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THE CHANGING BRAIN – INSIGHTS INTO THE MECHANISMS OF NEURAL AND BEHAVIORAL ADAPTATION TO THE ENVIRONMENT

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Abstract—The Kavli Prize in Neuroscience was awarded for the third time in September 2012, by the Norwegian Academy of Science and Letters in Oslo. The accompanying Kavli Prize Symposium on Neuroscience, held in Bergen and Trondheim, was a showcase of excellence in neuroscience research. The common theme of the Symposium presentations was the mechanisms by which animals adapt to their environment. The symposium speakers – Michael Greenberg, Erin Schuman, Chiara Cirelli, Michael Meaney, Catherine Dulac, Hopi Hoekstra, and Stanislas Dehaene – covered topics ranging from the molecular and cellular levels to the systems level and behavior. Thus a single amino acid change in a transcriptional repressor can disrupt gene regulation through neural activity (Greenberg). Deep sequencing analysis of the neuropil transcriptome indicates that a large fraction of the synaptic proteome is synthesized *in situ* in axons and dendrites, permitting local regulation (Schuman). The nature of the 'reset' function that makes animals dependent of sleep is being revealed (Cirelli). Maternal behavior can cause changes in gene expression that stably modify behavior in the offspring (Meaney). Removal of a single sensory channel protein in the vomero-nasal organ can switch off male-specific and switch on female-specific innate behavior of mice in response to environmental stimulation (Dulac). Innate behaviors can be stably transmitted from parent to offspring through generations even when those behaviors cannot be expressed, as illustrated by the elaborate burrowing behavior in a rodent species, in which independent genetic regions regulate distinct modules of the burrowing pattern (Hoekstra). Finally, at the other extreme of the nature-nurture scale, functional magnetic resonance imaging (fMRI) analysis in children and adults identified a brain area specifically involved in reading (Dehaene). As the area must originally have developed for a purpose other than reading, such as shape recognition, this illustrates the use of a previously formed neural structure to tackle a new challenge.

INTRODUCTION

The Kavli Prizes were awarded for the third time in Oslo, Norway on 4 September, 2012 to seven of the world's most prominent scientists in astrophysics, nanoscience and neuroscience. David Jewitt of the University of California, USA, Jane Luu of the Massachusetts Institute of Technology, USA, and Michael Edwards Brown of the California Institute of Technology, USA shared the astrophysics prize for discovering and characterizing the Kuiper Belt leading to a major advance in understanding the evolution and history of our planetary system. The nanoscience prize was awarded to Mildred Dresselhaus of the Massachusetts Institute of Technology, known as the 'Queen of Carbon', for pioneering research on phonons, electron–phonon interactions, and thermal transport in nanostructures. The joint recipients of the neuroscience prize were Cornelia Isabella Bargmann of the Rockefeller University, USA, Winfried Denk of the Max Planck Institute for Medical Research, Germany, and Ann M. Graybiel of the Massachusetts Institute of Technology, USA. They received the prize for elucidating basic neuronal mechanisms underlying perception and behavior.

The Kavli Prize, founded and funded by Dr. honoris causa Fred Kavli, is awarded by the Norwegian Academy of Science and Letters and is a joint venture by the Academy, the Kavli Foundation, and the Norwegian Ministry of Education and Research (http://www.kavliprize.no/). The prize committees are appointed by the Academy among renowned researchers nominated by the world's leading scientific academies and operate entirely independently. Based on Fred Kavli's vision that curiosity is the root of human culture and success, the Kavli Foundation is dedicated to advancing basic research for the benefit of humanity,

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Abbreviations: ACTH, adrenocorticotropin; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; AOB, accessory olfactory bulb; BDNF, brain-derived neurotrophic factor; CAMKIIα, α-Ca^{2+}/calmodulin kinase II; CpG, –cytosine–phosphate–guanine–; CREB, cAMP response element-binding protein; CRF, corticotropin-releasing factor; ER, estrogen receptor; fMRI, functional magnetic resonance imaging; GluR1, L-glutamate receptor 1; GR, glucocorticoid receptor; HPA, hypothalamic–pituitary–adrenal; LG, licking and grooming; LTP, long-term potentiation; L-VSCC, L-voltage-sensitive calcium channel; MeA, medial amygdala; MeCP2, methyl-CpG binding protein 2; mPOA, medial preoptic area; PSD, post-synaptic density; TRPC2, transient receptor potential cation channel 2; Ube3a, ubiquitin protein ligase 3a; VNO, vomero-nasal organ; VNOx, vomero-nasal organ surgically removed; VWFA, visual word form area.

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promoting public understanding of scientific research, and supporting scientists and their work.

On 6 September 2012, the University of Bergen and the Norwegian University of Science and Technology – NTNU, Trondheim, participated in the week-long Kavli Prize celebration, simultaneously hosting speakers and guests for the Kavli Prize Symposium on Neuroscience, which was previously held at the University of Oslo (Sander et al., 2009; Bergersen et al., 2011). As in 2008 and 2010, the goal of the 2012 Symposium was to celebrate excellence in neuroscience research. At the Symposium, seven leading neuroscientists described their leading-edge research, which focused primarily on two fundamental questions: by what molecular mechanisms does the environment influence neural structure and function in developing and mature organisms?; and what neural and genetic features control innate patterns of behavior (i.e., environmental adaptation at the development of species level)?. The Symposium speakers in Bergen were Michael E. Greenberg of Harvard University, Boston, USA, Erin M. Schuman of the Max Planck Institute for Brain Research, Frankfurt, Germany, Chiara Cirelli of the University of Wisconsin, Madison, USA, and Michael Meaney of Agency for Science Technology and Research – A*STAR, Singapore and McGill University, Montreal, Canada; in Trondheim the speakers were Catherine Dulac of Harvard University, Cambridge, USA, Hopi Hoekstra of Harvard University, Cambridge, USA, and Stanislas Dehaene of Institut National de la Santé et de la Recherche Médicale Cognitive Imaging Unit – INSERM-CEA, Saclay, France.

The 2012 Kavli Prize Symposium on Neuroscience was organized, on behalf of the Norwegian Academy of Science and Letters, by Linda H. Bergersen, Clive R. Bramham, Kenneth Hugdahl, Edvard I. Moser, May-Britt Moser, and Jon Storm-Mathisen (Chairman of the Kavli Prize committee on neuroscience). The participants in the Symposium expressed their gratitude for the opportunity to take part in the great celebration of science, the legacy of Fred Kavli, and the achievements of the winners of the 2012 Kavli Prizes. Main points of the presentations are summarized below. For a more detailed consideration of any of the topics discussed at the Symposium readers are referred to references cited throughout the text.

EXPERIENCE-STIMULATED NEURAL PLASTICITY: FROM CAT VISION TO REGULATING THE DNA METHYLOME

In the 1950s, David Hubel and Torsten Wiesel performed ground-breaking studies on the visual system of the cat, becoming the first researchers to provide direct evidence that sensory input, in the form of light stimuli, influences brain development, structure and function in a living animal (Hubel and Wiesel, 1959, 1962). Since these seminal studies, which demonstrated that experience modulates cognitive function and development, this idea has been reinforced and confirmed by researchers in social and biological sciences, from psychology to neurophysiology, and has become an accepted tenet of modern neuroscience. However, the extent to which environmental context and a human being's experience in a specific environment influences his or her brain structure and function has been and continues to be a matter of discussion and investigation, commonly referred to as the 'nature' vs. 'nurture' debate.

Extending from these early studies, neuroscientists have recently investigated and begun to elucidate the precise molecular mechanisms by which the environment modulates neurological development. One such mechanism is cognitive-activity-dependent gene expression. This area of research was the focus of several talks presented at the 2012 Kavli Prize Symposium on Neuroscience. Early studies on 'brain–environment' interactions, alluded to above, led to the hypothesis that synaptic activity promotes a series of events, including neurotransmitter release, membrane depolarization, Ca^{2+} ion influx, intracellular Ca^{2+} increase, activation of Ca^{2+}-dependent protein kinases, and kinase target activation, leading to changes in expression in specific genes in specific brain regions. Among the first gene targets of such a response network to be identified were c-fos and brain-derived neurotrophic factor (BDNF), with many more to follow (reviewed in Flavell and Greenberg, 2008). It is noteworthy that defective alleles of several widely-studied activity-regulated genes, including L-voltage-sensitive calcium channel (L-VSCC), ribosomal S6 kinase 2, methyl-CpG binding protein 2 (MeCP2), cAMP response element-binding protein (CREB), ubiquitin protein ligase 3a (Ube3a) and deleted in autism 1 have been linked to human neurological diseases that feature altered patterns of behavior and/or cognitive dysfunction. Two of the better known examples are MeCP2, linked to Rett Syndrome (Amir et al., 1999), and Ube3a, linked to Angelman Syndrome (Greer et al., 2010). Rett Syndrome is an X-linked hereditary disease that causes a profound defect in cognitive development, including failure to develop language skills, in infants 6 months and older, despite apparently normal development *in utero* and for the first 6 months of post-natal life. Angelman Syndrome is another neurodevelopmental disorder, characterized by motor dysfunction, mental retardation, hyperactivity and a high prevalence of autism.

Michael E. Greenberg (Harvard University, Cambridge, USA) has pioneered studies on activity-dependent gene expression and its role in neurological development (Ebert and Greenberg, 2013), including recent studies conducted in his laboratory on the molecular defect(s) associated with Rett Syndrome in humans and in knock-in mice with a Rett Syndrome like phenotype. MeCP2 encodes a protein that binds methylcytosine in –cytosine–phosphate–guanine– (CpG) dinucleotides in DNA, which, in a general sense, is thought to act as a repressor of gene expression and as a guardian of the 'methylation state' of chromatin (Cohen et al., 2011). Defective alleles of MeCP2 that cause Rett Syndrome lose the ability to repress target