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"Cortical plasticity and memory"

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These are preliminary lecture notes, intended only for distribution to participants.

Cortical plasticity and memory

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The roles of extrinsically modulated, plastic Hebb-like synapses and dynamic cortical cell assemblies underlying cortical plasticity in learning and memory operations are described. From our understanding of the distributed form of representation of learned behaviors in somatosensory and auditory cortical fields, and given new findings about the nature and distribution of responses representing learned and remembered stimuli in the inferior temporal cortex, a hypothetical picture of the cortical engram representing learned behaviors and memories is posited.

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Introduction

Our objective is to summarize aspects of studies of cortical representational plasticity that have contributed to our understanding of the 'cortical engram' representing learned behaviors and memories. Many thousands of reports have contributed to our concept of cortical plasticity and its role in learning and memory. In this brief review, we focus on a fraction of the work relevant to this subject that has been reported over the past 2 years. The reader is urged to use this as a starting point, as the majority of reports cited here have important and usually manifold precedents and parallels.

Representational plasticity in adult cortex: non-declarative memory

Studies conducted in our laboratory over the past 2 years have demonstrated that distributed changes in neuronal responses in the primary somatosensory [1•,2••] and auditory [3•] cortical fields of adult monkeys probably account for training-induced changes in specific behavioral discriminative abilities. During frequency-discrimination training, an increase in the cortical territory of representation of a narrow band of sound frequencies is strongly correlated with a many-fold improvement in frequency difference limens in that range. Cortical representational changes emerge progressively as a monkey becomes more proficient at this behavioral task. Specifically, the narrow frequency band employed in behavioral training comes to be represented in correspondingly finer spatial grain in the cortex. Psychophysical changes are largely if not exclusively restricted to the neighborhood of the frequency range at which the monkey is behaviorally trained. Physiological changes are restricted to the neighborhood of the zone of representation of the behaviorally delivered frequencies in cortical field A1. If training is shifted to a second more distant frequency, discriminative abilities at the originally trained frequency band progressively deteriorate toward the naive condition.

In the somatosensory cortex, behavioral frequency difference limens have been determined in monkeys trained in a flutter-vibration frequency discrimination task [1•,2••,4]. In these experiments, low-amplitude stimuli were delivered to a small invariant spot on one finger. An examination of the frequency discrimination abilities on nearby skin surfaces revealed that some training-induced performance gains also applied to nearby, but probably not to distant, untrained skin surfaces. An initial training period to enable the monkeys to become proficient at this behavior was followed by several weeks of further training, during which major changes in the details of the cortical spatiotemporal representations of the surfaces of roughly three fingers were induced. This occurred in parallel with progressive gains in frequency discrimination abilities. The spread of changes into the zones of representations of the remainder of the stimulated finger and into the territories of representations of adjacent fingers suggests that much of the change induced by this behavior in the primary somatosensory cortical field is attributable to plasticity in the cortical network itself, and that cortical neuronal response selectivity is strongly influenced from the surrounding cortical network.

Severalfold increases in receptive field sizes have been recorded as a consequence of training in these monkeys [4]. However, neither these dramatic changes in response selectivity, nor commonly recorded increases in cortical representational territories, or often observed increases in population response magnitudes correlate very strongly with gains in frequency discrimination performance. On the other hand, a striking increase in distributed neuronal response coherence for individual cycles of the vibratory frequencies applied in training

Abbreviations

ACh—acetylcholine; **ICMS**—intracortical microstimulation; **LTP**—long-term potentiation.

does correlate with frequency discrimination capabilities, with a correlation coefficient of 0.98. Thus, as a consequence of behavioral training, a progressively more temporally coherent representation of the individual events of these sequenced inputs results in their progressively more salient representation. This increase in response coherence is hypothesized to principally result from an increase in the strength of positive coupling of neurons in the behaviorally engaged sector of these cortical fields [2••,5].

In both auditory and somatosensory frequency discrimination tasks, plastic changes are induced in attended, rewarded behaviors. In control studies with equivalent stimulation procedures in which stimuli are unattended, no significant representational changes are recorded [2••,3•].

In a second series of experiments studying tactile flutter-vibration frequency discrimination behavior in primates, Mountcastle and colleagues demonstrated that strongly discrimination-dependent responses are evoked in the primary motor cortex in well trained macaque monkeys [6•]. Because these highly selective responses are task specific, they almost certainly emerge in magnified form as a consequence of training. In primary somatosensory cortex, the evolution of a progressively more coherent representation of these signals with training [2••], probably provides a major source of motor cortex input from which these discrimination-dependent motor cortex responses are generated.

In these discrimination training studies in somatosensory, motor and auditory cortices, investigators emphasized that the enduring representations of these behaviors are distributed. In sensory cortices, behavioral performance could only be accounted for by spatiotemporally reconstructing emergent responses across their distributed cortical representations. No single neuron conveyed the information required for making these discriminations: stimulus representation involving very large numbers of neurons across a wide cortical zone accounted for discrimination coding.

The emergence of enduring, robust distributed responses with learning has also been noted in a mapping experiment conducted in a kinesthetic representational field, area 3a [7•], and in single-unit waking monkey studies conducted in prefrontal [8•] and inferior temporal [9,10••,11••] cortex. In these studies, very highly stimulus-selective responses emerged for the majority of neurons sampled across a broad region [7•] or across a large continuous sector of a cortical zone previously driven by other inputs [8•] as a direct consequence of behavioral training. In other studies, remarkable response selectivity to complex stimuli appeared to arise as a direct consequence of a limited period of learning (for examples, see [9,10••,11••]). It is now reasonable to conclude that training-induced changes substantially account for neuronal response selectivity in at least most awake monkey experiments constructed around a detection, discrimination or stimulus recognition training base. The refined activity recorded in most such preparations emerges during training. At the same time, it should be noted that over-training leading to a little-attended habit (see [2••,3•]) can result in a consequent dramatic reduction of task-specific responses [12].

The pace of representational plasticity studies is also accelerating in studies of the human neocortex. Studies of subjects practicing a complex motor skill show that local blood flow progressively increases during the period of a few practice trials in motor cortex, in supplementary motor cortex, and in the pulvinar [13•]. Evoked-potential mapping experiments have tracked major representational changes over the course of sequenced-movement training (see [14,15]). Again, the distributed changes recorded during the early period of training for a complex sensorimotor task can be reduced dramatically by an intensive practice period [16•].

While distributed representational changes are generated by classical or operant conditioning in the primary auditory and somatosensory cortex, they have yet to be explored at the same level of detail in primary visual cortex. On the other hand, psychophysical experiments have demonstrated severalfold changes in the temporal [17••] and spatial [18] processing of perceptual 'primitives' of preattentive vision that are argued to arise from area 17 plasticity. These contemporary psychophysical studies continue a rich history of perceptual learning/non-declarative memory experiments, conducted mainly in the visual sense, which manifest the plasticity of the most fundamental aspects of perception [19–21].

Recent studies of cortical representational remodeling following restricted retinal lesions (see [22,23]) document a probable capacity for at least limited learning-inducible plasticity in area 17. Results from studies of lateral contributions to the selective responses of visual cortical neurons, revealed by the use of visual blanking stimuli (see [24]) or local injections of GABA (see [25]), are consistent with the distributed cell-assembly genesis of area 17 response selectivity, which is presumably subject to significant modification in detail in adults (for reviews, see [26,27]). Important evidence for primary visual cortex plasticity is also provided by the studies of Fregnac, Schulz and colleagues [28••,29••], who have performed a direct assessment of the capacity for alteration of receptive field selectivity for single neurons in primary visual cortex. They have shown that coupling of natural teaching stimuli (which have orientations or binocular disparities that differ from those recorded originally) with local cortical stimulation, which results in depolarization of studied neurons, results in progressive changes in neuronal response selectivity in the direction of the teaching model. While the capacity for modification is much greater in critical period preparations than in adults, there is still a substantial capacity for shifting response selectivities in adults. As with the somatosensory plasticity studies recounted earlier, these experiments strongly support the two hypotheses that: first, selective visual response properties are in large part the product of horizontal influences across cortical networks, i.e. a product of distributed cortical cell assemblies; and second, that modification of response selectivity during learning can be achieved by altering

the specific identities and strengths of these local cortical network influences.

More dramatic cortical representational plasticity recorded in peripheral lesion experiments

Cortical representational plasticity experiments conducted after large-scale peripheral deafferentations have recorded representational translocations over surprising distances in adult brains. The recent studies of Pons and colleagues [30••] have shown that the entire zone of representation of the arm and hand in primary somatosensory cortex — more than a centimeter across in the somatosensory koniocortical field, cortical area 3b — can be occupied by an expanded representation of limited surfaces of the face in adult monkeys, in which dorsal rhizotomies had been performed to denervate one or both arms 9 or more years previously. It should be noted that changes in cortical field representations in patients suffering spinal root lesions probably differ from those in patients with arm amputations (for a review, see [31•]). In rhizotomy or extensive brachial plexus-lesioned patients, phantom limbs never shorten perceptually, and the nature of sensations generated by stimulation of the stump skin are immutable. By contrast, in amputees, the perceived phantom limb perceptually shortens ('telescopes'), often dramatically, and severalfold changes in tactile sensitivity and acuity emerge on the stump skin. Moreover, while stimuli on the amputation stump are always correctly located to the stump skin, in parallel with telescoping, sharply localized sensations are also often evoked on the phantom limb. These second, 'ghost' sensations can be mapped topographically by probing the surfaces of the stump in an orderly way (see [31•]).

Reinforced by physiological evidence from a primate model (see [32]), these perceptual changes have been interpreted as revealing a competition-based translocation of the cortical representation of the stump, which comes to occupy the cortical zones formerly representing the skin of the now-missing member (see [31•,32]). Such studies have been reinvigorated over the past year by the discovery by Ramachandran and colleagues [33•] that stimulation of the face in arm amputees can also evoke sharply localized 'ghost' sensations on the phantom hand. These anomalously referred sensations can be evoked by face stimulation within days after the amputation. Over a subsequent period they change progressively to more completely involve the phantom hand, and can be mapped on the phantom hand in topographic detail by applying stimuli in orderly patterns across the face. An intriguing possibility is that the mapping of these progressive sensational changes might provide a method for tracking progressive input competition-based changes in cortical representations.

In studies of movement representations in humans suffering limb amputations, a several centimeter-distance lateral translocation of the zones from which surviving proximal limb and shoulder movements can be evoked has been recorded [34•]. These movement representation studies should, however, be interpreted with the appreciation that proximal movements are normally at least weakly, convergently represented in the cortical area 4 zone of representation of more distal movements (see [35••]). Thus, these dramatic and rapid changes in movement representations over long cortical distances do not necessarily involve representational translocations that are equivalent to those described for the skin surface representations following amputation.

Recorded cortical representational remodeling and the parallel psychophysical observations following surgical amputation have been interpreted as manifesting the basic competitive nature of the processes governing cortical plasticity and learning [32]. After amputation, the competitive effectiveness of afferents innervating a large skin surface and large deep afferent region that normally dominate neuronal responses over wide sectors of a number of cortical fields is completely lost. The normally active inputs from surrounding skin surfaces appear to move quickly to competitively occupy these 'vacated' central representational zones. The topographic remapping of the expanded inputs of the surrounding intact skin indicates that new, highly selected responses must be generated in topographic order, across long cortical distances. From the point of view of memory processes, these observations, along with studies of representational plasticity in learning models, demonstrate (see [32]) that 'perceptual constancy' is not explained by locational constancy (see also [36•]), and that there is a much greater capacity for alternative forms of stimulus representation in the primary somatosensory and motor cortices than was earlier believed.

In the pragmatic realm, these studies point to possible strategies for ameliorating phantom limb pain, to more direct models of the genesis of learning-based movement disabilities, and to experimental approaches for studying the neurological bases of recovery from peripheral and brain injury (see [32]). An especially interesting recent representational plasticity model in this last respect comes from studies in rats with motor cortex lesions [37•]. It reveals that recovery of previously learned movement behaviors can be achieved when 'correct' movements are rewarded by ventral tegmental nucleus stimulation through a rehabilitation period. Successful rehabilitation is dependent upon delivering this 'cognitive' signal; without ventral tegmental nucleus stimulation, rats never recover behavioral abilities, despite an intensive behavioral retraining regimen.

Neural bases of representational remodeling

Hebb-like synapses

Many experiments conducted over the past 2 years have reinforced the conclusion that cortical response changes are temporal coincidence-based and accounted for by Hebb-like synapses, and as Hebb envisioned, by the

modification of cortical cell assemblies or groups induced by these synaptic effectiveness changes in distributed cortical networks. Changes in the effectiveness of extrinsic inputs, and changes in local neuronal memberships and intrinsic input effectiveness in local cell assemblies, together confer neuronal response selectivity.

We have already discussed several lines of evidence that suggest that cortical cell assemblies contribute to the response selectivities of individual cortical neurons. Recent evidence for the possible early genesis of coupled neuronal groups or 'columns' has been provided by the startling finding that neighboring neurons within restricted, sharply bounded columns are actually directly electrically coupled through a period of early cortical development [38••]. This is a plausible basis for the generation of locally favored synaptic connections over relatively strictly bounded neuronal 'columns,' 'groups' or 'segregates' [39] in the developing cortex. Another manifestation of coupled neuronal groups, this time in adult cortex, has been provided by the cortical slice studies of Silva, Connors and colleagues [40]. They have shown that when a cortical slice is weakly depolarized, discretely bound columns of neurons several hundred microns across all discharge with in-phase oscillations that originate from a patch of coupled layer 5 bursting neurons. In still another approach to the question of the functional nature of cortical 'mini-columns' or 'groups', intracortical microstimulation (ICMS) experiments have demonstrated that the neuronal memberships of functional mini-columns with nearly identical stimulus response characteristics can be enlarged by up to several hundredfold by a period of very low level ICMS [41••]. In parallel with these representational changes, local network coupling is strongly positively increased [42]. Such experiments are interpreted as indicating that the neuronal members of relatively strongly coupled neurons comprising cortical 'mini-columns' are continually plastically changing in adult cortex [5,41••,42]. Montague and colleagues [43•] have pointed out the important implications for neuronal group or column formation of the presence of a highly diffusible second messenger, e.g. nitric oxide [44••]. These authors forcefully argue that nitric oxide release probably spreads synaptic effectiveness changes from any given local release site tens to hundreds of microns across cortical networks. This induces event-linked changes in horizontal connections and thereby alters selective neuronal responses over a significant surrounding columnar zone [43•].

It should be noted that much of the change generated in cortical plasticity is not attributable to strictly 'Hebbian' effects. Hebb hypothesized that changes in synaptic strength might apply for inputs received by neurons that are driven to discharge by just-preceding inputs. However, the genesis of enduring synaptic effectiveness changes in the cortex does not necessarily require postsynaptic neuronal discharge [41••,45]. Indeed, the many instances of recorded cortical representational translocations in which neurons come to discharge when driven by newly effective inputs implies that the effectiveness of subthreshold activity can be progressively altered with experience. Finally, the release of highly diffusable second messengers can provide a signal for induction of synaptic effectiveness changes that is not strictly Hebbian. At the same time, all of these effects might be regarded as 'Hebb-like,' in the sense that they all result in the mutual strengthening of inputs that are delivered to cortical neurons nearly simultaneously in time.

Studies of representational changes following digital syndactyly and training in tactile discrimination tasks, innervated skin island transfers and peripheral nerve transections/reconnections, provide strong evidence that the details of somatosensory cortical representations are time-coincidence based (for examples, see [2••,32,46••,47]), and that the recorded changes are probably accounted for by the operation of Hebb-like synapses. The experiments of Fregnac, Schulz and colleagues [28••,29••], in which enduring changes in input effects were generated by coupling a new stimulus with cell depolarization, provide a direct instantiation for the operation of Hebbian synapses in the visual cortex. Another demonstration is reported in an interesting study by Ahissar and colleagues [48••]. Positive changes in connection strengths between neurons were readily induced by using spike events to trigger afferent stimulation. This study adds further weight to a growing mass of evidence that argues that the strengths of positive coupling, presumably implemented via the intrinsic collaterals of cortical pyramidal cells, are being continuously remodeled during learning.

Studies of long-term potentiation (LTP) in *in vivo* and *in vitro* cortical preparations are steadily increasing in number (for a review, see [49•]). LTP has been generated using several associative stimulus paradigms in motor [50–52] and somatosensory [53,54] cortex. Cortical LTP appears to involve NMDA receptors [55] (see also [49•]). Strengthened or altered responses can emerge very rapidly in both LTP and natural stimulation single-unit recording [56] models. *In vivo* voltage-clamp studies of pyramidal cells in the motor cortex have shown that changes in synaptive effectiveness are paralleled by cellular resistance changes [57]. By labeling the cells in which LTP is induced, it has been demonstrated that changes in synaptic effectiveness can be generated in both pyramidal and non-pyramidal (inhibitory?) neurons [58]. The plasticity of the input strengths of inhibitory neurons has now been demonstrated in at least one other model [59]. Interestingly, remarkable changes in synaptic numbers (> 25 %) are reported to be inducible by using a stimulus regimen that generates LTP in acute experiments [60] (see also [61]). While cortical LTP experiments have not yet defined the influence of prior synaptic activity on the genesis of plasticity generated by associative conditioning, similar experiments in the hippocampus have revealed strong effects [62].

Modulation of synaptic effectiveness changes

Another growing area of research on cortical representational changes induced in learning and memory has involved the more direct study of the effects of extrinsic modulators of representational remodeling. Studies continue to reinforce the conclusion that acetylcholine

(ACh) and norepinephrine probably play a major (see [63•,64,65,66•,67]) and synergistic [68] role in facilitating cortical response plasticity. Interestingly, a loss of ACh can be substituted for by dopamine, at least in a hippocampus LTP model [69]. Such cooperative or synergistic effects may account for the somewhat surprising recent finding that macaque monkeys [70], but not other studied mammals, with basal forebrain lesions apparently do not have permanent deficits for learning a long-term memory requisite behavior. Dopamine has been specifically implicated as acting in cortical zones that contribute to short-term or procedural memory, but not necessarily to non-declarative learning or memory [71•,72]. Of course, other neuromodulators are also implicated in the plastic cortical changes underlying learning and memory (for a review, see [73•]).

As our knowledge of the mechanisms underlying the neuromodulatory control of learning and memory processes grows, we gain a better understanding of those influences that might enable or freeze learning systems. In this respect, it is interesting that the best studied modulators, such as ACh and dopamine, are delivered on a timescale that is not consistent with signaling in learning. They might be interpreted as modulators that enable learning, and not as the cognitive signal itself. Thus, for example, the loss of a main cortical ACh source in the basal forebrain can apparently be substituted for by introducing ACh-rich grafts in widely separated cortical patches [60], which can provide neither temporally nor spatially controlled ACh release. When dopamine release is triggered, its effects are highly diffuse, and span long time intervals [74].

Cortical contributions to long-term memory

Recent evidence from animal studies is beginning to challenge the earlier widely held view that the amygdala and hippocampus play a major role in long-term memory in primates (for a review, see [75•]). Complete destruction of the amygdala has no apparent impact on monkeys performing a delayed match to sample task [76•]. Similar conclusions have been drawn from experiments in monkeys with discrete hippocampal lesions. At the very least, involvement of the perirhinal cortex in hippocampal lesions exacerbates the losses in this kind of declarative memory assessment [77]. In fact, lesions restricted to the rhinal cortex alone appear to generate severe deficits at a delayed match to sample declarative memory task [78], while leaving the recognition and discrimination of complex objects unaffected. These studies indicate that long-term memories are not necessarily recorded in the amygdala and/or hippocampus in macaque monkeys, and support a growing consensus that the cerebral cortex is a main repository of both declarative and non-declarative memory.

Distributed form of 'cortical engrams'

As described earlier, a practiced behavior is represented by behaviorally-refined temporal discharge characteristics within a complex distributed cell assembly that has been shaped by learning. The coupling of this cell assembly, reflected by its distributed response coherence, and therefore the salience of its output, becomes progessively stronger with practice. Improvements in discriminative performance can only be accounted for by a system that reads much or all of the distributed neuronal response representation of the learned behavior.

Does this constitute a fair general description of a 'cortical engram'? How does it agree or conflict with the view of scientists who have tried to understand the form of cortical engrams accounting for stimulus recognition and memory? This issue is somewhat confused at present, in no large part because studies have addressed this great question almost exclusively by employing single-unit recording sampling methods in alert behaving macaques, or by deriving PET or electrical stimulation interference reconstructions that are inadequately spatially resolved. Alert monkey and human electrophysiological preparations provide good information about the temporal structures of responses, but a more limited basis for reconstructing the cell assemblies engaged by learned stimuli. Results are also somewhat difficult to interpret because investigators use different stimulus sets and record in different sectors of recognition/memory (usually inferotemporal) cortex. Thus, for example, Tanaka and colleagues [79••,80•] provide evidence that there is a columnar representation of different complex visual stimulus features, with a composite of columns required for the representation of real whole objects. Several miles across Tokyo and in another sector of inferotemporal cortex, Sakai and Miyashita [10••] describe neurons whose responses are selective for specific, complex learned visual images, and for pairs of behaviorally associated images. In their preparation, simultaneously recorded neurons only occasionally have related neuronal response selectivities, and there is little evidence of a columnar organization of neurons with associated responses.

In what may be the same cortical zone, Miller, Li and Desimone [81••,82•] have demonstrated that a stimulus match in a delayed match to sample behavioral task results in a stimulus-specific neuronal response suppression, which they argue might signal the match. Their NIH research colleagues (see [11••]), possibly sampling from a different inferior temporal cortical zone, have described neurons that respond with a stronger response to a stimulus match. They present the interesting argument that a match probably involves a multiplication of the neural representation of the stimulus with a conserved or retrieved extrinsically-stored representation of the match [83••]. Like Miller and colleagues, Villa and Fuster [9] have also recorded response suppression for inferior temporal neurons responding to a stimulus match in a memory task, but along with Eskandar and colleagues

[11••,83••] emphasize differences in temporal response patterns as the likely basis of signaling a stimulus match.

Several of these investigators have noted that at least for the closed stimulus sets that their monkeys are trained with, stimuli are reasonably specifically encoded by the temporal patterns of responses in their neuronal samples [11••,82•] (see also [84]). Indeed, temporal representational models constructed from a sample of single neuron responses evoked by closed stimulus sets provide a basis for identifying the response to a stimulus in this set, and only a moderately poorer basis for identifying a related new stimulus [85•].

There have been only limited attempts to map the distributed representations of learned stimuli in the requisite fine spatial grain. Investigators seem to agree that complex learned or remembered stimuli are represented by a sparsely distributed, widely scattered neuronal cell assembly [86,87]. 'Sparse' is a relative word, as it is not difficult for experimental scientists to locate relatively specific responses to elements of learned stimulus sets at separated locations across the inferior temporal cortex. Clearly, very many thousands, or even millions of neurons scattered across cortical zones several square millimeters in extent must be participating in the representations of any learned or remembered complex stimulus, within 'recognition cortex' alone.

How strong are the cell assembly islets that contribute to these complex distributed array representations? As noted earlier, simultaneous recordings from neurons in inferotemporal cortex commonly have different response selectivities, and only about 40 % of simultaneously recorded neuronal pairs (and 11 % of pairs recorded 500 μm across the network) can be demonstrated to be directly coupled [88,89]. It must be remembered, however, that influences in a cortical network can be passed via intervening neurons over significant distances. Because coupling in some models is manifested only by the use of specific stimuli (for recent evidence, see [89]), simple two-unit coupling experiments probably underestimate its contributions to neuronal response selectivity or stimulus context.

How are the separated, distributed patches that contribute to a cortical engram linked? Studies of distributed response coherence linking zones of representation that appear to contribute to complex behaviors are in their infancy, but there can be no doubt that they are plastic (for examples, see [5,41••,48••,89]). One current hypothesis supported by some evidence [89–92] is that these patches are driven to respond in phase, thereby temporally linking what can be widely distributed, fractionated cell assemblies. A consideration of the evidence supporting this intriguing hypothesis, and the neural bases for generating correlated responses across multiple cortical levels and wide cortical sectors is beyond the scope of this review.

How does the picture of the cortical engram emerging from inferior temporal cortex experiments differ from that generated by studies in primary somatosensory or auditory cortical fields? In the latter case, responses of simultaneously recorded and nearby neurons carry more common information, and simultaneously recorded neurons are more likely to be strongly positively coupled. Of course, a major reason for this difference could be the dramatically different spatiotemporal distributions of inputs that feed primary cortical fields, when compared with recognition-level cortical fields. In primary cortical fields, inputs are topographically ordered, and are relatively robust; convergence and divergence of inputs is anatomically restricted. As a consequence, heavy schedules of strongly coherent inputs are delivered away from any source of activity out into the network. In inferior temporal cortex, inputs are topographically dispersed in an all-to-all projection scheme. As a result, inputs are relatively diffused both spatially and temporally.

The consequences of an all-to-all anatomical projection scheme can be simulated in a primary cortical field by transecting and then surgically reconnecting large peripheral cutaneous nerves [32]. This manipulation results in the creation of a nearly all-to-all anatomy for a wide sector of primary somatosensory cortical fields [93]. As a result, any given skin surface comes to be represented in a series of spatially separated 'islets', akin to the islets of representation recorded in inferotemporal cortex. Any restricted part of the skin can now be accurately described as being represented by a 'sparse' distributed code. The fact that these islets have more strongly coupled inputs and larger populations of neurons with common information than is recorded in inferior temporal cortex, could be a result of the more powerful statistical predictability and coherent structure of their input array, i.e. the densely reinnervated skin surface.

Conclusion

Over the past few years a hypothetical picture of a cortical engram has begun to emerge. In our own working version of this model, a cortical engram is a widely distributed group of neurons that is probably comprised of many small neuronal islets or patches that in some areas might be reduced to very small neuronal memberships. Its origin is input coincidence-based, and derived from the operation of plastic Hebb-like synapses. Competitive and cooperative cortical network influences powerfully contribute to the genesis of, and limitations of, contributing neuronal patches. With substantial overlap, the contributions of different neuronal patches appear to represent different aspects of complex stimuli. The real, whole learned or remembered stimulus is represented by the entire cell assembly. This representation is dynamic, not static. That is, temporal response events over time provide the assembly with dynamically shifting and modulating spatial patterns that operate collectively to represent a learned behavior or memory. Distributed parts of this cell assembly are linked, and their temporal response coherence is strengthened by stimulus repetition. Response coherence can be equated with stimulus salience.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1. • RECANZONE GH, JENKINS WM, HRADEK GH, MERZENICH MM: **Progressive Improvement in Discriminative Abilities in Adult Owl Monkeys Performing a Tactile Frequency Discrimination Task.** *J Neurophysiol* 1992, 67:1015–1030.

Frequency discrimination abilities of adult monkeys progressively improve over a many week long training period, in a monkey that performs this task with few false-positive responses. Improvements attributed to training are partly conferred on nearby, but probably not to distant skin locations. With cessation of training, performance is altered progressively back toward naive performance levels.

2. •• RECANZONE GH, MERZENICH MM, SCHREINER CE: **Changes in the Distributed Temporal Response Properties of SI Cortical Neurons Reflect Improvements in Performance on a Temporally Based Tactile Discrimination Task.** *J Neurophysiol* 1992, 67:1071–1091.

Progressive improvements in flutter-vibration frequency discrimination with practice are accounted for by a progressive change in the distributed response coherences of neurons that represent behaviorally important stimuli in cortical area 3b. Changes are conferred beyond the zone of representation of the directly stimulated skin spot into a wide surrounding cortical network region. Other interesting behaviorally induced changes in the engaged sector of somatosensory cortical fields 3b and 3a are described.

3. • RECANZONE GH, SCHREINER CE, MERZENICH MM: **Plasticity in the Frequency Representation of Primary Auditory Cortex Following Discrimination Training in Adult Owl Monkeys.** *J Neurosci* 1993, 13:87–103.

Progressive, manyfold improvements in sound frequency discrimination with practice appear to be accounted for by a parallel, progressive change in the territory representing those sound frequencies in the primary auditory cortical field, A1.

4. RECANZONE GH, MERZENICH MM, JENKINS WM, GRAJSKI KA, DINSE HR: **Topographic Reorganization of the Hand Representation in Cortical Area 3b of Owl Monkeys Trained in a Frequency-Discrimination Task.** *J Neurophysiol* 1992, 67:1031–1056.

5. RECANZONE GH, MERZENICH MM: **Alterations of the Functional Organization of Primary Somatosensory Cortex Following Intracortical Microstimulation and Behavioral Training.** In *Memory: Organization and Locus of Change.* Edited by Squire LR, Weinberger NM, Lynch G, McGaugh JL. New York: Oxford University Press; 1991: 217–238.

6. • MOUNTCASTLE VB, ATLURI PP, ROMO R: **Selective Output-Discriminative Signals in the Motor Cortex of Waking Monkeys.** *Cerebr Cortex* 1992, 2:277–294.

About one third of neurons that respond in cortical area 4 in a monkey performing a flutter-vibration frequency discrimination task responded selectively just prior to the monkey making a correct discrimination. There was no evidence that the discrimination operation was localized to any particular area.

7. • RECANZONE GH, MERZENICH MM, JENKINS WM: **Frequency Discrimination Training Engaging a Restricted Skin Surface Results in an Emergence of a Cutaneous Response Zone in Cortical Area 3a.** *J Neurophysiol* 1992, 67:1057–1070.

Area 3a has been hypothesized to provide inputs that signal movement initiation. It is usually dominated by inputs from muscle afferents and other 'deep' receptors. In a task involving a reaction-time hand movement signaled by low amplitude skin stimulation with the hand immobile, only cutaneous (not muscle afferent or other deep) inputs could trigger movement initiation. In adult monkeys trained in such a task, there was a massive practice-induced substitution of effective skin inputs for deep inputs in cortical area 3a.

8. • MITZ AR, GODSCHALK M, WISE SP: **Learning-Dependent Neuronal Activity in the Premotor Cortex: Activity During the Acquisition of Conditional Motor Associations.** *J Neurosci* 1991, 11:1855–1872.

Roughly half of the neurons sampled in premotor cortex studied through the course of training developed response characteristics specific to the behavioral task and concurrent with learning.

9. VILLA AE, FUSTER JM: **Temporal Correlates of Information Processing During Visual Short-Term Memory.** *Neuroreport* 1992, 3:113–116.

10. •• SAKAI K, MIYASHITA Y: **Neural Organization for the Long-Term Memory of Paired Associates.** *Nature* 1991, 354:152–155.

Monkeys were trained in a paired-association task using complex, paired visual patterns. After training, many anterior temporal cortex neurons selectively responded to both complex stimuli of specific paired associates.

11. •• ESKANDAR EN, RICHMOND BJ, OPTICAN LM: **Role of Inferior Temporal Neurons in Visual Memory I. Temporal Encoding of Information About Visual Images, Recalled Images, and Behavioral Context.** *J Neurophysiol* 1992, 68:1277–1295.

The responses of inferior temporal neurons stimulated by the visual presentation of Walsh patterns as well as those evoked when the monkey did or did not receive a matching stimulus are documented in this study. It extends earlier experiments by this group demonstating highly specific temporal neuronal response representations of different training stimuli, by showing that information about previously presented images is carried forward into the non-matching and matching sample periods. It also shows that there are significant differences in responses to these stimuli that are dependent upon stimulus context. See also [83••].

12. AIZAWA H, INASE M, MUSHIAKE H, SHIMA K, TANJI J: **Reorganization of Activity in the Supplementary Motor Area Associated with Motor Learning and Functional Recovery.** *Exp Brain Res* 1991, 84:668–671.

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14. NIEMANN J, WINKER T, GERLING J, LANDWEHRMEYER B, JUNG R: **Changes of Slow Cortical Negative DC-Potentials During the Acquisition of a Complex Finger Motor Task.** *Exp Brain Res* 1991, 85:417–422.

15. LANG W, BEISTINER R, LINDINGER G, DEECKE L: **Changes in Cortical Activity when Executing Learned Motor Sequences.** *Exp Brain Res* 1991, 89:435–440.

16. • HAIER RJ, SIEGEL BV JR, MACLACHLAN E, SODERLING E, LOTENBERG S, BUCHSBAUM MS: **Regional Glucose Metabolic Changes After Learning a Complex Visuospatial/Motor Task: a Positron Emission Tomographic Study.** *Brain Res* 1992, 570:134–143.

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17. •• KARNI A, SAGI D: **Where Practice Makes Perfect in Texture Discrimination: Evidence for Primary Visual Cortex Plasticity.** *Proc Natl Acad Sci USA* 1991, 88:4966–4970.

Subjects performing a backward masking task improved markedly with training. The limitation of these striking training effects to the trained eye and to the sector of the visual field at which training was applied, led the authors to conclude that these striking changes in preattentive vision arose from area 17.

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21. MERZENICH MM, SCHREINER C, JENKINS W, WANG X: **Neural Mechanisms Underlying Temporal Integration, Segmentation and Input Sequence Representation: Some Implications for the Origin of Learning Disabilities.** *Ann NY Acad Sci* 1993, in press.

22. CHINO YM, KAAS JH, SMITH EL, LANGSTON AL, CHENG H: **Rapid Reorganization of Cortical Maps in Adult Cats Following Restricted Deafferentation in Retina.** *Vision Res* 1992, 32:789–796.

23. GILBERT CD, WIESEL TN: **Receptive Field Dynamics in Adult Primary Visual Cortex.** *Nature* 1992, 356:150–152

24. PETTET MW, GILBERT CD: **Dynamic Changes in Receptive Field Size in Cat Primary Visual Cortex.** *Proc Natl Acad Sci USA* 1992, 89:8366–8370.

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26. GILBERT CD: **Horizontal Integration and Cortical Dynamics.** *Neuron* 1992, 9:1–13.

27. EYSEL UT: **Lateral Inhibitory Interactions in Areas 17 and 18 of the Cat Visual Cortex.** *Prog Brain Res* 1992, 90:407–422.

28. •• FREGNAC Y, SHULZ D, THORPE S, BIENENSTOCK E: **Cellular Analogs of Visual Cortical Epigenesis. I. Plasticity of Orientation Selectivity.** *J Neurosci* 1992, 12:1280–1300.

These important studies (see also [29••]) document the mutability of orientation response selectivity in area 17, demonstrated by the delivery of oriented visual stimuli in conjunction with weak depolarization of area 17 neurons. The capacity for alteration of response selectivity is retained in adults, but on a lower scale than was recorded in pre-critical-period cats. Interestingly, progressive changes in orientation were recorded with this manipulation. If the training orientation varied enough from that initially recorded, the orientation achieved by conditioning moved toward the training orientation and stabilized at a value intermediate between the original and teaching-stimulus orientations. Such observations provide strong evidence for the participation of a significant surrounding region of the cortical network in the genesis and maintenance of orientation tuning.

29. •• SCHULZ D, FREGNAC Y: **Cellular Analogs of Visual Cortical Epigenesis. II. Plasticity of Binocular Integration.** *J Neurosci* 1992, 12:1301–1318.

See [28••].

30. •• PONS TP, GARRAGHTY PE, OMMAYA AK, KAAS JH, TAUB E, MISHKIN M: **Massive Cortical Reorganization After Sensory Deafferentation in Adult Macaques.** *Science* 1991, 252:1857–1860.

The entire cortical area 3b zone of representation of the hand and arm was found to be occupied by inputs from the face, in an adult macaque monkey that had had its arm deafferented by dorsal rhizotomy as a young adult a number of years earlier.

31. • KATZ J: **Psychophysiological Contributions to Phantom Limbs.** *Can J Psychiat* 1992, 37:282–298.

This review provides a good summary of the interesting perceptual changes recorded in humans following limb amputation.

32. MERZENICH MM, RECANZONE GH, JENKINS WM, GRAJSKI KA: **Adaptive Mechanisms in Cortical Networks Underlying Cortical Contributions to Learning and Nondeclarative Memory.** *Cold Spring Harb Symp Quant Biol* 1990, 55:873–887.

33. • RAMACHANDRAN VS, ROGERS-RAMACHANDRAN D, STEWART M: **Perceptual Correlates of Massive Cortical Reorganization.** *Science* 1992, 258:1159–1160.

In patients with arm amputations, localized sensations referred to the phantom hand are evoked by face stimulation. These 'ghost' sensations, which arise very soon after amputation, can be mapped topographically onto the phantom hand by systematically stimulating the surfaces of the ipsilateral face.

34. • COHEN LG, BANDINELLI S, FINDLEY TW, HALLET M: **Motor Reorganization After Upper Limb Amputation in Man.** *Brain* 1991, 114:615–627.

In this human study, movements of the proximal limb were seen to progressively occupy the motor cortex zone of representation of the missing limb, eventually extending over a cortical territory of several centimeters.

35. •• NUDO RJ, JENKINS WM, MERZENICH MM, PREJEAN T, GRENDA R: **Neurophysiological Correlates of Hand Preference in Primary Motor Cortex of Adult Squirrel Monkeys.** *J Neurosci* 1992, 12:2918–2947.

This landmark study documents the differences in the detailed representations of movements from the preferred and non-preferred hands in the primary motor cortices of adult monkeys. Movement representations of preferred hands are significantly more complex, by a variety of distributed-response measures.

36. • ROE AW, PALLAS SL, KWON YH, SUR M: **Visual Projections Routed to the Auditory Pathway in Ferrets: Receptive Fields of Visual Neurons in Primary Auditory Cortex.** *J Neurosci* 1992, 12:3651–3664.

This is a continuation of an important series of experiments from this laboratory that demonstrate that when visual inputs are rerouted in development into the auditory thalamus, they create neuronal response selectivities and representational topographies in the auditory cortex that are akin to those normally generated in the primary visual cortex. These studies can be interpreted as indicating an equipotentiality of the cortex for generating selective responses that primarily arise as a consequence of the spatiotemporal forms of their inputs, regardless of their specific anatomical origins.

37. • CASTRO-ALAMANCOS MA, GARCIA-SEGURA LM, BORRELL J: **Transfer of Function to a Specific Area of the Cortex After Induced Recovery from Brain Damage.** *Eur J Neurosci* 1992, 4:853–863.

While most cortical plasticity modulation experiments conducted over the past 2 years have focused on blocking plasticity, Castro-Alamancos and colleagues temporally coupled ventral tegmental nucleus stimulation with correct limb movement performance in animals in which the performance was greatly degraded after frontal cortex lesions. Positive results with this manipulation, but not in behaviorally-trained rats lacking ventral tegmental reinforcement, suggest that manipulation of modulatory inputs might be powerfully employed to accelerate learning and memory processes in brain-damaged individuals.

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Coupled neuronal groups are a developmental fact, but do they have any enduring expression in the mature cortex?

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40. SILVA LR, AMITAI Y, CONNORS BW: **Intrinsic Oscillations of Neocortex Generated by Layer 5 Pyramidal Neurons.** *Science* 1991, 251:432–435.

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The physical dimensions and neuronal memberships of functionally-defined mini-columns are greatly enlarged by a period of very low current level intracortical microstimulation.

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