1985) reports that "in studies of the turkey erythrocyte membrane beta-adrenergic/adenylate cyclase system, it was shown that agonist, but not antagonist, affinities for beta-adrenergic receptors increase at lower temperatures . . . The binding of agonists is enthalpy-driven, with marked net decreases in entropy, whereas the binding of antagonists seems to be almost completely entropy-driven." (Creese 1985, p. 227.)

It may well be at the level of receptor kinetics rather than at that of conventional circuitry, that the questions I have raised here, concerning the differential entropy-reducing functions of slow-wave and REM sleep, may finally be settled.

ORGANIZATIONAL NOTE

The book is divided essentially into two sections. Chapters 1–7 deal with neocortical organization, sleep functions and memory.

Chapters 8–14 and the Appendix have to do with the organization of the limbic, mesolimbic and reticular systems, and the relations of these to higher-level central nervous activity.

CONTENTS

CHAPTER 1

How Stable are Stable Networks?; Implications for Memory Theory; General Plan of Cortical Organization; Implications of the Plan

HOW STABLE ARE STABLE NETWORKS?

The work of Mountcastle (from 1957) and of Hubel and Wiesel (early 1960s) led many to the conclusion that prime receiving cortex was "hard-wired," except in early developmental stages (e.g. in kittens before 4–8 weeks). In other words these divisions of prime receiving cortex set early in life and were thenceforth, in effect, nonmemory forming.

Subsequent work has shown that neither visual nor somesthetic cortex is as functionally rigid as had been thought. Kaas et al. (1981) reported that in adult monkeys, after section of the median nerve, the deafferented cortex in parietal areas 3b and 1 was silent. Over a period "of a few weeks" units that had fallen silent then became active again, responding to stimulation of other, still-innervated hand areas. These authors suggest that "cortical maps, even in adults, are probably subject to constant modifications based on the use or activity of the peripheral sensory pathways." (Kaas et al., 1981, p. 257.)

In the visual system, Creutzfeldt and Heggelund (1975) obtained a different but related result. They reported striking increases in the ratio of "uncommitted" to "committed" cells in the striate cortex of mature cats, following visual deprivation for 308 out of 336 hours. (This experiment is reviewed in detail in chapter 4.)

Blakemore (1974) said: "Perhaps it is the mere probability of experience that determines the final preference of a cell. Perhaps each neuron selects, as its preferred stimulus, the feature that it has seen most often." The Creutzfeldt-Heggelund experiment appears to support him. Neurons responding as he has suggested I will describe as working on Blakemore's

Principle. In short, supposedly stable networks such as striate cortex may not be truly that.

IMPLICATIONS FOR MEMORY THEORY

Neurons that work on Blakemore's Principle are by definition memory forming. In prime receiving cortex, however, their tendency to develop probabilistically determined response preferences may be masked under normal conditions by the fact that the range of inputs available to them is limited. The experiments reported by Kaas et al. (1981) imply that there is *some* choice perhaps available to such units, appearing in the form of alternate response preferences when originally preferred inputs have been shut off.

Such units may represent a population distinct from those, e.g., of temporal association cortex, some of whose response preferences may be selectively made more enduring by the mechanism of long-term potentiation (LTP) and associated Ca^{2+} mediated membrane changes. Reference is to the model of long-term memory (LTM) formation proposed by Lynch and Baudry (1985) discussed in chapter 6.

The processes underlying LTM formation, in systems lying closer to the effector side of the central nervous system (CNS), are as yet unknown. The fact that Milner's (bilateral hippocampal) patient Henry was unable to form "new" memories lasting more than 10 to 15 minutes, but still showed a normal learning curve for a mirror-writing task (Milner, 1964) appears to differentiate "procedural" from "declarative" learning. That is, it tells us that the two can function independently in the human nervous system, but beyond that, very little.

That neurons in specific projection areas show an unexpected plasticity suggests the conclusion that virtually all cortical neurons, which are not subject to special "fixing" mechanisms, may have short-term memory (STM) functions. The duration of the probabilistically established response preferences postulated to underlie STM may then vary according to the cortical areas in which they are established.

In areas such as striate 17, which are tightly linked via the thalamus to the periphery, and in which diversity of traffic is constrained accordingly, STM functions may ordinarily not be apparent. However, if input to such cortex is sufficiently reduced for a sufficient period, the results suggest both some memory-loss and some loss of functional organization, the two perhaps being the same.

In the experiments of Kaas et al. (1981), as the authors suggested, deafferentation by median nerve section may have left the parietal units still with "competitive" inputs to which they responded by default. In the Creutzfeldt-Heggelund (1975) experiment, the sufficient conditions for

functional disorganization may more nearly have been met. It is discussed in chapter 4. Its relation to the findings in human sensory deprivation experiments is discussed in chapter 5.

GENERAL PLAN OF CORTICAL ORGANIZATION

Graybiel (1974) divides association cortex into proximal and distal sectors. The essential features of that division are that:

1. In both pre- and post-cruciate areas, proximal association cortex lies synaptically closer to the phylogenetically newer sectors of cortex—the specific thalamocortical, and the frontal supplementary and premotor systems.
2. Posterior distal association cortex receives less direct input than does proximal, from the specific receiving system, and more direct input from the limbic system (in particular the hippocampus). (See figure 1–1, from Graybiel 1974.)
3. The frontal distal division comprises the prefrontal association areas, making it further than frontal proximal cortex from the pyramidal outflow pathways, and more closely connected with the limbic system (in particular the amygdala).
4. The foregoing relations are systematically reflected in the posterior-anterior connections of the two divisions, such that each posterior division forms a loop with its frontal equivalent (see figure 1–1), the distal loop being the longer, and having the larger subcortical component.
5. Studies in the monkey (Pandya and Kuypers 1969; Jones and Powell 1970) have shown these relations to be maintained in the return projection-routes from frontal cortex. "Posterior association cortex receives a massive afferent system from the frontal lobe that is divisible into a *premotor* component directed preferentially toward areas most closely linked to the major sensory fields, and a *prefrontal* component distributed to the parietotemporal regions that represent distal association cortex." (Graybiel 1974, italics original.)

The projections just described are not shown in figure 1–1. They presumably include fronto-temporal connections via the arcuate and uncinate fasciculi, the latter arising in orbital cortex; and, of course, the bi-directional perforant path connecting temporal association cortex, via entorhinalis, with the dentate gyrus and hippocampus.)

The older idea that sense data are "elaborated" in stages, e.g., from area 17 to 18–19, has been replaced by a more thalamically based model, in which "families" of receiving systems (Graybiel and Berson 1981) are reached, in part serially, partly in parallel, by the same incoming data,