Development of mesocortical dopamine is a gradual process that continues until early adulthood. Because of its extended maturational 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, to adulthood.

**Methods:** We used LgDel mutant mice that carry the same 1.5 Mb deletion of the human 22q11.2DS. In parallel, we also used patients with 22q11.2DS.

**Results:** We first unraveled in mice altered startle responses at pre-pubertal ages (postnatal day PND 14) that ameliorated in early development from PND 19. Moreover, sensorimotor gating deficits started to appear as early as PND 19 lasting throughout adulthood. Motor coordination assessed with the Rotarod Test, instead revealed in LgDel mice motor deficits in pre-pubertal period (PND 15–16), that disappeared from adolescence (PND 35). Next, in an implemented 5-Choice Serial Reaction Time Task, we found that LgDel adolescent mice showed selective higher distractibility than controls as it has been shown in patients with schizophrenia. All these developmental behavioral alterations were accompanied by selective altered maturation of the prefrontal cortex, as demonstrated by parallel studies in mice and humans.

**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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1Stanley Medical Research Institute; 2Neuroscience Research Australia: Schizophrenia Research Laboratory

**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 interneurones, 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 postsynaptic GABAα 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 GRIN2B, 2D and 3A all decrease throughout life, GRIN1 remains stable and GRIN2A decreases after childhood. More recent 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
damage, is expressed at very low levels at birth but then increases significantly with age and is highest in adulthood, suggesting that significant changes in complement may occur after brain maturation is complete.

**Discussion:** Together these findings show very dynamic and complex patterns of expression from birth to adulthood, with the most active growth phase and dynamic changes occurring in the early years before adolescence. Thus, an insult during these early years could profoundly affect the developmental trajectory.

24. FROM DUSK TILL DAWN: LIFELONG TRAJECTORIES OF COGNITIVE FUNCTIONING IN PSYCHOTIC DISORDERS AND THEIR IMPLICATIONS FOR FUNCTIONAL RECOVERY AND TREATMENT DECISION

Eva Velthorst
Icahn School of Medicine at Mount Sinai

**Overall Abstract:** This symposium will draw together state of the art findings on the lifelong cognitive trajectories, on key-predictors of cognitive functioning and the functional consequences of cognitive impairments in schizophrenia and related psychotic disorders from developmental epidemiological, prodromal, and clinical research. Four speakers will take the audience through new findings on the cognitive course of the lifespan, ranging from childhood to old age. Specifically, the talks will address four key-questions:

1) Which areas of cognitive functioning are impaired and when does this impairment start?
2) How well can cognitive functioning predict the development of a psychotic illness, as well as diagnostic and functional outcome?
3) Does cognitive functioning remain stable after illness onset or are psychotic disorders characterized by continuing decline? When does decline occur and is it possible to predict it?
4) And what is the functional sequelae of specific cognitive impairments in older adults with schizophrenia?

Specifically, Dr. Mollon will present new data examining the origin of cognitive impairment across the psychosis spectrum using a population-based cohort followed prospectively from birth. Her findings demonstrate that while individuals with affective psychosis, subthreshold psychotic experiences and even depression experience some degree of cognitive impairment across the first two decades of life, only those who go on to develop non-affective psychosis exhibit widespread and increasing deficits.

Most studies of neurocognitive functioning in Clinical High Risk (CHR) cohorts have examined group averages, likely concealing heterogeneous subgroups. The study of Dr. Velthorst therefore used two independent methods to identify neurocognitive subgroups in a large population at Clinical High Risk for developing psychosis. Her findings show that neurocognitive profiles vary substantially in their severity and are associated with diagnostic and functional outcome, underscoring neurocognition as a predictor of illness outcomes.

Dr. Fett will present recent research on cognitive functioning in a large sample of patients at first hospitalization for a psychotic disorder who have been followed 20-years into the illness. Her findings indicate that cognitive functioning in psychotic disorders continues to decline after illness onset, that this decline is not specific to schizophrenia but present across psychotic disorders, and that, relative to never-psychotic individuals, impairments on some key-cognitive domains worsen with age. Decline could not reliably be predicted by key patient characteristics at baseline.

Lastly, Dr. Harvey will share novel data on the course of cognitive functioning in middle aged and older patients with schizophrenia. His findings demonstrate that cognitive impairments are moderated in their impact on everyday outcomes by the presence of severe communication abnormalities.

Interestingly, verbal under-productivity and disconnected speech had different functional correlates, with under-productivity impacting clinician rated social outcomes and performance on measures of interpersonal social competence. A lifetime focus on cognition is paramount in order pinpoint critical periods for prevention and intervention. This symposium seeks to present a comprehensive overview of the cognitive landscape of psychotic disorders by integrating findings on predictors and consequences of lifelong cognitive functioning of individuals diagnosed with a psychotic disorder.

24.1 NEUROCOGNITIVE DEVELOPMENT FROM INFANCY TO EARLY ADULTHOOD IN THE PSYCHOSIS SPECTRUM

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**Background:** The majority of patients with psychotic disorders experience severe neuropsychological impairment. The onset and course of this impairment, however, is debated. Moreover, the course of neuropsychological functioning in other psychiatric conditions remains largely unexamined. This study used longitudinal data from infancy to early adulthood to chart the course of general and specific neuropsychological functions in individuals with psychotic disorders, psychotic experiences and depression.

**Methods:** Data were from the Avon Longitudinal Study of Parents and Children (ALSPAC), a prospective cohort study comprising all live births between 1991 and 1992 in Avon, UK. All participants who underwent cognitive testing at 18 months, 4, 8, 15 and 20 years, and psychiatric assessment at age 18 were included. Individuals with non-affective psychotic disorder, affective psychotic disorder, subclinical psychotic experiences and depression were compared to controls on full-scale, verbal and non-verbal IQ, and measures of processing speed, working memory, language, visuospatial ability and attention.

**Results:** Individuals with non-affective psychosis showed continually increasing deficits between infancy (18 months) and adulthood (20 years) in full-scale IQ (effect size of change (ESA) = −1.09, p = .02), and non-verbal IQ (ESA = −0.94, p = .008). The depression group showed a small, increasing deficit in non-verbal IQ (ESA = −0.29, p = .04) between infancy and adulthood. Between ages 8 and 20, the non-affective psychosis group exhibited developmental lags (i.e. slower growth) on measures of processing speed, working memory and attention (ESA = −0.68, p = .001; ESA = −0.59, p = .004; ESA = −0.44, p = .001), and large, static deficits on measures of language and visuospatial ability (ES = −0.87, p = .005; ES = −0.90, p = .001). There was only weak evidence for neuropsychological deficits in individuals with affective psychosis, depression, and subclinical psychotic experiences.

**Discussion:** These findings suggest that the origins of non-affective psychotic disorder involve dynamic neurodevelopmental processes, which effect both verbal and non-verbal abilities throughout the first two decades of life. These neurodevelopmental processes do not manifest in other psychotic disorders, such as affective psychotic disorder and depression.

24.2 NEUROCOGNITIVE PROFILES IN THE PRODROME TO PSYCHOSIS IN NAPLS-1

Eva Velthorst*,1, Carrie Bearden2, Eric Meyer1, Anthony Giuliano3, Jean Addington4, Kristin Cadenhead5, Tyrone Cannon2, Barbara Cornblatt6, Thomas McGlashan2, Diana Perkins8, Ming Tsuang9, Elaine Walker10, Scott Woods7, Larry Seidman11

1Icahn School of Medicine at Mount Sinai; 2University of California, Los Angeles; 3College of Medicine, College Station; 4College of Medicine, College Station; 5College of Medicine, College Station; 6College of Medicine, College Station; 7College of Medicine, College Station; 8College of Medicine, College Station; 9College of Medicine, College Station; 10College of Medicine, College Station; 11College of Medicine, College Station

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