Abstracts:

Joshua Berke *Dissociable dopamine dynamics for learning and motivation*

The dopamine projection from ventral tegmental area (VTA) to nucleus accumbens (NAc) is critical for motivation to work for rewards, and reward-driven learning. How dopamine supports both functions is unclear. Dopamine spiking can encode prediction errors, vital learning signals in computational theories of adaptive behavior. By contrast, dopamine release ramps up as animals approach rewards, mirroring reward expectation. This mismatch might reflect differences in behavioral tasks, slower changes in dopamine cell spiking, or spike-independent modulation of dopamine release. Here we compare spiking of identified VTA dopamine cells with NAc dopamine release in the same decision-making task. Cues indicating upcoming reward increased both spiking and release. Yet NAc core dopamine release also covaried with dynamically-evolving reward expectations, without corresponding changes in VTA dopamine cell spiking. Our results suggest a fundamental difference in how dopamine release is regulated to achieve distinct functions: broadcast burst signals promote learning, while local control drives motivation. I will further present initial results that cholinergic interneurons are responsible for the local control of motivation-related dopamine release.

Avrama Blackwell *The role of dopamine and post-synaptic signaling molecules in synaptic plasticity and relapse to alcohol use*

The basal ganglia are involved in normal learning and motor behavior as well as diseases such as Parkinson's disease, and addiction. Dopamine inputs to the striatum are involved are required for learning goal directed actions and habit formation. Spiny projection neurons of the striatum integrate cortical, thalamic, and dopaminergic input to learn critical associations via cortico-striatal synaptic plasticity. The tendency to relapse after withdrawal from addiction is partly due to the strong habits learned from the overly strong dopamine stimulation caused by drug use. However, it is unclear how dopamine interacts with acetylcholine and glutamate to control activation of memory kinases implicated in synaptic plasticity. We implemented a model of signaling pathways activated by dopamine D1 receptors, acetylcholine receptors, and glutamate receptors to investigate how spiny projection neurons discriminate different temporal patterns of stimulation, and the degree of spatial specificity exhibited by signaling molecules underlying LTP and LTD. We use our novel, computational efficient simulator, NeuroRD, to simulate stochastic interactions both within spines and between spines arranged along a dendrite. Dopamine release during theta-burst and 20hz stimulation was extrapolated from voltammetry data. Our results show that the combination of activity of several key kinases can predict the occurrence of LTP in response to theta-burst stimulation and LTD in response to 20hz stimulation. To investigate spatial interactions, we stimulate two spines, either adjacent or separated on a 20 um dendritic segment, and investigate how the distance between stimulated spines influences molecule activation. Our results show that molecules underlying LTP exhibit spatial specificity, whereas the endocannabinoid 2AG exhibits a spatially diffuse elevation. We also implement changes in NMDA receptors, adenylyl cyclase, and G protein signaling that have been measured following chronic alcohol treatment and withdrawal. Simulations under these conditions demonstrate enhanced LTP and a change from LTD to LTP, which predict rapid re-learning and cue-induced relapse and suggest that the molecular changes can account for some aspects of alcohol use disorder.

Dynamic diversity underlying pauses and bursting in SNc dopamine neurons

Carmen Canavier and Chris Knowlton

In the absence of synaptic input, midbrain dopamine (DA) neurons are spontaneous pacemakers. Salient and reward-related stimuli elicit bursts and disappointment can elicit a pause in firing. Although DA neurons were once thought to be a homogeneous population, there is in fact significant diversity with the population with respect to the processes involved in pauses and bursts. A morphologically realistic, multi-compartmental model was used to suggest mechanisms for axonal projection-specific responses of tonically firing nigral dopamine neurons to a prolonged hyperpolarization, such as those that presumably underlie pauses in vivo. Bursting mechanisms also appear to be diverse in that medial neurons may rely

more on slow recruitment of K-ATP channels for burst termination whereas other current, such as the ERG K+ current, may be sufficient in lateral neurons. The model predicts that the degree to which the T-Type (CaV3) Ca2+ channels are de-inactivated controls whether DA neurons projecting to the dorsolateral striatum (DLS) exhibit a short latency rebound spike or longer latencies due to the presence of a subthreshold oscillation. Deeper hyperpolarizations favor the latter, because the larger Ca2+ influx activates the SK K+ channel sufficiently to prevent an action potential on at least one cycle of a subthreshold oscillation produced by a T/SK channel interaction. Setting the SK or T-type conductance to zero eliminated subthreshold oscillatory responses and produced substantial transient increases in rebound spike frequency, consistent with experimental observations using pharmacology. Another important result was that simply increasing conductance density of A-type (Kv4.3) K+ channels in the model eliminated both the fast rebound responses and the subthreshold oscillation; instead, the model produced only delayed post-inhibitory responses associated with a continuum of ramp-like subthreshold responses consistent with observations in DMS-projecting DA neurons. Increased A-type conductance in DMS is shown to be consistent with more ramp-like interspike intervals in DMS projecting cells, deeper after-hyperpolarizations and a lower basal frequency relative to DLS projecting cells. Overall, a lateral to medial increase in KV4.3 and decrease in CaV3 are consistent with the ramp responses.

Possible roles of dopamine in model-free and model-based decision and learning

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The response of dopamine neurons to unpredicted rewards and reward predictive sensory events is considered as the key learning signal for TD-type model-free reinforcement learning. The role of dopamine in model-based action selection and reinforcement learning is less clear, but its involvement has been suggested in fMRI studies (e.g., Daw et al. 2011).
Here we reconsider a hypothesis that dopamine neurons respond to internal events of finding a better-than-standard candidate during model-based action search, and the corresponding dopamine pulse can serve as the Go signal for the found action (Doya 1999) in view of recent experimental findings.

A dendrite-specific striatonigral circuit facilitates dopamine rebound

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Dopamine neurons in the substantia nigra pars compacta (SNc) are often inhibited by aversive events. A subset of these neurons rebound following an aversive pause in activity. The functional circuit underlying both the aversive inhibition and the rebound are currently unknown. Retrograde viral tracing studies show that dopaminergic neurons receive diverse inhibitory input from nearly all nuclei in the basal ganglia. However, the functional strength, specific receptors activated, and dendritic location of each input have not yet been tested. Here we use two-photon imaging and local optogenetic activation to functionally map the inhibitory inputs from basal ganglia nuclei onto dopamine neuron dendrites. We compare the strength and location of genetically-defined inhibitory subpopulations in the striatum (striosome and matrix) and globus pallidus (Parvalbumin and Lhx6). We find that the striosomal inputs selectively inhibit the ventrally-projecting “SNr dendrite” of the dopamine neurons. Although isolated to the SNr dendrite, this connection exerts strong control over the entire cell, pausing action potentials and facilitating rebound firing. By contrast, the Lhx6 neurons of the globus pallidus inhibit dopamine neurons at the soma and proximal dendrites but do not result in rebound firing. We find that striosomal input facilitates rebound firing because it activates GABAb receptors, which strongly hyperpolarize the SNr dendrite. Because the globus pallidus inputs selectively activate GABAa receptors, they pause firing without recruiting rebound conductances. We use a computational model to show that dendrite-specific inhibition more effectively generates rebound action potentials than either somatic inhibition or broad inhibition of the entire dendritic arbor. Finally, we show that striosomes preferentially inhibit the subset of SNc dopamine neurons which express intrinsic rebound mechanisms. Therefore, we describe a distinct striatonigral circuit for generating dopamine neuron rebound activity.

Arif Hamid *Wave-like spatio-temporal patterns organize dopamine transient into compartmentalized decision signals*

Dopamine is a potent regulator of plasticity in the striatum, and is critical for reward learning. The dopamine-reward prediction error (RPE) hypothesis emphasizes that dopamine conveys deviations from expectation in reinforcement learning (RL) theory. This influential view generally treats dopamine as a "global", spatio-temporally uniform signal that is thought to be broadcast to postsynaptic targets. A key limitation of this "global" view is that scalar RPEs are neither computationally advantageous, nor reflected in forebrain dopamine dynamics, as striatal sub-regions are functionally specialized. Thus, we lack a clear understanding of organizational principles of dopamine dynamics across the striatum, and the extent these organizational rules reflect postsynaptic computational specialization.

I will describe results from a recent project that imaged large-scale organization of dopamine axons across 60-80% of dorsal striatum. I will report a novel set of spatio-temporal trajectories of DA axons that are organized into traveling waves that deliver correlated dopamine transients to functionally related striatal sub-regions. Further, rewards (and locomotor behaviors) immediately resynchronized activity into directional waves.

I will close with providing an initial interpretation of the computation functions of dopamine waves. Specifically, I will argue that opponent wave directions implement vector-valued RPEs (or rather spatio-temporally weighted decision signals) to underlying striatal sub-experts. Together, these results demonstrate that waves promote a spatio-temporal specialization of striatal dopamine axons that help tailor dopamine release to sub-region's computational requirements.

Effects of phasic dopamine in sensory representations and their perceived salience

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Novelty and reward expectancy evoke bursts in the firing of dopaminergic midbrain neurons. This burst firing evokes phasic dopamine release that is considered a teaching signal in reinforcement learning. It is established that phasic dopamine release modifies behavior and induces synaptic plasticity. Yet, it is not entirely clear how phasic dopamine release modifies stimulus representations in striatal circuits that evaluate sensory stimuli and transform them into actions. We addressed this question in the ventral striatum that receives both dense olfactory and dopaminergic inputs. We found in awake mice that evoked phasic dopamine induced plasticity selectively for the coincidently presented stimulus and increased its distinctness from other stimuli. Phasic dopamine thereby enhanced the decoding of previously paired stimuli and increased their perceived salience. These findings may provide a network mechanism of how dopaminergic learning signals promote value assignment to specific stimuli.

Dopamine-endocannabinoid interactions mediate bidirectional spike timing dependent plasticity in the striatum

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Dopamine modulates striatal synaptic plasticity, a key substrate for action selection and procedural learning. While plasticity under prolonged activation is well elucidated, its expression in response to few spikes remains less documented. Using spike-timing dependent plasticity (STDP), we unraveled a new form of plasticity in the dorsolateral striatum: a spike-timing dependent potentiation (tLTP) induced by few coincident pre- and post-synaptic spikes (~5-15), mediated by endocannabinoids (eCB-tLTP) through a signaling pathway that relies on the activation of type-1 cannabinoid receptor (CB_1R) and transient receptor potential vanilloid type-1 (TRPV1) and on eCB dynamics. Whether this eCB-tLTP interacts with the dopaminergic system and consequently be affected in Parkinson's disease remained to be investigated. Here, we report that eCB-tLTP is controlled by dopamine, impaired in Parkinson's disease and rescued by L-DOPA. We found that opto-inhibition of dopaminergic neurons prevents eCB-tLTP induction and that eCB-tLTP involves specifically dopamine type-2 receptors (D_2R) located presynaptically in corticostriatal glutamatergic afferents. Combining our experimental results and mathematical modeling, we show that dopamine controls not only the induction but also the polarity via presynaptic D_2Rs (tLTP vs tLTD) of eCB-plasticity by modulating the effective eCB thresholds. While usually considered as depressing synaptic function, our results show that eCBs in presence of dopamine constitute a versatile system underlying bidirectional plasticity implicated in basal ganglia pathophysiology.

Martin Vinck *Tuning of neuronal interactions in the lateral Ventral Tegmental Area by dopamine sensitivity*

The Ventral Tegmental Area (VTA) contains a considerable population of rhythmically firing dopaminergic neurons. These neurons are influenced by auto-inhibition due to extra-synaptic dopamine release resulting in volume transmission. Using a Multi-Electrode-Array we simultaneously recorded in vitro from multiple VTA dopamine neurons in the rat and studied their mutual interactions. Neurons were synchronized at frequencies around their intrinsic oscillation frequency, and exhibited resonance to inputs around these frequencies. We observed that the dopamine sensitivity (EC50) of the neurons (i.e. the relation between dopamine concentration and firing rate) was quite variable within the recorded population. The interactions between pairs of neurons were quantified using the Granger causality. We found that the dopamine sensitivity determined the role of a neuron in the local VTA population. Highly sensitive neurons became followers (of the population rhythm), whereas less sensitive dopamine neurons played a more leading role. This was confirmed by the application of sulpiride which reduces the dopamine sensitivity of all neurons through competition and abolishes the structure in the interactions. These findings imply that therapeutics, which have an easy to understand effect on firing rate, could have a more complicated effect on the functional organization of the local VTA population, through volume transmission principles.

Timing of dopamine directs synaptic plasticity

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Dopamine dependent synaptic plasticity in the striatum is a candidate mechanism for certain forms of reinforcement learning. In this model, dopamine released in response to rewarding events acts at the cellular level to strengthen synapses that were active in the behaviour that led to reward. In natural learning, rewards are delayed until after the actions that lead to them, and thus after the relevant neural activity. To overcome this credit assignment problem, computational models of reinforcement learning assume the existence of an eligibility trace, which may take the form of a silent synaptic signal activated by presynaptic and postsynaptic activity, which later is converted into a long-term synaptic change by the conditional action of dopamine. Despite its conceptual appeal, direct experimental evidence for a silent eligibility trace has been limited We tested the silent eligibility trace hypothesis by measuring time-dependent modulation of synaptic plasticity by dopamine in adult mouse striatum, using whole-cell recordings of synaptic responses to corticostriatal inputs in striatal spiny projection neurons. Presynaptic cortical input followed by postsynaptic action potentials caused spike-time dependent long-term

depression in spiny projection neurons expressing dopamine D-1 receptors. To test for an eligibility trace, dopamine was uncaged at specific time-points before and after pre- and post-synaptic conjunction of activity. Dopamine caused potentiation selectively at synapses that were active two seconds before dopamine release, but not at earlier or later times. Our results provide direct evidence for a silent eligibility trace in the synapses of striatal neurons. This dopamine-timing-dependent plasticity may play a central role in striatal reinforcement learning, in which timing of the dopamine signal directs synaptic plasticity.

Specialized dopamine projection neurons work cooperatively to maximize reward reinforcement

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Dopamine neurons of the ventral tegmental area (VTA) regulate multiple aspects of reinforcement. Here, I will describe our work to determine how dopamine neurons coordinate distinct aspects of reinforcement through the regulation of reward association and motivation. We have identified two distinct populations of dopamine-producing neurons in mice that differentially innervate the nucleus accumbens core and shell subdivisions of the ventral striatum. Although these neurons encode reward-related information similarly, they perform distinct functions. Dopamine neurons projecting to the nucleus accumbens core facilitate learning to associate an action with an outcome, but do not drive motivated behavioral responses. In contrast, dopamine neurons projecting to the nucleus accumbens shell do not facilitate action-outcome associations, but facilitate the maintenance of actions previously associated with a rewarded outcome. I will provide further evidence that the coordinated action of these two dopamine projection populations is critical for maximal reward reinforcement and discuss the implications for having specialized dopamine populations that work optimally as a cooperative group.

Role of VTA GABAergic neurons in high-frequency firing of dopaminergic neuron

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Dopaminergic (DA) neurons play a key role in reinforcement learning and motivation system. In particular, their activity encodes reward value [1]. DA neurons show three types of behavior: a tonic mode (spontaneous spiking) providing a background level of DA concentration; a phasic (high frequency) bursts corresponding to positive rewards; and a silent state (spiking is almost absent) in the case of a negative reward value. *In vitro* DA neurons are active spontaneously and their high frequency activity may be evoked by bath application of NMDA agonists (for example, [2]). *In vivo* tonic DA neuron firing is a result of balanced NMDA and GABA inputs [3,4]. To increase firing frequency, one may disinhibit DA neurons (to suppress GABA neurons activity) or increase the glutamatergic inputs. On the other hand, there is a body of evidence that GABA neurons may play a more complex role in DA firing beyond only tonic inhibition and disinhibition processes. In particular, we have shown that simultaneous activation of GABA and AMPA receptors may change the DA neuron excitability type (from type I to II) allowing for DA neuron synchrony and increased DA release [5]. Furthermore, recent data suggest “paradoxical” excitations of the DA neurons by GABA inputs [6-8] and their definitive role in producing bursts as opposed to elevated tonic frequencies [7,8]. We hypothesize that one of the possible mechanisms explaining such “paradoxical” effects on DA neurons activity is based on the short time synchronization of GABA networks. The VTA interneurons may be synchronized by multiple mechanisms: e.g. glutamatergic inputs from the PFC or phasic activation of nicotinic acetylcholine receptors. In this case the synchronized population of GABA neurons generates a strong high frequency input pulse train “forcing” synchronization of DA neurons at the frequency of GABAergic neurons [9,10] (fig. 1). In summary our computational work points out how temporally structured GABA input to the DA neurons may lead to increased burst firing and sculpt the ensuing DA release.

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