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

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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 neurocircuity dysfunction triggered by drugs and for prevention.

Bita Moghaddam 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 mPFC, 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-mPFC 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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Background: Recent work with a dopamine 2 receptor (D2R) over-expressing (D2R-OE) mouse has suggested that this receptor over-expression leads to a highly plastic increase in bridging collaterals from the associative striatum (AST) to the external segment of the globus pallidus (GPe). Because of the densely interconnected nature of basal ganglia-thalamo-cortical signaling circuitry, we hypothesized and demonstrated in a recent publication that the resting state functional connectivity (RSFC) of AST to multiple cortical and thalamic subregions is broadly disrupted in unmedicated patients with schizophrenia. In this talk, I will present novel simultaneous multi-slice (aka "multiband") fMRI data that provides the spatial resolution necessary to image smaller basal ganglia substructures (such as the GPe/GPi), and show that unmedicated patients with schizophrenia exhibit specifically disrupted AST-GPe connectivity, as predicted directly from the D2R-OE mouse model findings.
In addition, recent work with a 22q11 deletion mouse, which models a similar syndrome in humans that is strongly associated with schizophrenia, has shown that these mice exhibit a D2R-mediated reduction in the strength of excitatory post-synaptic potentials in primary auditory cortex in response to stimulation of the medial geniculate nucleus (MGN) of the thalamus. Consistent with this finding, I will present multiband fMRI data that employs both RSFC and an audio-visual localizer task to demonstrate a specific reduction in RSFC between the MGN and primary auditory cortex, consistent with these findings in the 22q11 mouse.
Methods: Partially-overlapping samples of 19 and 14 unmedicated patients with schizophrenia and 15 and 16 matched healthy participants participated in two sets of studies. For both studies, multiband fMRI images were acquired on a GE MR 750 system at the New York State Psychiatric Institute, with a multiband acceleration factor of 6, 2 mm isotropic voxel resolution, and 850 ms TR. Thirty minutes of RSFC data was collected in each participant, and participants in the auditory study also completed a 15 minute audio-visual localizer task that employed sparse temporal sampling with either auditory (9 seconds of a randomized and rapidly-varying musical stimulus) or visual (7.5 Hz alternating checkerboard) stimulation between each acquisition cluster. Basal ganglia subregions were identified via manual drawings conducted by an experienced rater, and the MGN and LGN were identified using the audio-visual localizer task.
Results: Unmedicated patients with schizophrenia showed a significant reduction in RSFC strength between the dorsal caudate and GPe (Cohen's $d = 0.87$, $P = 0.017$), but no other striatal or pallidal subregion pairs, consistent with a specific alteration in anatomical projections between these two regions. In addition, patients with schizophrenia showed a reduction in RSFC between the MGN and primary auditory cortex, as well as between the LGN and primary visual cortex ($P < 0.05$, alphasim corrected for whole-brain analysis).
Discussion: These findings provide initial support for the existence of D2R-mediated alterations in functional neuroanatomy, first observed in animal models of schizophrenia, in a clinical sample of unmedicated patients. In addition to providing early evidence for potential mechanisms of psychotic phenomena, this work suggests that the use of non-invasive multiband RSFC is a promising approach to translating basic neuroscience findings in animal models back into a clinical setting. Altered circuitry was shown in the D2OE mice to underlie motivational deficits, and we propose that they may have a similar functional impact in patients.

27.2 THE DOPAMINE MOTIVE SYSTEM IN ADDICTION

Nora Volkow*,[1]
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Background: We have investigated the role of bidirectional interactions between the dopamine reward and motivation system and executive function in addicted individuals, with a particular focus on the intersection between the role of D2 receptor (D2R) signaling in the striatum and perturbations in prefrontal brain activity.
Methods: Using brain imaging we have studied these interaction for various types of addiction and explored how their involvement affect behavior including impulsivity and compulsiveness. We have also investigated the mechanisms associated with vulnerability to drug use disorders as linked with disrupted executive function including the effects of genetics and physiological factors such as circadian rhythms, sleep deprivation and obesity.
Results: We found that: a) chronic drug use reduces striatal levels of D2R and perturbs metabolism in frontal brain regions, emotional reactivity and executive control; b) that higher-than-normal striatal D2R availability in nonalcoholic members of alcoholic families appear to play a protective role against alcoholism by regulating circuits involved in inhibiting behavioral responses and in controlling emotions; c) that chronic sleep deprivation is associated with increased striatal dopamine, lower D2R availability, and metabolic changes in several cortical brain regions; and, d) that newly characterized variable number tandem repeat (VNTR) polymorphisms in the genes coding for PER2 and the AKT1 proteins (a kinase that has been implicated in schizophrenia and psychosis) appear to modulate striatal D2R availability in the human brain.
Discussion: Although the studies have focused on the effects of drugs, the DA striato cortical pathway is of direct relevance to schizophrenia as well as that of other psychiatric disorders. We will discuss the implications of our findings as they relate to the prevention and treatment of substance use disorders and schizophrenia.

27.3 DISCRETE AND COORDINATED ENCODING OF REWARDED ACTIONS BY PREFRONTAL CORTEX AND DOPAMINE NEURONS

Bita Moghaddam*,[1]
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Background: Co-morbidity of schizophrenia and drug use has been attribute to common pathophysiology of mesocortical circuit. We modeled a behavioral disruption to this circuit in rodents by using a task where actions were consistently rewarded but probabilistically punished. Our data reveal dynamic coding schemes of the VTA-mPFC neural circuit in representing risk of punishment and punishment-based modulation of rewarded actions.
Methods: Spike activity and local field potentials were recorded during simultaneously from ventral tegmental area and medial prefrontal cortex (PFC), two reciprocally connected mesocortical regions, in rodents as they performed a task where actions were consistently rewarded but probabilistically punished. This model allowed us to reveal dynamic coding schemes of the VTA-mPFC neural circuit in representing risk of punishment and punishment-based modulation of rewarded actions.
Results: At the single unit level (n=167 mPFC n=102 VTA units), we found that ensembles of VTA and mPFC neurons encode the contingency between action and punishment. At the network level, we found that coherent theta oscillations synchronize the VTA and mPFC in a bottom-up direction, effectively phase-modulating the neuronal spike activity in the two regions during punishment-free actions. This synchrony declined as a function of punishment contingency
Discussion: During reward-seeking actions, risk of an aversive outcome and anxiety disrupts dopamine neuron-driven synchrony between PFC and VTA

27.4 STRUCTURAL, FUNCTIONAL, AND BEHAVIORAL INSIGHTS OF DOPAMINE DYSFUNCTION REVEALED BY A DELETION IN SLC6A3

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