Cognitive neuroscience

Thomas D Albright*, Eric R Kandel† and Michael I Posner‡

The last decade of the 20th century has seen the development of cognitive neuroscience as an effort to understand how the brain represents mental events. We review the areas of emotional and motor memory, vision, and higher mental processes as examples of this new understanding. Progress in all of these areas has been swift and impressive, but much needs to be done to reveal the mechanisms of cognition at the local circuit and molecular levels. This work will require new methods for controlling gene expression in higher animals and in studying the interactions between neurons at multiple levels.

Addresses
*Howard Hughes Medical Institute and Salk Institute, 10010 North Torrey Pines Road, La Jolla, California 92037, USA;
e-mail: tom@salk.edu
†Howard Hughes Medical Institute and Center for Neurobiology and Behavior, College of Physicians and Surgeons of Columbia University, 722 West 168th Street, New York, New York 10032, USA;
e-mail: erk5@columbia.edu
‡Sackler Institute, Department of Psychiatry, Box 140, Weill Medical College of Cornell University, 1300 York Avenue, New York, New York 10021, USA; e-mail: mip2003@mail.med.cornell.edu

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Abbreviations

5-HT	5-hydroxytryptamine
CaMKII	Ca^{2+}/calmodulin-dependent protein kinase II
CRE	cAMP-responsive element
CREB	CRE binding protein
CS	conditioned stimulus
E-LTP	early-stage LTP
ERP	event-related potential
fMRI	functional magnetic resonance imaging
I-LTP	intermediate form of LTP
IT	inferior temporal
L-LTP	late-phase LTP
LTD	long-term depression
LTP	long-term potentiation
MST	medial superior temporal
MT	middle temporal
NMDA	*N*-methyl-D-aspartate
NR1	NMDA receptor type 1 subunit
PET	positron emission tomography
PKA	cAMP-dependent protein kinase
PP1	protein phosphatase 1
rtTA	reverse tTA
tetO	tet operator
tTA	tetracycline-responsive transcription factor
US	unconditioned stimulus

Introduction

The last decade of the 20th century, the Decade of the Brain, has also been the Decade of Cognitive Neuroscience. It has been the decade in which the merger of cognitive psychology and neural science has begun to realize its promise. The joining of neural science and cognitive psychology is the most recent in a series of scientific unifications that have brought together the disparate subfields of biology into one coherent discipline. Almost all of the other unifications have been spearheaded by the synthetic power of molecular biology. Cognitive neuroscience is distinctive in that the important impetus has come from other sources; in particular, a large part of the impetus has come from psychology and from systems neuroscience.

That psychology should be a driving force for such a synthesis is perhaps not surprising. Psychology provides the agenda for the brain sciences; it poses the questions about mental activity that we ultimately want to address. In addition, within the first half of the 20th century, psychology underwent a remarkable increase in explanatory power, evolving from a philosophical tradition based on introspection to an independent scientific discipline centered on psychophysics and behaviorism. As psychology matured in the first half of the 20th century, it increasingly advocated an empirical behaviorist approach that ended up reducing the focus of interest in psychology to observable aspects of behavior. Psychologists argued that attempts to quantify non-observable mental events, such as perception, imagery, thinking, retention, problem solving, or consciousness were at best speculative and unstable. This emphasis on observable indices of behavior resulted in making psychology a rigorously experimental discipline but one that was so narrowly focused that it excluded from the study of behavior most of the really fascinating features of mental life. The reawakening of interest in internal events led to the emergence of modern cognitive psychology by making us realize that our knowledge of the world is based on perception, and that perception is an act of construction that depends not only on the information inherent in the stimulus but also on the mental structure of the perceiver. Ulric Neisser laid out the task of cognitive psychology. In his classic monograph of 1967 [1], he wrote:

> "…the world of experience is produced by the man who experiences it…There certainly is a real world of trees and people and cars and even books, and it has a great deal to do with our experience of these objects. However, we have no direct immediate access to the world, nor to any of its properties… Whatever we know about reality has been mediated not only by the organs of sense but by complex systems which interpret and reinterpret sensory information."
> ". . . the term 'cognition' refers to all the processes by which the sensory input is transformed, reduced, elaborated, stored, recovered and used . . ."

Neisser, and the other earlier pioneers in cognitive psychology, pointed out that to study mental operations,

cognitive psychologists needed to focus on the flow of sensory information, from its transduction by appropriate sensory receptors to its eventual use in memory and action. This implied that each perceptual or motor act has an internal representation in the brain, evidenced by a pattern of activity in a specific set of interconnected cells. The pattern of connections also stores information, in memory, about the perception and the motor act.

In the 1970s and 1980s, the early years of cognitive psychology, most types of internal representations were not really accessible for a meaningful experimental analysis (for interesting exceptions, see [2–4]). Fortunately, the emergence of cognitive psychology was soon followed by, and indeed helped stimulate, significant progress in systems neural science and in brain imaging. By the 1990s, these approaches had come together, making it possible, for the first time, to study directly internal sensory and motor representations in both nonhuman primates and human beings. A major goal of this new direction was to map elementary cognitive functions onto specific neuronal systems.

We cannot, in this brief review, document the substantial progress that has been made in mapping internal representations of cognitive functions. We therefore will restrict our review to three areas in which we have direct experience: memory storage, perception, and higher mental functions. Our purpose in considering memory storage is to illustrate that some elementary aspects of cognitive processes, in particular the switch from short- to long-term memory, can now be studied at the molecular level. In discussing perception, we illustrate the influence that psychophysics, especially psychophysical studies in intact, awake behaving primates, has exerted on the study of the neuronal organization and function of the visual system. Finally, we illustrate the remarkable power that we have gained in the study of complex cognitive processes in humans from the ability to image the living, behaving human brain.

Memory storage

During the past decade, the study of memory storage has been characterized by the attempt to map the molecular biology of synaptic plasticity onto ideas about memory systems that emerged from cognitive psychology in the 1980s. The earlier, cognitive psychological studies of patients with brain lesions made it apparent that memory was not a unitary faculty of mind but had at least two major forms: a declarative (explicit) form concerned with the knowledge of what something was about — a knowledge about facts and events — and a procedural (implicit) form concerned with the knowledge of how to do something — a knowledge about perceptual and motor procedures. In studying these two independent memory processes, it has proven convenient to divide the study of memory storage into two parts: the systems problem of memory, which is concerned with where in the brain memories are stored, and the molecular problem of memory, which is concerned with how memories are stored in different sites within the brain. We briefly consider the systems problem before focusing on the molecular problems of storage (for a current review, see [5]).

The systems problem of memory

Procedural (implicit) memory: there are multiple forms

It is now generally accepted that declarative (explicit) memory requires for storage the medial temporal lobe and the hippocampus, whereas procedural (implicit) memory does not. One of the advances of the past decade has been the further documentation that procedural memory has many subcomponents, and that essentially all cognitive systems — be they perceptual or motor — involving a large variety of different neural systems may be capable of storing some types of procedural memory. For example, various types of motor learning involve the cerebellum; learned fear the amygdala; operant conditioning and habit learning the basal ganglia; priming the neocortex; and perceptual learning, including habituation and sensitization, the primary sensory pathways. This distribution of procedural memory across neural systems was already well appreciated in the 1980s, and, in some cases, such as motor learning involving the cerebellum, the circuitry involved in learning was already well studied (see reviews in [6–10]). Here, we illustrate how our knowledge of implicit memory mechanisms has expanded in the 1990s by focusing briefly on just two examples, fear conditioning in the amygdala and motor learning in the cerebellum.

The amygdala and emotional memory

Considerable evidence from both humans and experimental animals now indicates that the amygdala is critical for the expression of emotion and intervenes between the hypothalamus and brainstem nuclei — the regions concerned with the somatic expression of emotion — and the cingulate, parahippocampal, and prefrontal cortices — the neocortical areas concerned with conscious feeling. For example, electrical stimulation of the amygdala in humans produces feelings of fear and apprehension, whereas damage to the amygdala in experimental animals produces tameness. Consistent with this idea, studies using positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) clearly show that recognition of emotional expression in faces involves the amygdala [11].

As early as 1956, Lawrence Weiskrantz [12] had demonstrated that lesions of the amygdala in experimental animals also impair learned fear. In subsequent work, Michael Davies [13], Michael Fanselow [14], Joseph LeDoux [15] and their colleagues have delineated the outlines of a neural circuit for learned fear. They found that one subnucleus of the amygdala, the lateral nucleus, is required for procedural memory of fear conditioning to a neutral tone [15]. Information about the CS, the tone, is carried to the lateral nucleus via two pathways: the thalamo-amygdala projection from the auditory thalamus and the cortico-amygdala projection from the auditory cortex. Long-term potentiation (LTP) has been observed *in vivo*

in the projection from the thalamus to the amygdala after tetanization of the thalamic input [16]. Importantly, synaptic change resembling LTP has been observed in this pathway after naturally occurring fear conditioning [17].

Because of the anatomical complexity of the amygdala (especially when compared with more ordered structures such as the hippocampus and the cerebellum), precise molecular characterization of the plasticity at these defined synapses has not yet been achieved. However, recent findings have begun to make some progress. Thus, blockade of noradrenaline receptors has been found to interfere with formation of emotional memory in humans, suggesting that the cAMP pathway in the amygdala may be required [18]. Disruption of cAMP-dependent kinase (PKA) in fact disrupts fear conditioning [19,20]. More recently, LTP has been described in slices of the amygdala at both the synapse from the thalamus and the cortex to the lateral amygdala, and, like LTP in the hippocampus, it has been found to have an early phase and a protein-synthesis-dependent late phase [21]. The induction of the early phase is postsynaptic, but the expression is presynaptic and also requires PKA [22,23].

Memory for motor acts and the cerebellum

Well into the 1970s and 1980s, many neural scientists still thought that the function of the cerebellum was restricted to coordinating voluntary movements: gait, posture, speech, and other skilled movements. This view began to change in the early 1980s, when a series of studies by Richard Thompson, Masao Ito, Mitchell Glickstein, Tom Thach and their colleagues provided a variety of independent evidence that the cerebellum is also critical for the formation of learned motor responses ([6–9]; for early theoretical discussions, see also [24,25]). For example, Thompson and co-workers [6,26,27] found that lesions of the cerebellar cortex produced deficits in conditioned eyeblink responses while sparing the unconditioned responses. The site for this plasticity appears to reside in the mossy-fiber–parallel-fiber Purkinje cell synapse [27]. Indeed, conditioned responses can be obtained by simply substituting for the CS direct electrical stimulation of brainstem (pontine) nuclei and pairing that with electrical stimulation of fibers from the inferior olive as the US [27].

The work on eyeblink conditioning is part of a larger tradition of work on the role of the cerebellum in learning, a tradition that includes the studies of Masao Ito [9] on the modification of the vestibular–ocular reflex and the studies of Thomas Thach [28] on the role of mossy and climbing fibers in monkeys learning to adjust their wrist movements to unexpected changes in load.

A comparison of learning in the vestibular–ocular reflex to learning of classical eyeblink conditioning by Raymond *et al.* [10] suggests that these two quite different behaviors show a surprisingly conserved role for the cerebellum in motor learning. In each case, the plasticity is distributed between the cerebellar cortex and the deep nuclei, with each playing a different role. The cerebellar cortex has the special function of learning the timing of movement. In so doing, the cerebellar cortex guides the learning in the deep nuclei, which may allow learning to be transferred from the cortex to the deep nuclei. Since one of the issues in declarative learning is the transfer of information from the hippocampus and the medial temporal lobe to other areas of neocortex, this insight may prove to be of general significance (see discussion of Declarative memory storage below).

Recent studies indicate that the cerebellum probably does even more than participate in motor learning; it also participates in associative word learning [29], learning of tactile mazes [30], and perception of time intervals between successive stimuli [31].

Declarative (explicit) memory storage: the medial temporal system appears to have only a temporary role

A key feature of declarative memory is that the medial temporal lobe is involved in memory for a limited period of time. The initial evidence came from studies of the patient H.M., as well as the two other patients described by Penfield and Milner [32] who had good memory for remote events that occurred years before their surgery. Recently, studies in experimental animals have tested this idea rigorously and obtained clear evidence for temporally graded retrograde amnesia, which covered a period ranging from a few days to about a month before surgery (reviewed in [5]).

These data have given rise to the idea that the medial temporal lobe structures direct a gradual process of reorganization and stabilization by changing the organization of cortical representations, perhaps by binding together the separate cortical regions that store memory for a whole event [33,34]. After sufficient time has passed, the hippocampal formation may not be needed to support storage or retrieval of declarative memory, and long-term memory is fully dependent on the neocortex (reviewed in [35]).

The molecular mechanisms of memory storage

A role for CREB in procedural (implicit) and declarative (explicit) memory

Although declarative and nondeclarative memory use different neural systems and different logic, the two memory systems have in common distinct temporal phases. There is a short-term memory lasting minutes to hours, and a long-term memory lasting days or even longer. In both memory systems, long-term memory differs from short-term memory not only in time course but also in molecular mechanisms. Long-term memory, but not short-term memory, requires the synthesis of new protein (reviewed in [36,37]). Studies during the past decade in *Drosophila*, *Aplysia*, and mice suggest that cAMP, PKA, and the cAMP-responsive transcription factor CREB are critically involved in the conversion of short-term to long-term memory for both declarative and nondeclarative memory.

Indeed, in both *Drosophila* and *Aplysia*, CREB learning-related transcriptional activation appears to be the rate-limiting step in the conversion of short-term to long-term synaptic plasticity and behavioral memory. This was first shown for synaptic plasticity by injecting into the nucleus of the sensory neuron of *Aplysia* an oligonucleotide with a cAMP-responsive element (CRE) [38]. This oligonucleotide selectively blocked long-term facilitation without affecting short-term facilitation. A similar result was later obtained by injecting antibodies specific for CREB1 [39]. Conversely, injecting a phosphorylated form of the recombinant CREB1a protein, a key regulator of transcription, was sufficient to induce long-term facilitation [40]. Injection of antibodies against *Aplysia* CREB2 (ApCREB2), a negative regulator that inhibits CREB1-mediated transcription, led to long-term facilitation accompanied by a growth of new synaptic connections [40] when paired with a single pulse of 5-HT (which normally produces short-term facilitation). Thus, ApCREB2 acts as a repressor of long-term facilitation by functionally competing with the CREB1a activator. In parallel experiments in *Drosophila*, the behavioral switch from short- to long-term memory was found to be regulated by changing the activity ratio between CRE binding activator dCREB2a and repressor dCREB2b proteins, the fly homologues of mammalian CREB and *Aplysia* CREB1 [36,41]. For example, when the expression of the CREB activator is induced before training, a single odor–shock pairing produces a long-term memory for the odor.

These results in *Drosophila* suggest that this CREB-mediated induction of transcription is necessary to produce the long-lasting changes in synaptic strength required for the long-term storage of memories [36,37]. The results in *Aplysia* suggest that the CREB switch functions at the level of the individual synapse to convert a short-lasting increase in synaptic strength produced by covalent modifications of existing proteins to one that is long-lasting and produced by the synthesis of new proteins (see also [42,43]).

Reverse genetics in the mouse

What about the switch to long-term declarative memory? In the past decade, methods for modifying individual genes in mice have become available and have helped define the mouse as the mammalian model system *par excellence* for the genetic study of declarative memory storage. Mice exhibit a memory for space and objects that corresponds to human declarative memory, requiring the hippocampus and the medial temporal lobe. Moreover, the hippocampus has a form of synaptic plasticity, called LTP, thought to be a candidate mechanism for this sort of memory storage. Pharmacological experiments in the 1980s and early 1990s first indicated that LTP itself has stages, much like long-term facilitation in *Aplysia*. There is an early-stage LTP (E-LTP) that requires covalent modification mediated by Ca^{2+}/calmodulin-dependent protein kinase II α (CaMKIIα) and the tyrosine kinase fyn [44,45], and a late-phase LTP (L-LTP) that requires protein synthesis and the kinase PKA [46]. Moreover, there is increasing evidence for rapid receptor insertion and remodeling during E-LTP and for actual structural changes during L-LTP (reviewed in [47]).

Development of gene targeting by homologous recombination in embryonic stem cells has made it possible to test some of these ideas genetically. The initial studies examined mice with targeted knockout of CaMKII and the tyrosine kinase fyn, kinases that had previously been implicated in LTP in pharmacological studies [44,48]. The genetic studies revealed that mice lacking CaMKIIα displayed a partial loss of E-LTP in the CA1 neurons of the hippocampus and severe impairment on spatial memory tasks [49–51]. Similarly, analysis of mice with targeted deletions of the tyrosine kinase fyn also showed deficits in E-LTP as well as in spatial memory. Mice with deletions of the non-receptor tyrosine kinases src and yes were normal [52]. By contrast, expression of a dominant-negative inhibitor of PKA in neurons of the forebrain using the CaMKIIα promoter [53] resulted in mice that had a normal E–LTP but a dramatically attenuated L-LTP. These genetically modified mice learned a contextual task as well as wild-type animals, had a perfectly good short-term memory when tested 1 hour after training, but were impaired in selective long-term memory when tested 24 hours later. Thus, as in *Aplysia* and *Drosophila*, the PKA signaling pathway in mice seems to be important for maintaining both LTP and memory for prolonged periods of time.

Previously, Roussoudan Bourtchouladze *et al.* [54] had examined the role of CREB in the mouse. They found that a deletion that eliminated only the alpha and delta isoforms led to impairment in LTP and in long-term memory storage [54]. The memory deficit was similar to that seen in mice expressing the PKA inhibitor; initial learning and short-term memory were intact, whereas long-term memory was impaired. Moreover, work by Daniel Storm and colleagues [55,56] has provided further strong evidence that CREB is indeed involved in mouse synaptic plasticity. They produced a transgenic mouse in which a *lacZ* reporter gene is activated by a CREB-responsive promoter, and they found that this reporter is activated both by L-LTP *in vitro* [55] and by certain forms of hippocampus-dependent learning *in vivo* [56]. This demonstrates that CREB or CREB-like transcription factors are in fact activated under circumstances that lead to plasticity and suggests a causal role similar to that seen in *Aplysia* and *Drosophila*.

Regionally and temporally restricted gene expression

The traditional genetically modified mouse lines mentioned above have identified some genes that are necessary to develop a normal learning and memory phenotype in the adult, and suggest genes that may vary in their allelic form in a normal population to give rise to the normal variation in cognitive ability. These lines of mice, however, suffer from the limitation that many molecules likely to be important for adult learning are also likely to be important for normal

development. In addition, these gene manipulations often affect a variety of different brain regions. One example of how to circumvent this problem is provided by work on regional and regulated gene expression in the brain [57–59].

Mice with a targeted deletion in the NR1 subunit of the NMDA receptor die shortly after birth [60]. Previously, Joe Tsien and colleagues [57,58] succeeded in obtaining conditional deletion restricted to forebrain neurons by using the CRE-*loxP* systems. By combining the forebrain-specific CaMKIIα promoter with the bacterial CRE-loxP recombinase system, they were able to knock out the NR1 gene specifically in the CA1 region of the postnatal hippocampus, without affecting other structures. This restricted knockout avoided the perinatal lethality of a complete NR1 knockout. As predicted, the mice showed a deficit in CA1 LTP and a severe deficit in spatial learning, strongly supporting a role for NMDA-dependent LTP in hippocampus-dependent learning. More recently, Tsien and colleagues [61] have carried out the reverse experiment. They expressed a mutant form of NR1 that allows greater Ca^{2+} influx, and found that it enhances LTP and memory storage.

A further advance has been the ability to regulate gene expression not just regionally but also temporally, using the tetracycline system (see e.g. [62]). In a group of experiments, a cell-type-specific promoter, such as the CaMKIIα promoter, is used to drive expression of the tetracycline-responsive transcription factor tTA in forebrain neurons of one line of mice. In a second line, the transgene to be regulated is linked to a promoter consisting of multiple repeats of the tet operator (tetO) linked to a minimal eukaryotic promoter element. When these two lines are mated so that both transgenes are introduced into a single mouse, the tetO-linked gene is activated specifically in those cells that express tTA. The expression of the tetO-linked transgene can then be suppressed by oral administration of the tetracycline analogue doxycycline [59]. In another class of experiments, a mutant form of the tetracycline repressor is used that induces transcription only in the presence of doxycycline [62]. This reverse tTA, or rtTA, has been used to obtain inducible and reversible expression of a Ca^{2+}-activated protein phosphatase calcineurin in forebrain neurons [63,64]. Calcineurin opposes the action of PKA and other protein kinases. Calcineurin has a high affinity for Ca^{2+}, even higher than that of CaMKIIα. At low-frequency stimulation, the amount of Ca^{2+} coming into the cell through the NMDA receptor is small and activates calcineurin but not CaMKIIα. Calcineurin, in turn, can dephosphorylate protein phosphatase Inhibitor-1, which activates protein phosphatase 1 (PP1) and leads to long-term depression (LTD) of synaptic transmission, which is the mirror opposite of LTP [65]. In contrast, higher frequencies of stimulation lead to greater Ca^{2+} influx. This, in turn, activates kinases, including PKA, that phosphorylate and block Inhibitor-1, thereby shutting off the phosphatase cascade. In fact, PKA and calcineurin target the same residue on Inhibitor-1.

Overexpression of calcineurin leads to an impairment in an intermediate form of LTP (I–LTP) in hippocampus and to a defect in spatial memory in the Morris water maze [63,64,66]. Since the transgene can readily be switched on and off by giving or removing doxycycline, it has the great advantage that it can be used to study not only memory storage but also memory retrieval. Mutant mice that express the calcineurin transgene transiently, after learning has been acquired and after spatial memory has already been stored, have an apparent defect in the retrieval of the spatial information. This retrieval defect is not attributable to a disruption in memory storage because it could be reversed when the transgene expression was turned off by stopping doxycycline administration. Thus, with the use of regulated genetic modification one can not only control for potential developmental abnormalities associated with a genetic change but also begin to explore the various phases of memory acquisition, storage and retrieval [64].

Future directions

The use of mouse genetics to investigate complex behavioral traits such as learning and memory is at an early stage, but it promises to extend cognitive neuroscience into a new, molecular genetic direction. Moreover, the work in both invertebrates and mice suggests that many of the basic molecular mechanisms for memory may be conserved across species, allowing insights from invertebrates to be applied to the mammalian brain. In the fly, for example, the characterization of a new learning and memory mutants will hopefully provide a fuller understanding of the critical genes involved in memory storage. However, since the developmental integrity of many brain regions is necessary for the proper performance of even the simplest memory task, and since memory storage requires some of the most basic cellular signaling mechanisms, there will be many developmentally important genes that affect learning and memory. The difficult task facing the field, therefore, will be to distinguish those mutations that affect the core cellular signaling mechanisms that are used to encode memories from those mechanisms that modulate these mechanisms or affect the development of the basic circuits important for performing the learning task or for storing the learned information. The use of progressively better anatomically restricted and temporally regulated genetic modification in the mouse will be critical for distinguishing those genes that directly affect memory encoding from those that affect memory indirectly through developmental, motivational, or perceptual mechanisms.

Vision

In his pioneering text, which first appeared 50 years ago, Donald Hebb [67] observed that “we know virtually nothing about what goes on between the arrival of an excitation at a sensory projection area and its later departure from the motor area of the cortex…” “Something like *thinking* intervenes,” and although it would be hard to disagree with that proposition, the goal of cognitive neuroscience has been to flesh out that ‘something’ in a form that is more satisfying

to both psychologists and neurobiologists alike. In part because its operations span the chasm that Hebb lamented, the visual system has served as a proving ground for this goal. By tracing the flow of visual information from retina to motor control circuits we can, in principle, determine how its representation by the brain contributes to the various cognitive processes that constitute thinking, such as perception, recognition, imagery, decision making, and motor planning.

The 1990s will long be remembered as a turning point in this effort. As often recorded in these pages, recent advances in cognitive neuroscience are many. This state of affairs owes much to the fact that neurobiologists have with increasing frequency turned to experimental psychology (and vice versa) for guidance, inspiration, and tools. Products of this new-found interdisciplinary success include discoveries regarding the correspondence between neuronal and perceptual events, the role of context in perceptual processing, the neuronal substrates of attention and decision making, the plasticity of adult sensory representations, and the role of such in perceptual learning and sensory–motor spatial coordinate transformations.

Linking neuronal and perceptual events

We entered the past decade secure in the knowledge that the stimulus selectivities of visual neurons resemble the basic elements of perceptual experience, such as simple forms, motions, and colors. Lacking, however, was evidence for a specific causal relationship between neuronal and perceptual events. The problem was remedied by William Newsome and colleagues, who united classic methods from experimental psychology with modern neurobiological techniques (for a review, see [68]). These investigators discovered a close relationship between perceptual motion sensitivity and the sensitivity of neurons in cortical visual area MT [69], which strongly suggested that neuronal activity within area MT is a constituent of the perceptual experience of motion. Icing came in the form of another study in which Newsome and colleagues modified the perceptual experience of motion by artificially activating small collections of MT neurons [70]. The results from these experiments have offered sound reassurance that the stimulus selectivities of visual neurons account for perceptual experience, and they have paved the way for an understanding of the underlying mechanisms.

Sensation versus perception

The Newsome experiments solved one puzzle, but as many neurobiologists of the 1990s gained sophistication in perceptual psychology, they were forced to confront another: as understood up to that point, the stimulus selectivities of visual neurons encoded properties of the retinal stimulus. But things perceived reflect the 'meaning' of the stimulus, as defined by the content of the visual scene that leads to its appearance. Several studies carried out during the past decade have sought to distinguish neuronal representations of sensory and perceptual events.

In a set of experiments conducted by Thomas Albright, Gene Stoner, and colleagues [71–73], contextual cues unrelated to visual motion (e.g. luminance or stereoscopic cues that elicit a percept of surface depth ordering) were found to markedly alter perceived motion, even though retinal stimulus motion remained unchanged. In addition, the responses of many motion-sensitive neurons in cortical visual area MT were found to co-vary with perceived motion rather than with retinal motion, demonstrating that the formation of perceptual or 'scene-based' neuronal representations is accomplished at early stages in the visual processing hierarchy [73–75].

Related evidence for scene-based representations has come from experiments in which perceived features are not physically present in the retinal stimulus, but their presence in the visual scene is implied by contextual cues. In one such study, Rüdiger von der Heydt and colleagues [76] studied the neuronal basis of a perceptual phenomenon known as 'illusory contours', in which contextual cues imply the presence of an occluding surface and the edges of the surface are seen, even though they are not actually present in the stimulus. These investigators discovered that many neurons fire in a way that matches the percept, as though a real contour had been placed in the receptive field. In another study, John Assad and John Maunsell [77] exploited the fact that observers generally infer the continuous motion of an object when it moves behind an occluder. By using remote contextual cues to place the path of occluded motion within the receptive fields of motion-sensitive MT neurons, these investigators found that many neurons respond in a way that matches the perceptual inference of motion, in the absence of any real motion in the receptive field. The significance of these findings lies, of course, in the fact that the neuronal representations reflect — as does perception — the enduring structural and relational qualities of the observer's external environment [78].

Visual attention

The primate visual system has a limited information processing capacity. An exciting area of research in the 1990s has been that addressing the means and conditions under which this limited capacity — visual attention — is dynamically allocated. Work in this area has revealed two basic types of attentional phenomena, which may have distinct neuronal substrates. One effect, known as 'attentional facilitation', is the improved processing of a stimulus when it appears at an attended location. Early investigations of the effects of focal brain lesions in humans implicated the parietal lobe in attentional facilitation. In subsequent physiological studies of parietal cortex in non-human primates, Michael Goldberg and colleagues [79] found that for many neurons an attended visual stimulus elicited a much larger sensory response than did an identical unattended stimulus. Similar facilitatory effects have since been reported for other cortical visual areas [80,81].

The other basic attentional effect that has been studied extensively is known as 'attentional selection'. This effect refers to the phenomenon in which a target stimulus (i.e. the thing you're looking for) is selected from among other stimuli that are competing for attention. In the mid-1980s, Robert Desimone and colleagues [82] found that receptive field profiles of individual neurons in cortical areas V4 and IT contract around the attended stimulus, excluding unattended stimuli. These findings of selection at the neuronal level imply that information about an attended stimulus is carried to higher processing stages, at the expense of information about unattended stimuli. Selective effects have now been reported for many visual areas, including areas V1, V2, V4, MT, MST, and IT (see e.g. [83–86]), indicating that selective mechanisms operate simultaneously on multiple feature maps.

Physiological studies are beginning to target the underlying mechanisms of selective attention. Much of the work in this area has been inspired by the 'biased competition' model advocated by Desimone and Duncan [87]. According to this view, pieces of incoming sensory information compete for neuronal representation (and, ultimately, control of the observer's actions), and the competition is biased such that behaviorally relevant inputs are facilitated. Support for this model comes from a recent study by Desimone and colleagues [86], who found that the neuronal response to two unattended stimuli placed together in the receptive field was approximately the average of the responses elicited by the two stimuli presented independently. By contrast, when either stimulus was attended — thus giving it a competitive advantage — the neuronal response approximated that elicited by the attended stimulus alone. Although these findings beg important and difficult questions regarding the source of the biasing signal, as well as the local circuit and synaptic interactions that lead to changes in the receptive field profile, they provide a striking example of the gains afforded by the convergence of psychology and neurobiology.

Perceptual decisions

While intelligent behavior depends upon knowledge of one's external environment (i.e. perception), it also requires deciding which actions are appropriate given that knowledge. This 'decision process' has been the focus of several revealing experiments over the past decade. One goal has been to identify neuronal activity that is correlated with the decision to execute a particular action in response to a particular sensory stimulus, rather than simply correlated with either stimulus or action alone. In a series of studies, Earl Miller and colleagues [88] found that the responses of neurons in prefrontal cortex — an area long believed to play a role in the organization of complex behavior — change as new sensory–motor relationships are learned, such that individual neurons come to represent new behaviorally relevant conjunctions of stimulus and action. Other groups have adopted a different approach to the decision process, the principal feature of which is a search for neuronal responses that 'predict' an impending motor response to a visual cue (see e.g. [89]). In a recent study, Michael Shadlen and colleagues [90] exploited the fact that difficult decisions generally require time to accumulate relevant information, hence predictive neurons should exhibit responses that increase in magnitude in parallel with the observer's decision confidence. These investigators found that neurons in prefrontal cortex do exactly that. Collectively, these novel studies of the decision process have identified relevant neuronal substrates and have led to promising theories regarding ways in which visual information is flexibly mapped to action.

Perceptual learning

It is a central tenet of neurobiology that the sensory neocortex reaches its mature state of organization following a brief period of postnatal plasticity known as the critical period. One of the most important discoveries of the past decade, however, is the large extent to which this plasticity continues throughout life. Adult plasticity enables forms of cognitive flexibility such as perceptual learning, which is the improvement with practice in the ability to discriminate sensory attributes. Early hints of this plastic potential came from studies demonstrating that the adult cortex undergoes a local functional reorganization to compensate for damage to the sensory periphery [91–93]. This compensation may be mediated by intrinsic cortical connections, which appear to undergo rapid changes in synaptic efficacy, as well as a slower process of sprouting and synaptogenesis [94,95]. The belief that this form of plasticity also underlies adult perceptual learning is supported by evidence that training on perceptual tasks leads to reorganization of cortical sensory maps [96] and improvements in the sensitivities of cortical neurons [97].

Transforming signals from visual space to motor space

Another success story from cognitive neuroscience in the 1990s centers on the problem of converting visual inputs to signals that can guide actions. One long-standing view holds that retinal signals, which represent visual space in a coordinate frame that shifts with every movement of the eyes, are re-mapped into a more generic and stable coordinate frame based, for example, on the positions of objects relative to the observer's head or body. Consistent with this view, Richard Andersen and colleagues [98] discovered that the magnitude of response to a visual stimulus varies with the angle of gaze. Because they take eye position into account, these 'gain field' responses yield a head-centered map of visual space that is distributed across a population of parietal neurons [99]. More recent studies have obtained intriguing evidence for explicit cellular representations of space in pre-motor cortex. Carl Olson and Sonya Gettner [100], for example, found that some premotor neurons represent spatial location relative to the parts of a visible object (i.e. 'object-based' coordinates), independent of the position of the object's image on the retina. Perhaps even more remarkable are the findings of Michael Graziano, Charles Gross and colleagues [101], who reported the existence of

premotor neurons that represent the position of a visual stimulus relative to the position of the observer's forearm. Body-part-centered representations of this sort appear well suited for orchestrating specific limb movements to stimuli that are near those body parts.

The binding problem

In reviewing major themes of cognitive neuroscience research in the 1990s, we would be remiss to exclude a topic that has captured enormous attention in disciplines ranging from visual physiology to philosophy, while nonetheless remaining one of the most unsettled. The topic in question is the use of temporal binding codes to represent complex conjunctions of information carried by individual neurons. The potential utility of such codes has long been recognized. Empirical support came in the form of physiological data from Charles Gray, Wolf Singer and colleagues [102], which suggested that visual features (e.g. edges) perceived as parts of the same object are represented by neurons that fire synchronously. Others, however, have failed to find such support (or have raised objections on theoretical grounds), and the unprecedented polarization of opinions on the subject remains palpable as the decade draws to a close (e.g. see reviews in the October 1999 issue of *Neuron*). In light of the importance of the binding problem for both a functional and mechanistic understanding of cognition, and the attention and resources that have been directed at the problem in recent years, this persistent lack of consensus is both surprising and greatly disappointing. One can only hope that resolution will come from the application of new concepts and techniques in the next decade.

Imaging higher cognitive functions

Imaging has been critical for the localization of mental processes

As one reads journals devoted to cognitive neuroscience or human brain mapping, it is hard to imagine that there could ever have been doubts that there was a specific anatomy related to higher mental processes. Only in the past decade have neuroimaging studies using PET and fMRI demonstrated a pervasive form of localization in a wide variety of cognitive and emotional tasks [103,104]. The localization of mental operations, as described in the first section of this review, has made psychology a full partner in efforts to understand human brain mechanisms.

The distributed nature of the activations in any real cognitive task helps explain why Karl Lashley [105] and others could have thought that the brain operated as a whole. However, in tasks involving language, mental imagery, spatial navigation and working memory, where we have been able to dissect them into plausible computations, it is these components not the task themselves that are localized. Of course localization is only a start toward the achievement of cognitive neuroscience. As described below, imaging has provided an important impetus for exploring the evolution of mental operations, their organization into circuits, their pathologies and change with experience.

Imaging has strengthened the correspondences between the brain anatomy of humans and that of experimental animals

A major advance in making cross-species comparisons has been the development of flat maps that provide a two-dimensional surface for mapping the complex folds of the human brain [106]. There has been progress in efforts to relate retinotopic human visual areas to the maps obtained from cellular recording in primates [107]. Evidence that attention enhances activity in V1 (for a review, see [108]), has made it possible to explore attentional influences in a brain area where the detailed cellular structure is better understood. Cellular studies in monkeys indicate the importance of attention in integrating visual effects that occur outside the classic receptive field of V1 neurons, for example, in perceiving contours [109]. The interaction of attention with V1 circuitry may also be important in understanding the early visual system plasticity described in the previous section.

Integration of human and animal studies is not limited to the early visual system. Studies of parietal neurons, located within brain areas shown to be active in imaging studies of spatial attention [110,111], have provided evidence of a map of locations organized by their current importance [112] that could serve as the basis for human working memory for location [113]. Using new fMRI methods, it has been possible to separate operations performed by the superior and inferior areas of the parietal lobe. These results [111] suggest that the temporal–parietal junction is critical for shifts of attention toward unexpected visual stimuli, a finding that supports the importance of this area in the neglect of space opposite the lesioned hemisphere found in patients suffering from strokes that affect the temporal–parietal junction.

Timing and the functional connectivity of neural circuits

Of equal importance to precision in space is the ability to say exactly when and for how long an anatomical area is active and when information is being exchanged between areas. Because mental operations occur in the range of tens to hundreds of milliseconds, it has been useful to relate areas of activity found in imaging studies to the distribution of electrical activity recorded from the scalp [114] or by depth electrodes [115]. For example, using combined ERP and fMRI methods, it has been shown that although attention influences activity in primary visual cortex, this takes place only after the information has been processed in prestriate areas [116].

A different approach to the circuitry of high-level cognition is to examine functional connectivity by studying the correlation between brain areas on the basis of hemodynamic [117] or electro-magnetic [118] measurements. These efforts provide an approach to the transfer of information

between brain areas by specifying within a task exactly the time when their activity is correlated.

Recently, an adaptation of magnetic imaging called diffusion tensor imaging has been used to produce images of the white matter connecting brain areas [119,120]. The time course of myelination of neuronal pathways can be used to test theories of when in development particular behaviors emerge. Perhaps this method, when combined with measuring correlations in electrical activity, will allow us to predict when a given brain circuit is sufficiently developed to support the learning of complex skills. In a recent study [121], for example, differences in white matter tracts in the temporal parietal area of the left hemisphere were related to reading skill within both a normal and a reading-impaired population.

Pathology: the search for subtle functional changes in disease

Brain damage due to strokes and tumors can be observed readily in structural images, but other abnormalities may involve more subtle functional changes. The use of structural images to map brain lesions has allowed investigators to combine the data from sets of patients with large cerebral lesions showing by the overlap in lesion location the brain areas that appear to cause the deficit. For example, a set of patients with large lesions of the left hemisphere all showed expressive aphasia provided that they had a loss of neurons in the anterior insula [122]. This finding supported results obtained with PET showing that the insula is an important pathway for highly automated verbal output, such as reading words aloud [123].

Tasks involving monitoring of emotion and cognition activate separate areas of the frontal midline [124–126]. In some studies, the cognitive and emotional areas appear to be mutually inhibitory, with cognitive tasks reducing blood flow in areas related to emotion, as well as the reverse [126]. These areas appear to be important in some forms of psychopathology. For example, PET scans of patients with schizophrenia who have never been on medication indicated an abnormality in the left globus pallidus [127], which is the outflow of a major dopamine circuit that modulates cellular activity in midline frontal areas such as the anterior cingulate gyrus [128]. This abnormal function might help to explain both the curious neglect of the right side of space shown in early schizophrenia and the changes in circuitry within the anterior cingulate observed in the brains of schizophrenic patients postmortem [129].

Plasticity and shaping of neural circuits by experience

A major achievement of infancy research in the past decade has been to show that human infants enter the world with some mechanisms related to the processing of language, objects, faces and numbers, as well as with the ability to imitate motor routines (for a review, see [130]). How does experience shape these initial mechanisms into the complex skills present in the adult?

Neuroimaging studies have provided us with some mechanisms by which experience at different time scales might change anatomy or circuitry on a temporary or permanent basis. One way in which brain circuitry can be altered is called priming, which refers to changes in the efficiency of processing a target when part or all of the pathway involved has been previously activated. Combined neuroimaging and cellular studies show that priming works by reducing or tuning the number of neurons required to process the target [131]. Studies in human subjects have shown that priming can take place within a second and that it may take place even when the person is unaware of the identity of the prime [132]. Priming may help account for moment-to-moment differences in the thoughts generated in response to a given environmental challenge or strategies used to solve a problem.

A few minutes of practice has been shown to be sufficient to change the circuit that processes information from one that involves a high level of complex computation to one that has an already compiled answer waiting for output [123,133]. Changes of pathways can help explain the shifts that take place when extensive practice renders a skill automatic.

Somewhat slower are the task-related increases in cerebral tissue found in sensory [134] and motor [135] systems with extended practice. These changes in visual areas were discussed in the previous section. The effects of extensive practice have also been documented in studies of adults who learned languages either as children or later in life [136] and musicians who had extensive practice on musical instruments [137]. Although there are strong hints that the relative plasticity of these skills may differ between children and adults, full documentation of this form of critical period is still to be developed.

The next decade?

Donald Hebb and his fellow pioneers in cognitive neural science would surely be pleased at the promiscuous bedfellows that psychologists and neurobiologists have now become, and with their offspring, which is a fuller demonstration that specific cognitive information is represented in the activities of specific neuronal populations. These recent successes notwithstanding, it seems likely that Hebb would also recognize the weakness in our current view: lack of information about how these neuronal representations are achieved mechanistically. How, for example, are contextual cues assessed by cortical neurons to form visual representations that coincide with perceptual experience? And how are such representations altered as a function of experience? Answers to these and other mechanistic questions require, at the very least, detailed information about the patterns of anatomical connections in the cerebral cortex, and the functional properties conferred by specific circuit components.

Determining the local circuit organization of the cerebral cortex and how that organization relates to the processing

of region-specific information is, however, dauntingly complex, and its elucidation — important though it may be — is among the most formidable challenges facing cognitive neuroscience in the next decade. Hope lies in some remarkable new experimental approaches, which promise both fine-scale assessment of functional circuitry in the cortex and pictures of the global patterns of neuronal activity associated with specific cognitive states.

One of the most exciting prospects for fine-scale analysis of functional circuitry can be found in methods for regionally restricted and temporally regulated control of gene expression. These methods took the stage in the 1990s in the form of mouse germ line transgenic manipulations, and they have become extremely powerful tools for analysis of the cellular and molecular bases of learning and memory. Can we reasonably expect to use these new molecular tools to study neural systems in animals such as non-human primates, animals that possess a rich and human-like repertoire of cognitive skills, but for which germ line gene transfer is all but impossible? Much cause for optimism stems from newly developed methods that employ viruses as vectors for gene transfer, which promise to eliminate dependence upon germ line transgenics and thus allow technology for temporal and cell-type specific gene regulation to be imported to primates. Imagine, for example, the incredible possibilities for analysis of functional circuit components afforded by the ability to switch on and off a specific class of cells in a specific cortical area while a monkey is engaged in a cognitive task!

At the other end of the continuum of mechanistic issues, we face the problem of measuring and interpreting the interactions between individual neurons and between groups of neurons. Work of the past decade attests that the single neuron approach to perception and cognition has been profoundly successful. As we move beyond the representational phenomenology of single neurons to confront mechanistic questions, however, we find that it is impossible to proceed without a more global approach to neural coding. If, for example, we expect to understand the mechanisms that underlie the interactive contributions of a stimulus in the visual field and of working memory to selective visual attention, then it is essential that we be able to monitor simultaneously neuronal events in all the relevant interconnected brain regions. This is not an easy task, nor is the associated problem of interpreting the multitude of potential neuronal interactions. New techniques based on multielectrode recording, optical imaging of neuronal activity, and fMRI — each used in conjunction with the behavioral methods that have proved so valuable over the past decade — are beginning to make important inroads in this area.

In the decade of the 1990s, cognitive neuroscience thrived by bringing together psychology and neurobiology. We now have every reason to expect that the next decade will yield a similarly mature molecular biology of cognition, in which powerful molecular and genetic tools find their calling in the service of cognitive neuroscience, and that the field will continue to advance through a global circuit-based approach to cognitive representation by the brain. These are indeed heady times for the young field of cognitive neuroscience. Although, as noted by Hebb 50 years ago, there still is "a long way to go before we can speak of understanding the principles of behavior to the degree that we understand the principles of chemical reaction", the time for that understanding is now — at least — in full view.

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