slowing and the cluster showing dyskinesia and abnormal NSS have different cortical-striatal connectivity compared to UHR who show average motor behavior and healthy controls.

**Discussion:** These results provide evidence for etiological theories highlighting altered cortico-striatal networks and the importance of examining motor behavior prior to the onset of psychosis. Taken together, this approach may reflect a novel strategy for promoting tailored risk assessment as well as future research developing individualized medicine.

### 26.2 Cortical Stress Regulation is Disrupted in Schizophrenia but Not in Clinical High-Risk for Psychosis

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**Background:** While striatal dopamine in psychosis and stress has been well studied, the role of dopamine in the prefrontal cortex (PFC) is poorly understood. To date no study has investigated the PFC dopamine response to stress exclusively in schizophrenia or its putative prodrome, even though medial PFC is known as a key area in stress regulation. The present study uses the high-affinity dopamine D2/3 receptor radiotracer [11C]FLB437 and positron emission tomography (PET) together with a validated psycho-social stress challenge to investigate if the PFC dopamine response to stress is dysregulated in schizophrenia and clinical high risk (CHR) for psychosis.

**Methods:** Fourteen antipsychotic-free patients with schizophrenia, 14 CHR and 12 matched healthy volunteers underwent two [11C]FLB437 PET scans, one while performing a Sensory Motor Control Task (control) and another while performing the Montreal Imaging Stress Task (stress). PET data were analyzed using the Simplified Reference Tissue Model with non-displaceable binding potential (BPND) as outcome measure. Dopamine release was defined as percent change in BPND between control and stress scan (ΔBPND).

**Results:** We observed an increased dopamine release, indexed by ABPND, in the medial PFC in schizophrenia patients but not CHR compared to healthy volunteers. Further, associations between stress-induced dopamine release and increase in cortisol levels observed in healthy volunteers and CHR, were absent in schizophrenia, similar to associations with symptoms, distress and anxiety.

**Discussion:** These findings provide first direct evidence of a disrupted cortical dopamine-stress regulation in schizophrenia.

### 26.3 Salience Signaling and the Emergence of Psychopathology in Youth at Clinical High Risk for Psychotic Illness

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**Background:** The early identification of people who appear to be at high risk for conversion to psychosis has become a central thrust of mental health research, with the hope that early intervention may alter the course of psychotic illness. Importantly, both positive and negative symptom dimensions have been found relate to risk for conversion in clinical high risk (CHR) populations. Neuroimaging work points to a role for dopamine pathway activity in both the positive and negative symptoms of psychotic illness. A role for dopamine pathways in signaling various kinds of salience is well-established, and several authors have proposed that excessive dopamine transmission in the striatum might contribute to psychotic symptoms by bringing about erratic, or “aberrant”, salience signaling. By contrast, a reduced ability to identify salient events as such, and signal salience “adaptively”, could result in impairments in learning and motivation. I will describe results from a study in which we examined the impact of salient events on learning and behavior: the probabilistic stimulus selection task (PSST; Frank et al., 2004) and the Salience Attribution Task (SAT; Roiser et al., 2009). Both adaptive and aberrant salience signals were operationalized in the context of each task. Successful performance of the PSST depends on the adaptive signaling of mismatches between expected and obtained outcomes, called reward prediction errors, which are one form of salient event. The SAT requires participants to respond as quickly as possible to a response prompt, which is preceded by conditioned stimuli that potentially predict reward availability for a fast response. The comparison of reaction time (RT) between responses following the frequently vs. infrequently rewarded conditioned stimuli offers a measure of adaptive salience coding with the expectation of faster RT for reward predicting stimuli. The comparison of RT between responses to the two levels of the irrelevant dimension offers a measure of aberrant salience coding with the expectation of equal RT for stimuli equally-predictive of reward. We assessed whether experimental measures of both adaptive and aberrant salience showed correspondences with SIPS ratings for symptoms along both the positive and negative dimensions.

**Results:** We observed significant correlations between multiple performance measures from the PSST and measures of both positive and negative symptoms. We found that positive symptom severity, in help-seeking youth, correlated positively with an implicit measure of aberrant salience from the SAT, and negatively with an explicit measure of adaptive salience.

**Discussion:** These results, consistent with our previous findings in both first-episode psychosis patients and patients with chronic schizophrenia, suggest that experimental measures of salience signaling may provide a psychosis risk signal in treatment-seeking youth. Further research is necessary to understand the potential predictive role of these measures for conversion to psychosis.

### 26.4 Language Disturbance as a Predictor of Psychosis Onset in Youth at Enhanced Clinical Risk

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**Background:** Language offers a privileged view into the mind; it is the basis by which we infer others’ thoughts. Subtle language disturbance is evident in schizophrenia prior to psychosis onset, including decreases in coherence and complexity, as measured using clinical ratings in familial and clinical high-risk (CHR) cohorts. Bearden et al previously used manual linguistic analysis of baseline speech transcripts in CHR to show that illogical and referential thinking, and poverty of content, predict later psychosis onset. Abstracts for the Sixth Biennial SIRS Conference
Then, Bedi et al used automated natural language processing (NLP) of CHR transcripts to show that decreased semantic coherence and reduction in syntactic complexity predicted psychosis onset. To determine validity and reproducibility, we have applied automated NLP methods, with machine learning, to Bearden's original CHR transcripts to identify a language profile predictive of psychosis.

**Methods:** Participants in the Bearden-UCLA cohort include 59 CHR, of whom 19 developed psychosis (CHR+) within 2 years, whereas 40 did not (CHR-), as well as 16 recent-onset psychosis and 21 healthy individuals, similar in demographics; speech was elicited using Caplan's "Story Game. Participants in the Bedi NYC cohort include 34 CHR (29 CHR+), with speech elicited using open-ended interview. Speech was audiotaped, transcribed, de-identified and then subjected to latent semantic analysis to determine coherence and part-of-speech tagging to characterize syntactic structure and complexity. A machine-learning speech classifier of psychosis onset was derived from the UCLA CHR cohort, and then applied both to the NYC CHR cohort and to the UCLA psychosis/control comparison, with convex hull (three-dimension depiction of model) and receiver operating characteristics analyses. Correlational analyses with demographics, symptoms and manual linguistic features were also done.

**Results:** A four-factor model language classifier derived from the UCLA CHR cohort that comprised three semantic coherence variables and one syntax (usage of possessive pronouns) predicted psychosis t with accuracy of 83% (intra-protocol) for UCLA CHR, 79% (cross-protocol) for NYC CHR, and 72% for discriminating psychosis from normal speech (UCLA psychosis/control). Convex hulls were defined as the smallest space containing all datapoints within a set for CHR- or healthy controls: these convex hulls showed substantial overlap, with CHR+ and psychosis speech datapoints largely outside these convex hulls. Coherence was associated with age, but speech variables did not vary by gender, race, or socioeconomic status in this study. While automated text features were unrelated to prodromal symptom severity, they were highly correlated with manual text features ($r = 0.7$, $p < .000001$).

**Discussion:** In this small preliminary study, we identified and cross-validated a robust language classifier of psychosis risk that comprised measures of semantic coherence (flow of meaning in language) and syntactic usage (usage of possessive pronouns). This classifier had utility in discriminating speech in individuals with recent-onset psychosis from the norm. It demonstrated concurrent validity in that it was highly correlated with manual linguistic features previously identified by Bearden et al., important as automated methods are fast and inexpensive. Automated language features were unrelated to sex, ethnicity or social class in these small samples, and semantic coherence increased with age, consistent with prior studies of normal language development. Of interest, overlapping convex hulls could be defined for groups of individuals without psychosis (UCLA CHR-, NYC CHR- and UCLA healthy), suggesting a constrained hull of normal language in respect to syntax and semantics, from which pre-psychosis and psychosis speech deviates. The RDoC linguistic corpus-based variables of semantic coherence and syntactic structure hold promise as biomarkers of psychosis risk and expression, with initial validation and reproducibility. Next steps in biomarker development include larger multisite studies with standardization of protocols for speech elicitation, test-retest, and attention to traction/feasibility, acceptability, cost, and utility. Mechanistic studies can also yield neural and physiological correlates of abnormal semantic coherence and syntax.

### 27. THE ROLE OF DOPAMINE IN SHAPING CIRCUITRY RELATED TO SCHIZOPHRENIA AND ADDICTION

**Anissa Abi-Dargham**  
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**Overall Abstract:** Dopamine plays a central role in shaping circuitry within the brain, thus affecting learning and behavior. It also plays a central role in schizophrenia and addiction. This panel will examine the impact of dopaminergic signaling on specific circuits that may create special vulnerability for the emergence of comorbidity between schizophrenia and addiction. The talks will include two presentations in clinical samples using molecular and functional imaging and two presentations in animal models.

**Jared Van Snellenberg** will discuss connectivity of striatal substructures to the rest of the brain in drug-free patients with schizophrenia and their relationship to abnormal cortical D2 signaling and psychotic symptoms. He will present recent unpublished work, motivated by pre-clinical studies with a D2 receptor over-expressing mouse model, using simultaneous multi-slice (multiband) functional MR imaging in these patients. These results suggest that unmedicated patients have altered connectivity between specific basal ganglia subnuclei, consistent with the animal model.

Nora Volkow will focus on the role of bidirectional interactions between dopamine reward system and prefrontal regions in the addicted brain with emphasis on the role of D2 receptor signaling in the striatum. She will discuss the functional impact of these interactions on reward/motivation and executive-function networks and will discuss the variables that influence D2 receptor function including genes, sleep and social stressors and how they interact with drug exposures to provide resilience or vulnerability to substance use disorders or schizophrenia. Finally, she will discuss how this knowledge can be used to tailor interventions to remediate or buffer neurocircuitry dysfunction triggered by drugs and for prevention.

Bita Moghadam will present an animal model of behaviorally induced dysfunction in the mesocortical circuit by using a task where actions are consistently rewarded but probabilistically punished. Spike activity and local field potentials are recorded during this task simultaneously from VTA and nPFC, two reciprocally connected mesocortical regions. Under no risk of punishment, a synchronous interaction at multiple time scales between PFC and VTA dopamine neurons is observed. This synchrony collapsed as a function of punishment contingency during reward-seeking actions, with risk of punishment diminishing VTA-driven neural synchrony between the two regions. These data reveal a dynamic coding scheme in VTA-nPFC neural circuits in representing aversion-based modulation of rewarded actions. These data suggest that driving VTA dopamine neurons by drugs of abuse may reverse the diminished synchrony and serve as self-medication in comorbid conditions.

Finally, Aurelio Galli will discuss the structural, functional, and behavioral insights into the dopamine dysfunction of comorbid conditions as modeled by a deletion of the SLC6A3 affecting the function of the human dopamine transporter (hDAT). Genetic variants in hDAT have been associated with neuropsychiatric disorders. An in-frame deletion in hDAT at N336 (ΔN336) leads to abnormal DA homeostasis. He demonstrated these dysfunctions in brains of Drosophila melanogaster expressing hDAT ΔN336. Furthermore, these flies are hyperactive and display fear and impaired social interactions, traits associated with impaired DA neurotransmission. Insights from X-ray crystallography, electron paramagnetic resonance, molecular dynamic simulations, electrophysiology and behaviors describe how a genetic variation causes DA dysfunction resulting in combined behavioral alterations and psychostimulant use.

### 27.1 TRANSLATIONAL EVIDENCE OF DOPAMINE-RELATED ALTERATIONS OF BASAL GANGLIA AND THALAMO-CORTICAL NEUROCIRCUITRY IN SCHIZOPHRENIA: A FULL CLINIC-TO-BENCH-TO-CLINIC BACK-TRANSLATION

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