INTERNATIONAL ATOMIC ENERGY AGENCY
UNITED NATIONS EDUCATIONAL, SCIENTIFIC AND CULTURAL ORGANIZATION
INTERNATIONAL CENTRE FOR THEORETICAL PHYSICS
I.C.T.P., P.O. BOX 586, 34100 TRIESTE, ITALY, CABLE: CENTRATOM TRIESTE

SMR.853 - 10

ANTONIO BORSELLINO COLLEGE ON NEUROPHYSICS

(15 May - 9 June 1995)

"Cortical Representation of Learned Behaviors"

Michael M. Merzenich
Departments of Otolaryngology and Physiology
University of California at San Francisco
San Francisco, CA 94143
U.S.A.

Memory concepts - 1993. Basic and clinical aspects
P. Andersen, Ø. Hvalby, O. Paulsen and B. Hökfelt, eds.

Cortical Representation of Learned Behaviors

M. M. Merzenich and W. M. Jenkins

W. M. Keck Center for Integrative Neurosciences and Coleman Laboratory, University of California at San Francisco, San Francisco CA 94143-0732

INTRODUCTION

The mammalian forebrain is a self-organizing machine with a relatively stable anatomical framework established early in life, whose local functional connections are remodeled in detail throughout life by our experiences. Our purpose in this review is to summarize recent evidence that contributes to our understanding of the basic operational "rules" and the mechanistic bases of the adaptive connection-remodeling processes in the cortex that underlie its contributions to learning and skill acquisition.

PERSPECTIVE

In the late 19th Century, if we are to take William James' word on the matter, it was widely agreed that learning resulted in the natural creation of altered circuits in the brain that occurred as a predictable consequence of their repetitive activation [1]. It is the basic nature of physical systems, James argued, to deepen and widen and strengthen and facilitate pathways as a function of their repeated engagement, an argument echoed by contemporary theorists [2,3]. When physiologists began looking for evidence of learning-induced plasticity in the cerebral cortex in the late 19th and early 20th Century, they found it. Thus, for example, in brilliantly imaginative studies, Brown-Sequard described changes on a major scale induced in motor and sensory cortices by associative conditioning, in his case by temporally pairing electrical shocks to anterior and posterior brain regions [4; also see 5]. Sherrington and colleagues provided compelling evidence that large sectors of motor cortex could be representationally remodeled by repeated, localized surface electrical stimulation [6,7; for an earlier precedent, see 8] or by stimulation of a peripheral nerve innervating muscles [6], and believed that this rapid remodeling of mapped, stimulus-evocable movements reflected the kinds of change that were induced in cortex by repetitive movements during skill acquisition. In the early 1920's, Lashley provided additional strong evidence that movement representations in cortical area 4 were dynamic constructs, changing over time in the details of how specific movements were represented within them [9]. Taken together, these and other experiments provided a compelling early argument that cortical representations are dynamic, functional constructs, remodeled continually in detail by life's experiences.

In the middle of the Century, when physiological psychologists gained the methods necessary for directly determining whether or not the responses of cortical neurons were altered by behavioral training in ways that could account for learning, they conducted many learning-plasticity experiments, first using electroencephalographic and evoked response recording [e.g., see 10 for review], then later employing single unit recording [see 11-13 for review]. The great majority of these experiments succeeded, in the sense that they demonstrated that changes in neuronal responses were generated on a large and easily recordable scale by behavioral training. Because they usually employed non-specific sensory or electrical stimuli, early experiments did not very directly address issues of sensory response specificity of the behaviorally-induced changes, except in the domain of temporal patterning. Focussing principally on the elegant models of associative conditioning provided by Pavlov and his early-Century contemporaries, they did not very specifically relate the features of change to alterations in discriminative abilities or skills. Nor did they reconstruct the enduring cortical record of the learned behavior as it was distributed across engaged cortical sectors, although these experiments as well as numerous ablation/behavioral studies bore powerful implications for its distributed form. Despite these limitations, taken as a whole these cortical plasticity/associative conditioning experiments confirmed a number of the hypotheses that Pavlov had posited about the cortical origins of learning [14], and provided compelling, direct evidence in the middle decades of this Century that the cerebral cortex is a dynamic machine, remodeled continually by our experiences. By inescapable logical extension, they demonstrated that the responses of many millions of cortical neurons could be altered by a relatively brief period of Pavlovian conditioning, with those alterations at least roughly reversed when the associative conditioning inducing these neuronal response changes was behaviorally "extinguished".

In parallel with these advances, there was an early understanding that activity coincidence and time-place concurrence or juxtaposition were key features of the learning process [1,15,16]. The concept of coincident-based synaptic plasticity is most often attributed to Donald Hebb [17]. In fact, Hebb himself regarded coincident input-based plasticity as a generally excepted concept in his time. Indeed, the roots of considering input coincidence as a general cortical organizing principal dates at least back to Thorndike [15], Tanzi [16] and James, who noted that "the time- and space-relations between things... stamp copies (of) themselves within. Things juxtaposed in space impress us, and continue to be thought, in the relation in which they exist there. Things sequent in time, ditto" [1]. At the same time, Hebb made a major contribution by his consideration of this concept in more specific hypothetical neurological terms, both a) by positing plausible hypotheses about what could underlie coincidence-based plasticity, and b) by explaining some implications of coincident input-based changes for the creation of stimulus-specific "assemblies" of cortical neurons. Such assemblies, Hebb understood, would necessarily be created by behaviorally important stimuli if coincident input-based synaptic plasticity is put into play in neuronal networks. Hebb also hypothesized that these emergent assemblies would likely be reverberant and to some extent self-perpetuating, and as such, could provide a basis for the stable representation of a learned input or behavior, a general proposition that had important precedents [especially 18], as well as many echoes in contemporary neuroscience.

After Hebb posited his hypotheses about coincidence-based synaptic plasticity and the creation of input-specific cell assemblies, he and later many other investigators began to look for evidence for them. Again, these experiments were initially conducted using extracellular recording techniques, then later using *in vitro* and *in vivo* intracellular methods. The great majority of the latter class of experiments have been conducted in the past decade. Both classes of these studies were usually successful [e.g. see, 19-21,13 for reviews of cortical versions

of these experiments]. Coincident or nearly coincident inputs were commonly mutually strengthened in their effectivenesses for exciting forebrain neurons, especially when that excitation was behaviorally significant. If we take the evidence of the numerous experiments of this class as a whole, they again lead us to the inescapable conclusion that the mammalian forebrain including the cortex itself is a dynamical structure that continually remodels itself on the bases of these widespread, intrinsic, adaptive, coincident input-based processes.

Finally, Cajal may have been the first to posit that physical changes in synaptic structures resulting in facilitated transmission underlies learning, a logical extension of his advocacy of the "neuron theory" [22]. Many subsequent investigators have looked for structural changes induced with learning, measuring the physical dimensions of the cerebral cortex and of its compartments, layers and component neurons. Investigators have described changes in cortical thickness, proportional extent of neuropil, numbers of spines, turnover of spines, local features of spines, dendrite elaboration, synapse number, synaptic turnover, areas of synaptic contacts --- as well as more microscopic changes --- *all* significantly altered by engaging a cortical region in behaviorally important experience or in learning [for reviews, see 23-27]. If we consider this literature collectively, we see evidence for local change induced on a *massive* scale involving innumerable synaptic active zones and spines and boutons and dendritic branchlets continually emerging and undergoing changes in morphology, throughout life, under the impetus of new experiences and learning.

In parallel and ultimately largely superseding this compelling historical flow of evidence, a strong countercurrent model emerged in neuroscience that has dominated thinking about learning and the cortex over the past several decades. By that opposing view, the selectivity of responses of cortical neurons were believed to be determined by anatomical development of specific connections in a brain that establishes nearly all of its mature connections in the main studied model systems (visual cortical area 17, somatosensory cortical area S1) within the first days or weeks of life. This view of aplastic mature cortex was paralleled by studies in cognitive psychology and artificial intelligence that analogized brain operations to computer architectures. In such machines, commonly invoked in artificial models of higher cognitive processes, learning is accomplished by resident software, and not by the continual remodeling of the details of machine wiring.

This extreme alternative view positing a post-developmental anatomical and functional neuronal response rigidity has been the pre-eminent position of mainstream neuroscience for several decades. It has been again challenged in the current era, by experiments that have provided more specific evidence about the nature of the establishment and plasticity of cortical neuronal response specificity, and for a lifelong capacity for learning expressed by cortical representational remodeling. That new evidence is the subject of this review.

CORTICAL REPRESENTATIONAL PLASTICITY

Plasticity induced by restricted peripheral or central input losses

Central representations of the skin surface, the retina and the cochlea rapidly reorganize following a spatially restricted input loss, e.g., as induced by

2.

peripheral nerve section [e.g., 28-34], or by restricted retinal [35,36] or cochlear [37] lesions. In that reorganization, surrounding sensory epithelial surfaces expand in representation to occupy the cortical zones formerly predominantly representing the now-missing inputs. When a peripheral lesion induces such a loss, there are of course immediate changes in overt input effectivenesses, termed "unmasking", that can be attributed to local sensory system/cortical network imbalances induced by the loss input subset [31,38-40]. Interestingly, in motor cortex, sensory input losses or changes induced by altered limb positions, motor nerve transections or a period of peripheral nerve stimulation [41-43, 6] also result in almost immediate changes in stimulus-evokable *outputs*.

Immediately "unmasked" inputs partly occupy cortical zones deprived of their primary inputs by the peripheral lesion with relatively less specific or 'detuned' (e.g., large receptive field) input combinations from sensory zones that surround dennervated retinal or skin or cochlear sensory epithelial surfaces [31,35-37]. From the point in time of the peripheral lesion forward, learning-based changes operating in the unusual competitive conditions that apply to a cortical sector that has been deprived of its original dominating inputs appear to govern the subsequent reoccupation process, which occurs progressively over a subsequent several week long period [30, 35, 37]. These slower, progressive processes result in the creation of a more topographically refined representation of the surrounding retinal or skin or cochlear sensory epithelial surfaces. At least in the somatosensory case, they are marked by the emergence of normal or greater than normal neuronal response specificity, e.g., by the emergence of normal or smaller than normal cortical receptive fields. It has been argued that this greater-than-normal response selectivity can occur because the lesion has elimited inputs that have vacated cortical network space. That space can now be occupied by competitive inputs from non-disturbed sources, which can thereby be represented in this larger territory in correspondingly finer representational grain [31,32,44; see 45-48 for review].

Because of the regenerative capacity of the distal axons conveyed in peripheral cutaneous nerves, and because innervated skin can be translocated across the body surface with its skin innervation zone maintained intact, several other interesting input manipulations have been studied in the somatosensory system that have resulted in large-scale cortical plasticity and that bear important implications for the underlying competitive, learning-related remodeling process [45-50]. For example, representational remodeling has been tracked a) after cutting and reconnecting peripheral cutaneous nerves [51,52]; b) after cross-connecting peripheral cutaneous nerves [52,53]; c) after fusing fingers [54,55]; d) after separating long-fused hand digits [56]; and e) after moving innervated islands of skin across the hand to new peripheral skin locations [46,49,57]. The representations of the hand surfaces in somatosensory cortical areas are remodeled dramatically in all of these cases, substantially on the basis of the altered input time structures of shuffled or fused or separated or translocated skin inputs. That is, most of the changes that follow such manipulations are predicted on the basis of cortical plasticity mechanisms operating with Hebb-like synapses. For example, transection and reconnection of peripheral cutaneous nerves results in a re-establishment of small receptive fields and local topographic order from shuffled skin-to-central nervous system inputs that must be coincident input-based [52,46,48-50]. Fusing of digits results in the breakdown of representational discontinuities that normally separate their cortical representations, presumably because it results in a heavy schedule of nearly coincident inputs from digital surfaces that were formerly apart, i.e., substantially temporally independently stimulated [54,55]. Reversal of digital syndactyly results in the rapid emergence of a separate cortical representation of digits that were formerly represented in a highly overlapping manner, presumably because with finger separation, adjacent, formerly-fused digits now deliver a more temporally independent input schedule into the somatosensory afferent system [56]. Cross-connection or transfers of innervated skin islands across the hand results in a novel emergence of a topographic representation of the translocated skin in the part of the cortical hand representation that receives the transferred skin or nerve. This emergence of a new, orderly representation of the island skin in a novel cortical sector must involve coincident input-based plasticity mechanisms [46,49,52,53,57].

Similar representational plasticity has also been documented in a growing number of models following induction of central tract or restricted cortical lesions [e.g., 58-63]. These studies provide a growing body of evidence documenting the contributions of cortical plasticity to functional recovery following brain injury or stroke.

Cortical representational plasticity induced by "experience"

Representational plasticity is also generated by any episodic change in behaviorally driven inputs, e.g., by a change in behaviorally important sensory "experience". For example: 1) The representation of the ventral aspect of the trunk of a female rat expands roughly 2X in the primary somatosensory cortex (S1) as a consequence of the female nursing a litter of pups for 10-19 days [64]. Receptive field distributions on the trunk recorded in S1 shift significantly to disproportionately favor nipple locations, and cutaneous receptive fields sizes are reduced to about 1/3rd their normal extents. 2) The cortical territories of representation of the long vibrissae of adult rats maintained in an enriched environment expand severalfold over a period of several weeks, when other vibrissae are cut on a regular schedule [65,66]. With that S1 representational expansion, the domain of short-latency responses recorded in layer 5 also enlarges severalfold, and commonly extends across the areal domains of several cortical "barrels" [66; but see 67]. 3) The representations of intracortical microstimulation evoked movements mapped in cortical area 4 in adult monkeys are dramatically altered by a brief period of practice at a small object retrieval task [68]. Positive representational changes are specific for movements employed in the behavior. 4) The representations of the hand surfaces that a monkey uses to palpate and retrieve the same small objects expand approximately 2X after a few days of practice at this behavior. Roughly inverse changes in receptive field sizes and significant changes in local representational topographies are recorded in parallel [69]. 5) The representations of species-specific vocalizations of an adult marmoset monkey come to be very highly selective for the vocalizations of a mate that was first introduced several weeks earlier [70]. 6) The representation of the reading-engaged digital surfaces in a human Braille reader who initiates reading in the middle years of childhood appears to be substantially greater than are the representations of the same surfaces of control hands [71]. Motor cortical representations of key movements for Braille reading also appear to be representationally enlarged in these subjects [72].

This class of contemporary studies extend a more than 30-year history of study of the positive physical neurological consequences of a period of "environmental enrichment" for the cerebral cortex. Such studies have repeatedly shown that behavioral experience results in highly significant changes in cortical thickness, neuropil area and connectional complexity (see 23-25, for review), with a capacity for change a) recorded over at least most of the neocortex, and b) maintained almost equivalently throughout life, fading only in senescence [73,24,25]. These contemporary studies show that any new, behaviorally important experiential epoch will generate changes in cortical representations on a major scale. Those cortical changes clearly constitute a large part of the emergent, evolving behavior.

Cortical plasticity in the representation of specific stimuli induced by classical (Pavlovian) conditioning

In perhaps the best studied contemporary classical conditioning cortical plasticity model employing more specific sensory stimuli, changes in the selective responses to tones have been induced by a brief period of classical conditioning in auditory cortical fields studied in rats [74], guinea pigs [75,76], rabbits [77], cats [78-81] and monkeys [82]. By that conditioning, an exaggerated representation of the specific sound frequencies used in associative conditioning [74-81] and an increase in the coupling of neurons across the cortical zone that is engaged by the conditioned stimulus [82] emerges. Changes endure as long as conditioning is sustained --- indeed, over the durations of test periods extending up to as much as 8 weeks [83] --- and are at least roughly reversed by behavioral extinction [74,77,78-82]. Dimensionally similar changes in the cortical representations of the conditioned response and the unconditioned stimulus have also been recorded in their appropriate cortical areas [e.g., 84-87]. In fact, studies of the plasticity of conditioned responses --- and of cortically mediated motor learning in general --- have provided a second major model for studying the cortical processes underlying associative conditioning [e.g., 84,89,27,12].

In both a rodent [75] and primate [82] auditory cortex plasticity model, negative representational changes have also been recorded for non-associated (S-) stimuli applied as a part of an alternative S+ (associated) / S- (non-associated) Pavlovian conditioning paradigm --- as predicted must be the case on the basis of classical S+ / S- conditioning experiments conducted by Pavlov [14]. Moreover, as noted above, in the macaque monkey S+ conditioning has been demonstrated to generate specific input-strengthening effects not only for afferent inputs to the cortex, but as Hebb predicted must occur [17], for intrinsic cell-assembly connections within the cortical network itself. S- schedules weaken such connections.

The significance of the generation of both learning and "unlearning" effects has important theoretical implications that have been perhaps most extensively considered by Cooper, Bienenstock and colleagues [90,91; also see 92]. Evidence for cellular mechanisms underlying the "long term depression" (LTD) that presumably contributes to "unlearning", and its relationship to "long term facilitation" (LTP) that contributes to associative learning have further affirmed their probable joint and connected roles in representational plasticity mechanisms accounting for cortical contributions to learning [93,94; see 21 for review].

Plasticity induced by operant or instrumental conditioning

It was historically argued that the changes induced by Pavlovian conditioning might occur on a greater scale than with operant conditioning [e.g., 95]. In fact, relatively few early studies of cortical response plasticity have used operant conditioning procedures. Moreover, classical conditioning most commonly employed an aversive unconditioned stimulus, confounding comparisons with operant conditioning studies employing relatively weaker food reinforcement.

Several operant conditioning models developed over the past several years have revealed changes like those induced by classical conditioning. They include: 1) Changes in the representations of long vibrissae indistinguishable from those recorded in vibrissal "experience" studies were recorded over a much shorter time course (after only hours of training), when adult rats were conditioned to perform a surface roughness discrimination Y-maze behavioral task [66]. 2) The cortical representations of behaviorally engaged finger surfaces were enlarged several-fold in extent in monkeys trained in a manual task requiring the maintaining of digit contact pressures for several seconds per food reward [96]. Receptive fields representing these behaviorally engaged skin surfaces were a fraction of their pre-training sizes. 3) The population of neurons in somatosensory cortical area 3b driven by specific tactile stimuli in a flutter-vibration stimulus detection task did not significantly increase in its extent with training, but the temporal coherence of cortically evoked neuronal responses sharpened progressively, presumably due to a strengthening of intrinsic connections in the engaged sector of somatosensory cortex. This progressive change in local positive network coupling accounted for a dramatic (more than 10X) improvement in flutter-vibration stimulus detection thresholds with practice [97]. 4) The population of neurons engaged by a tactile probe in a vibratory frequency difference discrimination task enlarged progressively as the animals' performance at the task improved. Receptive fields representing the engaged skin zone were usually enlarged severalfold, and responses representing ongoing stimulus cycles became progressively more strongly temporally coherent. This latter change, believed to be mainly due to progressively stronger positive pyramidal cell coupling in the engaged cortical network sector, correlated strongly with these animals' training-based improvements in frequency discrimination abilities [98-100]. 5) The extent of cortex engaged by behaviorally important stimuli expanded several-fold, in adult monkeys trained in an auditory frequency discrimination task [101]. Significant changes in receptive field bandwidths were also recorded within the directly excited cortical area A1 sector. The former measure was correlated with these monkeys' progressive improvements in sound frequency discrimination abilities. 6) Training a monkey in a visual target-specific reaching task resulted in the rapid emergence of responses that were progressively more selective for the target or reach trajectory, within a premotor cortical area [102]. 7) Training a monkey in an auditory-cued motor task resulted in modification of unit responses that came to more closely represent the sound-cued movement set, within a premotor cortical area [103]. 8) Performance improvements achieved by training a monkey in a visual tracking task were closely paralleled by changes in unit response behavior by neurons in the middle temporal visual cortical field (field MT) [104]. 9) Training of monkeys in a taste aversion behavior could apparently be attributed to physical changes induced in a small gustatory cortex zone [105]. 10) Training monkeys in a motoric task resulted in the emergence of specific, trained-movement-related responses for neurons studied in the supplementary motor cortex [106]. 11) Brief training of monkeys in the recognition of a specific face resulted in significant positive changes in neuronal responses to that face in the appropriate sector of temporal cortex [107]. 12] Significant positive areal representational changes were induced in frontal cortical areas including primary motor cortex, in humans practicing a sequenced finger movement [108]. 12] Training monkeys in a delayed nonmatch-to-sample or stimulus-pair association behavior resulted in a rapid emergence of highly stimulus-specific responses in several subdivisions of the inferotemporal cortex [e.g., 109-111; see 112 for review).

Thus, changes induced by operant conditioning have been recorded in all major sensory systems and all across the motor hierarchy, in virtually every cortical area that has been studied in a learning context. Moreover, recorded changes are commonly specifically relatable to performance gains attributable to behavioral training.

DISTRIBUTED REPRESENTATIONS OF LEARNED BEHAVIORS

Neural changes induced with learning; some principles

Before summarizing what we now understand about the specific distributed forms of representations of learned behaviors, it is useful to review some basic "rules" of the cortical plasticity that generates them. Among those principles are the following:

1) *There is an input coincidence rule for synaptic effectivenesses changes.* Again, contemporary studies demonstrate that a main determinant of cortical representational detail is a coincident input basis for the alteration of synaptic effectivenesses, as initially formally hypothesized by Hebb. Considered in detail, cortical representations are time-based constructs. The many topographic representations that occupy much of the cerebral cortex, when considered in detail, actually represent input time continua [45,48-50,113,114]. Coincident input-based processes are especially powerful in representing behaviorally important stimuli because they provide a versatile basis for input *selection*. That is, *any* combination of inputs that a) nearly co-concur in time, and b) are delivered into convergent cortical network space in a given cortical area can be selected together to generate specific responses to numerous --- or in some cortical areas, virtually innummerable --- particular input combinations. Historically, specific responses of neurons in the cortex were regarded to be the product of inherited anatomical structures, or to represent an excitatory peak in a background sea of inhibition. We now understand that a) each cortical location receives a rich input repertoire that is operated on by coincident input-based Hebb-like co-selection mechanisms to mold representational detail to adapt to new behaviorally-driven conditions; and b) that each specific cortical response is the product of a coupled cortical neuronal "group" [113-115] or "cell assembly" [17] (see below). The input selection process involves both directly linked excitatory and inhibitory and learning and unlearning plasticity effects.

It should be noted that some aspects of cortically recorded changes are often termed "non-Hebbian", i.e., do not follow the specific hypothetical rule for change (input effectivenesses increased when they arrive at the time that a neuron is depolarized by a preceding input) postulated by Hebb (e.g., 116-121). At the same time, described alternative mechanisms, with one possible exception [122], are still approximately time-coincidence based, although a) they may effectively prolong the operational integrative time constant for the cortical input selection machinery, and b) change synaptic effectivenesses for nearby but not directly stimulated neurons, e.g., by the persistence of a diffusible second messenger.

2) *Competition for synaptic space; 'normalization' or 'zero-sum' learning rules.* Cortical representational changes induced in learning are also clearly *competitive* by nature. Competition reflects an apparent vying for effective synaptic dominance of cortical neurons, and by reasonable presumption, of their synaptic space. In computational models of cortical plasticity following a Hebb-like coincident input-based learning rule, limits in the extents of inducible changes -- a "normalization rule" or "zero-sum synapse substitution rule"-- are commonly imposed for any small part of the neocortex to simulate changes recorded in *in vivo* models. A competitive "Hebbian network" model operating with limited synaptic space in a simulation including pyramidal and inhibitory neurons can provide a reasonable replication of the main findings of *in vivo* cortical plasticity/learning experiments [e.g., 123-124]. It might be noted that relative, but not strict synapse number limits probably apply in real cortex, as overall synapse numbers can apparently be significantly increased in a differentially engaged cortical sector by a period of enriched experience [125] or associative conditioning [27].

Competition has been manifested in most contemporary plasticity studies. Thus, for example: a) Cortical representations of nearby, always-innervated sectors of sensory epithelia rapidly move to occupy sectors that are silenced by deafferentation [e.g., 28-37,126-128], in some carnivore, monkey and human cases over cortical distances of up to several centimeters [33,34,126-128]. Note that the thalamic, cortical and other extrinsic inputs that are functionally disabled by such manipulations are all physically intact, but are competitively disarmed by their relative quiescence. b) As has been demonstrated in almost every plasticity study employing specific conditioning stimuli and requiring specific responses, training of rodents, lagomorphs, carnivores or primates with application of specific behaviorally important tactile or auditory or visual stimuli and/or evoking specific regular movements commonly results in enlarged cortical zones of representations of those stimuli or movements, at the necessary expense of other, previously-dominant afferent inputs and/or outputs. c) Receptive fields are progressively and systematically reduced in size in training experiments in which stimuli move across the skin or vary in sound frequency, consistent with the operation of competitive network mechanisms. In that case, each small skin or cochlear locus is an effective source of coincident input in a competitive network organizing itself on the basis of a coincident input-based learning rule [e.g., 64,69,96]. d) When stimuli are delivered to an absolutely invariant skin location in a behavioral task, receptive fields can enlarge severalfold, consistent with the operation of competition-based remodeling in which there is a competitive winner, i.e., that specific, heavily differentially engaged skin spot [99,100]. e) Intracortical microstimulation at a particular location in somatosensory or motor cortex can result in the competitive enlargement of the representation of the specific inputs initially overtly represented only at the conditioning site [129,130] --- or of the specific movements evoked by intracortical microstimulation only at that site [131]. These newly effective inputs --- in the case of motor cortex, newly evoked movements --- come to be represented over progressively larger cortical territories, achieved by a dramatic competitive substitution for previously dominant inputs and/or effective outputs.

3) *Neuronal group/cell assembly formation.* As has been earlier emphasized, Hebb initially postulated that nearly simultaneously activated cortical neurons will strengthen their mutual connections in a cortical net, and thereby become progressively more strongly coupled members of cooperative cell assemblies. Edelman and later other investigators refined and extended those arguments [see 114,2,3, for reviews] a) by positing that functional groups of cooperating neurons constitute the input co-selecting machine, and b) by demonstrating that such groups form from realistically configured cortical network models driven to change using coincident input-based learning rules [113, 2, 132].

In support of this general view, experimentalists and theorists have pointed out that: a) Single neurons convey relatively little information about behaviorally important stimuli [e.g., 133-135]. Distributed population responses are required to account for stimulus recognition or for the representations of learned behavioral capabilities [136-138,97,100]. b) In several important test cases, it would appear that progressively strengthened coupling of neurons in the cortical network that emerges with behavioral training accounts for the increasingly stronger distributed neuronal response coherence that underlies improvements in behavioral performances [97,100]. c) Neurons recorded together at any given cortical locus have a significant probability of responding like their neighbors, although that probability declines as one ascends sensory system hierarchies [e.g., 133-135]. d) Dense-sample response mapping experiments have provided a direct reconstruction of neuronal groups in the primary somatosensory cortex. There, large groups of neurons up to a millimeter or more across can emerge in behavioral experiments that engage cortical networks with powerfully coherent, repetitive inputs [49,99,100]. The thousands of pyramidal cells within a given layer in these large groups of cooperative neurons have virtually identical response properties, and appear to be so strongly positively coupled that they respond nearly simultaneously to behaviorally important stimuli. e) Finally, the neuronal memberships of cooperating cell groups have been experimentally manipulated. In intracortical microstimulation conditioning experiments, for example, the populations of neurons representing a specific input combination can be easily enlarged several hundred-fold [129,130]. These striking neuronal group membership changes are closely paralleled by changes in coupling strengths between neuron members of the remodeled neuronal group [139], and as an apparent consequence, by a dramatic sharpening of the distributed temporal coherence of stimulus-evoked responses [140].

It might be noted that the formation of very large, continuous neuronal groups that participate together in generating cortical response specificity is more powerfully expressed in cortical areas that have more anatomically topographic and less convergent/divergent inputs, because they are delivered proportionally more powerful temporally coherent inputs into the cortical net.

There is a growing appreciation that the specific responses of cortical neurons are also contributed to by cortical activity in a broad surround --- as revealed, for example, by manipulating those perimeter influences [e.g., 141-144]. Pavlov perhaps first understood that the engagement of a specific input in a learning task conferred changes that applied for widely surrounding inputs [14]. Such "stimulus generalization" effects imply conferred changes away from the most directly engaged cortical network zone into a significant surround. Such effects have now been directly demonstrated in cortical learning studies [99,100; 97].

4) *Multiple-field representation of learned behaviors.* Any real behavior engages many cortical areas. There are on the order of 100 functional areas in the human cerebral cortex [145,146]. These cortical areas have field-specific a) input sources, b) input dispersions, c) functional response properties, and d) output projection destinations. Any new behavior engages many cortical fields, and behavioral performance gains are almost invariably accounted for by changes in multiple areas, which make area-specific contributions to emergent or refined abilities. To cite a specific studied example, if a monkey is trained to detect a difference between stimuli applied to the hand when it is held in static position, signalling that detection by moving the hand, a) changes in cortical area 3b are induced that reflect progressive improvements in fine discriminative abilities [99,100]; b) almost equally significant representational changes can be induced in cortical area 1, although their contributions to the evolving behavior are not clear; c) marked changes in cortical area 3a are believed to reflect the role that this cortical area plays in providing inputs to area 4 that contribute to the initiation of a hand movement [147]; and d) on the basis of other studies, we know that cortical area 4 would be remodeled to exaggerate the representation of the specific hand movement adopted as the motor response. Another dozen or more sensory and motor cortical areas would also be relatively directly engaged by this simple behavior. Given the near universality of positive cortical plasticity changes recorded in learning experiments within every cortical system and area in which they have been looked for, it is likely that all or nearly of these fields would be modified by this evolving behavior, and that each would contribute individually to its practice-based improvement.

5) *Modulation of plastic changes as a function of behavioral state; stable representational platforms and the formation of "habits".* In operant conditioning studies, changes in cortical representations are induced in attended behaviors, but not by application of equally heavy, passively received inputs [99,100,101]. In classical conditioning studies, changes are directly correlated with the emergence or conditioning, endure as long as conditioning endures, and are reversed by behavioral extinction [e.g., 74,77-82,87].

In the development of many learned behaviors, initial practice trials are closely attended to, but as the behavior progresses it comes to be more and more automatically performed. In the initial, closely attended epoch of learning, cortical engagement appears to be far greater [148, and unpublished results]. As the behavior is repeatedly performed it becomes progressively more automatic, and at least some of the cortical representational changes induced in the early learning period will fade, returning cortical representations back to a base form.

This reversion of cortical "maps" to a base form was hypothesized to occur by Leyton and Sherrington [7], in their studies of the plasticity of movement maps in great apes. William James had earlier emphasized the advantages of the cortex operating as a learning machine that could carry learning to the level of automatic behavior ("habit") --- at which point the plasticity machinery would no longer have to be directly engaged to sustain the behavior [1].

There are at least two ways that an adept movement behavior or fine discriminative ability might be sustained as the behavior passes into a more automatic performance epoch. Both may come into play in sustaining trained abilities. First, the behavior may be sustained substantially extracortically, with a powerful cortical form of representation contributing as a teacher to the creation of parallel basal ganglion and/or cerebellar and/or other representations whose subsequent maintenance does not necessitate close behavioral attention or behavioral reinformement. Second, some crucial aspects of the representation of the behavior may be sustained in the cortex while other initially-induced representational changes fade. In practice, we overpractice core behaviors that come to be relatively automatic and that can be sustained with limited attended rehearsal over long periods of time. In learning such behaviors, the cortex is massively engaged, and subject to dramatic representational remodeling, which reverts back in the direction of a base form as the behavior comes to be automatic. These core behaviors constitute relatively predictable platforms for their many refinements and extensions that mark our behavioral progress in life. Maintenance of behavioral refinements require attentive practice to develop, and often require continual attentive practice to sustain. This lifelong learning and active behavioral maintenance presumably continually heavily engages the learning machinery of the cerebral cortex.

Summary. Main features of spatiotemporal response patterns induced by learning

On the basis of these contemporary studies of cortical plasticity induced by learning, we have a growing understanding of the basic form of the cortical representations of learned behaviors and memories -- the long-sought "cortical engram" [149; also see 12]. What can we now say about its specific form?

1) *Main spatial features.* When learning engages the cerebral cortex, emergent or improving behaviors are represented at multiple system levels. Each cortical area that is relatively directly engaged by the behavior is remodeled by it. By that remodeling, the behavior is represented in a more salient way, in two respects. First, through initial, closely attended practice repetitions, it is represented by progressively larger neuronal populations. Second, as learning progresses, excited neurons are progressively more stronger positively coupled to form more salient and more robust neuronal groups and distributed assemblies.

In relatively anatomically constrained cortical areas like cortical area 3b, new behaviors commonly deliver powerfully coherent inputs into the cortical network zones that they engage. Nearly simultaneously delivered inputs are co-selected there by the operation of competitive, coincident input-based selection processes. Further, progressively more coherently responding groups of cortical neurons provide strongly temporally synchronized schedules of inputs that are delivered into the cortical network itself. This growing cortical source of synchronized activity contributes to the recruitment of neuron members to enlarging cooperative cortical neuronal groups that are representing the key sensory inputs that are crucial to the behavior. Moreover, these powerful cortical foci of temporally synchronous activity have proportionally strong influences on input selection over a wide cortical surround. Such distributed horizontal network effects confer the behavioral gains that emerge for surrounding skin or retinal or cochlear regions that were not directly engaged in the behavioral training.

In relatively anatomically constrained cortical areas, i.e., that are a) more strictly topographic, b) fed by less divergently and convergently projected afferents c) that are delivered in a simpler form from fewer input sources --- fields like cortical areas S1 or A1 --- the neurons representing key sensory inputs crucial to the behavior can be arrayed in largely continuous patches that can extend over cortical distances of more than a millimeter, with tens of thousands of pyramidal cells over continuous sectors having nearly identical stimulus-specific response characteristics. The spatial form of representation of pieces of learned behaviors contributed by different cortical areas must differ systematically at progressively more divergently and convergently connected cortical zones, i.e., at successively "higher" levels in the limited hierarchies of cortical "systems". These differences arise because more temporally dispersec inputs are delivered into these levels. Higher-level inputs come from progressively more diverse cortical sources, and are progressively more widely anatomically distributed into these fields --- until, at the "top" of serial cortical systems, cortical areas receive virtually all-to-all inputs that are complexly derivative from many "lower" cortical areas. Operating on the basis of coincident input-based selection mechanisms in a high-level field, a given, behaviorally important input can very rapidly dominate neuronal responses because no specific earlier input can ordinarily establish a competitive stranglehold. However, that rapidly emergent representation can apply only for small, scattered neuronal islands. While neuronal memberships in the locally coupled groups at higher representational levels appear to be very small, response sampling results derived in hundreds of waking monkey experiments indicate that many thousands, or tens or hundreds of thousands of such small neuronal groups must contribute to the representation of any practiced behavior or memory at high system levels. At all involved cortical areas and levels, hundreds of thousands or millions of cortical neurons must be engaged in their representation.

2) *Main temporal features.* Cortical plasticity carried into the cortical network generates progressively more strongly coupled cell assemblies. That progressive increase in coupling strengths contributes to representational salience, in two main ways. First, it results in the production of a progressively more temporally coherent responding, more sharply marking all temporal events in the representation of behaviorally important stimuli. Second, with this increased distributed response synchronicity, the more temporally coherent outputs of the cortical cell assemblies representing pieces of the learned behavior provide a far more powerful input to higher-level areas that are undergoing parallel remodeling on the basis of a coincident-input plasticity rule. Abeles, Gerstein and others [150,151] have emphasized that progressive changes in network coupling will generate progressively more synchronous cortical responses. Recent studies have repeatedly confirmed that the alignment of distributed responses in time due to increased positive coupling in cortical networks is a main feature of learning-induced plasticity.

It should be noted that temporal input coincidence-based learning systems will use *all* temporal events as a basis for generating a complex stimulus representation. Inputs are delivered into the cortical network over time from multiple extrinsic and intrinsic sources. The temporal structure of the input stream is enriched by these other stimulus-induced and cognitively-generated input sources, which add important temporal complexity to stimulus representations. While this subject is beyond the scope of the present review [see 152-154], it should be understood that this temporal event signature is what the cortex operates on to produce its context-sensitive, temporal coincident-based representational constructions.

ACKNOWLEDGMENTS

Research conducted by our W. M. Keck Center group was supported by NIH Grant NS-10414, the Coleman Fund, and Hearing Research, Inc. The authors thank the many collaborators who have contributed to these studies, especially Drs. Randolph Nudo, Terry Allard, Sharon Clark, Kamil Grajski, Gregg Recanzone, Bret Petersen, Xiaoqin Wang, Koichi Sameshima and Dean Buonomano.

REFERENCES

1 James, W. The Principles of Psychology, Vol. 1. New York: Dover, 1890.
2 Malsburg C von der, Singer W. In: Rakic P, Singer W, eds. New York:Wiley,1988; pp. .
3 Churchland PS, Sejnowski TJ. The Computational Brain. Cambridge MA: MIT Press, 1992.
4 Brown-Sequard CE Comptes Rendus Mem Soc Biol 1884:36:301-333.
5 Baer A Pflüger's Arch 1905: 106:523-567.
6 Graham Brown T, Sherrington CS Proc Roy Soc Lond 1912: 85:250-277.
7 Leyton ASF, Sherrington CS Q J Exptl Physiol 1917: 11:135-222.
8 Wedensky NE Pflüger's Arch 1903: 100:1-144.
9 Lashley KS Am J Physiol 1923: 65:585-602.
10 Thatcher RW, John ER. Foundations of Cognitive Processes, New York: Wiley, 1977.
11 Woody CD. Conditioning: Representation of Involved Neural Functions. New York:Plenum, 1982.
12 Woody CD Ann Rev Psychol 1986: 37:433-493.
13 Farley J, Alkon DL Ann Rev Psychol 1985: 36:491-494.
14 Pavlov I P. Conditioned Reflexes. An Investigation of the Physiological Activity of the Cerebral Cortex. London: Oxford Univ Press, 1927.
15 Thorndike EL. The Animal Intelligence. An Experimental Study of Associative Processes in Animals. New York: MacMillan, 1898.
16 Berlucchi G, Bentivoglio M Neurosci Abstr 1992: 18:182.
17 Hebb DO. Organization of Behavior. New York: J. Wiley, 1949.
18 Lorente de Nó R. In: Physiology of the Nervous System. Fulton JF, ed., London: Oxford Univ. Press, 1949; pp. 288-313.
19 Bures J, Buresova O. In: Short-term changes in Neural Activity and Behavior. Horn G, Hinde RA, eds., Cambridge: Cambridge Univ Press, 1970; pp. 363-403.
20 Tsumoto T, Prog Neurobiol 1992: 39:209-228.
21 Bear M F, Kirkwood A Curr Opin Neurobiol 1993: 3:197-202.
22 Ramon y Cajal S. In: Cajal on the Cerebral Cortex. An Annotated translation of the Complete Writings. DeFilipe J, Jones EG, eds., New York: Oxford Univ Press, 1911;pp. 465-490.
23 Rosenzweig MR, Bennett EL, Diamond MC Sci Amer 1972: 226:22-29.
24 Rosenzweig MR, Bennett EL, Diamond MC. In: Studies on the Development of Behavior and the Nervous System. Vol. 4. Early Influences. Gottlieb G, ed., New York:Academic Press, 1978;pp. 289-327.
25 Greenough WT, Chang FF. In: Cerebral Cortex. Vol. 7. Development and Maturation of Cerebral Cortex. Peters A, Jones EG, eds., New York:Plenum, 1988;pp. 335-392.
26 Calverley RKS, Jones DG Brain Res Revs 1990: 15:215-249.
27 Keller A, Arissian K, Asanuma H J Neurophysiol 1992: 78:295-308.
28 Franck JI Brain Res 1980: 186:458-462.
29 Kalaska J, Pomeranz B J Neurophysiol 1979: 42:718-633.
30 Rasmusson DD J Comp Neurol 1982: 205:313-316.
31 Merzenich MM, Kaas, JH, Wall JT, Sur M, et al. Neurosci 1983: 10:639-665.
32 Merzenich MM, Nelson RJ, Stryker MP, Cynader MS, et al. J Comp Neurol 1984: 224:591-605.
33 McKinley PA, Jenkins WM, Smith JL, Merzenich MM Dev Brain Res 1987: 31:136-139.
34 Pons TP, Garraghty PE, Ommaya AK, Kaas JH, et al. Science 1991: 252:2857-2860.
35 Chino YM, Kaas JH, Smith EL, Langston AL, et al. Vision Res 1992: 32:789-796.
36 Gilbert CD, Wiesel TN Nature 1992: 356:150-152.
37 Robertson D, Irvine DRF J Comp Neurol 1989: 282:456-471.
38 Cusick CG, Wall JT, Whiting JH Jr, Wiley RG Brain Res 1990: 537:355-358.
39 Calford MB, Tweedale R J Neurophysiol 1991: 65:178-187.
40 Calford MB, Tweedale R Somato Motor Res 1991: 8:249-260.
41 Gellhorn E, Hyde J Jhysiol 1953: 122:371-385.
42 Sanes JN, Wang J, Donoghue JP Cerebral Cortex 1992: 2:141-152.
43 DonoghueJP, Suner S, Sanes JN Exptl Brain Res 1990: 79:492-503.
44 Teuber, Krieger and Bender, cited in Haber WB, Ann NY Acad Sci 1958: 74:14-24.
45 Merzenich MM, Jenkins WM, Middlebrooks JC. In: Dynamic Aspects of Neocortical Function. New York:Wiley, 1984; pp.397-424.
46 Merzenich MM, Jenkins WM J Hand Ther 1993: 8:89-104.
47 Kaas JH Ann Rev Neurosci 1991: 14:137-167.
48 Merzenich MM, Recanzone GH, Jenkins WM, Allard TT, et al. In: Neurobiology of Neocortex. Rakic P, Singer W, eds., Chichester:Wiley, 1988; pp. 41-67.
49 Merzenich MM, Recanzone GH, Jenkins MM. In: Natural and Artificial Parallel Computations. Arbib M, Robinson JA, eds., New York:MIT Press, 1990; pp. 177-201.
50 Merzenich MM, Grajski KA, Jenkins WM, Recanzone GH, et al. Cold Spring Harb Symp Quant Biol 1990: 55:373-887.
51 Wall JT, Kaas JH, Sur M, Nelson RJ, et al. J Neurosci 1986: 6:218-233.
52 Allard TA, Clark SA, Grajski KA, Merzenich MM (unpublished findings)
53 Grajski KS, Allard T, Clark SA, Merzenich MM Exptl Brain Res (in press)
54 Clark SA, Allard T, Jenkins WM, Merzenich MM Nature 1988: 332:444-445.
55 Allard T, Clark SA, Jenkins WM, Merzenich MM J Neurophysiol 1991: 66:1048-1058.
56 Mogilner A, Grossmann JA, Ribary U, Joliot M, et al. Proc Natl Acad Sci USA 1993: 90:3593-3597.
57 Merzenich MM, Clark SA, Jenkins WM, Allard T J Neurosci (to be submitted)
58 Wall PD, Egger MD Nature 1971: 232:542-545.

59 Jenkins WM, Merzenich MM, Recanzone G Neuropsychologia 1990: 28:573-584.
60 Jenkins WM, Merzenich MM In: Progress in Brain Research. Seil FJ, Herbert E, Carlson BM, eds., Amsterdam: Elsevier, 1987.
61 Pons TP, Garraghty PE, Mishkin M Proc Natl Acad Sci USA 1988: 85:5279-5281.
62 Xerri C, Jenkins WM, Merzenich MM, Petersen B, et al. Neurosci Abstr 1991: 16:843.
63 Castro-Alamancos M A, Garcia-Segura LM, Borrell J Eur J Neurosci 1992: 4:853-863.
64 Xerri C, Stern J, Merzenich MM J Neurosci 1993 (in press)
65 Kossut M Prog Neurobiol 1992: 39:389-422.
66 Guic E, Rodriguez E, Caviedes P, Merzenich MM Neurosci Abstr 1993: 19:163.
67 Fox K J Neurosci 1992: 12:1826-1838.
68 Milliken GW, Nudo RJ, Grenda R, Jenkins WM, et al. Neurosci Abstr 1992: 18:506.
69 Xerri C, Jenkins WM, Peterson B, Santucci S, et al. Neurosci Abstr 1993: 19:1570.
70 Wang X, Beitel R, Schreiner CE and Merzenich MM Neurosci Abstr 1993: 19:1422
71 Pascual-Leone A, Torres F Brain 1993:116:39-52.
72 Pascual-Leone A, Cammarota A, Wasermann EM, Brasil-Neto JP, et al. Ann Neurol 1993: 34:33-37.
73 Rosenzweig MR, Bennett EL, Krecht D J Comp Physiol Psychol 1964: 57:438-439.
74 Disterhoft JF, Stuart DK J Neurophysiol 1976: 39:266-281.
75 Bakin JS, Weinberger NM Brain Res 1991: 536:271-286.
76 Edeline JM, Weinberger NM Behav Neurosci 1993: 107:82-103.
77 Kraus N, Disterhoft JF Brain Res 1982: 246:205-215.
78 Kitzes LM, Farley GR, Starr A Exp Neurol 1978: 62:678-697.
79 Buchhalter J, Brons J, Woody C Brain Res 1978: 156:162-167.
80 Diamond DM, Weinberger NM Brain Res 1986: 372:357-360.
81 Weinberger NM, Ashe JH, Metherate R, McKenna TM, et al. Concepts Neurosci 1990: 1:91-132.
82 Ahissar E, Vaddia E, Ahissar M, Bergman H, et al. Science 1992: 257:1412-1415.
83 Weinberger NM, Javid R, LepanB Proc Natl Acad Sci USA 1993: 90:2394-2398.
84 Woody CD, Engel J J Neurophysiol 1972: 36:230-241.
85 Woody CD, Black-Cleworth P J Neurophysiol 1973: 36:1104-1116.
86 Woody CD, Gruen E, Birt D Brain Res 1991: 539:76-84.
87 Aou S, Woody CD, Birt D J Neurosci 1992: 12:549-559.
88 Iriki A, Pavlides C, Keller A, Asanuma H J Neurophysiol 1991: 65:1435-1441.
89 Keller A, Iriki A, Asanuma H J Comp Neurol 1990: 300:47-60.
90 Bienenstock EL, Cooper LN, Munro PW J Neurosci 1982: 2:39-48.
91 Clothiaux EE, Bear MF, Cooper LN J Neurophysiol 1991: 66:1785-1804.
92 Stanton PA, Sejnowski TJ Nature 1989: 339:215-218.
93 Dudek SM, Bear MF J Neurosci 1993: 13:2910-1918.
94 Kirkwood A, Dudek SM, Gold JT, Aizenman CD, et al. Science 1993: 260:1518-1521.
95 Marsh JT, McCarthy DA, Sheatz G, Galambos R EEG Clin Neurophysiol 1961: 13:224-234.
96 Jenkins WM, Merzenich MM, Ochs, M, Allard T, et al. J Neurophysiol 1990: 63:82-104.
97 Jenkins WM, Beitel R, Xerri C, Peterson B, et al. Neurosci Abstr 1993: 19:162.
98 Recanzone GH, Jenkins WM, Hradek, GH, Merzenich MM J Neurophysiol 1992:67:1015-1030.
99 Recanzone GH, Merzenich MM, Jenkins WM, Grajski KA, et al. J Neurophysiol 1992: 67:1031-1056.
100 Recanzone GH, Merzenich MM, Schreiner CS J Neurophysiol 1992: 67:1071-1091.
101 Recanzone GH, Schreiner CE, Merzenich MM J Neurosci 1993: 13:87-103.
102 Mitz AR, Godschalk M, Wise SP J Neurosci 1991: 11:1855-1872.
103 Germain L, Lamarre Y Brain Res 1993: 611:175-179.
104 Zohary E, Celebrini S, Britten KH, Newsome WT Science, 1993 (in press)
105 Rosenblum KN, Meiri N, Dudai Y Behav Neural Biol 1992: 59:49-56
106 Aizawa H, Inase M, Mushiake H, Shima K, et al. Exptl Brain Res 1991: 84:668-671.
107 Rolls ET, Bayles GC, Hasselmo ME, Nalwa V Exptl Brain Res 1989: 76:153-168.
108 Frafton ST, Mazziota JC, Presty S, Friston KJ, et al. J Neurosci 1992: 123:2542-2548.
109 Miyashita Y, Chang HS Nature 1988: 331:68-70.
110 Sakai K, Miyashita Y Nature 1991: 354:152-155.
111 Eskandar EN, Richmond BJ, Opticon LN J Neurophysiol 1992: 68:1277-1295.
112 Miyashita Y Ann Rev Neurosci 1993: 16:245-263.
113 Edelman GM, Finkel LH. In: Dynamic Aspects of Neocortical Function, Gall E, Edelman GM, eds., New York: Wiley, 1985;pp. 653-695.
114 Edelman GM. Neural Darwinism: The Theory of Neuronal Group Selection. New York:Basic, 1987.
115 Edelman GM. In: The Mindful Brain, Edelman GM, Mountcastle VB, eds., Cambridge, MA: MIT Press, 1972;pp. 51-100.
116 Kossel A, Bonhoeffer T, Bolz J Neuroreport 1990: 1:115-118.
117 Alonso A, deCurtis M, Llinas R Proc Natl Acad Sci USA 1990: 87:9280-9284.
118 Fox K, Daw NW Trends Neurosci 1993:16:116-122.
119 Aroniadou VA, Maillis A, Stefanis CC Neurosci Letters 1993:151:77-80.
120 Montague PR, Gally JA, Edelman GM Cerebral Cortex 1991: 1:199-220.
121 Dawson TM, Dawson VL, Snyder SH Ann Neurol 1992: 32:297-311.
122 Verna A, Hirsh DS, Glatt CE, Ronnett GV, et al. Science 1993: 259:381-384.
123 Grajski KS, Merzenich MM. In: Neural Information Processing Systems, Vol. 2. Touretzky DL, ed., San Mateo, CA: Morgan Kaufman, 1990;pp. 52-59.
124 Mazzoni P, Andersen RA, Jordan MI Proc Natl Acad Sci USA 1991: 88:4433-4437.
125 Renner MM, Rosenzweig MR. Enriched and Impoverished Enironments: Effects on Brain and Behavior. New York:Springer, 1987.

126 Cohen LG, Bandinelli S, Findley TW, Hallett M Brain 1991: 114:615-627.
127 Fuhr P, Cohen LG, Dang N EEG Clin. Neurophysiol 1992: 85:43-60.
128 Yang TT, Gallen C, Ramachandran V, Cobb S, et al. Neurosci Abstr 1993: 19:162.
129 Recanzone GH, Dinse HA, Merzenich MM Cerebral Cortex 1992: 2:181-196.
130 Recanzone GH, Merzenich MM. In: Memory: Organization and Locus of Change. New York: Oxford Univ. Press, 1991: pp. 217-238.
131 Nudo RJ, Jenkins WM, Merzenich MM Somato Motor Res 1990: 7:463-483.
132 Pearson JC, Finkel LH, Edelman GM J Neurosci 1987: 7:4209-4223.
133 John ER Science 1972: 177:850-864.
134 Gochin PM, Miller EK, Gross CG, Gerstein GL Exptl Brain Res 1991: 84:505-516.
135 Gawne TJ, Richmond BJ J Neurosci 1993: 13:2758-2771.
136 Lehky SR, Sejnowski TJ, Desimone R J Neurosci 1992: 12:3568-3581.
137 Young MP, Yamane S Science 1992: 256:1327-1331.
138 Rolls ET Proc Roy Soc Lond 1992: 335:11-20.
139 Dinse H, Recanzone GH, Merzenich MM Neuroreport 1993 (in press)
140 Dinse HR, Recanzone GH, Merzenich MM. In: Parallel Processing in Neural Systems and Computers. Eckmitler R, Hartmann G, Hauske G, eds., New York: Elsevier, 1990;pp. 65-70.
141 Eysel ET Prog Brain Res 1992: 90:407-422.
142 Jacobs KM, Donoghue JP Science 1992: 251:944-947.
143 Gilbert CD Neuron 1992: 9:1-13.
144 Ramachandran VS, Gregory RL, Aiken W Vis Res 1993:33:717-721.
145 Merzenich MM, Kaas JH. In: Progress in Psychobiology and Physiological Psychology. Sprague J, Epstein A, eds., New York: Academic Press, 1980; pp. 1-42.
146 Felleman DJ, Van Essen DC Cerebral Cort 1991: 1:1-47.
147 Recanzone GH, Merzenich MM, Jenkins WM J Neurophysiol 1992: 62:1057-1070.
148 Haier RR, Siegel BV Jr, MacLachlan E, Soderling E, et al. Brain Res 1992: 570:134-143.
149 Lashley KS Symp Soc Exptl Biol 1950: 4:454-482.
150 Abeles M Corticonics: Neural Circuits in the Cerebral Cortex. New York, Cambridge University Press, 1991.
151 Gerstein GL, Bedenbaugh PH, Aertsen AM IEEE J 1989: 36:4-14.
152 Richmond BJ, Optican LM, Spitzer H J Neurophysiol 1990: 64:351-379.
153 Singer W Ann Rev Physiol 1993: 55:349-374
154 Tononi G, Sporns O, Edelman GM Cerebral Cortex 1992: 2:310-335.

AUTHOR INDEX