Plenary

22. THE NEAR FUTURE FOR SCHIZOPHRENIA (PSYCHOSIS) RESEARCH
William T. Carpenter, Jr.
University of Maryland School of Medicine

Overall Abstract: Implications of a heterogeneous clinical syndrome such as schizophrenia have long been known but little attended. Fundamental problems persist, such as schizophrenia as the phenotype in GWAS studies. But the 21st Century has brought substantial attention to limitations in acquisition of new knowledge. New concepts and methods are being implemented. Selected examples will be reviewed and potential scientific advances that influence clinical care will be outlined. This will include advances in mechanism knowledge, identification of novel targets for therapeutic discovery, re-conceptualization of psychopathology for regulatory purposes, a new integration of behavioral and biological science to inform nosology, enhanced testing of neural circuit hypotheses, and serious attention to primary prevention.

Concurrent Symposia

23. FRONTAL CORTEX DEVELOPMENT AND RISK FOR PSYCHOPATHOLOGY: MOLECULAR AND GENETIC MEDIATORS AS POSSIBLE BIOMARKERS?
Francesco Papaleo
Instituto Italiano Di Tecnologia

Overall Abstract: This panel includes 4 females and 1 male, 2 early career scientists, 2 clinicians. From 5 different countries, 3 different continents. Prefrontal cortex (PFC) dysfunction is associated with alterations in cognitive processing impaired in schizophrenia. The development of the PFC is a protracted process, which peaks in adolescence and ends only in early adulthood. Its extended development renders the PFC particularly susceptible to environmental influences, but we know very little about the underlying neurobiological mechanisms. More importantly, we need to understand how risk or protective factors can affect PFC development. This could have an impact towards the development of early and/or preventive treatments for cognitive dysfunctions relevant to a number of psychiatric disorders including schizophrenia.

We will discuss recently-discovered processes involved in different stages of prefrontal cortex development, including gestation and adolescence, and how alterations to these events may lead to schizophrenia-relevant phenotypes. A multidisciplinary group of preclinical and human researchers will discuss recently-identified molecular, genetic, and hormonal events that shape PFC development. We will also show compelling new evidence that disruption to these developmental processes is linked to psychiatric conditions.

The data we will present include:

1. Signaling events implicated in the migration of newborn neurons into emerging cortical layers and their relevance to schizophrenia and autism spectrum disorder (Helen Cooper).
2. Mechanisms related to adolescent axonal growth and connectivity in the PFC and how they are disrupted by ongoing experiences (Cecilia Flores).
3. Findings from human and mouse studies regarding the impact of the 22q11.2 microdeletion on PFC development and cognitive maturation (Francesco Papaleo).
4. The molecular development of the postnatal human cortex, including the maturation of interneurons, molecular changes in neurotransmitter signaling pathways, synaptic development and developmental changes in those immune related molecules that may impact synaptic development (Maree Webster).

Collective discussion of these data (Maude Schneider) will highlight important implications for prevention and early intervention strategies in schizophrenia.

23.1 UNDERSTANDING THE ROLE OF SCHIZOPHRENIA/AUTISM GENES IN CORTICAL DEVELOPMENT
Helen Cooper*, 1, Amanda White2, Conor O’Leary2
1Queensland Brain Institute, The University of Queensland; 2Queensland Brain Institute

Background: The fidelity of neocortical development is dependent on the highly polarized morphology of the neuroepithelial stem cell (NSC) within the embryonic brain. NSCs project long processes to the pial surface along which newborn neurons migrate to establish the cortical plate. Perturbation of NSC morphology prevents neuronal migration into the emerging cortical layers, leading to cortical malformations. Disruption of the laminar architecture due to failed neuronal migration is thought to contribute to the etiology of schizophrenia and autism. Therefore, elucidating the signaling events that precisely control NSC morphology is essential to our understanding of corticogenesis and the aberrant processes that contribute to neuropsychiatric disorders.

Maintenance of NSC morphology and function requires the formation of cadherin-based cell-cell adhesion (adherens junctions) between NSCs and loss of junctional integrity results in failed neuronal migration. Junctional stability is critically dependent on the closely apposed actin cytoskeleton and the actin remodeling protein Cyfip1 known to promote actin polymerization. Cyfip1 has been implicated in schizophrenia and autism and its loss results in cortical malformations. However, the molecular mechanisms governing Cyfip1 activity in NSCs are poorly understood.

Methods: In this study we investigate the signaling mechanisms that regulate Cyfip1 activity in the developing mouse cortex using both gain- and loss-of-function approaches. Short interfering RNAs or cDNA expression constructs were electroporated, in utero, into the embryonic day 12 mouse cortex. Phenotypic analysis was then performed several days later.

Results: Here we identify the netrin/RGM receptor, Neogenin, as a direct binding partner for Cyfip1. We provide evidence that Neogenin is a critical upstream regulator of Cyfip1 activity during corticogenesis and is therefore a key component of NSC junctions. We show that blocking Neogenin/ Cyfip1 interactions in the embryonic mouse cortex results in NSC junctional collapse and severe perturbation of the emerging cortical architecture due to aberrant neuronal migration. Our study therefore reveals that Neogenin’s interaction with Cyfip1 is essential for NSC morphology and function.

Discussion: In conclusion, we have identified a novel signaling pathway that governs the development of the neocortex. The emergence of neuronal migration defects and cortical malformations when Neogenin-Cyfip1 interactions are prevented emphasizes the fundamental role of this interaction in establishing the correct cortical architecture. Intriguingly, mutations in the Neogenin gene have recently been linked to autism. Therefore, our study implicates the Neogenin/Cyfip pathway in the etiology of neuropsychiatric disorders.

23.2 NETRIN-1 RECEPTORS CONTROL MESOCORTICAL DOPAMINE CONNECTIVITY IN ADOLESCENCE
Cecilia Flores* 1
1McGill University

Background: Adolescence is an age of heightened vulnerability to develop psychiatric disorders that involve alterations in prefrontal cortex circuitry and cognitive dysfunction. The maturation of prefrontal cortex function is linked to the establishment of dopamine connectivity in this region.