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MEETING REPORTS

The Tenth Annual Meeting of the Winter Conference on Neural Plasticity St. Lucia, West Indies February 21 – 28, 1998

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The 10th Annual Meeting of the Winter Conference on Neural Plasticity was held in Reduit Bay, St. Lucia from February 21 to 28, 1998. The Conference was attended by approximately 75 participants from six countries. Most of the participants were neuroscientists from universities and basic research departments of applied institutions. The primary focus of the conference is to annually review recent advances in the area of neural plasticity from multidisciplinary and lifespan perspectives. There was an initial Frank Morrell Memorial Lecture by Aryeh Routtenberg entitled "From the Mirror Focus to Memory: Bridging the GAP," followed by a "New Concepts Session," and nine scientific sessions, each lasting two hours.

NEW CONCEPTS

The New Concepts Session, chaired by **R. F. Thompson** (Univ. Southern California), allowed all participants five minutes and one slide to present their latest idea, finding, or technique. This allowed a broad exchange of ideas within a condensed format that fostered the presentation of the most recent and exciting findings from the laboratories of the various participants.

ENSEMBLE SINGLE-NEURON RECORDING IN HIPPOCAMPUS DURING LEARNING

This session was chaired by **J. Disterhoft** (Northwestern Univ. Medical School). It focused on recent developments in single neuron recording techniques that allow the

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monitoring of many cells simultaneously in the conscious animal during behavior. This approach allows a more realistic appraisal of the function of individual neurons because many more can be sampled. Perhaps more important is the opportunity this approach affords to explore how nearby neurons interact with each other during the acquisition and readout of learned behaviors. This symposium addressed modern single-neuron ensemble acquisition and analysis techniques as used to evaluate the function of the hippocampus during learning and consolidation of several different behavioral tasks.

S. Deadwyler (Bowman Gray School of Medicine) presented his linear and nonlinear description of hippocampal ensemble activity during delayed non-match to sample short-term memory performance in rats, and described the effects of ampakines on memory storage in this task. **J. Disterhoft** (Northwestern Univ. Medical School, Chicago, IL) described several unique stages of hippocampal activity that are especially prominent in the period preceding behavioral changes during the acquisition of trace eyeblink conditioning in rabbits, and discussed differences in neural activity between young and aging rabbits during learning. **H. Eichenbaum** (Boston Univ., Boston, MA) discussed experiments using two different approaches to explore the cues used in representations of places in the hippocampal cognitive map in young adult and aging rats and in genetically manipulated rats, which suggested that hippocampal spatial representation is not a unified map but rather a collection of linked encodings of various subsets of the cues and all manner of possible relations among them.

R. Muller (S.U.N.Y. Health Sciences Center) discussed experiments exploring the involvement of NMDA-mediated transmission in the formation of place cell maps, and demonstrated that the specific NMDA-receptor antagonist CPP destabilizes place cell maps of new environments. M. Wilson (Massachusetts Institute of Technology, Cambridge, MA) described recordings from mice in which the synaptic plasticity had been manipulated within restricted regions of the hippocampus using new genetic targeting techniques to determine the role of synaptic plasticity at specific synapses within the hippocampus in the acquisition of spatial memory and the formation of normal hippocampal place fields. He also described work beginning to examine interactions between the frontal cortex and hippocampus during spatial task performance.

INTRACELLULAR ANALYSIS OF NEURAL CIRCUITS AND THEIR PLASTICITY *IN VIVO*

The firing pattern of a neuron contains the information that it communicates to the rest of the network. This pattern in turn is determined by the activity of presynaptic neurons and local dendritic electrogenesis. Subtle subthreshold dynamics, therefore, determine the transformation from presynaptic to postsynaptic spike trains. This transformation is central to the computations performed by neural circuits but is invisible to extracellular recordings. In contrast, the cellular membrane potential reflects the dynamics of synaptic currents, the local electrogenesis in response to these currents, and the resulting action potential train. Intracellular recordings are therefore essential to further our understanding of neural circuits and their plasticity.

Although the first membrane potential recordings in the mammalian central nervous system were made *in vivo*, by far the majority of intracellular studies have focused on reduced preparations, such as slices. Slice studies, however, are difficult to interpret in terms of circuit function; these difficulties stem from the highly unnatural patterns of synaptic stimulation, the absence of background activity and modulatory inputs, and experimental factors such as temperature and others. This may be one reason why studies employing intracellular recordings of neuronal dynamics *in vivo* have recently experienced a bit of a renaissance. Another reason might be that new techniques (whole-cell recordings, functional imaging) and improvements on old techniques (sharp electrode recordings) have reduced the technical challenges in obtaining high quality intracellular recordings *in vivo*. The speakers in this session presented some recent highlights in intracellular analysis of neurons and circuits *in vivo*. The presentations showed that quantitative cellular physiology *in vivo* is routinely doable and that it provides unique, and often surprising insights into the workings of the brain.

C. Gray (Univ. California, Davis) discussed the mechanisms of excitation in the primary visual cortex of the cat. **D. Pare** (Univ. Laval, Quebec, Canada) described research on synaptic noise in the neocortex. **K. Svoboda** (Cold Sprung Harbor Laboratory, NY), who chaired the session, and **G. Buzsaki** (Rutgers Univ., NJ) discussed intracellular analysis of dendritic excitability in the neocortex and hippocampus, respectively.

EARLY NEURAL ACTIVITY AND THE DEVELOPING CENTRAL NERVOUS SYSTEM

One of the fundamental questions in developing neuroscience is the role of nature vs. nurture in shaping neural functions. There is now compelling evidence that the outgrowth of the brain is not exclusively pre-programmed genetically by turning on the expression of specific genes at different developmental stages. Early neural activity, generated spontaneously in the embryo, or by experience in neonates, plays a fundamental role in the elaboration of neural circuitry. Through modulation of neurite outgrowth, the establishment of synaptic connections, trophic interactions between neurons, and cell death, early neural activity builds and alters the circuitry of the developing central nervous system (CNS), enabling storage of information. Disruption of early neural activity may lead to irreversible functional changes in the mature CNS. Storage of information during early life ultimately determines adult behavioral patterns. This symposium gave examples of how early neural activity helps elaborate complex functions in the auditory system, the visual system and the motor system.

A. King (Univ. Oxford, UK) showed how the development of the map of auditory space in the superior colliculus and its correct alignment with the neural representations of other modalities is guided by both auditory and visual experience during early postnatal life. Using a combination of anterograde tracing and immunocytochemical techniques to identify the site and mechanisms underlying this experience-dependent plasticity, he discussed the way in which the pattern of auditory and visual afferents to the colliculus, and the neurotransmitter and neurotrophin receptors they

express, change during the normal course of development and after disruption of the sensory inputs. **E. Sernagor** (Univ. Newcastle upon Tyne, UK), who chaired the session, described the properties of the early spontaneous activity present in embryonic retinal ganglion cells long before visual experience at birth. This bursting activity is mainly driven by acetylcholine. it is synchronized between neighboring ganglion cells, resulting in waves of activity sweeping across the retina. She showed how disruption of early neural activity (either by chronic blockade of the spontaneous activity or by dark rearing) affects developing receptive fields of retinal ganglion cells, and presented evidence for the differential roles played by early spontaneous activity and visual experience in shaping these receptive fields.

M. Weliky (Duke Univ., NC) discussed the role of correlated neural activity during visual system development. He first described the patterns of spontaneous activity within the developing lateral geniculate nucleus, obtained from multi-electrode recordings in awake behaving ferrets. He discussed how feedforward/feedback connections regulate these patterns, and whether the correlational structure of these patterns are consistent with activity-dependent models of cortical map and receptive field development. Next, he demonstrated that the introduction of abnormal patterns of neural activity into the visual pathway disrupts cortical receptive field development. Short bursts of electrical pulses are applied to retinal ganglion cell axons in the optic nerve, producing artificial neuronal correlations. He showed that cortical orientation/direction selectivity is weakened following this stimulation, suggesting that activity plays an instructive role in shaping cortical receptive field tuning properties.

M. O'Donovan (National Institutes of Health, Bethesda, MD) showed that networks in the developing spinal cord exhibit spontaneous episodes of rhythmic activity. The networks responsible for this activity may be the precursors of adult locomotor circuits. He showed that these networks exhibit a surprising form of short-term plasticity that may be important in the regulation of network output.

MOLECULAR MECHANISMS OF NEURODEGENERATION AND REGENERATION

This session discussed mechanisms that play a role in neurodegenerative diseases such as Alzheimer's disease, Huntington's disease, and amyotrophic lateral sclerosis. First, oxidative injury and cytoskeletal abnormalities were highlighted as central participants that result in neurodegeneration. Next, regenerative mechanisms that occur in response to neurodegeneration were discussed along with their significance and consequences of such events to brain diseases. Finally, a neuroprotective mechanism was described utilizing genetically modified cells implanted into rodent and primate brains.

A significant body of evidence suggests that free radical damage and oxidative stress play pivotal roles in neurodegeneration. **M. Smith** (Case Western Reserve, Cleveland, OH) described experiments to identify the source(s) of damaging reactive oxygen species in the brains of patients with Alzheimer's disease. Sources for the generation of reactive oxygen species include neurofibrillary tangles and senile plaques, hallmark pathologic features of Alzheimer's disease. Treatment strategies

were discussed that specifically target sources of oxygen radicals which may have particular therapeutic efficacy.

G. Jicha (Albert Einstein College of Medicine, New York, NY) discussed cytoskeletal abnormalities as early events in neurodegeneration. The microtubule-associated protein, tau, forms paired helical filaments (PHF) in degenerating neurons during Alzheimer's disease. Monoclonal antibodies have been produced to characterize the complex structural changes that occur to tau during formation of PHF. Specific conformational changes and phosphorylation of tau occur prior to PHF formation, and it is important to determine if these abnormalities are causally linked to neurodegeneration. During the early stages of neurodegenerative diseases, regenerative events and neuronal sprouting occur in an attempt to compensate for neuronal injury.

R. Bowser (Univ. Pittsburgh, PA) described the re-activation of a specific molecular mechanism during the early stages of Alzheimer's disease and amyotrophic lateral sclerosis. This molecular mechanism also functions during brain development and after brain injury.

J. Kordower (Rush Medical Center, Chicago, IL) discussed the potential of transplanting genetically modified cells that secrete trophic factors as a mechanism of neuroprotection in models of Huntington's disease. Implantation of these modified cells prevents loss of multiple cell populations in rodent and nonhuman primate models of Huntington's disease. A hypothesis was presented to explain the robust neuroprotection of multiple cell types which are selectively vulnerable in Huntington's disease.

E. Mufson (Rush Medical Center, Chicago, IL) discussed the involvement of nerve growth factor and its high- and low-affinity receptors in basal forebrain cholinergic cell death in Alzheimer's disease. Data was presented implicating a deficit in high-affinity receptor expression as a major factor in cholinergic basal forebrain cell death in Alzheimer's disease. The session was co-chaired by E. Mufson and R. Bowser.

NEUROPLASTICITY OF HYPERALGESIA

The phenomenon of hyperalgesia is characterized by a decrease in pain threshold and an increase in sensitivity to painful stimulation and often occurs following nerve injury and/or inflammation. Hyperalgesia occurs in a wide variety of human pathological conditions, and is frequently resistant to treatment. On a physiologic level, hyperalgesia can be the product of either or both peripheral and central neuroplastic changes. These changes can be transient, as in primary afferent sensitization, or long term, as in novel gene expression and anatomical reorganization. Physiologic and genomic changes that may contribute to hyperalgesia, and novel approaches to the alleviation of hyperalgesia, were reviewed and discussed. The group of speakers assembled included scientists actively researching many aspects of hyperalgesia.

G. Pappas (Univ. Illinois, Chicago, IL) discussed morphologic changes in interneurons in the spinal cord that occur with hyperalgesia consequent to sciatic nerve constriction injury. Evidence was presented that indicates that these changes may underlie a loss of tonic inhibition leading to facilitation of pain transmission. Pappas

also discussed his extensive animal and human clinical work in the treatment of pain and hyperalgesia by means of spinal transplantation of adrenal medullary tissue.

D. Simone (Univ. Minnesota) discussed electrophysiological changes in nociceptive spinal neurons that contribute to hyperalgesia. It was demonstrated that excitability of spinothalamic tract (STT) neurons increase during hyperalgesia, and that increased evoked responses of STT neurons correlate with psychophysical measures of hyperalgesia in humans. Evidence was also presented showing that spinal neurons that possess substance P receptors are critical for the development of hyperplasia following certain injuries. This evidence includes nociceptive evoked internationalization of substance P receptors on spinal neurons, and the antihyperalgesic effects of selective immunotoxic destruction of these cells.

Finally, **D. Yeomans** (Univ. Illinois, Chicago), who chaired the session, presented evidence that behavioral hyperalgesia can be separately induced for nociception evoked by the activation of myelinated or unmyelinated primary afferents. Also discussed was how hyperalgesia mediated by these two afferent types can be differntially modulated pharmacologically. In addition, evidence was presented for a novel approach to the alleviation of hyperalgesia, which uses herpes viral vectors to induce the expression of gene products that inhibit the development of hyperalgesia. The group discussed the neural changes accompanying hyperalgesia and novel approaches to its study and treatment.

NETWORKS AND MEMORY MODULATION

It is commonplace in neuroscience to refer to particular brain structures (e.g., the hippocampus) as sites of particular behavioral functions (e.g., episodic memory). This symposium put forth a different perspective: that behavioral functions are governed by interactions among multiple, interconnected areas that form functional brain networks. Convergent results of several of the symposium participants fostered the conclusion that amygdala neurons modulate other areas that are parts of a learning network, and the other areas act back to significantly modulate the activities of amygdala neurons.

B. Kapp (Univ. Vermont) derived from his data the notion that a conditioned vigilance process rapidly mediated by the amygdala and related basal forebrain areas forms the basis of this circuit's downstream modulation of sensory processing and of more slowly acquired conditioned responses such as the eyeblink response of rabbits. **M. Gabriel** (Univ. Illinois, Urbana) asserted concordantly that the integrity of the amygdala is essential for the initiation of learning-relevant plasticity of sensory (medial geniculate) neurons as well as cingulothalamic neurons involved in mediating associative attention.

The work of **M. Fansclow** (Univ. California, Los Angeles), **M. Gabriel**, and **F. Helmstetter** (Univ. of Wisconsin, Milwaukee) has yielded convergent results with respect to network interactions of hippocampus, amygdala, and related areas during aversive conditioning. Fanselow's work indicates that the hippocampus is involved in a time-dependent consolidation of memory pertaining to representation of the training context. The amygdala receives this information and associates it with specific values of affect (fear). Gabriel's work indicates that an intact hippocampus is needed if be-

havior and amygdala neurons are to be modulated by changes in the learning context. Helmstetter showed that fear conditioning requires normal metabolic activity and the synthesis of new RNA and proteins at several network sites during training: the amygdala, hippocampus, periaqueductal gray, and medial geniculate nucleus. Each structure is involved in mnemonic storage of the training experience, yet each makes distinct functional contributions to the learned response. **G. Quirk** (Ponce School of Medicine) discussed the interactions of the amygdala and the neocortex during fear conditioning. The session was co-chaired by M. Gabriel and T. Shors.

INTERACTIONS BETWEEN FRONTAL AND POSTERIOR BRAIN SYSTEMS IN MEMORY AND ATTENTION

Growing evidence indicates rather extensive interactions between prefrontal cortices and other brain systems, including higher order sensory, parietal, and parahippocampal regions in the performance of various cognitive operations. New techniques make it possible to bring studies in humans and monkeys closer together, thereby providing the benefit of the detailed information found in the animal work and direct evidence for similar functions in human cortices.

This symposium, co-chaired by **G. Simpson** (Albert Einstein College of Medicine, New York, NY) and **J. Haxby** (National Institutes of Mental Health, Bethesda, MD), encompassed examples from two lines of research in monkeys and two related lines of research in humans. It raised issues regarding the compartmentalization of function in frontal and sensory systems and addressed the role of networks and the importance of timing of activity within these systems. Haxby discussed studies using functional magnetic resonance imaging to investigate the perceptual and mnemonic functions of human posterior and frontal cortices during object and spatial visual working memory tasks. This included findings regarding the compartmentalization of function in these areas and the relationships between these regions, elucidated in part by the temporal properties of their activation.

The prefrontal cortex is essential for working memory, a set of functions involved in planning complex behavior, reasoning, and problem solving. The work from **E. Miller's** group (Massachusetts Institute of Technology, Cambridge, MA) illustrated that the prefrontal neurons have properties consistent with a role in these operations. These neurons can select, from the many available sensory inputs and from long-term storage, the information currently relevant for behavior, integrate information from diverse sources, and rapidly form the arbitrary associations critical for rule learning, planning, and problem solving. Across all these studies, they see that the prefrontal cortex is a highly dynamic system. Its activity adapts to current behavioral demands. This suggests that the prefrontal cortex may have information about behavioral context, that is, the rules or task instructions needed to guide behavior.

F. Wilson (Univ. Arizona College of Medicine, Tucson, AZ) reviewed three studies that address areas of interaction between the frontal and temporal lobes in macaque monkeys: 1) Similarities and differences in function between the inferior prefrontal convexity (IFC), and inferior temporal (IT) cortex. Although neurons in IFC and IT have similar visual receptive field properties, IT neurons reflect the influence

of recognition memory, while IFC neurons do not; 2) areas 9 and 46 (prefrontal cortex) mediate spatial operations within an egocentric frame of reference, while the caudal parahippocampal gyrus mediates allocentric operations; and 3) the involvement of area 46 in the performance of the spatial-delayed (20 s) response task is critical shortly after stimulus presentation, but not 10 to 15 s later; the converse is true for the hippocampus.

NON-GENOMIC ACTIONS OF ESTROGENS

This symposium focused on the emerging body of evidence indicating that estrogens can exert important effects in the CNS via sites that are independent of genomic receptors. While rapid effects of estrogens have been observed for quite some time in the CNS, the mechanisms by which estrogens could exert these rapid effects remained elusive. In the past several years, results from several laboratories have shown that the non-genomic estrogen recognition sites can exert neurotrophic effects in cortical neurons and potentiate activity of AMPA and NMDA glutamate-regulated receptors. In addition, recently published data indicate that estrogens can potentiate LTP, an electrophysiological model of memory. Surprisingly, very recent data suggest that neuroprotective effects of estrogenic steroids are also independent of nuclear site of action.

T. Teyler (Northeast Ohio College of Medicine, Rootstown, OH) presented a historical perspective on the topic of non-genomic actions of estrogens and reviewed his now classic work on the electrophysiological effects of 17 β-estradiol in the hippocampus. **T. Berger** (Univ. Southern California) presented findings from his laboratory showing that 17 β-estradiol potentiates both AMPA- and NMDA-mediated currents in hippocampal neurons. **R. Thompson** (Univ. Southern California) presented findings from his laboratory showing that 17 β-estradiol potentiates long-term potentiation in the hippocampus. **R. Diaz Brinton** (Univ. Southern California), who chaired the session, showed that the neurotrophic effects of 17 β-estradiol, conjugated equine estrogens and SERMS are mediated through a plasma membrane site. **J. Simpkins** (Univ. Florida) presented findings from his laboratory on the neuroprotective effects of different estrogens and preliminary evidence suggesting that the estrogen-inducible neuroprotection is mediated by a non-genomic site of action. **T. Shors** (Princeton Univ., Princeton, NJ) discussed her observations that actions of 17 β-estradiol extends to the amygdala to regulate fear conditioning by potentially genomic and non-genomic mechanisms.

THE NEURODEVELOPMENTAL HYPOTHESIS OF SCHIZOPHRENIA

Heterogeneity characterizes the prototypic expression of schizophrenia, its etiological pathways, its fluctuations during the evolution of the disease, and the differences of its responsiveness to treatment. As yet, neither a singular dysfunction nor a discrete brain system can be singled out as prominent in the etiology of this disease. A variety of anatomical data provide suggestive evidence that the embryonic development of

telencephalic laminated structures may be abnormal in schizophrenia. One of the characteristics for the formation of functional neuronal networks is the specificity of neuronal migration and positioning which takes place during brain ontogenetic development. Among the factors that guide neuronal migration and positioning are proteins secreted by a class of pioneer GABAergic neurons, the Cajal – Retzius cells. They secrete reelin into the extracellular matrix, migrate from the ventricular zone at a very early stage of embryonic development, and quickly reach and reside in the marginal zone of the telencephalon.

If we accept the "two-hits theory" of the etiology of schizophrenia, the first hit consists of neurodevelopmental abnormalities in cell migration, perhaps related to reelin functional abnormalities. The second hit is probably triggered by hormonal events that occur in early adulthood, effecting the function of the second generation of reelin is expressed after birth in neocortical GABAergic interneurons, or act independently from reelin. In the adult, the function of reelin is not yet understood.

R. Murray (Institute of Psychiatry, London, UK) reported evidence from recent functional imaging studies suggesting that auditory hallucinations result from abnormal connectivity between frontal and temporal language areas. The dysfunctional connectivity and underlying structural brain abnormality appear to be developmental in origin.

F. Benes (Harvard Univ., Cambridge, MA) reported a series of new experiments that were designed to investigate possible causes for the down-regulation of glutamic acid decarboxylase in cortical and limbic structures. She also reported that this decrease of GABAergic tone is associated with an up-regulation of the $GABA_A$ receptor expression density. She suggested that alterations in the innervation of GABAergic interneurons by dopaminergic and/or serotonergic neurons may be a cause for GAD down-regulation.

E. Costa (Univ. Illinois, Chicago), who chaired the session, documented a generalized decrease by ~50% in the amount of mRNA encoding for reelin expressed in brain structures in schizophrenia. Since reelin is released in the extracellular matrix, and presumably indirectly interacts with mDab1 protein located in the neuroplasm of cells that do not store reelin, integrins may be involved in signaling from extracellular Reelin to intraneuronal mDab1. GABAergic neurons may play a role in schizophrenia.

J. Davis (Univ. Illinois, Chicago) presented new data on the efficacy of a second generation of antipsychotics for the treatment of schizophrenia. He emphasized that these new drugs, which inhibit D_2 and 5-HT_2 receptors, have greater efficacy than the typical antipsychotics which effect only D_2 receptors. He suggested that these drugs may act in part by limiting the down-regulation of GABAergic function present in schizophrenia, via a blockade of the inhibition predicated by these two receptors on GABA interneurons.