SWEBAGS Conference 2025

ABSTRACT BOOK

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Keynote Lecture 1: Ana Muñoz Manchado

Ana Muñoz Manchado is a neuroscientist who leads a research group working on genetics and neurodegenerative diseases, with a strong focus on Parkinson's disease and cell-type-specific mechanisms in the brain.

Keynote Lecture 2: Marcus Stephenson Jones

Marcus Stephenson-Jones serves as Group Leader and Principal Investigator at the Sainsbury Wellcome Centre, University College London (UCL).

Keynote Lecture 3: Marco Pignatelli

Marco Pignatelli is an Assistant Professor of Psychiatry and Principal Investigator at Washington University in St. Louis School of Medicine.

Session 1:

Spatiotemporal patterns of acetylcholine and their role in behavioral flexibility

Authors: Gideon A. Sarpong, Jeffery R. Wickens

Affiliations:

Okinawa Institute of Science and Technology Graduate University, Japan
Presenting Author: Gideon A. Sarpong

Abstract:

Introduction:

The ability to switch from established choices to new alternatives when conditions change – behavioral flexibility – is critical for survival. Recent findings indicate that cholinergic signaling

in the striatum contributes to such flexible behavior. However, until now, the timing and spatial patterns of striatal acetylcholine release following contingency changes have remained unknown, limiting conceptual understanding of its role in behavioral flexibility. In particular, high-resolution measurements of ACh spatiotemporal dynamics during behavioral tasks requiring flexible responses have been lacking. To address this gap, we monitored striatal ACh dynamics in awake, head-fixed mice performing a virtual-reality Y-maze task. Using a genetically encoded acetylcholine sensor and 2-photon imaging in the dorsal striatum, we visualized acetylcholine

release, with high temporal and spatial precision, during acquisition and reversal learning. Across the dorsal striatum, rewarded choices predominantly evoked phasic decreases in acetylcholine. In contrast, unexpected non-reward following reversal of task contingencies triggered widespread increases in acetylcholine, which were most pronounced on unrewarded trials that preceded a shift to the opposite arm. Conversely, chemogenetic inhibition of striatal cholinergic interneurons decreased this adaptive response. Spatial tiling analysis of 2-photon images revealed heterogeneous and temporally distinct ACh signals across the dorsal striatum, identifying functionally diverse microdomains with outcome-specific response profiles. These findings suggest that widespread and focal acetylcholine release during unexpected outcomes promotes adaptive response shifts and provide a mechanistic framework for understanding disorders such as addiction and obsessive-compulsive rituals.

Dopamine and serotonin co-transmission filters striatonigral synaptic activity via 5-HT1B receptor activation.

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Abstract:

The substantia nigra pars reticulata (SNr), a key basal ganglia output nucleus, is modulated by dopamine (DA) believed to be released locally from midbrain dopamine neurons. Although DA has been proposed to regulate GABA release from medium spiny neuron (MSN) terminals via presynaptic D1 receptors (D1Rs), the precise mechanisms remain unclear. Using presynaptic optical recordings of synaptic vesicle fusion, calcium influx in D1-MSN synapses together with postsynaptic patch-clamp recordings from SNr neurons, we found that DA inhibits D1-MSN GABA release in a frequency-dependent manner. Surprisingly, this effect was independent of DA receptors and instead required 5-HT1B receptor activation. Using two-photon serotonin biosensor imaging in slices and fiber photometry in vivo, we demonstrate that DA enhances extracellular serotonin in the SNr. Our results suggest that serotonin mediates DAergic control of basal ganglia output and contributes to the therapeutic actions of dopaminergic medications for Parkinson's disease and psychostimulant-related disorders.

Serotonin and serotonergic inputs modulate cholinergic interneurons in the striatum on different timescales

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Abstract:

The striatum, the major input hub of the basal ganglia, integrates converging glutamatergic and GABAergic inputs from cortical and subcortical regions, along with modulatory dopaminergic signals from the midbrain that are critical for motor initiation, learning, and reward. In addition, approximately one-third of serotonergic neurons in the dorsal raphe nucleus project to the striatum, yet the influence of serotonin on striatal circuits remains less well understood. Here, we examined how serotonin and serotonergic inputs affect striatal cholinergic interneurons (ChINs). ChINs regulate action selection and reinforcement signalling by exerting inhibitory control over medium spiny neurons and are interconnected through polysynaptic pathways, enabling widespread coordination across the striatum. Using paired whole-cell recordings combined with pharmacological manipulations, we found that serotonin modulates ChIN intrinsic excitability and suppresses polysynaptic inhibitory interactions between them via 5-HT2 receptors. Furthermore, optogenetic activation of striatal serotonergic fibres revealed a fast, monosynaptic glutamatergic input onto ChINs. Together, these findings identify previously unrecognized mechanisms by which serotonin and serotonergic projections modulate ChIN networks, highlighting the intricate interplay between acetylcholine, dopamine, and serotonin in shaping striatal function. Given the broad influence of ChIN activity, serotonergic modulation likely has widespread consequences for striatal circuits and may provide insight into the mechanisms underlying non-motor symptoms of Parkinson's disease.

Session 2:

Logic of spatial and functional organization of connectivity patterns on striatal parvalbumin and somatostatin interneurons

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Abstract:

The striatum, the main input structure of the basal ganglia, plays a key role in integrating cortical and subcortical information. While striatal projection neurons (SPNs) have been extensively studied, interneurons, particularly those expressing parvalbumin (PV) and somatostatin (SOM), remain less explored. These two types of interneurons exhibit distinct morphological, electrophysiological, and functional differences that influence their connectivity and their role in sensorimotor integration. PV interneurons are strongly connected to SPNs locally, with dense arborization and fast activity, whereas SOM interneurons form more diffuse and longer-range connections. These differences also vary across striatal regions (dorsolateral - DLS, and dorsomedial - DMS), suggesting complementary roles in the modulation of corticostriatal networks. Our work aims to characterize the connectivity patterns of PV and SOM striatal interneurons using anatomical and functional approaches. From an anatomical perspective, tracing with modified rabies virus combined with a semi-automated analysis of presynaptic cells allows us to map and compare the global connectivity of both striatal interneurons and compare these patterns between the DMS and the DLS. In parallel, we are testing the functional organization of connectivity from targeted cortical areas to each striatal interneurons, using patch-clamp electrophysiological recordings coupled with laser-scanning photostimulation (glutamate uncaging). We are mapping the cortical distribution and weight of the presynaptic cells from the primary and secondary somatosensory cortex (S1 and S2) to PV and SOM interneurons in the DLS. These experiments reveal much denser and more convergent innervation of PV interneurons compared to SOM interneurons, which may reveal functional specificities between both microcircuits, providing a deeper understanding of their contributions to sensorimotor integration.

A hypothalamus-brainstem circuit governs the prioritization of safety over essential needs

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[#]These authors contributed equally

Abstract:

Animals continuously adapt their behavior to balance survival and fulfilling essential needs. This balancing act involves prioritization of safety over the pursuit of other needs. However, the specific deep brain circuits that regulate safety-seeking behaviors in conjunction with motor circuits remain poorly understood. Here we identify a class of glutamatergic neurons in the lateral hypothalamic area (LHA) that target the midbrain locomotor-promoting pedunculopontine nucleus (PPN). Upon activation, this LHA-PPN pathway orchestrates context-dependent locomotion, prioritizing safety-directed movement over other essential needs such as foraging or mating. Remarkably, the neuronal activity of these circuits correlates directly with safety-seeking behavior. These circuits may respond to both intrinsic and external cues, playing a pivotal role in ensuring survival. Our findings uncover a circuit motif within the lateral hypothalamus that when recruited, prioritizes critical needs through the recruitment of an appropriate motor action.

Striatal Metabolic Alterations Link Maternal Alcohol Exposure to Offspring Motor Deficits

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Keywords: Maternal alcohol exposure, Sex-specific effects, Dorsomedial striatum, Neuronal excitability, Motor learning

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Abstract:

The dorsal striatum is a highly energy-demanding region and particularly vulnerable to developmental insults associated with lifelong motor deficits. Alcohol and its metabolites reduce striatal glucose utilization in patients and impair pyruvate dehydrogenase (PDHA1) activity in vitro. We therefore asked whether maternal alcohol use disrupts striatal bioenergetics in the offspring, contributing to long-term fetal alcohol spectrum disorder (FASD) motor symptoms. Striatal transcriptomic analysis revealed reduced long-term PDHA1 expression in males and compensatory upregulation in female progeny. Consistent with these molecular changes, DeepLabCut-based analysis revealed sex-specific behavioral impairments, with males showing pronounced motor deficits at adolescence. To test causality, we silenced PDHA1 in the dorsomedial striatum (DMS) using viral-mediated knockdown during postnatal development. PDHA1 downregulation induced widespread transcriptional remodeling, reduced neuronal excitability ex vivo, and decreased striatal engagement during locomotion and motor learning, as revealed by in vivo fiber photometry and c Fos mapping. Importantly, DMS-specific PDHA1 silencing reproduced the sex-specific behavioral phenotypes of alcohol-exposed offspring. Together, these findings uncover a metabolic mechanism by which maternal alcohol drinking disrupts striatal function and drives FASD-related motor impairments, highlighting PDHA1-dependent bioenergetics as a key vulnerability node in striatal development.

Session 3:

Comparing cell type-specific transcriptomics patterns in the parkinsonian and dyskinetic striatum

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Keywords: Striatum, Single-nuclei RNA sequencing, Parkinson's disease, Spiny projection neurons, Cell-cell communication

Abstract:

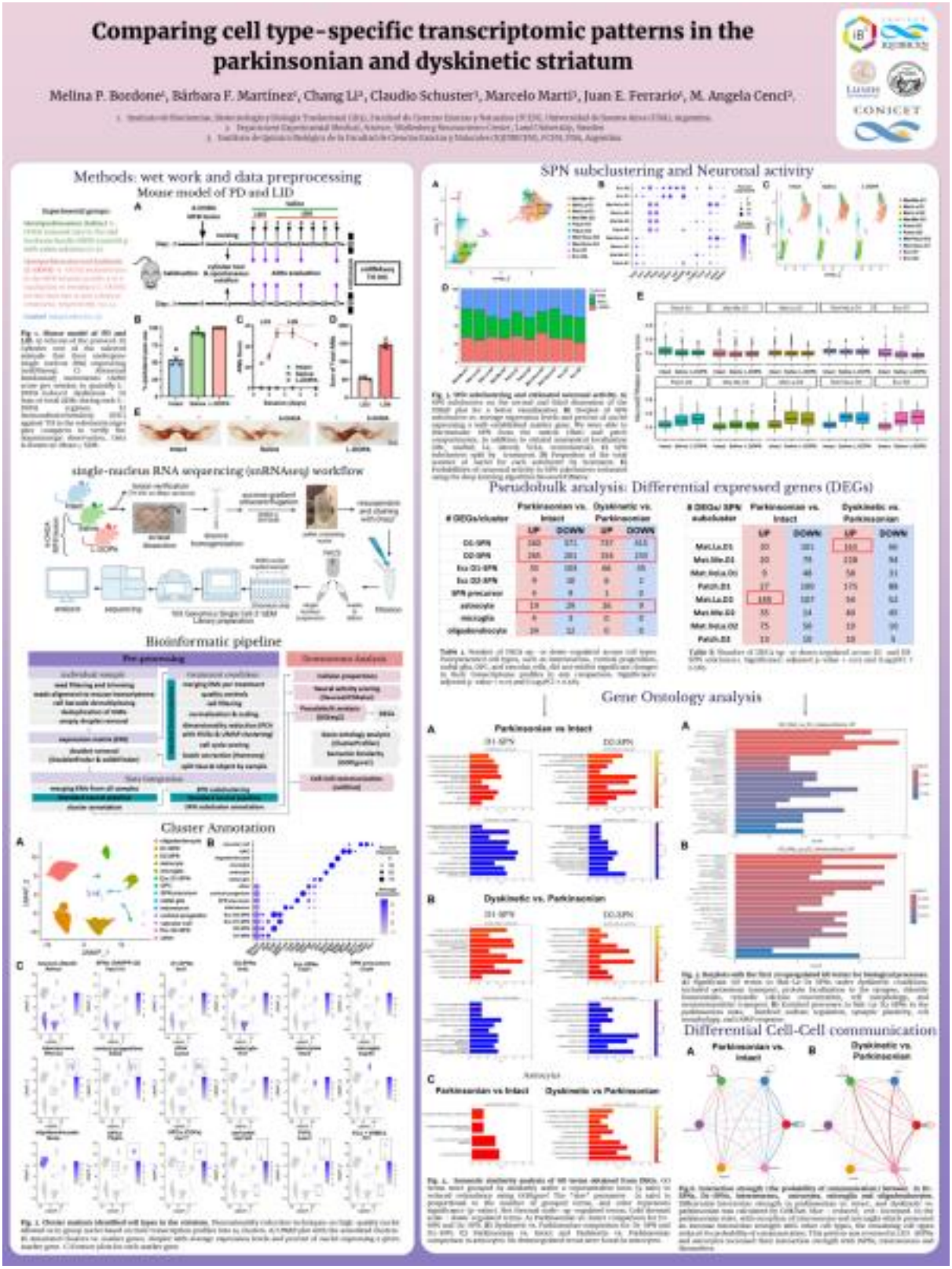
Striatal neurons exhibit pronounced physiological and structural changes in Parkinson's disease (PD) and L-DOPA-induced dyskinesia (LID). Here, we have used single-nuclei RNA sequencing (RNAseq) to identify cell type-specific transcriptional signatures in mouse models of parkinsonism and LID. Mice sustained unilateral 6-hydroxydopamine (6-OHDA) lesions of the nigrostriatal pathway. Animals with substantial motor deficits were randomly allocated to receive daily i.p. injections of L-DOPA or saline for 8 days. L-DOPA treatment (3 mg/kg/day for two days followed by 6 mg/kg/day for another six days) induced dyskinesia of moderate

high severity in all animals. A control group of intact mice was handled and processed in parallel. Striata were dissected for single-nuclei isolation 20 hours after the last injection (corresponding to the L-DOPA-off state). cDNA libraries were prepared and sequenced from FACS-sorted nuclei from 4 samples/group using a droplet-based RNA sequencing technology (10X Genomics). Data were pre-processed to generate high-quality expression matrices for each sample, which were then integrated, clustered and annotated based on well-established cell type-specific mRNA markers. We were able to positively identify 13 out of 14 cell categories: D1-spiny projection neurons (D1-SPNs), D2-SPNs, eccentric D1-SPNs, eccentric D2-SPNs, interneurons, microglia, astrocytes, oligodendrocytes, oligodendrocyte precursor cells, radial glia, vascular cells, SPN

precursors, and cortical progenitors. To analyze spatiomolecular signatures within the dorsal striatum, D1-SPNs and D2-SPNs were subclustered by compartment (matrix or patch) and spatial localization (medial, lateral or ventrolateral). For each SPN subtype, neural activity was predicted using NeuroeSTIMmator. Pseudobulk analysis was performed using DEseq2 to identify differentially expressed genes (DEGs) in the pairwise comparisons: 'Saline vs Intact' (lesion effect) and 'L-DOPA vs Saline' (L-DOPA effect). Functional enrichment analyses were performed with

clusterProfiler::enrichGO, and redundancy was reduced using the semantic similarity-based tool GO-Figure!. Differential cell-cell communication was analyzed using CellChat. Among all cell categories, D1-SPNs and D2-SPNs exhibited the largest number of changes when comparing both the lesion (> 400 DEGs) and L-DOPA effect (> 1000 DEGs in D1-SPN, > 300 DEGs in D2-SPN). Functionally important changes were detected also in astrocytes due to L-DOPA treatment. The lesion caused a decreased in cell-cell communication among SPNs and astrocytes, whereas interneurons and microglia showed an increased communication. L DOPA reversed these patterns, enhancing interactions of D1-SPNs with astrocytes, D2-SPNs, interneurons, and of D1-SPNs between themselves. Following SPN subclustering, most D2- SPNs (except those in the matrix and medial striatum) exhibit increased neural activity in both saline and L-DOPA groups.

This is the first study examining cell type-specific transcriptomic changes in dyskinetic animals in the "L-DOPA off" state, thus capturing persistent transcriptional changes rather than transient effects that are driven by high levels of dopamine receptor stimulation. We reveal robust transcriptional adaptations in D2-SPN that had gone undetected in previous studies. The observed shifts in cell-cell communication reveal an altered functional dynamic of striatal and glial networks in both parkinsonian-untreated and L-DOPA-treated-dyskinetic animals. Further investigations into these cellular interactions will provide insights of therapeutic translational importance.


Comparing cell type-specific transcriptomic patterns in the parkinsonian and dyskinetic striatum
Melina P. Bordone, Bárbara F. Martínez, Chang Li, Claudio Schuster, Marcelo Martí, Juan E. Ferrario, M. Angela Cenci
CONICET
Methods: wet work and data preprocessing
Mouse model of PD and LID
single-nucleus RNA sequencing (snRNAseq) workflow
Bioinformatic pipeline
Cluster Annotation
SPN subclustering and Neuronal activity
Pseudobulk analysis: Differential expressed genes (DEGs)
Gene Ontology analysis
Differential Cell-Cell communication

Exercise improves motor coordination and increases dopaminergic neuron excitability selectively in female mice

Authors: Valerie J. Lewitus[1], Chelsea B. Scott[1], Olivia M. Kruszewski[1], Joel A. Walker Jr.[1], Lindsey A. Russ[1], Zachary Colon[1], Giorgi Shautidze[1], Celine Ertekin[1], Asia Fernandez[1], Megan R. Croom[1], Rebekah C. Evans[1]

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Keywords: Substantia nigra pars compacta, Pedunculopontine nucleus, Aerobic exercise, Dopaminergic neurons, Sex differences

Abstract:

Aerobic exercise is one of the most accessible, low-cost interventions to boost motor function across the lifespan and to combat the effects of movement disorders such as Parkinson's disease (PD). Animal models have revealed that exercise promotes changes in multiple motor-related areas of the brain, including regions impacted by PD such as the substantia nigra *pars compacta* (SNc)
and the pedunculopontine nucleus (PPN). However, it is not known how exercise alters the intrinsic activity and properties of these key neuronal populations.

To address this question, we used the voluntary wheel running model of exercise in male and female mice in conjunction with a variety of *ex vivo* and *in vivo* techniques. Using the accelerating rotarod task we found that one week of voluntary exercise improves motor coordination in female but not male mice. Using *ex vivo* whole-cell patch clamp recording, we found that exercise increases the excitability of SNc dopaminergic neurons and increases excitatory synaptic activity onto PPN cholinergic neurons in females only. Finally, using *in vivo* calcium imaging with fiber photometry, we found real-time changes in PPN neural activity during exercise that differed among PPN subpopulations.

These results give us fundamental insight into the neuronal changes that exercise induces in key neuronal populations in motor circuitry. Further, in accordance with our behavioral results on motor coordination, the changes in neuronal properties that we observed only occurred in females. This knowledge opens new avenues to understanding the influence of biological sex and sex hormones on the motor effects of exercise. In particular, these results may have relevance for sex differences in PD as well as for the increase in motor impairments observed after menopause in women.

Session 4:

CLAWing toward threshold: how the dynamic interplay of cortico-basal ganglia-thalamic pathways shapes the decision-making process

Authors:

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Keywords: Cortico-basal ganglia-thalamic circuit, Decision-making, Dopamine-dependent plasticity, Drift-diffusion model, Learning dynamics

Abstract:

Significant effort has been spent looking at specific roles that specific neural populations in the cortico-basal ganglia pathways play in guiding decisions and learning from them. In this study, we take on the much less investigated questions of how activity evolves within the whole circuit during the course of individual decisions, the nature of variability within this process, and how this dynamic evolution changes with learning. To address these questions, we developed and used a novel computational framework that we call CLAW (Circuit Logic Assessed via Walks) to trace the instantaneous flow of neural activity as it progresses through stochastic, spiking cortico-basal ganglia-thalamic (CBGT) networks engaged in a virtual decision-making task. Our results uncover distinct deliberation and commitment phases characterized by which CBGT components are dominant and suggest how differences in subpopulation dominance underlie distinct decision strategies. Moreover, we show how dopamine-dependent synaptic plasticity based on decision outcomes can alter the nature of CBGT activity during decisions and shift the likelihood of decision strategies from deliberation to reward-directed commitment. Finally, we map these results to the drift-diffusion model (DDM) framework, recasting them in terms of gradual changes in DDM parameters that provide an algorithmic interpretation of how learning leads to improved decision speed and accuracy while preserving the capacity for caution.

Opponent control of reinforcement by striatal dopamine and serotonin

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Keywords: Nucleus accumbens, Dopamine, Serotonin, Associative learning, Reinforcement

Abstract:

The neuromodulators dopamine (DA) and serotonin (5-hydroxytryptamine; 5HT) powerfully regulate associative learning. Similarities in the activity and connectivity of these neuromodulatory systems have inspired competing models of how DA and 5HT interact to drive the formation of new associations. However, these hypotheses have not been tested directly because it has not been possible to interrogate and manipulate multiple neuromodulatory systems in a single subject. Here we establish a mouse model that enables simultaneous genetic access to the brain's DA and 5HT neurons. Anterograde tracing revealed the nucleus accumbens (NAc) to be a putative hotspot for the integration of convergent DA and 5HT signals. Simultaneous recording of DA and 5HT axon activity, together with genetically encoded DA and 5HT sensor recordings, revealed that rewards increase DA signalling and decrease 5HT signalling in the NAc. Optogenetically dampening DA or 5HT reward responses individually produced modest behavioural deficits in an appetitive conditioning task, while blunting both signals together profoundly disrupted learning and reinforcement. Optogenetically reproducing DA and 5HT reward responses together was sufficient to drive the acquisition of new associations and supported reinforcement more potently than either manipulation did alone. Together, these results demonstrate that striatal DA and 5HT signals shape learning by exerting opponent control of reinforcement.

Poster Session:

Dysregulated thalamostriatal connectivity and striatal long-term potentiation in the eIF4E-TG ASD mouse model

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Abstract:

Autism spectrum disorder (ASD) is associated with striatal dysfunction and behavioural inflexibility. We previously showed that overexpression of the SFARI ASD risk gene *eIF4E* in transgenic (eIF4E-TG) mice produces ASD-like inflexible behaviours and impairs dorsal striatal dopamine release. Here, we examined whether *eIF4E* overexpression alters striatal synaptic transmission and plasticity. Using microscopy, whole-cell electrophysiology, and optogenetics, we assessed dendritic morphology and excitatory synaptic properties of spiny projection neurons (SPNs). eIF4E-TG mice exhibited higher dendritic spine density, elevated AMPA and NMDA mEPSC frequency, and reduced AMPA mEPSC amplitude. We also observed selective dysregulation of thalamostriatal transmission and increased induction and magnitude of long-term potentiation (LTP) in SPNs, which was normalised by NMDA-receptor inhibition. These findings reveal that *eIF4E*-driven protein synthesis dysregulation alters thalamostriatal signalling and striatal LTP, providing new insights into the synaptic mechanisms underlying striatal dysfunction in ASD, and highlighting the critical interplay between dopaminergic and thalamic inputs in mediating ASD-like behaviours.

Investigation of the function of neurogliaform and tyrosine hydroxylase positive interneurons in a large-scale biophysically detailed model of the striatal microcircuit

Authors: Kadri Pajo [1] , Robert Lindroos [2] , Matthijs Dorst [1,3] , Alexander Kozlov [2] , J.J. Johannes Hjort [2] , GiladSilberberg [1] , Jeanette Hellgren Kotaleski [1,2]

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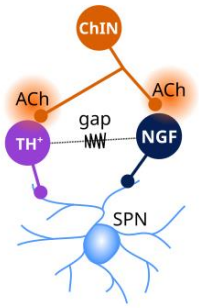
Abstract:

Recent experimental advances have made it possible to generate animal models that selectively target cell types using specific molecular markers. These developments have revealed a wide range of previously unidentified neuronal subtypes and states, underscoring the extraordinary complexity of neural tissue. Although the functions of many of these new subtypes remain poorly understood, emerging studies are beginning to clarify their roles. For instance, recent findings show that co-activation of GABAergic interneurons and glutamatergic synapses on striatal projection neurons can enhance glutamatergic input by amplifying dendritic spikes. In this study, we construct biophysically detailed models of neurogliaform interneurons and tyrosine hydroxylase–positive interneurons, embedding them within a large-scale model of the striatal microcircuit. Using the tool Snudda, we apply touch detection and pruning to generate biologically realistic connectivity patterns. This approach allows us to investigate the mechanisms and conditions through which co-activation of these GABAergic interneurons facilitates signal integration at glutamatergic synapses. In particular, we focus on the activation of GABAergic interneurons by striatal cholinergic interneurons.



Presymptomatic Parkinson's disease: locus coeruleus dysfunction and early neuronal alterations

Authors: Jone Razquin[1,2,3], Laura De Las Heras-García[1,3,4], Gloria Gonzalez-Aseguinolaza[5], Edgar Soria-Gómez[2,5,6],Jérôme Baufreton [4], Harkaitz Bengoetxea[2,3], Naiara Ortuzar[2,3], Jorge E. Ortega[1,3,8], Cristina Miguélez[1,3]

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Abstract:

Parkinson's disease (PD) is a neurodegenerative disorder characterized by the accumulation of Lewy bodies in multiple brain regions, dysfunction of several neurotransmitter systems, and the presence of both motor and non-motor symptoms. Non-motor symptoms often precede motor manifestations and strongly affect patients' quality of life. The locus coeruleus (LC), the main noradrenergic nucleus in the brain, is among the earliest sites of pathology in PD. It has been linked to non-motor symptoms and projects widely, influencing dopaminergic homeostasis as well as basal ganglia and hippocampal circuits.

The aim of this study was to investigate noradrenergic dysfunction in PD. To this end, we induced selective overexpression of human α-synuclein in LC neurons and assessed molecular, neurochemical, electrophysiological, and behavioural outcomes in male and female mice. Our findings revealed that α-synuclein expression in the LC induced sex

and time-dependent alterations at multiple levels, including neurochemical and electrophysiological changes, signs of axonal dysfunction, and selective non-motor phenotypes such as anxiety-like behaviour and cognitive deficits. Importantly, these effects occurred without dopaminergic cell loss or overt motor impairments, pointing to an early and specific role of the LC in shaping prodromal PD symptomatology.

These results provide new insight into noradrenergic dysregulation at the earliest stages of PD and highlight the LC as a potential target for therapeutic strategies aimed at delaying disease progression.

Two Sides of Learning: Enhanced and Impaired Basal Ganglia Functions in Tourette Syndrome

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Abstract:

Tourette syndrome (TS) is a neurodevelopmental disorder characterized by motor and vocal tics that arise from alterations within cortico-basal ganglia-thalamo-cortical circuits. These same basal ganglia circuits also support procedural memory—the gradual, implicit learning system that underlies skills and habits. This overlap makes procedural memory an ideal framework for understanding both adaptive and maladaptive forms of basal ganglia-based learning in TS. Here we present two experiments that examined procedural memory using probabilistic sequence learning tasks in children with TS and age-matched controls (Experiment 1: 21 children with TS and 21 age-matched controls, Age: MTS = 138.1 and MTD = 137.43 months; Experiment 2: 21 children with TS and 21 age-matched controls, Age: MTS = 148.43 and MTD = 149.38 months). Across both studies, children with TS showed enhanced probabilistic sequence learning, suggesting procedural hyperfunctioning. We contrast these findings with studies employing probabilistic classification tasks that have reported impaired learning in TS. Based on prior neuroimaging research on procedural learning, this pattern of enhancement versus impairment across task types reflects differential alterations of basal ganglia circuits in TS: specifically, an overactive sensorimotor circuit and an underactive associative circuit. Together, these findings illustrate how alterations in basal ganglia circuits can differentially affect components of procedural memory, shaping both motor and cognitive functioning in TS.

The superior colliculus strongly excites cholinergic and glutamatergic neurons in the pedunculopontine nucleus

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Abstract:

Sensory-motor integration in the brainstem is crucial for daily functioning and ultimately survival. Two structures involved in this process are the pedunculopontine nucleus (PPN) and the superior colliculus (SC), both of which are highly interconnected with basal ganglia nuclei and can be classified as part of an extended basal ganglia network. The PPN is a heterogeneous structure that is critical for sleep, arousal, and motor function and is implicated in both Parkinson's disease (PD) and epilepsy. Stimulation of the PPN is therapeutic in animal models of both disorders with a topography that is specific to cell type and location. The SC is important for integrating multisensory inputs to trigger motor responses, but the effect of SC projections to subregions and different cell types of the PPN is unknown. To address this gap in knowledge, we injected channelrhodopsin (ChR2) into the SC of ChAT-Cre/Ai9, Vglut2-Cre/Ai9, and Vgat-Cre/Ai9 (tdTomato) mice to determine functional connectivity between SC synaptic inputs to PPN subpopulations using optogenetics and whole-cell patch clamp recordings in ex vivo brain slices. We find that almost all cholinergic and glutamatergic PPN neurons recorded receive excitatory synaptic input from the SC compared to around 75% of GABAergic PPN neurons. Surprisingly, we also find inhibitory inputs from the SC to the PPN in around 40% of cholinergic and glutamatergic cells compared to around 25% of GABAergic cells. Since these cell types also show diverse motor effects across the rostral-caudal axis of the PPN, we separated this data into rostral and caudal subgroups. We find that the SC sends stronger excitatory projections to caudal PPN cholinergic neurons compared to rostral PPN cholinergic neurons, as measured by the amplitude of excitatory postsynaptic currents (EPSCs). Additionally, optogenetic stimulation of SC axon terminals more strongly excites firing in caudal cholinergic PPN neurons compared to rostral cholinergic neurons. Comparing across cell types, we find that the SC sends stronger excitatory input to caudal cholinergic neurons compared to caudal glutamatergic and GABAergic neurons. Given the important role the PPN plays in regulating arousal states and motor function, uncovering how the PPN responds to different inputs from the SC is important in understanding the modulation of movement

in response to sensory stimuli. These findings may provide insight into basic mechanisms underlying sensorimotor integration and help identify new, more precise targets within the extended basal ganglia circuit that are implicated in neurological disorders with basal ganglia dysfunction.

Signal integration and competition in a biophysical model of the substantia nigra pars reticulata

Authors: William Scott Thompson[1], J. J. Johannes Hjorth[2], Alexander Kozlov[1,2], Wilhelm Thunberg[2], Gilad Silberberg[1], Jeanette Hellgren Kotaleski[1,2] Sten Grillner[1]

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Abstract:

The substantia nigra pars reticulata (SNr) is a primary output for basal ganglia signalling. It plays an important role in the control of movement, integrating inputs from upstream structures in the basal ganglia, before sending organised projections to a range of targets in the midbrain, brainstem and thalamus. Here we present a detailed in silico model of the mouse SNr, including its major afferent inputs. The electrophysiological and morphological properties of SNr neurons are characterised in acute brain slices via whole cell patch-clamp recordings and morphological reconstruction. Using reconstructed morphologies, multicompartmental models of single neurons are instantiated within the NEURON simulation environment and populated with relevant modelled ion channels. Model parameters are optimised via an evolutionary algorithm, such that simulated neurons faithfully reproduce recorded electrophysiological behaviour. Using the simulation infrastructure software Snudda, single neuron models are incorporated into a circuit-level model, where the sparse connectivity within the SNr is recreated. We simulate the mouse SNr at scale, featuring realistic volumes and neuronal density. The unique synaptic properties and activity patterns of different afferent sources are captured in silico. Born out of ex vivo data, our model reporduces in vivo firing patterns. Our simulations suggest that paradoxical activity increases in response to experimental inhibition can be explained by lateral connectivity. In addition, our model predicts the functional implications of characteristic short-term synaptic plasticity in the indirect pathway of the basal ganglia. The model can be extended to include additional inputs and be connected with existing models of upstream basal ganglia nuclei, to further explore circuit dynamics.

Sex differences in the temporal progression of behavioural and neuropathological alterations in an A53T α-synuclein mouse model of Parkinson's disease

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Keywords: Parkinson's disease, sex differences, A53T alpha-synuclein, motor impairment, neurodegeneration, axonal pathology, neuroinflammation

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Abstract:

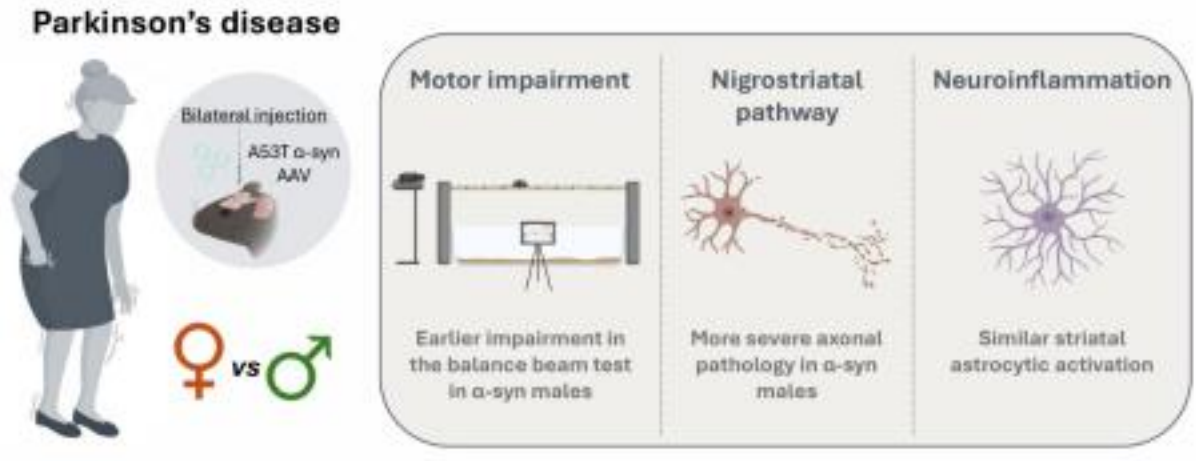
Parkinson's disease (PD) is characterised by progressive degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNc) and accumulation of misfolded α synuclein (α-syn). Neuroinflammation also contributes to disease onset and progression. Notably, PD exhibits sexual dimorphism in clinical presentation and treatment response. This study investigated sex differences in the temporal progression of behavioural and neuropathological alterations in a mouse model overexpressing A53T α-syn.

Male and female C57BL/6J mice received bilateral intranigral injections of adeno-associated viral vectors encoding mutant A53T α-syn or empty vectors. Motor function was assessed at 60- and 120-days post-surgery using open field, wire hang, pole, and balance beam tests. Brains were collected for immunohistochemical analyses of α-syn pathology, nigrostriatal integrity (tyrosine hydroxylase, TH), axonal degeneration, and neuroinflammation.

α-Syn overexpression induced early, subtle motor deficits primarily in males, despite preserved SNc neuronal density. Automated analysis of balance beam walking behaviour (DeepLabCut, SimBA) revealed increased immobility and reduced walking time in α-syn males. At 120 days only, striatal TH levels were significantly reduced, driven by reductions in α-syn males. Although undetected at 60 days, an axonal degeneration index (combining striatal TH optical density and axonal swellings) revealed

more advanced degeneration in α-syn males, suggesting faster disease progression. At both time points, α-syn mice showed increased striatal astrogliosis without sex differences, indicating α-syn-associated neuroinflammation.

These findings support a PD model of early axonal degeneration and reactive astrogliosis preceding neuronal loss. The sex differences in behavioural and neuropathological patterns underscore the importance of incorporating sex as a biological variable in preclinical models and developing tailored therapeutic strategies.



The novel D1/D2 agonist IRL1117 reverses motor deficits in 6-OHDA lesioned rats without the induction of dyskinesias or their related alterations in striatal gene expression

Authors: Gaia Tolone[1,2], Sabina Brandin[1], Li Rousk[1], Kristina Möller[1], Jenny Gunnergren[1], Malin Edling[1], Karin Önnheim[1], Daniel Andersson[1]

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Presenting Author: Gaia Tolone

Abstract:

Parkinson's Disease (PD) is a disabling neurodegenerative disease characterized by a progressive degradation of dopamine (DA) generating cells in the substantia nigra and subsequent loss of DA release in the striatum, leading to the manifestation of the core motor symptoms of the disease (akinesia, bradykinesia and tremor). Symptomatic treatment is centered around dopamine-based therapies, with L-DOPA having been the dominating treatment since the 1960s. However, after long-term use of L-DOPA, PD patients develop

fluctuations of motor functions and excessive involuntary movements, referred to as dyskinesias. This is believed to be largely correlated to the suboptimal pharmacokinetics of L DOPA, resulting in a high number of daily doses and, as a consequence, large fluctuations in striatal extracellular dopamine levels, with ensuing pulsatile stimulation of postsynaptic DA receptors and aberrant regulation of gene expression in striatal target neurons.

IRL1117 is a novel DA D1/D2 agonist currently being developed by IRLAB with the objective of providing a once-daily, high efficacy treatment option for the core motor symptoms of PD without the fluctuations and dyskinesia that are associated with chronic L-DOPA treatment. In previous studies IRL1117 treatment has been shown to induce contralateral rotations in 6- hydroxydopamine (6-OHDA)-lesioned rats for more than 24h after a single oral dose, thus demonstrating its potential as a once-daily treatment option.

In the current study, the effects of chronic IRL1117 treatment in 6-OHDA rats were investigated and compared to those of L-DOPA. 6-OHDA rats were given once-daily doses of vehicle, L-DOPA or IRL1117 for 20 consecutive days during which period they

were repeatedly assessed in the cylinder test for motor asymmetry as well as in the Abnormal Involuntary Movements (AIMs) test, alongside sham-lesioned control rats being treated with vehicle. Following treatment completion and a one-day washout rats were sacrificed, striatal tissue was dissected out, and striatal gene expression was analyzed by qPCR.

Results show that chronic IRL1117 treatment significantly improves cylinder test performance whilst not resulting in the development of dyskinesias, whereas L-DOPA-treatment results in the progressive development of dyskinesias and a variable cylinder test performance, as expected. In the ensuing qPCR analysis, IRL1117 treatment did not result in significantly different mRNA levels of neither prodynorphin (*pdyn*) nor proenkephalin (*penk*) as compared with vehicle-treated rats. L-DOPA on the other hand increased the expression of both *pdyn* (significantly) and *penk* (non-significantly) relative to controls, and when comparing L-DOPA treated rats to IRL1117-treated, the amount of both *pdyn* and *penk* mRNA was significantly lower in IRL1117-treated rats.

In conclusion, this study shows that chronic treatment with IRL1117 results in a statistically significant beneficial effect on motor symptoms in 6-OHDA rats, without inducing AIMs or the associated alterations in striatal gene expression. Consequently, the findings indicate that IRL1117 may be a promising candidate for the treatment of PD motor symptoms.

Distinct contributions of dopamine and noradrenaline dysfunction to sleep disturbances in a Parkinson's disease model

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Abstract:

A broad spectrum of sleep disturbances is associated with Parkinson's disease (PD), significantly impairing patients' quality of life and often persisting under pharmacological treatments. In this study, we examined sleep architecture in a PD mouse model generated by unilateral administration of the catecholamine neurotoxin 6-hydroxydopamine (6-OHDA) into the medial forebrain bundle.

Electroencephalogram and electromyogram electrodes were implanted over the left parietal cortex and neck muscles of both sham-lesioned and 6-OHDA-lesioned mice. Continuous 24-hour recordings were performed, and wakefulness, REM sleep, and non-REM (NREM) sleep states were classified and analysed using a MATLAB-based algorithm.

Mice with 6-OHDA lesions exhibited reduced wakefulness and increased NREM sleep during the active phase of the sleep-wake cycle, consistent with excessive daytime sleepiness (EDS). Additionally, these animals showed a higher number of NREM episodes with shortened duration during the inactive phase, indicative of sleep fragmentation. Notably, pre-administration

of desipramine, which preserves noradrenergic function, prevented sleep fragmentation but did not mitigate EDS. Treatment with reboxetine, a selective norepinephrine reuptake inhibitor, reduced the number of NREM episodes but failed to prolong their duration during the inactive phase.

These findings demonstrate that the PD mouse model employed in this study recapitulates sleep abnormalities observed in PD patients, including EDS and sleep fragmentation. Importantly, our results indicate that while nigrostriatal dopamine loss is sufficient to induce EDS, sleep fragmentation is primarily driven by noradrenergic dysfunction. Finally, the findings suggest that while targeting noradrenergic

transmission can modulate sleep architecture in this PD model, further refinement of therapeutic approaches is needed.

Identification of DARPP-32 as a novel sleep regulator in physiological conditions and experimental Parkinsonism.

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Abstract:

Excessive daytime sleepiness (EDS) and sleep fragmentation are common in Parkinson's disease (PD) and significantly reduce patients' quality of life. Effective treatments against these comorbidities remain elusive, likely due to an incomplete understanding of their etiology. Emerging evidence suggests that dopamine- and adenosine-mediated signaling in the striatum are involved in sleep regulation. A key intracellular effector of these neuromodulators is DARPP-32 (dopamine- and cAMP-regulated phosphoprotein of 32 kDa), but its role in sleep remains unknown.

Here, we investigated the contribution of DARPP-32 in D1 and A2A receptor (D1R and A2AR)-expressing neurons. Using targeted genetic depletion combined with EEG/EMG recording, we show that DARPP-32 plays a key role in the control of NREM sleep quantity and quality in distinct neuronal subpopulations. We found that disruption of DARPP-32 signaling in A2AR neurons reduces NREM sleep during the active phase of the sleep-wake cycle, whereas the same intervention in D1R neurons enhances NREM stability in the inactive phase. Notably, we also found that, in a 6-hydroxydopamine mouse model of PD, deletion of DARPP-32 in A2A neurons counteracts somnolence during the active period, thereby protecting against EDS.

In line with these results, we found that the selective A2AR antagonist istradefylline, a drug recently found to improve sleep disturbances in PD patients, reduces EDS in the mouse PD model. Our study provides a mechanistic explanation for this effect, opening the way for the development of interventions acting specifically on DARPP-32-mediated signaling in A2AR neurons to restore normal sleep patterns and enhance patient well-being.

Cell-type-specific neuronal activation the sensorimotor cortex in L-DOPA-induced dyskinesia

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Abstract:

Background and Objective:

Parkinson's disease (PD) is a progressive neurodegenerative disease characterized by the degeneration of nigrostriatal dopamine (DA) neurons. The most effective pharmacotherapy for PD is L-DOPA. However, the response to L-DOPA changes with disease progression, and most patients eventually develop abnormal involuntary movements called L-DOPA-induced dyskinesia (LID). While many studies on LID have focused on the striatum, little is known about the specific involvement of corticostriatal projections, which originate from both intratelencephalic (IT) and pyramidal tract (PT) neurons. We therefore set out to study changes in the activity of IT and PT neurons in motor and somatosensory cortices in a mouse model of LID. To this end, we used transgenic Arc-dVenus mice, expressing the short-lived fluorescent protein dVenus under the control of Arc, a neuronal activity dependent gene. Mice were injected unilaterally with 6-hydroxydopamine (6-OHDA) in the medial forebrain to induce a hemiparkinsonian motor phenotype. Two different cholera toxin B (CTB) axonal tracers were injected into the contralateral striatum or the ipsilateral pons to label cortical IT and PT neurons, respectively. Animals were treated with either L-DOPA or the selective D2 receptor agonist sumanirole for 6 consecutive days (as in Andreoli et al 2021 PMID: 34153463), and dyskinesia ratings were carried out every other day. Mice were perfusion-fixated 2 hours after the last L-DOPA injection. Confocal images were acquired from motor cortices (M1, M2) and different subdivisions of the primary somatosensory cortex (S1). RESULTS: A comparison between saline-treated 6-OHDA lesioned mice and sham-lesioned controls revealed that the dopaminergic denervation had caused a marked decline in the total number of Arc-dVenus positive neurons in both M1 and M2, but not in S1. The activity reduction affected both IT and PT neurons. Treatment with L-DOPA restored the total Arc-dVenus cell number to levels comparable to sham-lesioned controls, whereas Sumanirole treatment did not differ significantly

from saline. Analysis of Arc-dVenus expression in IT and PT neurons revealed treatment specific effects, as L-DOPA significantly activated both IT and PT populations (thought with a stronger effect on the IT cells), whereas the D2 agonist only raised PT activity. Indeed, layer 4 neurons in S1 were strongly Arc-dVenus-positive in the L-DOPA group ($p < 0.01$ vs all other groups). Taken together, our results reveal a different involvement of IT- and PT-neurons upon treatment with L-DOPA or D2 receptor agonists, and warrant a further investigation of S1 as a potential neuromodulation target to treat dyskinesia in PD.

Conditional iSPN D2 knockout reveals a primary D2-dependent pathway to dyskinesia

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Presenting author: Teodor Nyman, teodor.nyman@med.lu.se

Abstract:

Background: L-DOPA-induced dyskinesia is attributed to opposite activity changes mediated by D1 and D2 dopamine receptors in the two striatal output pathways. Whereas the causal role of direct-pathway D1 receptors is well established, the specific involvement of indirect-pathway D2 receptors in dopaminergic dyskinesias has remained elusive. **Objectives**: We used conditional knockout approaches in mice to determine whether indirect pathway D2 receptors causally contribute to dyskinetic and dystonic responses to dopaminergic agents. Methods: Studies were conducted in mice with unilateral 6-hydroxydopamine lesions of the nigrostriatal pathway receiving subchronic treatments with L-DOPA or D2/D1-selective agonists. Conditional knockout of indirect-pathway D2 receptors was produced either through the entire striatum (double-transgenic Adora2a-Cre/Drd2loxP/loxP mice) or selectively in the dopamine-denervated dorsal striatum (proenkephalin promoter-driven Cre vector delivery to Drd2loxP/loxP mice). **Results**: The severity of L-DOPA-induced abnormal involuntary movements and dystonia was halved in both knockout models compared to control mice, whereas normal motor behaviors were not reduced. All dyskinetic and dystonic features induced by the D2-selective receptor agonist sumanirole were completely abolished, whereas those induced by the D1-class agonist SKF38393 were unaffected. Using phosphorylated ribosomal protein S6 as an activity marker, we found that L-DOPA caused excessive neuronal activation in both striatum and external globus pallidus and sumanirole only in the latter. Whereas striatal phospho-S6 activity was mildly or not affected, both knockout animals showed normalized levels of activity in the globus pallidus. **Conclusions**: We provide experimental evidence that indirect-pathway D2 receptors are the primary mediators of D2-dependent dystonic responses and significantly contribute to dyskinesia during dopamine replacement therapy.

Homeostatic gene-therapy for levodopa-induced dyskinesia

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Presenting Author: Venu Narayanan

Abstract:

Levodopa alleviates several symptoms in Parkinson's disease (PD) and remains standard medication. However, over time, treatment efficacy often becomes limited by motor fluctuations and troublesome side effects, particularly levodopa-induced dyskinesia (LID). The pathophysiology of LID is not fully understood but a gradual sensitization to dopamine in striatal neurons, which in turn leads to electrical hyperexcitability, is thought to be an important underlying cause of LID. In particular, a subpopulation of spiny projection neurons (SPNs) expressing dopamine D1 receptors (D1Rs) with abnormally high levodopa-evoked firing rates has been identified, and experimental manipulations of these overactive SPNs robustly modifies LID, suggesting a direct causal role in the generation of dyskinesia.

Here we have evaluated a new homeostatic gene therapy approach aimed at specifically targeting this sub-group of overactive SPNs. The method was originally developed to treat epilepsy and is based on activity-dependent expression of an engineered Kv1.1 potassium channel (EKC) under an immediate early gene promoter, which makes it possible to selectively silence highly active neurons.

So far, behavioral evaluations of the anti-dyskinetic effects of EKC gene therapy have been evaluated in seven hemilesioned dyskinetic mice after EKC transfections in striatum and globus pallidus in comparison to a dyskinetic control group (n=6) over 5 months. Tests of LID were conducted via manual scoring of abnormal involuntary movements and automated quantification of locomotion/turning. Additionally, tests for potential side effects of EKC treatment and verification of maintained antiparkinsonian effects of levodopa were performed by characterization of spontaneous motor behavior in the open field.

All EKC treated mice displayed a significant reduction of LID (after 6mg/kg L-DOPA) compared to the control group. Tests have so far been performed up to 20 weeks after EKC expression demonstrating a pronounced and maintained antidyskinetic effect. Prokinetic effects of L-DOPA were seen in both groups, but EKC treated mice tended to display circular locomotion instead of the tight rotations shown by the control group resulting from axial LID.

Further studies in larger test groups will be needed to confirm these findings, and to clarify if gene expression is limited to D1R SPNs or if, for example, interneuron populations are also affected. Moreover, neurophysiological recordings will be needed to clarify how manipulations of these overactive neurons affect network dynamics in corticostriatal circuits, known to be associated with LID in both rodents and humans.

Unraveling the genetic architecture of autism: a multi-omic approach towards mirror neurons

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Abstract:

Background: Autism spectrum disorder (ASD) affects approximately 1% of the global pediatric population, characterized by persistent deficits in social communication, restricted behavioral patterns, and impaired socio-communicative signal processing. The mirror neuron system, recognized as fundamental for imitation processes, theory of mind, and social cognition, exhibits systematic dysfunctions in individuals with ASD. However, the genetic architecture underlying these alterations remains insufficiently characterized, significantly limiting the development of targeted interventions and personalized medicine approaches.

Objectives: To develop an integrative genomic framework that systematically identifies autism risk genes operating within mirror neuron circuits and characterizes their tissue-specific regulatory mechanisms.

Materials and Methods: An integrative multi-omic analysis was implemented combining

GWAS data from Grove et al. 2019 (9,112,386 SNPs from 18,381 ASD cases) with expression quantitative trait loci (eQTL) analyses from GTEx v8 consortium. Five candidate genes from the mirror neuron system (CACNA1C, CHD8, CNTNAP2, FOXP2, THEMIS) were analyzed across relevant brain tissues: cerebellar hemisphere, cerebral cortex, hippocampus, and nucleus accumbens.

eQTL analyses employed linear regression models with ±1Mb cis windows, followed by multiple statistical corrections using FDR and Bonferroni ($\alpha = 0.05$). GWAS-eQTL colocalization utilized ±250kb genomic windows with composite scoring incorporating statistical significance, genomic proximity, and directional allelic consistency. Classification criteria established thresholds: Strong (score >8.0), Moderate (5.0-8.0), Weak (2.0-5.0), and Minimal (<2.0). Methodological robustness was ensured through post-hoc statistical power analysis

(exceeding 99% detection capability), cross-validation via random data partitioning, sensitivity analysis varying critical parameters, and strict statistical corrections

resulting in 100% association survival for both multiple correction methodologies. Results: The analysis identified 215 statistically robust eQTL associations distributed across the five candidate genes. CACNA1C emerged as the principal gene with 136 eQTL variants, 39,292 colocalization analyses, and maximum score of 20.52, establishing itself as the highest priority therapeutic target. CHD8 demonstrated 20 eQTLs with colocalization score of 12.10, followed by CNTNAP2 (score 10.48, 20 eQTLs), FOXP2 (score 10.24, 37 eQTLs), and THEMIS (score 6.87, 2 eQTLs).

Tissue-specific effects concentrated in cerebellar hemisphere for CACNA1C and CHD8, cerebral cortex and hippocampus for CNTNAP2, and limbic structures for FOXP2. Network analysis revealed CACNA1C as a central hub in neuronal calcium signaling circuits. Evidence distribution (3,502 Strong signals, 6,614 Moderate, 12,398 Weak) demonstrated consistency with expected population genomic patterns.

Conclusion: This study establishes the first systematic framework connecting autism genetics with mirror neuron dysfunction through tissue-specific regulatory mechanisms. Identification of CACNA1C as the principal gene, with convergent multi-tissue evidence, provides solid molecular foundation for understanding social cognitive deficits in ASD. The identified target hierarchy (CACNA1C > CHD8 > CNTNAP2 > FOXP2) offers multiple directed therapeutic pathways, while the statistically rigorous methodology ensures validity and reproducibility for future translational research.

KEYWORDS: autism, mirror neurons, GWAS, eQTL, CACNA1C

Acute systemic inflammation alters the transcriptional and proteomic profile of the dorsal striatum in aged mice.

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Abstract:

Aging and inflammation are two of the most significant risk factors for neurodegenerative disease. Here, we investigated the impact of acute systemic inflammation on the dorsal striatum in male and female wild- type mice at 4- and 20-months of age using a lipopolysaccharide (LPS) model. LPS, a potent activator of toll-like receptors, was administered via two consecutive intraperitoneal injections (24 h apart), after which RNA and protein were extracted from a specific brain region, the dorsal striatum, for transcriptomic and proteomic profiling. RNA sequencing revealed robust upregulation of pathways associated with cytokine signaling and innate immune activation in response to LPS, with age exacerbating these effects. Proteomic analysis corroborated these inflammatory changes and further identified disruptions in synaptic signaling, including reduced expression of the dopamine transporter, a critical mediator of dopaminergic transmission in the dorsal striatum. Additional proteomic alterations implicated dysregulated lipid metabolism, impaired proteostasis, and mitochondrial dysfunction, all of which are hallmarks of neurodegenerative pathology. Together, these findings demonstrate that acute systemic inflammation reshapes the striatal molecular landscape, potentially impairing neuronal circuitry. This work suggests that during aging, systemic inflammatory challenges may contribute to striatal vulnerability and may represent a mechanistic link to sporadic neurodegenerative disease.

Depressive disorder in Parkinson's disease: involvement of monoaminergic systems

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Abstract:

Parkinson's Disease (PD) is a common neurodegenerative disorder characterized by depletion of dopamine in the nigrostriatal system, leading to the onset of motor and non-motor symptoms, including psychiatric disorders. Depression represents a major clinical challenge as it is generally unresponsive to dopamine replacement therapy and its neurological substrates are still elusive. PD typically leads to alterations in the noradrenergic and serotonergic systems, which are implicated in non-motor affective comorbidities.

To investigate the involvement of monoaminergic transmission in PD-associated depression, we examined noradrenergic activity and noradrenaline release in a 6-hydroxydopamine (6-OHDA) mouse model of PD exhibiting depression-like behavior. Using fiber photometry with calcium and noradrenaline sensors, we monitored neuronal activity and neurotransmitter release, respectively, during the tail suspension test, a despair-based paradigm for depression.

We found that struggling, reflecting the reaction of the animals to the inescapable stress of being suspended, increased the activity of noradrenergic neurons in the locus coeruleus (LC, the main noradrenergic nucleus in the brain) and enhanced noradrenaline release in the dorsal raphe nucleus (DRN, the primary source of central serotonin). Notably, when compared to control mice, 6-OHDA-lesioned mice displayed reduced activity of noradrenergic neurons in the LC and impaired noradrenaline release in the DRN during the tail suspension test.

These results indicate that the LC-to-DRN noradrenergic pathway plays a key role in the response to inescapable stress, but is impaired in the PD model, thereby representing a potential neuronal target to counteract depressive symptoms in PD.