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INTRODUCTION

The Center for the Neurobiology of Learning and Memory has organized many international conferences since being founded in 1982. The purpose of these forums has been to address the current status of enduring problems across the interdisciplinary spectrum of the field and to herald, where possible, new conceptual and empirical developments that have both broadened and deepened approaches to the neural substrates of learning and memory. The contributions of researchers that are reported herein represent the distillation of the Seventh Conference on the Neurobiology of Learning and Memory—*Making Memories in the Brain: Orchestration of Cells & Systems*. This conference, held in Irvine, California on November 7–9, 2001, also celebrated the 20th anniversary of the center. The conference was organized into four sessions: "Local Synaptic Processing in Memory Formation," "Interaction of Brain Systems in Memory Formation," "Stress and Memory," and "Addiction and Memory: Common Mechanisms?"

The first session focused on molecular events that are localized to synapses and are thought to contribute to long-lasting synaptic plasticity involved in memory formation. Kelsey Martin described her work using cultured sensory and motor neurons from the marine mollusk *Aplysia*. With her colleagues, she showed that local application of the biogenic amine serotonin (5HT) is capable of inducing branch-specific long-term synaptic facilitation (LTF) that is dependent on local protein synthesis. Using a cDNA library from isolated sensory neurites, she went on to show that there is a complex array of messenger RNAs (mRNAs) present in *Aplysia* synapses and that 5HT is capable of regulating their translation into protein. Tom Carew then presented evidence that he and his colleague Carolyn Sherff obtained showing that, in the CNS of *Aplysia*, several mechanistically distinct forms of LTF can be induced at sensori-motor synapses, depending upon the pattern and locus of 5HT application. One form, produced by repeated cell-wide 5HT application, requires presynaptic protein synthesis, whereas another form, induced by coincident application of a single pulse of 5HT to the cell body and synapse, requires local postsynaptic protein synthesis immediately, followed by delayed protein synthesis at the cell body. These results show that LTF expressed in the same time domain can result from different underlying mechanisms. Oswald Steward rounded out the session with his description of work that he and Paul Worley have carried out analyzing the cellular mechanisms that target newly synthesized mRNA transcripts to individual synapses, where they can be locally translated. They focused their attention on the mRNA of a particular immediate early gene called *Arc* (activity regulated cytoskelton-associated protein) and showed that synapse-specific targeting of Arc mRNA requires NMDA activation. This work revealed important aspects of a mechanism by which synaptic activity can induce both gene expression and target specific mRNA transcripts to synapses whose NMDA receptors have been activated.

The second session was concerned with the level of brain circuits and systems, and

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their various roles in mnemonic processes. The prefrontal cortex (PFC) has long been implicated in memory, as classically demonstrated by deficits in delay tasks consequent to prefrontal lesions. Three major issues are of contemporary interest: specialization in mnemonic function, localization of such specialization, and interaction of the PFC with other brain systems that may hold actual memories. Michael Petrides, emphasizing that PFC deficits do not necessarily imply PFC loci of information storage, reported functional and regional specializations with the use of position emission tomography (PET) and fMRI imaging in humans. He found that mid-dorsalateral PFC (areas 9 and 46) exhibits activation patterns consistent with the monitoring, not maintaining, of memory. In contrast, the mid-ventrolateral PFC (areas 45 and 47/12) is implicated in executive processes, such as the selection, comparison, and judgment of information during active retrieval in short- and long-term memory. This region is hypothesized to execute top-down control of posterior association fields that may be the sites of actual storage. Regardless of where they are stored, all memories can also be characterized by their strength. Jim McGaugh reviewed recent findings that he and his colleagues, Christa McIntyre and Ann Power, obtained on the role of the basolateral amygdala (BLA) in the posttraining modulation of memory strength, based on the BLA's established mediation of stress hormones released by emotional arousal. Studies in the rat reveal that the levels of norepinephrine (NE) release in the BLA during inhibitory avoidance learning are predictive of subsequent levels of retention. The BLA also plays a critical role in memory processes in other brain systems, as evidenced by the finding that memory modulation by direct manipulation of the caudate, hippocampus, and entorhinal cortex is dependent upon an intact BLA. Interestingly, the neuromodulatory effects of the BLA on brain regions that are the sites of actual memory storage appear to be mediated via the cholinergic nucleus basalis (NB). Thus, the widespread cortical and subcortical projections of the NB may enable memory modulation that is initiated by and dependent upon the basolateral amygdala. Leslie Ungerleider extended the systems approach to motor skill learning, presenting findings that she, Julian Doyon, and Avi Karni obtained during imaging studies in humans. They observed two phases (fast and slow) of behavioral learning and neural plasticity during repeated practice with patterns of finger movements. Motor cortical (M1) activity increases over weeks within the hand area, transforming a patchy representation of finger muscles into a more extensive representation; importantly, this plasticity is specific to the pattern of learned movements. They also found consolidation of motor memory over hours in the absence of additional practice. Cerebellar involvement was seen within a single training session but decreased as the striatum and supplementary motor cortex developed increased activity. The findings suggest that when a sequence of movements is well learned, the cerebellum is no longer a necessary substrate whereas a distributed system involving motor cortical areas and the striatum becomes sufficient. The neural substrates of motor consolidation constitute an intriguing problem for the future. Matt Wilson concluded the session with an account of recent findings on hippocampal representation of information storage, comparing the discharge patterns of place cells at multiple recording sites in CA1, for spatial exploration during waking with subsequent sleep. He reported that the hippocampus exhibits neural correlates of the reactivation of the waking experience during brief (e.g., 100 ms) periods of non-REM sleep, Moreover, he obtained evidence for the "replay" of sequential event memory over a long time scale by analysis of discharge patterns during REM sleep, over periods of tens of seconds to minutes. He hypothesized

that these findings provide a means for the transfer of information from the hippocampus to the cerebral cortex.

It is now generally appreciated that stress can have major effects on memory. Ron de Kloet led off the session on stress and memory by describing work that he and Jeannette Grootendorst, Adriaan Karssen, and Melly Oitzl have carried out examining the role of corticosterone on the interaction between genes and environment in mediating cognitive function. He focused on three issues: First, the role of corticosterone itself on the expression of networks of corticosterone-responsive genes; second, the experimental context that determines the timing and consequence of corticosterone actions; finally, the genetic context within which corticosterone acts. In this latter case, he presented intriguing evidence from experiments using apolipoprotein E (apoE) knockout mice that support the view that the apoE gene may play an important role in modulating some of the cognitive consequences of stress. While glucocorticoid hormones have been implicated in memory, both memory facilitation and impairment have been reported. Benno Roozendahl summarized his research indicating that the effects of these stress hormones depend on the phase of memory under investigation. Posttraining activation of relevant pathways facilitates memory consolidation and does so in a manner similar to the previously described effects of adrenal catecholamines, including dependence on noradrenergic activation of the BLA. In contrast, memory impairments are evident during retrieval in the presence of high circulating levels of glucocorticoids. Thus, a stressful experience can simultaneously strengthen memory for the precipitating event while interfering with the retrieval of previous memory. Roozendahl suggests that these apparently opposing effects work in concert to diminish retroactive interference from prior memories, thus favoring consolidation of the new stressful memory. The extent to which laboratory findings have relevance to clinical situations was addressed by Gustav Schelling. Most patients in intensive care report traumatic memories from their hospital stay, and many develop posttraumatic stress syndrome (PTSD). Those who have received stress hormones, e.g., epinephrine, norepinephrine, or cortisol, as part of their treatment later exhibit memory facilitation. Specifically, they exhibit greater vivid recall of nightmares, anxiety, respiratory distress, or pain without necessarily recalling factual events. Analysis of patients revealed that the number of categories of traumatic experience recalled increased as a direct function of the dosage of administered stress hormones and enhanced retention at least for 6 months. Thus, animal findings appear to be able to predict clinical findings in seriously ill humans.

The final session considered the fascinating question of whether there are commonalities in the mechanisms underlying addiction and memory. Nora Volkow began the session with a discussion of the work that she, Joanna Fowler, and Gene-Jack Wang have carried out examining drug addiction in humans. They used PET to investigate the role of dopamine (DA) in neural circuits that are thought to be involved in addiction. They showed that increases in DA are associated with the rewarding effects of drugs of abuse and that during withdrawal, drug abusers exhibit a significant decline in both DA receptors (specifically D2 receptors) and in DA release. She concluded with evidence showing that drug craving in abusers is associated with activation of several neural systems (e.g., the amygdala, hippocampus, and dorsal striatum), all of which have been implicated in some form of learning and memory and all of which receive DA innervation. Trevor Robbins reviewed his collaborative studies with Barry Everitt, analyzing drug addiction within the framework of normal learning and memory processes that are strengthened by the motivational effects

of drug-associated stimuli. He explained how both Pavlovian and instrumental conditioning processes ultimately induce drug-seeking behavior. Their findings in animal models implicate cortico-limbic-striatal systems that converge on the ventral striatum and habit-based learning dependent on the dorsal striatum Influences from the amygdala, hippocampus, cingulate, and medial prefrontal cortex are also involved in both drug-seeking and drug-taking behavior. Overall, their findings indicate the power and generality of known conditioning processes and mechanisms. The session concluded with a presentation by Eric Nestler, who described work from his laboratory and others that reveal several commonalities between the lasting changes in the brain that accompany the behavioral abnormalities underlying addiction on one hand, and learning and memory on the other. He pointed out that both types of changes are modulated by neurotrophic factors, share common intracellular signaling cascades, and depend on activation of transcription factors such as the cyclic AMP response element binding protein (CREB). Consistent with the observations of Nora Volkow described above, Nestler emphasized that similar forms of neural plasticity accompanying both addiction and memory formation are observed in a wide range of circuits including cortex, hippocampus, dorsal and ventral striatum, and amygdala.

In conclusion, the conference provided four lively sessions that shed new light on enduring problems as well as pointing the way to emerging areas in the analysis of learning and memory. When considering the conference as a whole, it is noteworthy that the field of the neurobiology of learning and memory now ranges so broadly, from the molecular biological analysis of single synapses to human drug addiction. Conferences such as this play a vital role in providing important conceptual and technical bridges across these diverse disciplines. This was evident not only from the presentations of the speakers but in equal measure from interchanges provided by the many participants at large.

Tom Carew
Norm Weinberger