22. THE NEAR FUTURE FOR SCHIZOPHRENIA (PSYCHOSIS) RESEARCH

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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?

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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 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

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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/Cyfip1 pathway in the etiology of neuropsychiatric disorders.

23.2 NETRIN-1 RECEPTORS CONTROL MESOCORTICAL DOPAMINE CONNECTIVITY IN ADOLESCENCE

Cecilia Flores*1
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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.
Development of mesocortical dopamine is a gradual process that continues until early adulthood. Because of its extended maturation course, this system is particularly susceptible to environmental influences. Yet there is a significant gap in our knowledge about the cellular and molecular mechanisms underlying adolescent prefrontal cortex dopamine development and how they are influenced by experience.

**Methods:** We examined the role of the Netrin-1 guidance cue receptor, DCC, and its microRNA repressor, miR-218, on adolescent mouse prefrontal cortex development. We used axon-initiated recombination and cell-specific knock-down techniques to characterize the spatiotemporal growth of mesocortical dopamine axons and the role that DCC and miR-218 play in this process. Next, we assessed whether stimulant drugs in adolescence alter miR-218/DCC signaling, thereby disrupting mesocortical dopamine axon growth. Finally, we determined whether altered dopamine axon growth influences prefrontal cortex development by quantifying pyramidal neuron morphology and cognitive performance in adulthood.

**Results:** Here we show, for the first time, that dopamine axons continue to grow from the nucleus accumbens to the prefrontal cortex during adolescence. We discovered that DCC receptors control the extent of this protracted growth by determining where and when dopamine axons recognize their innervation target. Exposure to stimulant drugs or to stress leads to disruption of DCC-dependent adolescent targeting events, causing dopamine axons that should innervate the nucleus accumbens, to grow ectopically to the prefrontal cortex. This effect profoundly changes prefrontal cortex structural and functional development, producing alterations in cognitive processes known to be impaired across psychiatric conditions, including schizophrenia. Importantly, miR-218 controls DCC receptor expression in dopamine neurons across postnatal development and acts as a molecular mediator of the effects of stimulant drugs on prefrontal cortex development.

**Discussion:** The prolonged growth of dopamine axons during adolescence represents an extraordinary period for experience to influence their growth and predispose to or protect against psychopathology. MicroRNA control of DCC receptor in dopamine neurons is a molecular link where genetic and environmental factors seem to interact in adolescence to influence the development and function of the prefrontal cortex.

### 23.3 DEVELOPMENTAL TRAJECTORIES OF SCHIZOPHRENIA-RELEVANT ABNORMALITIES IN A MOUSE MODEL OF 22Q11.2 DELETION SYNDROME

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**Background:** The hemizygous genetic deletion in the 22q11.2 locus causes a syndrome (22q11DS) characterized by developmental social and intellectual disabilities, high prevalence of attention deficit hyperactivity disorder (ADHD; ∼37%) during childhood and schizophrenia (∼41%) in adulthood. Although this peculiar behavioral alterations, the specific brain and molecular factors influencing these developmental trajectories are still unknown. Preclinical animal studies could help to disentangle these mechanisms. However, no studies in animal models had so far checked the impact of the 22q11.2 microdeletion in behavioral phenotypes from birth to adolescence until early adulthood. Because of its extended maturational course, this system is particularly susceptible to environmental influences through an altered maturation of the prefrontal cortex. This will be important in the context of the development of early diagnosis and preventive intervention.

**Discussion:** Overall, our experiments are starting to elucidate how clinically-relevant genetic alterations can influence the developmental trajectories of behavioral phenotypes through an altered maturation of the prefrontal cortex. This will be important in the context of the development of early diagnosis and preventive intervention.

### 23.4 MAPPING MAJOR MOLECULAR CHANGES IN THE DEVELOPMENT OF THE HUMAN CORTEX

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**Background:** The predominant neurodevelopmental theory of schizophrenia posits that there is a failure of normal synaptic loss believed to occur during normal adolescence. However, the most consistent neuropathology in the cortex of people with schizophrenia is a deficit in the γ-aminobutyric acid (GABA) inhibitory interneurons, not a reduction in presynaptic and postsynaptic elements. Thus, disruption to the normal development of cortical interneurons may lead to interneuron deficiency in schizophrenia. However, to understand if pathological changes in the brain of an adult with schizophrenia would be consistent with aberrant development, the known neuropathology must be placed in the context of normal human cortical development.

**Methods:** We examined the molecular changes that occur in the synapses, interneurons and the neurotransmitter systems during normal development of the human prefrontal cortex of 68 brains from healthy individuals (1 month - 49 years).

**Results:** Contrary to the prevailing view that synaptic pruning predominates during adolescent brain development, we found presynaptic mRNA and protein levels generally peak between 5–12 years of age and then remain stable through adolescence and into adulthood. Likewise, markers for dendritic spines peak in infancy and while mRNA levels then decline, protein levels are maintained throughout development. The various interneuron markers show three very distinct patterns of expression over development. Parvalbumin and cholecystokinin increase from infancy, whereas somatostatin, calretinin and neuropeptide Y decrease from infancy. Calbindin and vasoactive intestinal peptide peak in the toddlers and then decrease in adults in an inverted U-shaped pattern. Levels of mRNA for the GABA synthesizing enzymes GAD65 (GAD2) and GAD67 (GAD1) peak around 1 year of age and stay consistent through to adulthood. The post-synaptic GABAA receptor α1, β2 and γ subunits increase over the postnatal period to peak in adolescent/young adulthood whereas the α2 subunit shows the inverse pattern and decreases over the postnatal period. The dopamine receptor, D1, increase expression throughout the postnatal period to peak in early adulthood, whereas D2 and D5 show a continual decline throughout life. The NMDA receptors are highest in the first year of life and while subunits GRIN 2B, 2D and 3A all decrease throughout life, GRIN1 remains stable and GRIN 2A decreases after childhood. More recently data supporting the neuroinflammatory hypothesis of schizophrenia has merged with the neurodevelopmental hypothesis and posits that the strongest signal from GWAS studies in schizophrenia is in the C4 gene, which is a component of the complement cascade involved in normal synaptic development. We have initiated an examination of the various components of the complement cascade to determine if/when they are expressed in the human cortex and how they could be impacting the developing circuitry. Preliminary data shows C4 mRNA expressed at very low, but constant levels throughout postnatal life. In contrast, C3 mRNA is expressed at higher levels than C4, peaks in infancy and remains stable into adulthood. MAC protein (CD-59) mRNA which protects cells from complement mediated...