The Hong Kong Society of Child Neurology & Developmental Paediatrics

Annual Scientific Meeting

8 - 11 December 2000

Hong Kong

Language Development, Learning Disorders and Brain Plasticity: Research and Clinical Implications

Course Director :

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HKCNDP
Annual Scientific Meeting 2000
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Topic : "Language Development, Learning Disorders and Brain Plasticity"
Scientific Program

	Friday 8 Dec	Saturday 9 Dec	Sunday 10 Dec	Monday 11 Dec
AM		**Visit to local centre - CKCAC** 11:30-12:30 Presentation and discussion - Development of Services for SLD in Hong Kong	**Seminar III** 9:30-10:30 Lecture - Prof. A. Galaburda 10:45-13:00 Free paper Session	
Lunch		12:30 - 14:00 Lunch	13:00 - 14:00 Light Buffet	
PM		**Seminar II** 14:00 - 15:30 Lecture - Prof. A. Galaburda Discussion 15:30 - 17:00 Case Presentation and Discussion	**Seminar IV** 14:00 - 15:30 Lecture - Prof. Susana Camposano Discussion 15:40-17:00 Lecture - Prof Galaburda Discussion	
Evening	**Seminar I** 19:00 - 20:00 Light Buffet 20:00 - 22:00 Lecture - Prof. A. Galaburda Discussion			**Plenary Lecture:** 19:00 Cocktail 20:00 - 21:00 Lecture - Prof. A. Galaburda 21:00 - 22:30 Chinese Banquet Dinner
Venue	QEH M Block	AM session: CKCAC Lunch & PM session: QEH M Block	QEH M Block	Hong Kong Academy of Medicine Building

TABLE OF CONTENTS

Organizing Committee:

Dr. Chan Chok Wan
Dr. Catherine Lam Chi Chin
Dr. Philomena Tse
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COURSE DIRECTOR

Albert M. Galaburda, M.D.

Emily Fisher Landau Professor of Neurology and Neuroscience, Harvard Medical School, Chief of the Division of Behavioral Neurology, which includes the Dyslexia Neuroanatomical Research Laboratory, at the Beth Israel Deaconess Medical Center, Boston, Massachusetts.

AMG received his medical degree from Boston University School of Medicine, following which carried out residencies in Internal Medicine and Neurology at the Boston City Hospital, the latter under the direction of the late Norman Geschwind. After clinical training he received additional research training from Friedrich Sanides, Deepak Pandya and Thomas Kemper. Research areas of interest include the neurobiological foundations of cerebral dominance, developmental dyslexia and related learning disorders in children and adults, experimental developmental neuropathology, neurobiology of language, cognitive neuroscience, cerebral architectonics and connectivity, genetics of behavioral disorders, and brain plasticity and the organization of knowledge in the central nervous system. Memberships in organizations include the Society for Neuroscience, American Academy of Neurology, American Neurological Association, International Dyslexia Association, and International Academy for Research in Learning Disabilities. Membership in editorial boards include Cognition, Dyslexia, Journal of Learning Disabilities, NeuroImage, Reading and Writing. Author of 150 plus journal articles and book chapters. Recent books: *Cerebral Lateralization* (with N. Geschwind), MIT Press; *Cerebral Dominance* (with N. Geschwind), Harvard University Press; *The Neuro-Immune-Endocrine Connection* (with C. Cotman, R. Brinton, B. McEwen, and D. Schneider), Raven Press. From *Reading to Neurons,* M.I.T. Press/Bradford Books. *Neurobiology of Cognition* (with P. Eimas), M.I.T. Press/Bradford Books. *The Extra-ordinary Brain,* Harvard University Press. *Normal and Abnormal Development of the Cortex* (with Y. Christen), Springer.

SEMINARS

Brain organization of behavior in children and adults

Professor Albert M. Galaburda

Behavior in the brain is organized in a complex way, which includes various pathways of processing as well as hierarchical processing stages within each pathway. There may be more than one pathway within a given modality (e.g., several visual pathways), as well as pathways in different modalities (auditory, somatosensory, visual, olfactory, etc.). Behaviors are represented and processed at sensory/perceptual, cognitive/associative, and metacognitive levels, all in keeping with the multi-stage fashion of brain organization. There is a certain degree of modularity in the organization of behavioral systems, such that their function depends on different principles and operations that do not overlap, and breakdown can occur in one system while sparing another. On the other hand, there is a great deal of interaction among stages of processing that can take the form of bottom-up effects, in which low level stages affect the functioning of higher processors, or top-down effects, in which high level brain processors affect the function of low level stages. These interactions are active during the on-line execution of a behavior, as well as during the learning of a new behaviors and development. In fact, one of the most interesting discoveries of modern neuroscience has been the realization that the same molecules that are involved in learning are also involved in growth, development, and plasticity. Oftentimes, it is possible to demonstrate different brain substrates subserving different pathways and stages of processing, and often we see disease entities that affect the brain in such a way that some processing stages are affected while others are not.

Children are different from adults in this modular organization of behavior to the extent that the interaction between modules is different and the vigor of plasticity is greater. Thus, in children, in the absence of previous experience, cognitive function depends more on bottom up processes than on top down processes, as compared with adults. There are many interesting examples of this, which will be provided during the seminar.

SEMINARS

Outside of language, many of the so-called cognitive behaviors in humans have been studied in animals (e.g., memory, attention, vision, motor control, even consciousness). The ability to relate behaviors to brain function has been enhanced by the study of animals. More recently, it has been possible to introduce methods capable of demonstrating and changing brain activation during behaviors in living human subjects. There exists the ability to look for and find homologies in the implementation of equivalent behaviors between animals and humans. At best, however, there has been increased knowledge about the parts of the brain that participate in given behaviors, but very little additional knowledge about the exact way by which brain supports behavior: We know about parts of the brain involved in language, but we do not know how they carry out language; we know something about how memory works in the sea slug, down to the genes that are turned on and off, but little about human memory.

Most of the interesting cognitive behaviors take place with the participation of the cerebral cortex, while lower level behaviors require participation of the thalamus and basal ganglia. In children, as implied from comments made above, the thalamus may play a more important role for brokering behaviors than the same structure in adults. The cortex, in turn, is a highly complex structure, which challenges our ability even to visualize its anatomical organization - architecture and connectivity. In this seminar I will present a scheme for viewing the cerebral cortex as the anatomical structure that supports a broad gamut of human cognitive behaviors, which include language, mental imagery, memory, attention, motivation, and emotion.

SEMINARS

Cortical Development and the Problem of Dyslexia

Professor Albert M. Galaburda

Some learning disorders have been associated with disturbances in cortical development. Disturbances of cortical development may be visible to the naked eye, or may require microscopic examination of the brain. In some cases, disturbances are only visible at the molecular level and the brain is morphologically normal appearing. There has been a great deal of interest in recent years in the description of the genetic/molecular events underlying mental retardation and learning disability. In general, discovery of abnormal genes is only the first step in the process of discovery of the abnormal brain phenotype, and the way this abnormal brain explains abnormal brain function.

Developmental disorders of behavior may result from the effects of abnormal genes as well as from brain injury occurring during gestation. Brain injury occurring during gestation may result from agents external to the fetus (maternal factors, infection, injury, radiation, etc.), or endogenous to the fetus (a faulty gene leads to congenital heart disease, brain emboli, and stroke). The important point here is that an abnormal brain need not reflect an abnormal brain gene, but could result from abnormal genes that indirectly lead to brain damage.

The effect of brain injury, whether it is caused by a faulty gene or by epigenetic factors present in the intrauterine environment, depends on the severity of the injury, the timing of the injury, and in some cases the location of the injury. Part of the problem is the injury itself; and part of it is the reaction of the brain to injury. The same injury can produce dramatically different effects, for instance, when it occurs before, during, or after a critical window of development.

The formation of the cerebral cortex in the human brain takes place largely before birth. Early stages of pattern formation and cell and axonal fate determination, as learned from the study of the fruit fly initially, but now extrapolated to larger brains, are not detailed in the human brain. Subsequent steps involve assignment of neuroblasts to neuroproliferative zones, neuroblast proliferation, young neuron migration, clonal dispersion, neuronal maturation and connectivity, programmed cell death, synaptogenesis, maturation of receptors, expression of some genes and end of expression of others, establishment of connections, and myelination. In this seminar we will review cortical development, punctuating factors that can alter development at different stages and produce malformations of different types. This will serve as background for later seminars, when specific disorders of cortical development are considered for explaining learning disorders in children and adults.

Temporal Processing Deficits and Language in Dyslexia: Lessons from Animal Models

Professor Albert M. Galaburda

Dyslexics have problems processing sounds. It has been shown that they cannot handle rapidly changing sounds, whether they are language or general sounds. Dyslexics furthermore cannot easily play word games that require that they demonstrate knowledge about the sound structure of words. So, for instance, they have trouble with phoneme segmentation, rhyming, and phoneme deletion games. Are these findings related to one another? Are they related to the reading problem, and if so, how? We have used animal models to ask this question. First, we induce cortical malformations in rats, which are similar to the cortical malformations dyslexics have. Second, we study in detail the anatomical structure of the malformations -- their development, their chemical structure and connectivity, and histometric measures. Third, using tissue slices, we look at the physiological characteristics of neurons in the malformation and neurons in areas that are connected to the malformation. Fourth, we attach electrodes to rats (or specially chosen mice, in some cases) and look at the field electrophysiology, event related potentials, in relationship to tasks involving gap detection. Fifth, we test rats on operant conditioning paradigms that assess the animals' ability to detect different sorts of sounds. Finally, we study various startle reduction paradigms that also address the ability of the animal to detect short sounds. We correlate these measures and come to the conclusion that cortical malformations produce changes in the thalamus that are associated with disturbances in short duration temporal processing. So, we have found an animal model of at least one of the features known to fail in dyslexics. Ongoing research aims at finding out more about cognitive deficits in these animals that go beyond temporal processing deficits. We are also looking for ways to image malformations in vivo and ameliorate malformations using neuroprotective agents. We are looking at signals that exchange between the abnormal cortex and the thalamus during development of the abnormal sound processing systems. We are looking at genes in affected mice that may underlie cortical malformations of the type relevant to dyslexia. These findings will be illustrated during the seminar.

From Genes to Behavior: Challenges and Opportunities in Williams Syndrome

Professor Albert M. Galaburda

WMS is a compelling model of human cognition. Due to a hemideletion of human chromosome band 7q11.2, patients exhibit striking peaks and valleys in cognitive performance -- deficits in visual-spatial and global processing, relatively preserved language and face processing, hypersociability, and heightened affect. They also show characteristic neuroanatomical variations affecting parts of the cerebral cortex and cerebellum and characteristic functional features of neuronal processing as measured by event related potentials (ERP). A striking proportion of the findings may be explained by the hypothesis that dorsal brain development, as contrasted to ventral brain development, is specifically targeted by the defective genes. This dorsal-ventral dichotomy was introduced during the first seminar of this series.

To identify the genes whose deletion is responsible for these phenotypic features, we have used an integrated physical, genetic and transcriptional map of the WMS and flanking regions to determine the genes deleted and their relationship to neurocognitive phenotype in subjects with WMS who have common or smaller deletions. We are now in the process of reporting the molecular, neurocognitive, neuroanatomic, and ERP results characterizing a WMS patient with a smaller deletion that results in a single copy of all genes in the common WMS region except two that encode the functionally related transcription factors, GTF2I and GTF2IRD. We have compared the results from this subject to the normed results obtained from WMS with common deletions and matched diploid controls. These establish a region and consequent candidate transcription factors for a distinctive subset of the WMS neurocognitive features. We propose that functions of these transcription factors are in part responsible for a distinctive subset of cognitive functions that implicated the dorsal forebrain of the human brain and speculate that WMS neurocognitive features (global processing, variation in cerebral shape and morphology and ERPs for face processing) reflect an abnormality in the developmental expression of these genes. The main goal of much of this and similar research is to find the genetic substrate of complex behaviors in humans.

PLENARY LECTURE

Understanding Dyslexia from the Historical Perspective: Does 19th Century Neurology Apply to the 21st Century ?

Professor Albert M. Galaburda

I t is difficult to apply knowledge obtained during the 19th century to solve the problem of dyslexia, but many investigators still attempt to do just that. The 19th century was extremely important for the growth of neuroscience. Brains were for the first time adequately fixed at post mortem, allowing proper dissection and staining. The former outlined the relative uniformity of the main gyri and sulci, as well as the course of the principal fiber bundles. The latter gave a clearer picture of the architectonic organization of neurons in the cortex and subcortical nuclei, as well as information about the structure of individual neurons. This, coupled with the study of patients affected by focal brain lesions, slowly produced some consistencies in brain-behavior relationships. Thus, the left hemisphere emerged as the language organ, and within it, several subsets of language functions became 'localized' to specific cortical areas. In this context, Hinshelwood in Scotland, and others in the British Isles , Europe, and America proposed brain models for understanding developmental dyslexia.

However, the 20th century, particularly the second half of the century, saw the emergence of knowledge that has all but annihilated the so-called principles of cerebral organization and behavioral localization of function in their strongly phrenological versions. This occurred for a variety of reasons: First, the behaviors themselves were understood better, and curiously many of the behaviors that had been localized previously were found not to be real components of behavior; second, there was growing awareness of the problem of separating a behavioral picture that arose from the loss of a particular function by virtue of a brain lesion, from a picture that represented the emergence of new (abnormal) behaviors by virtue of brain plasticity (this, in fact, is at the crux of the problem of developmental learning disorders, more so even than acquired behavioral deficits in adults); and finally, the discovery through the introduction of other tools for studying brain-behavior relationships that brain lesions underestimated the amount of brain participating in a particular cognitive function, on the one hand, and overestimated the independence of separate brain lesions in the implementation of cortical behaviors.

The 21st century offers a bright future to our understanding of brain-behavior relationships and the eventual treatment and prevention of cognitive disorders in children and adults. Although the road ahead is long and difficult, whereby pathways must be elucidated after behavior relevant genes are discovered, there is now the strong possibility that we will learn meaningfully about how the brain is built and how this machinery is capable of learning. In this context, injury to the process of building the cognitive machine, the brain, or damage to its integrity after it has been built, which leads to cognitive dysfunction, developmental or acquired, will be better understood, prevented, and treated.