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RPPR Final Report
as of 14-Jul-2023

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Final Report for Period Beginning 30-Sep-2017 and Ending 30-Dec-2022
Title: Prefrontal Cortical Circuitry that Supports Learning in a Complex and Dynamic Environment
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End Performance Period: 30-Dec-2022
Report Term: 0-Other
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STEM Degrees: 2 **STEM Participants:** 4

Major Goals: Learning in a complex environment is an important cognitive ability requiring us to track choices, as well as the outcomes of those choices. Although several brain regions have been implicated in this type of learning, we proposed taking advantage of the extremely powerful genetic tools available in mice to target specific populations of neurons in order to monitor and manipulate their activity during behavior. The major goals of this project are to investigate the role of the prefrontal cortex (PFC) and its interactions with other brain regions in reinforcement learning.
The specific goals are:
1.Aim 1: To develop novel behavioral paradigms in mice well-suited for probing neural circuit mechanisms of reinforcement learning. Animals will be trained in a task that requires them to use previous history of choices and outcomes of those choices to guide behavior. The task is self-paced allowing us to investigate the neural circuitry underlying action selection (i.e. choice) as well as the pacing of the behavior (measured as trial initiation latency).
2.Aim 2: To identify regions within the prefrontal cortex (PFC) that are needed for reinforcement learning in our behavioral task. To investigate the causal role of neural activity in the PFC in reinforcement learning, we will optogenetically inactivate subsets of PFC neurons during behavior. Optogenetic manipulation allows for precise control over the timing of inactivation, so we are able to interrogate the precise timing of PFC involvement in the behavior by inhibiting during different epochs of the task.
3.Aim 3: To test the hypothesis that subpopulations of neurons in the prefrontal cortex that target distinct downstream structures differentially encode reward feedback and other features of the task. This aim involves imaging from subsets of PFC neurons as mice perform the task, as well as activating these neurons to test their causal role. We will use a retrogradely transporting AAV virus to target subsets of PFC neurons defined by their projection.

Accomplishments: Over the reporting period, we have broken important ground in understanding how reinforcement learning algorithms map on brain circuitry. I list our most significant discoveries below:

* Cox et al Nature Neuroscience 2023: Sex differences in the neural substrates of decision-making. While there is emerging evidence of sex differences in decision-making behavior, the neural substrates that underlie such differences remain largely unknown. We demonstrated that in mice performing a value-based decision-making

task, while choices are similar between the sexes, motivation to engage in the task is modulated by action value more strongly in females than in males.We found that the projection from a region of the prefrontal cortex to the dorsomedial striatum mediates this effect on motivation, without affecting choices in either sex.
* Willmore et al Nature 2022: Behavioral and dopaminergic signatures of resilience. Chronic stress can have lasting adverse consequences in some individuals, yet others are resilient to the same stressor. What mice may be learning during chronic stress to produce these different outcomes is not clear. Supervised and unsupervised behavioural quantification revealed that during stress, resilient and susceptible mice use different behavioural strategies and have distinct activity patterns in dopamine terminals in the NAc. Neurally, resilient mice have greater activity near the aggressor, including at the onset of fighting back. Conversely, susceptible mice have greater activity at the offset of attacks and onset of fleeing. We also performed optogenetic stimulation of NAc-projecting DA neurons in open loop (randomly timed) during defeat or timed to specific behaviours using real-time behavioural classification and found stimulation patterns that biased towards resilience Together, these data provide a link between DA neural activity, resilience and resilience-associated behaviour during the experience of stress.
* Bolkan et al Nature Neuroscience 2022: Neural substrates of state-dependent decision-making. A classic view of the striatum holds that activity in direct and indirect pathways oppositely modulates motor output. Whether this involves direct control of movement, or reflects a cognitive process underlying movement, was unresolved. We discovered that strong, opponent control of behavior by the two pathways of the dorsomedial striatum depends on the cognitive requirements of a task. Furthermore, a latent state model (a hidden Markov model with generalized linear model observations) revealed that—even within a single task—the contribution of the two pathways to behavior is state dependent. Specifically, the two pathways have large contributions in one of two states associated with a strategy of evidence accumulation, compared to a state associated with a strategy of repeating previous choices. Thus, both the demands imposed by a task, as well as the internal state of mice when performing a task, determine whether dorsomedial striatum pathways provide strong and opponent control of behavior.
* Parker et al Cell Reports 2022: Mapping reinforcement learning algorithms onto nucleus accumbens circuitry. How are actions linked with subsequent outcomes to guide choices? The nucleus accumbens, which is implicated in this process, receives glutamatergic inputs from the prelimbic cortex and midline regions of the thalamus. However, little is known about whether and how representations differ across these input pathways. By comparing these inputs during a reinforcement learning task in mice, we discovered that prelimbic cortical inputs preferentially represent actions and choices, whereas midline thalamic inputs preferentially represent cues. Choice-selective activity in the prelimbic cortical inputs is organized in sequences that persist beyond the outcome. Through computational modeling, we demonstrate that these sequences can support the neural implementation of reinforcement-learning algorithms, in both a circuit model based on synaptic plasticity and one based on neural dynamics.

* Engelhard et al Nature 2019: Specialized coding of sensory, motor and cognitive variables in VTA dopamine neurons. There is increased appreciation that dopamine neurons in the midbrain respond not only to reward and reward-predicting cues, but also to other variables such as the distance to reward, movements and behavioural choices. An important question is how the responses to these diverse variables are organized across the population of dopamine neurons. This fundamental question has been difficult to resolve because recordings from large populations of individual dopamine neurons have not been performed in a behavioural task with sufficient complexity to examine these diverse variables simultaneously. To address this gap, we used two-photon calcium imaging through an implanted lens to record dopamine neuron activity during a complex decision-making task. As mice navigated in a virtual-reality environment, dopamine neurons encoded an array of sensory, motor and cognitive variables. These responses were functionally clustered and anatomically organized, such that subpopulations of neurons transmitted information about a subset of behavioural variables, in addition to encoding reward. This organization may aid downstream circuits in correctly interpreting the wide range of signals transmitted by dopamine neurons.

Training Opportunities: This grant has supported numerous training and professional development opportunities forr one undergraduate student, three graduate students, one postdoctoral associate, and five non-student research assistants/technicians. Training encompassed conducting independent behavioral and brain imaging experiments that included data collection and analysis. In regards to professional development, the Princeton Neuroscience Institute hosted a series of seminars, colloquia, and other scientific presentations throughout each year that provided trainees with opportunities for interaction with other groups and scientists. Trainees were also highly encouraged to take advantage of resources outside the laboratory, including participating in University seminars on job search preparations and opportunities. The University has a renowned teaching center (The McGraw Center for Teaching and Learning) that ran multiple workshops on effective teaching techniques, preparing teaching statements, syllabus and course design, etc.

Results Dissemination: In addition to publishing papers, which are listed in one of the next sections, we gave talks and presented posters at scientific conferences and seminars to disseminate the work, listed below
Catecholamine GRC 2019. Sunday River, ME. Aug 2019.
CIFAR Azrieli Brain, Mind & Consciousness. London, ON. June 2019.
Cosyne Main Meeting 2019. Lisbon, Portugal. Feb 2019.
Kavli Workshop. Society for Neuroeconomics. Philadelphia, PA. Oct 2018.
Center for Neuroscience U Pittsburgh Retreat. Wheeling, WV. Sept 2018.
FENS 2018. Berlin, Germany. July 2018.
Inscopix webinar. Online seminar. June 2020.
Oxford Cortex Club. Online seminar. June 2020.
Champalimaud Center for the Unknown. Online seminar. Dec 2019.
BCH/HMS Neurobiology. Harvard U. Cambridge, MA. Dec 2019.
Virtual Dopamine (ViDA). Online conference. May 2020.
CRCNS Investigator Meeting. Austin, TX. Sept 2019.
Catecholamine GRC 2019. Sunday River, ME. Aug 2019.

Honors and Awards: 2017 Daniel X. Freedman Award
2017 NYSCF Robertson Investigator Award
2019 Grafstein Award in Neuroscience (Cornell Weill)
2021-2022 Brain Research Foundation Award.

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Technology Transfer: Nothing to Report

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Participant: Ilana Witten
Person Months Worked: 4.00 **Funding Support:**
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National Academy Member: N

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Person Months Worked: 4.00 **Funding Support:**
Project Contribution:
National Academy Member: N

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Person Months Worked: 3.00 **Funding Support:**
Project Contribution:
National Academy Member: N

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Project Contribution:
National Academy Member: N

Participant Type: Undergraduate Student
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Person Months Worked: 1.00 **Funding Support:**
Project Contribution:
National Academy Member: N

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Project Contribution:
National Academy Member: N

Participant Type: Non-Student Research Assistant
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Project Contribution:
National Academy Member: N

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Project Contribution:
National Academy Member: N

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Participant Type: Graduate Student (research assistant)
Participant: Iris Stone
Person Months Worked: 3.00 **Funding Support:**
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ARTICLES:

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Volume: Issue: First Page #:
Date Submitted: 8/31/20 12:00AM Date Published: 7/27/20 12:00AM
Publication Location:
Article Title: A comparison of dopaminergic and cholinergic populations reveals unique contributions of VTA dopamine neurons to short-term memory
Authors: Jung Yoon Choi, Heejae Jang, Sharon Ornelas, Weston Fleming, Daniel Furth, Jennifer Au, Akhil Bandi
Keywords: Dopamine, working memory, VTA
Abstract: We systematically compared the contribution of two dopaminergic and two cholinergic ascending populations to a spatial short-term memory task in rats. In ventral tegmental area dopamine (VTA-DA) and nucleus basalis cholinergic (NB-ChAT) populations, trial-by-trial fluctuations in activity during the delay period related to performance with an inverted-U, despite the fact that both populations had low activity during that time. Transient manipulations revealed that only VTA-DA neurons, and not the other three populations we examined, contributed causally and selectively to short-term memory. This contribution was most significant during the delay period, when both increases or decreases in VTA-DA activity impaired short-term memory. Our results reveal a surprising dissociation between when VTA-DA neurons are most active and when they have the biggest causal contribution to short-term memory, while also providing new types of support for classic ideas about an inverted-U relationship bet
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Article Title: Choice-selective sequences dominate in cortical relative to thalamic inputs to nucleus accumbens, providing a potential substrate for credit assignment
Authors: Nathan F. Parker, Avinash Baidya, Julia Cox, Laura Haetzel , Anna Zhukovskaya, Malavika Murugan, B
Keywords: Prelmibic, Nucleus accumbens, Imaging, Optogenetics
Abstract: How are actions linked with subsequent outcomes to guide choices? The nucleus accumbens, which is implicated in this process, receives glutamatergic inputs from the prelimbic cortex and midline regions of the thalamus. However, little is known about what is represented in these input pathways. By comparing these inputs during a reinforcement learning task in mice, we discovered that prelimbic cortical inputs preferentially represent actions and choices, whereas midline thalamic inputs preferentially represent cues. Choice-selective activity in the prelimbic cortical inputs is organized in sequences that persist beyond the outcome. Through computational modeling, we demonstrate that these sequences can support the neural implementation of temporal difference learning, a powerful algorithm to connect actions and outcomes across time. Finally, we test and confirm predictions of our circuit model by direct manipulation of nucleus accumbens input neurons. Thus, we integrate experiment and m
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Date Submitted: 8/31/20 12:00AM Date Published: 6/10/20 8:00AM
Publication Location:
Article Title: Distinct signals in medial and lateral VTA dopamine neurons modulate fear extinction at different times
Authors: Lili X Cai, Katherine Pizano, Gregory W Gundersen, Cameron L Hayes, Weston T Fleming, Sebastian H
Keywords: Dopamine, VTA, fear, extinction
Abstract: Dopamine (DA) neurons are known to encode reward prediction error (RPE), in addition to other signals, such as salience. While RPE is known to support learning, the role of salience in supporting learning remains less clear. To address this, we recorded and manipulated VTA DA neurons in mice during fear extinction, a behavior we observed to generate spatially segregated RPE and salience signals. We applied deep learning to classify mouse freezing behavior, eliminating the need for human scoring. Our fiber photometry recordings showed that DA neurons in medial and lateral VTA have distinct activity profiles during fear extinction: medial VTA activity more closely reflected RPE, while lateral VTA activity more closely reflected a salience-like signal. Optogenetic inhibition of DA neurons in either region slowed fear extinction, with the relevant time period for inhibition differing across regions. Our results indicate that salience-like signals can have similar downstream consequences to
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Article Title: Cholinergic interneurons mediate cocaine extinction through similar plasticity across medium spiny neuron subtypes
Authors: Weston Fleming, Junuk Lee, Brandy A. Briones, Scott Bolkan, Ilana B. Witten
Keywords: Nucleus accumbens, Imaging, Optogenetics
Abstract: The hypothesis that midbrain dopamine (DA) neurons broadcast an error signal for the prediction of reward (reward prediction error, RPE) is among the great successes of computational neuroscience1–3. However, recent results contradict a core aspect of this theory: that the neurons uniformly convey a scalar, global signal. Instead, when animals are placed in a high-dimensional environment, DA neurons in the ventral tegmental area (VTA) display substantial heterogeneity in the features to which they respond, while also having more consistent RPE-like responses at the time of reward. Here we introduce a new “Vector RPE” model that explains these findings, by positing that DA neurons report individual RPEs for a subset of a population vector code for an animal’s state (moment-to-moment situation). To investigate this claim, we train a deep reinforcement learning model on a navigation and decision-making task, and compare the Vector RPE derived from the network to population recordings from
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Article Title: Strong and opponent contributions of dorsomedial striatal pathways to behavior depends on cognitive demands and task strategy
Authors: Scott S. Bolkan, Iris R. Stone, Lucas Pinto, Zoe C. Ashwood, Jorge M. Iravedra Garcia, Alison L. Herma
Keywords: Nucleus accumbens, Optogenetic, Striatum, DMS
Abstract: The hypothesis that midbrain dopamine (DA) neurons broadcast an error signal for the prediction of reward (reward prediction error, RPE) is among the great successes of computational neuroscience1–3. However, recent results contradict a core aspect of this theory: that the neurons uniformly convey a scalar, global signal. Instead, when animals are placed in a high-dimensional environment, DA neurons in the ventral tegmental area (VTA) display substantial heterogeneity in the features to which they respond, while also having more consistent RPE-like responses at the time of reward. Here we introduce a new "Vector RPE" model that explains these findings, by positing that DA neurons report individual RPEs for a subset of a population vector code for an animal's state (moment-to-moment situation). To investigate this claim, we train a deep reinforcement learning model on a navigation and decision-making task, and compare the Vector RPE derived from the network to population recordings from
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Article Title: Inferring spikes from calcium imaging in dopamine neurons
Authors: Weston Fleming ,Sean Jewell ,Ben Engelhard,Daniela M. Witten ,Ilana B. Witten
Keywords: Dopamine, VTA, Imaging
Abstract: Calcium imaging has led to discoveries about neural correlates of behavior in subcortical neurons, including dopamine (DA) neurons. However, spike inference methods have not been tested in most populations of subcortical neurons. To address this gap, we simultaneously performed calcium imaging and electrophysiology in DA neurons in brain slices, and applied a recently developed spike inference algorithm to the GCaMP fluorescence. This revealed that individual spikes can be inferred accurately in this population. Next, we inferred spikes in vivo from calcium imaging from these neurons during Pavlovian conditioning, as well as during navigation in virtual reality. In both cases, we quantitatively recapitulated previous in vivo electrophysiological observations. Our work provides a validated approach to infer spikes from calcium imaging in DA neurons, and implies that aspects of both tonic and phasic spike patterns can be recovered.
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Publication Location:
Article Title: A neural substrate of sex-dependent modulation of motivation by value
Authors: Julia Cox, Adelaide R. Minerva, Weston T. Fleming, Christopher A. Zimmerman, Cameron Hayes, Samu
Keywords: to be determined
Abstract: While there is emerging evidence of sex differences in decision-making behavior, the neural substrates that underlie such differences remain largely unknown. Here we demonstrate that in mice performing a value-based decision-making task, while choices are similar between the sexes, motivation to engage in the task is modulated by action value more strongly in females than in males. Inhibition of activity in anterior cingulate cortex (ACC) neurons that project to the dorsomedial striatum (DMS) preferentially disrupts this relationship between value and motivation in females, without affecting choice in either sex. In line with these effects, in females compared to males, ACC-DMS neurons have stronger representations of negative outcomes and more neurons are active when the value of the chosen option is low. By contrast, the representation of each choice is similar between the sexes. Thus, we identify a neural substrate that contributes to sex-specific modulation of motivation by value.
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Article Title: Reproducibility of in-vivo electrophysiological measurements in mice
Authors: International Brain Laboratory*,Kush Banga,Julius Benson,Niccolò Bonacchi,Sebastian A Bruijns,Rob C
Keywords: To be Determined
Abstract: The hypothesis that midbrain dopamine (DA) neurons broadcast an error signal for the prediction of reward (reward prediction error, RPE) is among the great successes of computational neuroscience1–3. However, recent results contradict a core aspect of this theory: that the neurons uniformly convey a scalar, global signal. Instead, when animals are placed in a high-dimensional environment, DA neurons in the ventral tegmental area (VTA) display substantial heterogeneity in the features to which they respond, while also having more consistent RPE-like responses at the time of reward. Here we introduce a new “Vector RPE” model that explains these findings, by positing that DA neurons report individual RPEs for a subset of a population vector code for an animal’s state (moment-to-moment situation). To investigate this claim, we train a deep reinforcement learning model on a navigation and decision-making task, and compare the Vector RPE derived from the network to population recordings from
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Date Submitted: 3/27/23 12:00AM Date Published: 5/27/22 5:22PM
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Article Title: A vector reward prediction error model explains dopaminergic heterogeneity
Authors: Rachel S. Lee, Ben Engelhard, Ilana B. Witten, Nathaniel D. Daw
Keywords: To Be Determined
Abstract: The hypothesis that midbrain dopamine (DA) neurons broadcast an error signal for the prediction of reward (reward prediction error, RPE) is among the great successes of computational neuroscience1–3. However, recent results contradict a core aspect of this theory: that the neurons uniformly convey a scalar, global signal. Instead, when animals are placed in a high-dimensional environment, DA neurons in the ventral tegmental area (VTA) display substantial heterogeneity in the features to which they respond, while also having more consistent RPE-like responses at the time of reward. Here we introduce a new “Vector RPE” model that explains these findings, by positing that DA neurons report individual RPEs for a subset of a population vector code for an animal’s state (moment-to-moment situation). To investigate this claim, we train a deep reinforcement learning model on a navigation and decision-making task, and compare the Vector RPE derived from the network to population recordings from
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Article Title: Behavioural and dopaminergic signatures of resilience
Authors: Lindsay Willmore, Courtney Cameron, John Yang, Ilana B Witten, Annegret L Falkner
Keywords: Neural Circuits, Reward, Social behaviour, Stress and resilience
Abstract: Chronic stress can have lasting adverse consequences in some individuals, yet others are resilient to the same stressor1,2. Susceptible and resilient individuals exhibit differences in the intrinsic properties of mesolimbic dopamine (DA) neurons after the stressful experience is over3-8. However, the causal links between DA, behaviour during stress and individual differences in resilience are unknown. Here we recorded behaviour in mice simultaneously with DA neuron activity in projections to the nucleus accumbens (NAc) (which signals reward9-12) and the tail striatum (TS) (which signals threat13-16) during social defeat. Supervised and unsupervised behavioural quantification revealed that during stress, resilient and susceptible mice use different behavioural strategies and have distinct activity patterns in DA terminals in the NAc (but not the TS). Neurally, resilient mice have greater activity near the aggressor, including at the onset of fighting back. Conversely, susceptible mice h
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Article Title: Cholinergic interneurons mediate cocaine extinction through plasticity across medium spiny neuron subtypes
Authors: Weston Fleming, Junuk Lee, Brandy A. Briones, Scott S. Bolkan, Ilana B. Witten
Keywords: CP: Neuroscience; acetylcholine; cocaine; nucleus accumbens; plasticity.
Abstract: A classic view of the striatum holds that activity in direct and indirect pathways oppositely modulates motor output. Whether this involves direct control of movement, or reflects a cognitive process underlying movement, remains unresolved. Here we find that strong, opponent control of behavior by the two pathways of the dorsomedial striatum depends on the cognitive requirements of a task. Furthermore, a latent state model (a hidden Markov model with generalized linear model observations) reveals that—even within a single task—the contribution of the two pathways to behavior is state dependent. Specifically, the two pathways have large contributions in one of two states associated with a strategy of evidence accumulation, compared to a state associated with a strategy of repeating previous choices. Thus, both the demands imposed by a task, as well as the internal state of mice when performing a task, determine whether dorsomedial striatum pathways provide strong and opponent control of
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Article Title: Choice-selective sequences dominate in cortical relative to thalamic inputs to NAc to support reinforcement learning
Authors: Nathan F Parker, Avinash Baidya, Julia Cox, Laura M Haetzel, Anna Zhukovskaya, Malavika Murugan, I
Keywords: CP: Neuroscience; circuit modeling; imaging; learning; nucleus accumbens; optogenetics; prelimbic; reinforcement learning; thalamus.
Abstract: A classic view of the striatum holds that activity in direct and indirect pathways oppositely modulates motor output. Whether this involves direct control of movement, or reflects a cognitive process underlying movement, remains unresolved. Here we find that strong, opponent control of behavior by the two pathways of the dorsomedial striatum depends on the cognitive requirements of a task. Furthermore, a latent state model (a hidden Markov model with generalized linear model observations) reveals that—even within a single task—the contribution of the two pathways to behavior is state dependent. Specifically, the two pathways have large contributions in one of two states associated with a strategy of evidence accumulation, compared to a state associated with a strategy of repeating previous choices. Thus, both the demands imposed by a task, as well as the internal state of mice when performing a task, determine whether dorsomedial striatum pathways provide strong and opponent control of
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Article Title: Strong and opponent contributions of dorsomedial striatal pathways to behavior depends on cognitive demands and task strategy
Authors: Scott S. Bolkan, Iris R. Stone?, Lucas Pinto?, Zoe C. Ashwood, Jorge M. Iravedra Garcia, Alison L. Hern
Keywords: Neural circuits, Neural decoding
Abstract: A classic view of the striatum holds that activity in direct and indirect pathways oppositely modulates motor output. Whether this involves direct control of movement, or reflects a cognitive process underlying movement, remains unresolved. Here we find that strong, opponent control of behavior by the two pathways of the dorsomedial striatum depends on the cognitive requirements of a task. Furthermore, a latent state model (a hidden Markov model with generalized linear model observations) reveals that—even within a single task—the contribution of the two pathways to behavior is state dependent. Specifically, the two pathways have large contributions in one of two states associated with a strategy of evidence accumulation, compared to a state associated with a strategy of repeating previous choices. Thus, both the demands imposed by a task, as well as the internal state of mice when performing a task, determine whether dorsomedial striatum pathways provide strong and opponent control of
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Article Title: Perineuronal Nets in the Dorsomedial Striatum Contribute to Behavioral Dysfunction in Mouse Models of Excessive Repetitive Behavior
Authors: Brandy A. Briones,Miah N. Pitcher,Weston T. Fleming,Alexandra Libby,Emma J. Diethorn,Amanda E. H
Keywords: Dorsal striatum; Inhibitory signaling; Medium spiny neurons; Parvalbumin interneurons; Perineuronal nets; Repetitive behavior
Abstract: Excessive repetitive behavior is a debilitating symptom of several neuropsychiatric disorders. Parvalbumin-positive inhibitory interneurons in the dorsal striatum have been linked to repetitive behavior, and a sizable portion of these cells are surrounded by perineuronal nets (PNNs), specialized extracellular matrix structures. Although PNNs have been associated with plasticity and neuropsychiatric disease, no previous studies have investigated their involvement in excessive repetitive behavior. We used histochemistry and confocal imaging to investigate PNNs surrounding parvalbumin-positive cells in the dorsal striatum of 4 mouse models of excessive repetitive behavior (BTBR, Cntnap2, Shank3, prenatal valproate treatment). We then investigated one of these models, the BTBR mouse, in detail, with DiI labeling, in vivo and in vitro recordings, and behavioral analyses. We next degraded PNNs in the dorsomedial striatum (DMS) using the enzyme chondroitinase ABC and assessed dendritic spine
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Signature: Ilana Witten
Signature Date: 7/14/23 3:07PM

We have no pictures, charts, figures, etc. to report.