

## **Influence of Early Experience on Adult Brain Organization and Function**

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Chaired by Terry Sejnowski (Salk Institute) & Carla Shatz (Stanford University)

Sponsored by The Kavli Institute for Brain and Mind (KIBM)

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### ***Early brain trajectories and evolving oscillations: Template for mature function?***

April Benasich, Rutgers University

Ongoing research in my laboratory provides evidence that the ability to perform fine-grained acoustic analysis in the tens-of-millisecond range during infancy appears to be one of the most powerful and significant predictors of subsequent language development and disorders. Our prospective, longitudinal research using converging paradigms including dense-array EEG (dEEG) has shown that non-linguistic, spectro-temporally modulated, rapid auditory processing skills in the first year of life can serve as a "marker" of later language, and thus are of particular utility for early identification and proactive remediation. Although there is no consensus as to the extent to which developmental and neuropsychiatric disorders may reflect early disruption in dynamic coordination and/or a failure to establish well-formed structural and functional networks, accumulating evidence suggests that the emergence, function and maturation of oscillatory mechanisms are crucial to normative development. Identification of biomarkers that may characterize atypical development is therefore critical to elucidating the neurobiology underlying various developmental disorders. In this talk, I will present data from several studies that illustrate how dEEG measures of oscillatory synchrony and cross-frequency phase coupling differ in typically developing children and those at higher risk for developmental disorders or with clinically diagnosed developmental disorders.

### ***The effects of early life stress on brain and behavior***

BJ Casey, Yale University

Stress can have lasting effects on the brain and behavior. Delineating the impact of stress on the developing brain is fundamental for understanding sensitive periods of both risk and resilience. Studies of stress across species have provided essential insight into the mechanisms by which the brain changes and on the timing of these changes. This presentation will highlight how early-life stress can alter the course of brain development in parallel studies in humans and mice. The findings show that mice reared under conditions that mimic the type and timing of early-life stress experiences of orphanage rearing show early and persistent alterations in amygdala circuitry and function. These effects appear to persist long after the stressor is removed. These neural and behavioral findings are similar to human findings in children adopted from orphanages abroad. Evidence for buffering against early-life stress effects in humans will be presented that may promote resilience and positive outcomes. These findings will be discussed in the context of implications for early identification of risk and resilience factors.

### ***Neurobiology of the parental brain***

Catherine Dulac, Harvard University

Social interactions are essential for animals to reproduce, defend their territory, and raise their young. The conserved nature of social behaviors across animal species suggests that the neural pathways underlying the motivation for, and the execution of, specific social responses are also maintained. Modern tools of neuroscience have offered new opportunities for dissecting the molecular and neural mechanisms controlling specific social responses. This lecture will describe recent insights from our lab into the neural circuits underlying a particularly fascinating and important form of social interaction, that of parental care. We will discuss how these findings open new avenues to deconstruct maternal and paternal behaviors, and to help understand the neural basis of parenting in a variety of animal species, including humans.

### ***The amazing teen brain***

Jay Giedd, UC San Diego

Across cultures and millennia the teen years have been noted as a time of dramatic changes in body and behavior. Male/female body differences become more pronounced, social and sexual drives are intensified, there

are great leaps in cognitive abilities, and the ability to function independently ensues. It is also the peak time for onset of mental illness. More recently advances in imaging technologies, such as MRI, have demonstrated that the changes in body and behavior are accompanied by changes in the brain. White matter increases allowing faster and more efficient communication among disparate components of the brain. Gray matter changes reflect increasing specialization as the brain adapts to specific demands of the environment. Changes in connectivity and neurotransmitter receptors underlie behavioral changes in decision making. The ongoing changeability of brain biology during the teen years make adolescence a time of vulnerability but also a time of great opportunity.

### ***Making an old brain young? From developmental critical periods to Alzheimer's disease***

Carla Shatz, Stanford University

The brain is the most incredible computational machine imaginable. There are over one trillion nerve cells in the brain, and each cell can make 10,000 synaptic connections with other nerve cells. How are connections wired up during development? The wiring problem is solved sequentially first by forming a basic scaffold of connectivity according to genetic blueprints: strict molecular cues enable growing nerve connections to follow appropriate pathways to their correct target regions. Then, once this basic scaffold of connectivity forms, the exact details of each circuit emerge by pruning and sculpting synapses from the immature pattern of connections. The decision-making process that determines which synaptic connections remain and which are pruned is also genetically specified but in this case requires brain function. Even before birth, the brain generates its own internal neural activity patterns to jump-start the sculpting process. After birth once sensory systems, such as the eyes and ears, become mature enough, experience of the external world takes over to influence brain wiring during developmental critical periods. Neural activity and brain function regulate the expression of sets of genes including several previously thought to act only in the immune system. These activity-regulated genes- including Major Histocompatibility Class I family members and Paired immunoglobulin-like receptor B- are required in neurons for pruning and sculpting synapses during development, and they may also contribute to excessive synapse pruning in Alzheimer's disease. Thus, the baby's brain is not a miniature version of the adult, but rather is a dynamically changing structure in which neural activity and experience ultimately select and stabilize essential details of neural circuitry that make each of us different from one another.

### ***How immune cells sculpt developing synaptic circuits***

Beth Stevens, Harvard University

Our recent work revealed a key role for microglia and a group of immune related molecules called complement in normal developmental synaptic pruning, a normal process required to establish precise brain wiring. Emerging evidence suggest aberrant regulation of this pruning pathway may contribute to synaptic and cognitive dysfunction in a host of brain disorders, including schizophrenia. Recent research has revealed that a person's risk of schizophrenia is increased if they inherit specific variants in complement C4, gene plays a well-known role in the immune system but also helps sculpt developing synapses in the mouse visual system. Together these findings may help explain known features of schizophrenia, including reduced numbers of synapses in key cortical regions and an adolescent age of onset that corresponds with developmentally timed waves of synaptic pruning in these regions. I will discuss ongoing work to understand the mechanisms by which complement and microglia prune specific synapses in the brain. A deeper understanding of how these immune mechanisms mediate synaptic pruning may provide novel insight into how to protect synapses in neurodevelopmental and other disorders involving synapse loss and dysfunction.

### ***Using neurobiology to overcome genetic and environmental adversity***

Mark Bear, Massachusetts Institute of Technology

Proper brain function requires the sculpting of connections between neurons during early postnatal life. Synapses are formed and strengthened, weakened and lost, under the influence of sensory experience. Over five decades of research have culminated in a deep understanding of the mechanisms responsible for this brain plasticity. Insights derived from this line of research have recently suggested the remarkable possibility of developing treatments for developmental brain disorders previously believed to be intractable. We are poised to fulfill the promise of molecular medicine in which corrective treatments are developed from the bottom up—from gene discovery to pathophysiology in animals to novel therapeutics in humans.

### ***Traversing the path from spontaneous genetic mutations to neurobiology in autism spectrum disorders***

Matthew State, UC San Francisco

Autism Spectrum Disorders (ASD) are a group of diverse neurodevelopmental conditions defined by fundamental impairments in social communication as well as repetitive behaviors and highly restricted interests. After several

decades of frustration, the genetic underpinnings of ASD are now coming into sharp focus. Dramatic progress has been made in just the last 6 years in understanding how spontaneous changes in both chromosomal structure and DNA sequence can confer substantial risks to the individual. These insights are providing a rapidly growing set of reliable molecular clues to the biological underpinnings of ASD and have begun to shed some light on the interplay of environment and genetics in the origins of this syndrome. This lecture will summarize recent data on the role of new (de novo) rare mutation in ASD, provide evidence in support of the notion that gene discovery can be an important avenue to understand complex social behavior, and discuss the path forward in deepening the understanding of the causes of ASD.