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). 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, alphaFSPM 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 patients with schizophrenia exhibit specifically disrupted AST-GPe connectivity, as predicted directly from the D2R-OE mouse model findings.

27.2 THE Dopamine MoTIVE SYSTEM IN ADDICTION

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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

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Background: Co-morbidity of schizophrenia and drug use has been attributed 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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Abstracts for the Sixth Biennial SIRS Conference
Background: The human dopamine (DA) transporter (hDAT) mediates clearance of DA. Genetic variants in hDAT are associated to neuropsychiatric disorders. We investigated the structural and behavioral bases of an in-frame deletion in hDAT at N336 (ΔN336) associated with neuropsychiatric disorders.

Methods: This study bridges structural biology, molecular neuroscience and organism physiology culminating in a mechanistic model that relates precise alteration in a transport cycle with behavioral manifestations.

Results: We uncovered a previously unobserved conformation of the intracellular gate of the transporter promoted by ΔN336, representing likely the rate limiting step of the transport process. This state is defined by a “half-open and inward facing” state (HOIF) of the intracellular gate that leads to DA dysfunction. The HOIF state is regulated by a network of interactions conserved phylogenetically, as we observed it both in hDAT and in its bacterial homolog leucine transporter. We demonstrated these dysfunctions in brains of Drosophila melanogaster expressing hDAT ΔN336. These flies are hyperactive and display increased fear and impaired social interactions, traits associated with neuropsychiatric disorders.

Discussion: Here, we describe how a genetic variation causes DA dysfunction. We have recently revised and tested this phenomenological model, in particular distinguishing primary versus-secondary factors, in offering a bio-pheno-social model of schizophrenia spectrum disorders.

Results: The revised model is consistent with recent empirical findings and offers several advantages:

1) It helps account for the temporal variations of the symptoms or syndrome, including longitudinal progression, but also the shorter-term, situationally-reactive, sometimes defensive, and possibly quasi-agentive variability of symptom-expression that can occur in schizophrenia (consistent with understanding some aspects of self-disturbance as dynamic and mutable, involving shifting attitudes or experiential orientations).

2) It accommodates the overlapping of some key schizophrenic symptoms with certain non-schizophrenia spectrum conditions involving dissociation (depersonalization and derealization), including Depersonalization Disorder and Panic Disorder, thereby acknowledging both shared and distinguishing symptoms.

3) It integrates recent neurocognitive, neurobiological, and psychosocial (e.g., influence of trauma and culture) findings into a coherent but multi-factorial neuropsychological account.

Discussion: An adequate model of schizophrenia will postulate shared disturbances of core-self experiences that nevertheless can follow several distinct pathways and occur in various forms. Such a model is preferable to uni-dimensional alternatives—whether of schizophrenia or core self disturbance—given its ability to account for distinctive yet varying experiential and neurocognitive abnormalities found in research on schizophrenia, and to integrate these with recent psychosocial as well as neurobiological findings.

28.2 DISORDERS OF THE EMBODIED SELF IN SCHIZOPHRENIA: AT THE CROSSROAD BETWEEN DEVELOPMENT AND PSYCHOPATHOLOGY

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Background: Basic disorders of the embodied self (BDES) encompass a cloud of related clinical constructs (e.g. cnenesthesias, distortions of somato-physic unity, anomalous bodily experiences in a broad sense) that are immanently related to a profound transformation of subjectivity and with the developmental modulation of bodily awareness. They have been historically ascribed a potential role in the emergence of schizophrenia spectrum disorders. However, the clinical-phenomenological level of description has been only marginally integrated with novel insights from developmental psycho-pathology and neurosciences.

Methods: We conducted a conceptual literature review based on clinical analysis and heuristic synthesis.

Results: Despite often occurring in prodromal/clinical at-risk states, as well as in full blown schizophrenia spectrum conditions (where BDES play a pivotal psychopathogenetic role in the genesis of productive symptoms), they are relatively neglected both in research and in routine clinical examination. Furthermore, BDES also discriminate non help-seeking genetic high risk subjects from normal controls.

Discussion: Within the superordinate construct of Self-disorders, BDES are a potentially relevant dimensional phenotype for the characterization of broad Schizophrenia Spectrum vulnerability. Their contextualization within a developmental and neurophysiological perspective could further amplify their value for etio-pathogenetic research.