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01- Anatomical and Functional Connectivity

00004
Implication of GABAergic interneurons in nicotinic mediated striatal circuits

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Abstract

Striatal cholinergic interneurons (CINs) were believed to function largely in a neuromodulatory fashion, acting on muscarinic receptors which have been demonstrated to regulate nearly all aspects of striatal functioning. Recently, it was demonstrated that they also exert fast nicotinic synaptic effects in striatal networks in particular by targeting several populations of GABAergic interneurons. This notion was first suggested by evidence demonstrating nicotinic activation of recurrent inhibition in CINs. Subsequently, we demonstrated that optogenetic activation of CINs elicits very large, disynaptic compound GABAergic IPSP/Cs in projection neurons that are secondary to nicotinic receptor activation. Using double transgenic preparations we showed that theses GABAergic responses elicited in projection neurons is mediated by nicotinic activation of striatal GABAergic interneurons. Since then, our recent data demonstrate that at least five different populations of striatal GABAergic interneurons receive nicotinic (as well as muscarinic) input from CINs. These include the tyrosine hydroxylase expressing interneurons (THINs), the NPY-expressing neurogliaform (NGF) and low-threshold spike interneurons (LTS), the fast adapting interneuron (FAI) and the spontaneously active bursty interneuron (SABI). Furthermore, in addition to innervating the striatal projection neurons, LTS, NGF and THINs also provide reciprocal connections to the CINs, which potentially put them in a central position in these circuits. Using double optogenetic strategy in multiple double transgenic mice we investigated the contribution of those GABAergic interneurons in the two nicotinic mediated striatal circuits described above i.e. the recurrent inhibitory circuit among striatal CINs and the nicotinic-mediated disynaptic inhibition of SPNs. Our results point to a specific and selective participation of several striatal GABAergic interneurons in these two nicotinic mediated striatal circuits.

00008
Disynaptic inhibition promotes synchrony between striatal cholinergic interneurons and is regulated by dopamine via D2 receptors

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Abstract

Striatal activity is dynamically modulated by acetylcholine and dopamine, both of which are essential for proper basal ganglia function. Synchronized pauses in the activity of striatal cholinergic interneurons (ChINs) are correlated with elevated activity of midbrain dopaminergic neurons, whereas synchronous firing of ChINs induces local release of dopamine. The mechanisms underlying ChIN synchronization and its interplay with dopamine release are not fully understood. Here we show using multineuron patch-clamp recordings, voltammetry, optogenetics, chemogenetics, and *in vivo* recordings, that robust disynaptic inhibition between ChINs acts as an efficient synchronization mechanism. Inhibitory disynaptic responses were elicited by single action potentials in ChINs and showed a high degree of recurrence within the ChIN network. Disynaptic inhibition was attenuated by dopaminergic midbrain afferents acting on D_2 receptors. Our results present a mechanism supporting synchronization of activity and pauses across the ChIN population and a novel form of interaction between striatal acetylcholine and dopamine.

00015
Molecular, electrophysiological, morphological heterogeneity and circuit function of striatal Pthlh cells with differential Pvalb expression revealed by PatchSeq

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Abstract

Pvalb expressing fast-spiking basket cells across the telencephalon share the same developmental origin and have been considered a homogenous group with a canonical circuit function including feed-forward inhibition. Their unique high-frequency firing and dense local axonal arborization allows them to exhibit a strong somatic inhibition onto their target cells, making them crucial for fine-tuning the circuit output.

Using Striatal single-cell RNA-sequencing in combination with patch clamp recordings (PatchSeq) we reveal that *Pvalb* expression does not define a discrete subtype but is detected within a larger group of cells defined by the expression of *Pthlh*. Within this population *Pvalb* expression is detected in a gradient wise manner, with a spatial ventro-lateral bias across the striatum. Using PatchSeq we showed that Pthlh-cells exhibited another continuum of electrophysiological properties, correlated to *Pvalb* expression. Gradient like differences in both molecular profiles and intrinsic properties, raises the question if striatal *Pvalb*-high and low cells within the Pthlh-population could be states rather than discrete subtypes.

However, we also show that *Pvalb*-high show a more extensive axonal and dendritic arborization and receive greater glutamatergic input from motor cortex. As morphology and long-range connectivity are stable traits that will change minimally between dynamic states of a neuronal population, we can conclude that *Pvalb*-high and low cells are not highly dynamic states but rather more stable entities within the Pthlh-population that likely have distinct functions within the circuit.

00022
Ca2+ current decrease induced by muscarinic M4 receptors in DA-depleted direct striatal projection neurons is reversed by PP-1 inhibition

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Abstract

Direct striatal projection neurons (dSPN) express dopamine (DA) and muscarinic receptors. DA/PKA signaling phosphorylates Thr-34 of DARPP-32 inhibiting PP-1 (Greengard et al., 1998). DA-depletion plus a glutamate excess during parkinsonism (PS) (Galarraga et al., 1987) depresses DA/PKA-signaling through coactivation of p35/CDK5 via mGluR1 that phosphorylates Thr-75 of DARPP-32 inhibiting PKA, and activating NMDA receptors restrains DARPP-32 via PP-2B (Gould & Manji, 2005) disinhibiting PP-1. Activation of M_4–type receptors (M_4R) also need the coactivation of p35/CDK5 to phosphorylate Thr-75 of DARPP-32 (Liu et al., 2017) and CDK5 is known to regulate Ca^{2+}-current (ICa^{2+}) (Yarotsky et al., 2007).

Previously, we showed that activation of M_4R in control dSPNs increase ICa^{2+} through Ca_V1-channels leading to firing increase (Hernández Flores et al., 2015), making M_4R a target to recover firing in dSPNs during PS. However, activation of M_4R in DA-depleted animals produce a decrease in ICa^{2+} through Ca_V1-channels and a decrease in firing, suggesting that DA-depletion alters M_4R- ICa^{2+} interaction. Therefore the questions are: if M_4R actions also interact with the CDK5/DARPP-32 pathway, and whether DA-depletion enhances PP-1 activity via depression of the DA/PKA signaling, explaining decreases in ICa^{2+} after M_4R activation.

Here we demonstrate that the CDK5 inhibitor roscovitine (10-100 µM) antagonizes both positive and negative actions of M_4R in control and DA-depleted dSPNs,

respectively, suggesting that M_4R involve the CDK5/DARPP-32 cascade. In addition, we show that activation of M_4R can enhance ICa^{2+} through Ca_V1-channels in DA-depleted dSPNs when PP-1 is inhibited (1 µM okadaic acid).

Our results give evidence that in DA-depleted dSPNs M_4R activation decreases ICa^{2+} via Ca_V1-channels decreasing firing, that inhibition of CDK5 antagonizes the actions of M_4R in both control and DA-depleted dSPNs, and that inhibition of PP-1 restores M_4R control actions on ICa^{2+}.

00023
Firing properties of intralaminar thalamic neurons

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Abstract

The intralaminar thalamic nuclei: central lateral (CL) and parafascicular (Pf), constitute important afferents to the striatum. By identifying them via their primary striatal projections, the firing frequency properties of Pf and CL neurons were explored. We used mice of 4-6 weeks of age (VGlut2-Cre). Horizontal brain slices of 300 µm thickness including both intralaminar thalamic nuclei were kept in “in vitro” conditions. Patch clamp whole cell technique recordings in both intralaminar thalamic nuclei neurons were done. The recorded neurons were identified by intracellular labeling with biocytin and by double labeling with retrograde or anterograde neuronal VGlut2 tracings. Neurons were easily differentiated into two morphological subtypes: “diffuse” and “bushy” as previously described (Beatty, et al. 2009). As most thalamic neurons, cells from both nuclei showed the ability to produce firing in two modes: single action potential continuous discharge and high frequency bursting coming from transient low threshold spikes at more hyperpolarized membrane potentials (Jahnsen and Llinas, 1984). Continuous firing frequency was observed at i = 0 and was higher in Pf neurons which also had a faster firing frequency adaptation with two clearly different components (fast and slow). The afterhyperpolarizing potential (AHP) of Pf neurons also had fast and slow components, while that of CL neurons only had a slow component. The participation of Ca_V3 calcium channels, blocked by 10 µM NNC 55-0396 was observed underlying the transient low threshold spike in both CL and Pf neurons. During hyperpolarization, synaptic responses evoked by field stimulation with a bipolar concentric electrode of 50 µm in diameter in the intralaminar thalamic nuclei could generate high frequency bursting on top of low-threshold-spikes. CONACyT: 251144 and DGAPA-UNAM: IN201517, IN201417

CONACyT: 251144 and DGAPA-UNAM: IN201517, IN201417.

00026
Selection and oscillations in a spiking model of the Basal Ganglia

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Abstract

From a mean-field model of the Basal Ganglia based on extensive anatomical and electrophysiological primate data (Liénard & Girard, 2014), we have derived a leaky Integrate-and-Fire based spiking model. We show that this model keeps the biological plausibility properties of the mean-field model, and while it was not parameterized to fulfill any specific function, it is able to select among competing channel and to oscillate in the beta band in simulated Parkinson disease.

Liénard, J. & Girard, B. (2014). A Biologically Constrained Model of the Whole Basal Ganglia Addressing the Paradoxes of Connections and Selection. *Journal of Computational Neuroscience*, 36(3):445--468.

00040
Modulatory effect of serotonin on the basal ganglia circuits in rats: role of 5HT2A receptors

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Abstract

Serotonin (5-HT) has been linked to multiple disorders such as Parkinson's disease, obsessive-compulsive disorder or schizophrenia. It is also present in the sensorimotor (SM) and medial prefrontal (mPF) basal ganglia (BG) circuits, which are important for motor functions, or decision-making, goal-directed behaviour, motivation and cognition, respectively. The aim of this study was to assess the modulatory role exerted by 5-HT on SM and mPF BG circuits and the specific contribution of 5-HT2A receptors to this modulation. To that purpose, extracellular recordings of substantia nigra *pars reticulata* (SNr) neurons along with simultaneous electrical stimulation of motor or mPF cortex were performed in control and pCPA (5-HT synthesis inhibitor)-treated anaesthetized rats.

In the SM circuits, 5-HT depletion increased the amount of SNr neurons exhibiting bursting firing pattern, without modifying the spontaneous firing parameters in the mPF circuits. Moreover, transmission through the direct pathway was enlarged in both circuits after 5-HT synthesis inhibition. Systemic administration of the selective 5-HT2A receptor agonist, TCB2 (100 µg/kg), increased the firing rate of mPF-SNr neurons in control rats and reduced the number of neurons displaying burst activity in both control and pCPA groups. In addition, in the mPF circuits, TCB2 enhanced the duration of the inhibition but not in pCPA group.

These results suggest that 5-HT elicits a tonic control on SNr firing pattern and on the cortico-nigral information transfer through the direct pathway in both SM and mPF BG circuits. Additionally, 5-HT2A receptors facilitate the cortico-striato-nigral transmission in the mPF circuits by a 5-HT-dependent mechanism. Overall, these data may contribute to the development of 5-HT2A targeting drugs for treatment of BG related disorders.

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Keywords: Basal ganglia circuits, 5-HT2A receptor, pCPA

00043
A detailed in silico reconstruction of the striatal microcircuitry

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Abstract

Morphologial and electrophysiological data from mouse striatum are used to create a detailed network model with realistic neurons. This model includes the direct and indirect pathway striatal projection neurons (dSPN, iSPN) which represent 96% of all neurons, and in addition fast spiking interneurons (FSN), cholinergic interneurons (ChIN) and low-threshold spiking interneurons (LTS). The mouse striatum has in total around 1.76 million neurons.

The neuronal models are based on detailed reconstructed morphologies and recorded electrophysiology, with the distribution of ion channels guided by mRNA expression for each subtype. The channel conductances were optimised using BluePyOpt to match electrophysiological recordings. A family of parameters were generated for each neuron morphology, and the population statistics was compared to experimental data.

To create the network connectivity the range of somatodendritic-axonal morphologies were placed in a striatal volume. Smaller volumes used a cube, the full striatum used a striatal mesh downloaded from Allen Institute allowing us to place the full set of 1.76 million neurons. Putative synapses were placed where axons and dendrites were in close apposition, using a voxel based touch detection algorithm. For ChIN and LTS neurons a probabilistic method was used to place the synapses, since only limited axon reconstructions were available. The set of synapses were then pruned to match pairwise connection probabilities seen in experiments.

A reduced volume of the whole striatum was simulated using Parallel NEURON. Our modelling pipeline and the data used will be available on the HBP Brain Simulation Platform, and on github.

This study is funded by: Horizon2020 grant agreement 720270 and 785907 (Human Brain Project, SGA1 and SGA2); The Swedish Research Council; Swedish e-Science Research Center. The network model is simulated on a Cray supercomputer provided by the Swedish National Infrastructure for Computing (SNIC) at PDC KTH.

00045
Loss of cannabinoid modulation on cortical information transmission through the sensorimotor and medial prefrontal basal ganglia circuits after dopaminergic denervation

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Abstract

Basal ganglia (BG) circuits, among which are the sensorimotor (SM) and medial prefrontal (mPF) circuits are heavily influenced by dopamine, as well as by cannabinoids. Here, we aimed to study the changes in cortical information transmission through the SM and mPF BG circuits and in its modulation by cannabinoids after dopaminergic denervation. To do so, simultaneous electrical stimulation of motor or medial prefrontal cortex and single-unit extracellular recordings of substantia nigra pars reticulata (SNr) neurons, were carried out in anaesthetized SHAM and 6-Hydroxydopamine (6OHDA)-lesioned rats.

After 6OHDA lesion, both SM and mPF-SNr neurons showed lower firing rates and more irregular firing pattern. In addition, information transmission through the direct and indirect pathways of the SM circuits, and the indirect pathway of the mPF circuits was impaired. SM-SNr neurons showed less triphasic and inhibiton+late excitation responses, whilst more neurons responded only with an early excitation; mPF-SNr neurons showed more monophasic inhibitory responses. As previously shown, administration of WIN 55,212-2 (125 µg/Kg, i.v.) (WIN) modulated trans-striatal pathways in SM circuits of SHAM rats, but had no effect after dopaminergic denervation. Regarding the mPF circuits, WIN administration impaired information transmission through the three pathways in SHAM rats, whilst only the hyperdirect pathway was affected in 6OHDA-lesioned animals. The CB1 receptor antagonist AM251 (2 mg/Kg, i.v.), blocked the effects exerted by WIN.

These results show a functional interaction between dopamine and cannabinoids and contribute to understand how they modulate BG circuitry, and the relationships between these two neurotransmission systems.

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The authors declare no conflict of interest.

Keywords: basal ganglia circuits, dopamine, cannabinoid, electrophysiology

00061
Functional dissociation of basal ganglia circuits during the temporal rescaling of action

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Abstract

Many species, including humans, show a remarkable capacity to adjust the timing of their actions to match the temporal requirements of the environment. Prior evidence implicates the cortico-basal ganglia circuitry in generating temporally efficient sequences of action. However, the necessary mechanisms that coordinate the temporal rescaling of previously consolidated actions throughout learning remains unknown. Here we designed a novel instrumental conditioning paradigm by which mice made self-paced adjustments to the timing of their action sequences. In early training, time between individual actions in a sequence became compressed, but as instrumental requirements progressed, animals adapted the timing of their actions by prolonging the average duration of each sequence. Using high-throughput reconstructions of signalling activity in large ensembles of neurons, we found that animals adjusting their action duration showed profoundly reduced signalling activity in the posterior dorsal striatum (pDStr), which inversely correlated with increased molecular activity in the subthalamic nucleus (STN). Conversely, animals that were not scaling the timing of their actions, expressed high signalling in the pDStr and low signalling in the STN. The depression of signalling in the pDStr during temporal rescaling was observed in both direct and indirect projection systems, suggesting that an external circuitry may be mediating a pDStr-STN functional dissociation. We explored this possibility by revisiting the anatomical connections of the hyperdirect pathway using transynaptic labelling and circuit-specific tracing. Our study identified a shared cortico-basal ganglia projection linking the motor cortex with both the pDStr and the STN. Overall, our results suggest that downstream basal ganglia circuits undergo dissociations of molecular activity during the temporal adjustment of action, and that the hyperdirect pathway could be key to promoting such adaptations during learning.

00065
Pause in cholinergic firings modulate the direction of corticostriatal synaptic plasticity in dorsomedial striatum.

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Abstract

The cholinergic interneurons (CINs) of the striatum are crucial for behavioral flexibility. CINs of the dorsomedial striatum (DMS) play a role in strategy switching. However, how CINs modulate the neural circuitry underlying strategy switching is unclear. The glutamatergic afferents from the cerebral cortex to the striatum display activity-dependent plasticity in the corticostriatal synapses, and may be involved in certain types of learning. One hypothesis is that strategy switching may be realized by a modulatory effect of CINs on corticostriatal plasticity. Here, we investigated the effect of CINs on activity-dependent plasticity in the corticostriatal synapses. To control tonically firing of CINs, AAV encoding halorhodopsin (NpHR) was injected into DMS of ChAT-cre mice. AAV injected mice expressed NpHR in CINs and we can optogenetically inactivate CINs firing. We recorded EPSPs induced by electrical stimulation of corpus callosum using ex vivo slice whole-cell recording from spiny projection neurons (SPNs), which are the output neurons of the striatum. Activity dependent synaptic plasticity was induced by high-frequency stimulation under the Mg-free conditions. This conditioning stimuli combined with optogenetically inactivation of CINs during HFS induced the long-term potentiation in some SPNs. However, other group of SPNs showed long-term depression to the same conditioning stimuli. This result might indicate that CIN activity modulate corticostriatal plasticity in different manner between direct and indirect SPNs.

00067
Respective roles of the distinct populations of Medium Spiny Neurons of the Nucleus Accumbens in reward processing

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Abstract

The nucleus accumbens (NAc) is a major structure that plays a key role in action selection and execution as well as reward processing and reward-dependent learning. It is largely composed of GABAergic Medium Spiny Neurons (MSN) that are divided into two distinct subpopulations, those expressing the dopamine D1 receptor (D1R; dMSNs), and those expressing the D2 receptor (D2R; iMSNs). Based on the model of the dorsal striatum, it has been proposed that dMSNs and iMSNs of the NAc play antagonistic effects on reward processing, but their respective roles are still largely debated (Carvalho Poyraz et al. 2016; Soares-Cunha et al. 2016). Herein, we aimed at deeper exploring the implication of these two populations of MSNs of the NAc core on various components of reward processing. Using operant conditioning tasks and pharmacogenetic approaches we show that activation of iMSNs decreases motivation to obtain a food reward but increases food consumption, while inhibition had the opposite effect, with no impact on hedonic reactivity. Interestingly, in vivo electrophysiology experiments in anesthetized animals revealed that the increased iMSN excitability boosts the activity of dopaminergic VTA neurons. Surprisingly, we observed that both inhibition and activation of dMSNs led to a decrease in performance in motivational tasks, likely related to a strong modulation of consummatory processes. Our data shed light on the complex function of dMSNs and iMSNs of the NAc core in reward processing and highlight differential effects on consummatory vs. motivational processes.

00074
Cerebellar degeneration correlates with motor symptoms in Huntington's disease

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Abstract

Objective: Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder characterized by variable motor and behavioural symptoms attributed to major neuropathology of mainly the basal ganglia and cerebral cortex. The role of the cerebellum, a region involved in movement coordination, in HD neuropathology has been controversial. This study utilises post-mortem human brain tissue to investigate whether Purkinje cell degeneration in the neocerebellum is present in HD, and how this relates to disease symptom profiles.

Methods: Unbiased stereological counting methods were used to quantify the total number of Purkinje cells in 15 HD cases and 8 neurologically normal control cases. Based on their predominant symptoms, the HD cases were categorised into two groups: "motor" or "mood".

Results: The results demonstrated a significant 43% loss of Purkinje cells in HD cases with predominantly motor symptoms, and no cell loss in cases showing a major mood phenotype. There was no significant correlation between Purkinje cell loss and striatal neuropathological grade, post-mortem delay, CAG repeat in the IT15 gene or age at death.

Interpretation: This study shows a compelling relationship between Purkinje cell loss in the HD neocerebellum and the HD motor symptom phenotype, which, together with our previous human brain studies on the same HD cases, provide novel perspectives interrelating the variable cerebellar, basal ganglia and neocortical neuropathology with the variability of motor/mood symptom profiles in human HD.

00076
Differential ultrastructural alterations in the Vglut2 (STN) glutamatergic input to the substantia nigra pars compacta/pars reticulata following nigrostriatal dopamine loss in a progressive mouse model of Parkinson's disease.

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Abstract

According to the model of basal ganglia circuitry, loss of nigrostriatal dopamine (DA) results in increased activity of the subthalamic nucleus (STN). The STN sends axonal projections to both the substantia nigra pars compacta (SNpc) and pars reticulata (SNpr). The vesicular glutamate transporter 2 (Vglut2) is localized within STN terminals synapsing in the SN. Following DA loss, there is a decrease in the extracellular levels of striatal glutamate, which is inversely associated with an increasein the density of nerve terminal glutamate immuno-gold labeling. The aim of this study was to determine if there were differential changes in the density of glutamate immuno-gold labeling within the SNpc/SNpr originating from the STN (i.e., Vglut2+) and in the proportion of Vglut2+ terminals synapsing on tyrosine hydroxylase (TH)+ or TH- labeled dendrites following chronic MPTP treatment. There was no change in the density of nerve terminal glutamate immuno-gold labeling in the SNpc. There was a shift in Vglut2+ terminals contacting TH+ vs TH- labeled dendrites in the VEH vs MPTP treated group, respectively: TH+: 81.6% vs 50.2%; TH-: 21.7% vs 51.8%. In the SNpr, there was a decrease in the density of glutamate immuno-gold labeling in Vglut2+ terminals contacting TH+ (37%, p = 0.031) and TH- (39%, p = 0.023) dendrites. There was no change in the percentage of Vglut2+ terminals contacting TH+ or TH- labeled SNpr dendrites. There was an increased shift in the percentage of Vglut2+ terminals contacting TH+ vs TH- labeled dendrites following MPTP in the SNpc but not in the SNpr. There was no change in the density

of glutamate labeling within the SNpc following MPTP, suggesting no change in glutamate release. There was a differential effect within the SNpr, where the decrease in the density of glutamate immunogold within Vglut2+ terminals suggests an increase in glutamate release, a finding consistent with the model of basal ganglia function in Parkinson's disease.

00088
Characterization of inputs from the Striatum and Globus pallidus into the substantia nigra pars reticulata neurons in control and Parkinson's disease mice models.

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Abstract

The substantia nigra pars reticulata (SNr) is the main output structure of the basal ganglia (BG), and the activity of SNr neurons is primarily controlled by GABAergic inputs from striatal direct-pathway spiny projection neurons (dSPN) and the external globus pallidus. In Parkinson's disease (PD) the activity of SNr neurons is profoundly altered, switching from an irregular single spike pattern of activity to a synchronous bursty mode of discharge. The SNr is composed of several cell types but until now this neuronal diversity has never been taken into consideration regarding normal and pathological functioning of this nucleus.

In this study we record SNr neurons in acute brain slices obtained from PVCre::Ai9T mice which allow to distinguish PV-expressing SNr neurons (SNr-PV+) from other SNr cell types (SNr-PV-) and compare their excitability. We also perform optogenetic manipulation of striato-nigral (STR-SNr) and pallido-nigral (GP-SNr) inputs in order to determine if PV+ and PV- SNr neurons receive equivalent inputs from these two nuclei. We tested the impact of STR-SNr or GP-SNr activation on the activity of SNr neurons in cell-attached configuration and then switched to whole-cell voltage-clamp to characterize short-term plasticity of these synapses. Our results show that both SNr-PV+ and SNr-PV- neurons are innervated by the STR and the GP. They also reveal that GP-SNr synapses display stronger short-term depression than STR-SNr synapses as previously reported.

We are currently testing the impact of dopamine depletion on the excitability of SNr neurons and on STR-SNr and GP-SNr synaptic transmission using the 6-OHDA mouse model of PD.

00096
Changes in midbrain dopaminergic circuitry in the maternal immune activation rat model of schizophrenia

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Abstract

Schizophrenia is a debilitating neuropsychiatric disorder with ~1% prevalence. Despite extensive research, little is known about the microscopic changes in neural circuits that may contribute to the behavioural manifestations of schizophrenia. We have identified a complex pattern of inputs onto the dopaminergic neurons in the posterior ventral tegmental area (pVTA) of the midbrain, involving inhibitory inputs from the rostromedial tegmental nucleus (RMTg), which in turn are modulated by excitatory glutamatergic inputs. Here, we investigated the hypothesis that an underlying causal mechanism of schizophrenia is altered synaptic input onto pVTA dopaminergic neurons, which results in a characteristic excessive release of dopamine. We combined lentiviral vector technology and peroxidase-immunogold double labelling methods to selectively label pVTA dopaminergic neurons and RMTg GABAergic neurons. Three-dimensional serial transmission electron microscopy was used to analyze the synaptic inputs to the pVTA in the maternal immune activation (MIA) rat model of schizophrenia versus controls. In identified synapses between RMTg GABAergic neurons and pVTA dopaminergic neurons, we found a statistically significant decrease in the volume of both the presynaptic terminal and the postsynaptic density in MIA rats versus controls. For excitatory synapses on the RMTg GABAergic inputs, we found a statistically significant decrease in the thickness of the postsynaptic density in MIA rats versus controls. All anatomical deficits correlated significantly with decreased pre-pulse inhibition. These data suggest that in schizophrenia, impaired inhibition of pVTA dopaminergic neurons could result in excessive release of dopamine, leading to a hyperdopaminergic state of the brain and the manifestation of schizophrenic symptoms.

00100
Modulation of nigrostriatal dopamine release by GABAA/B receptors

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Abstract

Nigrostriatal dopamine (DA) is critical to action selection and learning. Axonal DA release can be strongly influenced by local striatal neurotransmitters. Cholinergic interneurons (ChIs) gate DA release via ACh action at nicotinic receptors (nAChRs) identified on DA axons. Striatal GABA is thought to modulate DA, but GABA receptors have not been documented conclusively on DA axons and their impact on DA release is not fully understood. However, ChIs express GABA receptors and are candidates for mediators of GABA regulation of DA.

We addressed whether striatal GABA and its receptors can modulate DA release directly, independently from any impact on nAChR activity, by detecting DA in dorsal striatum in slices from male mice using fast-scan cyclic voltammetry. We also assessed how GABA receptors impact on short term plasticity (STP) of DA release.

DA release evoked either by single electrical pulses in the presence of the nAChR antagonist DHβE or by optogenetic stimulation of DA axons, was reduced by GABA or agonists of GABAA or GABAB receptors, indicating that striatal GABA receptors can inhibit DA release independently from actions on nAChRs. Furthermore, GABA receptor antagonists, particularly GABAB blockers, enhanced DA release evoked by optogenetic or electrical stimuli, revealing a tonic inhibition of DA release by striatal GABA operating particularly through GABAB receptors.

Furthermore, GABA receptor activation or antagonism slightly modified the frequency sensitivity of DA release during short stimulus trains, but in addition played a critical role in determining whether manipulation of axonal excitability by other means (varying extracellular [K+]) modified short-term plasticity.

Together these data reveal that striatal GABA can inhibit DA output through a tonic GABA inhibition, and that GABA receptors influence the sensitivity of DA output to local modulation by other mechanisms, offering a potential means to promote signal gain.

00105
D1/D2 detection from action-potential properties using machine learning approach in the dorsal striatum

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Abstract

Striatal medium spiny neurons (MSNs) are segregated into two subpopulations, the D1 receptor-expressing MSNs (the direct striatonigral pathway) and the D2 receptor-expressing MSNs (the indirect striatopallidal pathway). The fundamental role of MSNs as output neurons of the striatum, and the necessary distinction between D1- and D2-expressing neurons accentuate the need to clearly distinguish both subpopulations in electrophysiological recordings *in vitro* and *in vivo*. Currently, fluorescent labelling of the dopaminergic receptors in mice enables a clear differentiation. However, multiplying *in vivo* the number of genetic markers (optogenetics, fluorescence) hinders possibilities for other genetic manipulations. Moreover, electrophysiological properties of fluorescents neurons can slightly differ from “native” cells and false-positive can be observed. The lack of a proper way to separate D1- and D2-MSNs based on electrophysiological properties led us to devise a detection algorithm based on action potential profile. We used more than 450 D1/D2 labelled MSNs from *in vitro* patch-clamp recordings (different experimentalists, different setups and protocols), to characterize and identify properties that facilitate the MSN discrimination. After analyzing passive and active MSN membrane properties, we built an extensive dataset and fed it into classical machine learning classification methods. The training of the different algorithms (k-nearest neighbors, random forest, deep neural networks, …) was performed with the *scikit-learn* Python library, and the optimized classifier was able to correctly discriminate neurons in the dorsolateral striatum at 76% (and up to 83% if we allow the classifier to reject some MSNs). This study developed an efficient classification algorithm for D1/D2-MSNs, facilitating cell discrimination without specific genetic fluorescent labelling, leaving some room for other genetic markers and optogenetic.

00112
Decorrelation is Augmented along the Cortical-Basal Ganglia Main Axis

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Abstract

The cortical-basal ganglia (BG) network has two functionally related subsystems: a main axis and the neuromodulators that adjust activity along the main axis. The BG main axis is considered to be a feed-forward organization in which converging input from numerous cortical and thalamic areas project to cortical and brainstem motor centers. However, the characteristics of information processing in the BG main axis remain unclear.

We recorded the activity of the BG main axis neurons and neuromodulators from six monkeys engaged in a classical conditioning task. Comparison of thousands of pairwise signal correlations indicated that the skewness of the signal correlation distribution decreases, i.e., decorrelation is augmented, at the transition from the striatum to the external globus pallidus. The striato-pallidal transition is also the point of significant change in the spiking features of the BG neurons (e.g., from a low to a high discharge rate) and in the number of neuronal response assemblies. However, regression analysis revealed that the BG decorrelation is not confounded by the spiking features of the cells.

Hence, decorrelation of evoked neuronal activity is a main feature of information processing in the cortical-BG main axis, that probably enables optimal compression of information at the striato-pallidal level.

00116
Predicting Inhibition and Disinhibition of Substantia Nigra pars Reticulata Neurons

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Abstract

The globus pallidus (GPe) projects directly to substantia nigra pars reticulata (SNr), making strong inhibitory connections onto SNr neurons. To investigate the impact of this pathway, we characterized GPe-mediated synaptic currents in SNr neurons, and simulated the effects of GPe output on the spiking activity of SNr neurons and neuron models. To characterize GPe to SNr synaptic inhibition, a virus encoding a Cre-inducible channelrhodopsin was injected into GPe of Parvalbumin-Cre mice, targeting the subtype of GPe neurons that project to SNr. Brain slices were prepared, and unitary IPSCs from GPe axons were evoked by minimal photo-stimulation and recorded in whole-cell voltage-clamp mode. Based on these synaptic data, we constructed synaptic conductance waveforms incorporating the measured synaptic conductance amplitudes, rise time, decay time constant, and number of unitary connections detected, as well as previously described synaptic depression. Conductance waveforms representing 3 unitary GPe inputs were applied to both SNr neurons recorded in vitro, and SNr neuron models constructed based on our phase resetting data. Cell data and model spike times were analyzed and quantified in peristimulus time histograms (PSTH). Relatively sparse, yet strong GPe-mediated conductance created a sustained inhibition of SNr neuron activity. Disinhibition from GPe-mediated input results in an overshoot transient in the SNr neuron PSTH that does not require post-inhibitory rebound currents. The features of the disinhibitory PSTH are determined largely by the shape of the phase resetting curve. The characteristic phase resetting curve of the SNr neurons produces a powerful and short latency overshoot which accurately predicted that seen in the cells. These results show that SNr neurons respond rapidly and precisely to relief from sustained inhibition despite the absence of post-inhibitory rebound ion channels.

00118
Impact of cholinergic interneurons on corticostriatal transmission: an in vivo approach combining intracellular recordings and optogenetics in anesthetized mice

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Abstract

The cerebral cortex massively innervates the striatum, the main basal ganglia (BG) input stage, where it targets the two populations of striatal projection neurons (MSNs), at the origin of the "direct" and "indirect" pathways, as well as interneurons. Although in small numbers (<2%), striatal cholinergic interneurons (CINs) show morphofunctional features, notably an extended neuritic arborization and a tonic firing (around 4 Hz in vivo), that place them as key players in the BG functioning, at the interface of striatal input systems and MSNs. However, the role of CINs in modulating corticostriatal transmission in vivo remains parcellar. Here we addressed this issue by examining the impact of optogenetic inhibition of CINs expressing halorhodopsin on basal and evoked corticostriatal transmission, using intracellular recordings of MSNs in vivo in anaesthetized mice. Our results show that short inhibition of CIN firing (500 and 1000 ms), consistent with the duration of the pause observed in vivo in response to salient and to conditioned stimuli in reinforcement learning, had no effect on the MSN membrane potential that oscillates between two preferred potentials known as Up and Down states. Photoinhibition during 5 sec had an overall hyperpolarizing effect that, however, was unrelated to CIN inhibition as it was also observed in control mice that do not express halorhodopsin. Furthermore, CIN photoinhibition had no impact on cortically-evoked EPSPs or EPSPs paired-pulse ratio measured in MSNs. Altogether, these data surprisingly suggest that, in control situation, the tonic firing of CINs does not modulate corticostriatal transmission. Since we have previously shown that CIN photoinhibition alleviates motor symptoms in 6-OHDA hemi-parkinsonian mice, we are currently analyzing the impact of CINs photoinhibition on corticostriatal transmission in those mice. (Supported by CNRS and AMU)

00121
The tecto-subthalamic projection: A source of short-latency auditory input to the subthalamic nucleus

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Abstract

We have shown that the superior colliculus (SC), a subcortical sensory-motor structure, directly projects to the subthalamic nucleus (STN) and is a crucial source of visual input to this structure (Coizet et al., 2009). The SC is well known to process multi-sensorial signals. Furthermore, visual and auditory stimuli potentiate neuronal responses in SC deep layers when both stimuli are colocalised (Stein and Meredith, 1983). According to the interrupt hypothesis of the STN, this neuronal modulation in SC is likely to be transmitted to the STN, for a better interruption of the ongoing behavior. This hypothesis relies on the transmission of auditory stimuli from the SC to the STN. Our objective was to characterize auditory responses in the STN and test whether the SC was a crucial relay. Using a technique of extracellular electrophysiology in anesthetized rats, we recorded 85 STN cells in response to auditory stimulation. Among the 47 cells responding to the stimulation (47/85, 55 %), 38 cells responded at a short latency (70-100 ms) with a short duration. We observed that this phasic response was not constant with the repetitive presentation of the 120 trials and found evidences of sensory habituation and sensitization. We also observed a tonic response, with 21 (25 %) and 26 (31 %) cells increasing and decreasing their baseline firing rate with the introduction of the auditory stimulation, respectively. To test if the SC was the afferent structure relying auditory signals to the STN, we lesioned the SC using the European Synchrotron Radiation Facilities (ESRF, Grenoble). SC lesion by irradiation was confirmed with DTI tractography and histological analysis and significantly decreased the number of responding cells (18%), confirming its crucial role as a relay. This suggests that SC neuronal potentiation between co-localized visual and auditory stimuli may be transmitted to the STN for a better behavioral interruption and attentional re-orientation.

00122
The spatial organization of dorsal striatum spontaneous activity

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Abstract

A comprehensive description of the brain requires the understanding of how communication among brain areas and circuits occurs. We are interested on the flow of cortical information to the basal ganglia. To that end, we are focus in the striatum the main synaptic entrance to the basal ganglia. In rodents, the dorsal region of striatum has been functionally divided in two poorly anatomically defined regions, named dorsolateral and dorsomedial, which receive partially overlapping cortical projections. In order to understand the functional connectivity to dorsal striatum, we simultaneously performed whole-cell patch-clamp recordings in striatal Medium Spiny neurons (MSNs) together with extracellular recordings in different cortical areas in anesthetized mice. Hence, we could study how the functional connectivity of each cell influenced its dynamics during the well-known slow wave oscillation (SWO1Hz). We found that lateral and medial regions of dorsal striatum shown different features in their SWO, such as state transition speed or wave shape. Such differences were enough to classify MSNs on dorsolateral or dorsomedial regardless of their position in the mediolateral axis. These results were supported by a different excitatory/inhibitory balance during *Up states* onto MSNs across striatal regions. These differences were not fully explained by cortical excitatory projections suggesting a role of the striatal microcircuitry in the encoding of the SWO.

At last, we studied whether these differences in the functional corticostriatal connectivity were noticeable at the level of the direct and indirect pathway. We show how inherited cortical SWO is common to both striatal subpopulations, thus providing a homogenous input to all MSNs of each region.

In conclusion, dorsolateral and dorsomedial striatum receive different excitatory/inhibitory balance during Up states, leading to different but reliable dynamics that were sufficient to classify MSNs based on their ongoing activity.

00128
Modulation of corticostriatal transmission by striatal cholinergic interneurons in normal and parkinsonian conditions: electrophysiology and optogenetics ex vivo

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Abstract

Although striatal cholinergic interneurons (CINs) are few in number, they have morpho-functional features that place them as critical players in striatal functions. CINs contact the two populations of striatal output neurons (also called medium spiny neurons, MSNs) that express either D1 or D2 dopaminergic receptors. Correct execution of movement requires a balanced activity between MSNs that is disrupted in Parkinson's disease (PD) in favor of D2 MSNs. Alteration in the strength of corticostriatal synapses contributes to this imbalance. *In vivo*, CINs exhibit a tonic activity that is inhibited in a synchronous manner (pause) during associative learning. This pause disappears in animal models of PD, suggesting that CIN inhibition rather than activation is the relevant message for striatal functions. What is still unknown is whether CIN activity modulates corticostriatal transmission and contributes to the imbalance of striatofugal pathways in PD. To address this question, we combined electrophysiology and optogenetics in brain slices from control and parkinsonian mice. We show that a brief pulse of light in halorhodopsine-expressing CINs induces a complete inhibition of their firing whose features are similar to the characteristics of the pause observed *in vivo* in terms of duration and synchronization. CIN photoinhibition does not modulate corticostriatal synaptic transmission in both D1 and D2 MSNs in normal condition. This lack of effect, which is not due to insufficient cholinergic tone in slices, questions CIN role in the physiology of the corticostriatal network. In PD condition, CIN pause selectively potentiates corticostriatal transmission in D1 MSNs. This potentiation could counteract the hypoactivity of D1 MSNs and provide a cellular substrate to the antiparkinsonian effect of CIN inhibition that we previously showed. Supported by Fondation de France, CNRS and AMU.

00143
Modulation of a local SNc-SNr circuit by leptin

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Abstract

Cross-talk between metabolic hormones and midbrain dopamine (DA) neurons is increasingly well-appreciated. The adipose-tissue derived hormone leptin has been demonstrated to play a role in regulating DA synthesis and somatodendritic DA stores in ventral tegmental area (VTA), but whether leptin influences the activity of DA neurons in substantia nigra pars compacta (SNc) or other aspects of basal ganglia circuitry is unknown. Using whole-cell patch clamp recordings in ex vivo midbrain slices, we found that leptin increased DA neuron excitability and somatodendritic DA release in the SNc. This enhancement was lost after intracellular application of a leptin receptor (OBR) antibody or antagonism of IP3 receptors. These data implicate OBR-dependent activation of intracellular calcium (Ca2+) stores in both effects of leptin. Leptin also caused an increase in substantia nigra pars reticulata (SNr) GABA neuron excitability. Strikingly, however, this proved to be an indirect effect that was prevented in the presence of a D1 receptor antagonist, by DA depletion, or by application of a TRPC3 channel blocker. Thus, leptin enhances somatodendritic SNc Da neuron activity and DA release, which leads to excitation of SNr GABA neurons via D1 receptors and downstream TRPC3 channel activation, via a previously described local circuit (Zhou et al. 2009). These data suggest that leptin could act through this novel SNc-SNr circuit, to regulate motor activity. Moreover, an imbalance in energy status during disease states, including obesity and Parkinson's disease, that include altered leptin levels or signaling would influence DA neuron activity, and impact motor function in these disorders.

00145
Neuronal density and distribution of interneurons in the primate striatum

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Abstract

Classically, the striatal interneurons are grouped into two main classes: the interneurons that use acetylcholine as a neurotransmitter, and the gabaergic interneurons. These interneurons have specific afferent inputs and synaptic connections that result in the formation of important functional networks. Of all types of striatal interneurons, those expressing the calcium-binding protein calretinin (CR) are the most abundant in human and nonhuman primates, while those expressing tyrosine hidroxylase (TH) are relatively few. In Parkinson's disease (PD) the dopamine (DA) deficit affects not only the striatal projection neurons but also various types of striatal interneurons. The numbers of TH-ir and CR-ir striatal neurons have been shown to increase with dopaminergic depletion in animal models of PD. However, the effects of levodopa (L-DOPA) treatment and of the degree of DA striatal denervation as conditioning factors of the numbers of these neurons are unclear.

Here, we provide a detailed account of the morphological characteristics, topographical distribution and numerical densities of TH-ir and CR-ir types of interneurons in monkeys rendered parkinsonian by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) intoxication. The monkeys had different degrees of nigrostriatal lesion and included pre-symptomatic and symptomatic subjects. We also analyzed the effects of L-DOPA. Our results show that the numbers of TH cells increases very early in the evolution of the nigrostriatal DA deficit, including the stage when no motor signs are present. L-DOPA treatment abolished the numerical increase of TH cells. The numbers of small and medium size CR neurons did not change, whereas the numbers of large CR neurons were slightly increased in parkinsonian monkeys. These findings support a modulatory role of DA in the molecular phenotype of some striatal interneurons, which are known to play a crucial role in PD pathophysiology.

00154
Novel population of nucleus accumbens direct-pathway MSNs express stress-associated neuropeptide corticotropin releasing hormone

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Abstract

The neuropeptide corticotropin-releasing hormone (CRH) has been shown to increase dopamine and acetylcholine transmission in the nucleus accumbens (NAc). These effects are accompanied by facilitation of appetitive behaviors. The endogenous source(s) of CRH to the NAc remain unclear. While recent evidence points to CRH containing afferents to the NAc from several limbic regions, there is also an uncharacterized population of CRH-expressing cells that resides in ventral NAc. Using fluorescent in situ hybridization, we characterized the cellular identity of neurons positive for *Crh* mRNA within the NAc of male mice using markers for both medium spiny projection neurons (*Drd1*, *Pdyn*, *Drd2*, *Penk*) and distinct interneuron classes (*Chat*, *Npy*, *Th*, *Sst*, *Nos1*, *Pthlh*). After analyzing the entire rostro-caudal and medial-lateral expanse of the NAc, we found that CRH-expressing cells make up 2.4% of all cells in the NAc and that there is a distinct rostro-caudal gradient, with greater numbers in the caudal aspect of the NAc. Interestingly, the results indicate that CRH-expressing cells in the NAc are predominantly direct pathway medium spiny projection neurons (dMSNs) (86.1% *Drd1*+, n=2338 *Crh*+ cells, 4 mice; 75.1% *Pdyn*+, n=1493 *Crh*+ cells, 4 mice). A smaller percentage were either *Drd1*/*Drd2* co-expressors or only positive for *Drd2* indicating that they were indirect pathway medium spiny projection neurons (iMSNs) (25.2% *Drd2*+, n=2234 *Crh*+ cells, 3 mice; 33.5% *Penk*, n=1493 *Crh*+ cells, 4 mice). Our findings suggest that interneurons account for little of NAc CRH expression (% of *Crh*+ cells: 0.13% *Chat*+, 0.10% *Npy*+, 0.93% Th+, 1.22% *Sst*+, 1.79% *Nos1*+) with the exception of *Pthlh*+ interneurons (10.3% of *Crh*+ cells). These findings add insight into the conditions in which endogenous CRH is released to regulate NAc circuitry. Next steps include examining the role these cells play in motivation and exploration using behavioral assays with conditional knockout mice.

00158
Optogenetic stimulation of thalamocortical projections alters cortical activity and coherence

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Abstract

Studies of phase-amplitude coupling (PAC) have become popular to examine the coherence between the slow and fast oscillations of a recorded signal due to its offline computation capability and its ease to compute over a wide range of frequencies. Recently, the coupling of the amplitude of gamma band oscillations to the phase of alpha- or beta-range oscillations has been shown to increase in electrocorticogram (ECoG) signals recorded in parkinsonian patients and primates (compared to recordings in normal individuals or those with other diseases), leading many to believe that it may be suitable as a possible biomarker for the disease and its associated motor symptoms. The reasons for the cortical PAC changes are not clear, but it is likely that cortical PAC patterns are heavily dependent on thalamic efferents to the cerebral cortex. We studied this issue directly with a series of optogenetic experiments in Rhesus macaques.

We virally transfected neurons in the basal ganglia receiving territory of the ventral motor thalamus to express the excitatory opsin C1V1 in one hemisphere. We then recorded ECoG signals from the primary motor cortex and the supplementary motor area during somatic (thalamic) stimulation. We compared PAC during stimulation with single pulses or with trains of pulses of light stimulation with PAC results based on pre- or post-stimulation ECoG recordings, using the Kullback–Leibler divergence method of quantifying PAC, in addition to the evoked potentials (EPs) during this same time period. We found that optogenetic stimulation caused significant PAC in gamma amplitude during periods of light pulses while the effects the in EPs were significant in only one hemisphere.

00160
Can functional connectivity reveal the network mechanisms underlying the beta-band oscillations?

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Abstract

Emergence of β-band (15-30Hz) oscillations in the basal ganglia (BG) is one of the main signatures of Parkinson's disease (PD). Several hypotheses has been proposed that could potentially explain the emergence of these oscillations in the BG. Recently, experimentalists have been using functional connectivity (FC) metrics in the hopes of untangling the complex mechanism behind generation of β-rhythms. It is unclear whether FC metrics can correctly identify the network interactions that generate β-band oscillations. The critique of FC metrics is well grounded in the fact that statistical dependencies among remote neurophysiological events in a steady state system are not sufficient to make inferences about the underlying model.
To evaluate whether any meaningful conclusions can be drawn from FC, we constructed large-scale network of BG and generated β-band oscillations using two different models: increased activity of D2 type medium spiny neurons of the striatum and increased connectivity between the subthalamic nuclei and globus pallidus externa. Specifically, we investigated whether FC (measured using a non-parametric directionality estimate) can be related to the models structure in a steady-state system when it is generating oscillations. Our analysis showed that no distinction can be made between the two models of β-band oscillations based on the FC alone. Moreover, FC estimated from the steady-state of the BG network activity system was unable to capture the change in reciprocal strength between key nuclei of the BG. Nevertheless, we constrained the model using the available FC data and we found that in PD the BG network may operate in a twilight zone in the parameter space determined by a combination of the two aforementioned mechanisms. Finally, we show that instead of steady state FC, transient response of the BG network upon selective stimulation of specific subnuclei can reveal the network structure underlying the emergence of β-band oscillations.

00174
Selective innervation of striatal cell types by distinct pallidal neurons

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Abstract

The globus pallidus pars externa (GPe) is a highly interconnected nucleus within the basal ganglia. Two major types of projection neuron have been identified in the GPe; so-called prototypic and arkypallidal neurons. Prototypic GPe neurons can innervate both ‘downstream’ basal ganglia nuclei (globus pallidus pars interna, subthalamic nucleus, and substantia nigra pars reticulata) and ‘upstream’ nuclei (striatum), whereas arkypallidal neurons only send projections to the striatum. The striatal microcircuit is itself composed of at least two major classes of projection neuron, as well as a variety of interneurons. As such, there could be much diversity and selectivity in pallidostriatal connections.

The aim of this study was to characterise and quantify the innervation of different striatal cell types by prototypic and arkypallidal neurons of the mouse GPe. To address this, we carried out trans-synaptic retrograde tracing of inputs to genetically-restricted cell types in striatum. We then generated estimates of the numbers of molecularly-defined GPe neurons monosynaptically innervating two major classes of projection neuron, two populations of GABAergic interneuron, and cholinergic interneurons in striatum.

Our data confirm previous reports that arkypallidal neurons provide an extensive innervation of the striatum. Results indicate that prototypic and arkypallidal neurons do indeed selectively innervate different striatal cell types. This study provides insight into the underlying connectivity of the GPe and striatum which will guide our understanding of the network in health and disease.

00176
Functionally Distinct Connectivity of Developmentally Targeted Striosome Neurons

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Abstract

The striatum plays a critical role in behaviors ranging from action selection to motor control. One model of how the striatum might mediate such functions divides striatal neurons into populations called striosomes and matrix. While anatomical evidence suggests that striosome and matrix neurons may have distinct connectivity, limited methods for isolating these populations has hindered examination of their functional differences. Here, we validate 599CreER mice as a tool for developmentally targeting striosome MSNs. Using this tool, we demonstrate that striosome and matrix neurons receive biased input from limbic and sensorimotor structures such as the prelimbic cortex and primary motor cortex. We also identify pathway-specific differences in how striosome and matrix neurons convert excitatory input into spiking. Lastly, we demonstrate that striosome neurons have unique output to midbrain neurons, including dopamine neurons in the substantia nigra pars compacta. Together, these results identify striosome and matrix neurons as functionally distinct striatal pathways.

00178
Temporal dynamics of thalamocortical interactions during beta bursts in Parkinsonism

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Abstract

Excessive neural activity in the beta-frequency band, and particularly discrete epochs of high beta power named ‘beta bursts’, are potential biomarkers of Parkinson’s disease (PD). Indeed, frequent and long-duration beta bursts in the subthalamic nucleus (STN) have been positively correlated with PD motor symptoms, negatively correlated to ON medication state, and linked to an enhanced inter-site coupling between the basal-ganglia and the cortex (Tinkhauser et al., 2017a, 2017b., Cagnan et al., 2019 [in review]). Recent computational work suggests that transitions from low to high beta power are supported by complex interactions within and between cortex and thalamus (Reis et al., 2019). Nevertheless, how neuronal activity in thalamacortical circuits evolves during defined beta bursts is unclear.

To address this, we analysed neuronal activity from multichannel and single unit recordings made in different nuclei of the thalamus (anterior ventral nucleus, the basal-ganglia recipient zone of motor thalamus, the cerebellar-recipient zone, and the reticular nucleus) as well from the substantia nigra pars reticulata (SNr) and motor cortex of anaesthetized Parkinsonian rats.

Our preliminary results show that from the five subcortical regions (of which 4 are thalamic nuclei) only the thalamic nucleus receiving inputs from basal-ganglia (Nakamura et al., 2014) and the SNr, present statistically significant periods of increased beta activity and enhanced thalamocortical coupling when aligned to the onset of cortical beta bursts. These results contribute to a better understanding of PD’s pathophysiology by supporting the view that oscillatory dynamics of beta activity in PD are driven by a dynamically coupled network rather than a local phenomenon.

00181
The zona incerta: a new node in the reward pathway

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Abstract

The Zona Incerta (ZI) is a little known structure, of which the anatomical connections and the function are poorly understood. Yet, clinical studies of deep brain stimulation in the neighbouring subthalamic nucleus suggest that the zona incerta plays a part in the pathophysiology of Parkinson's disease or the effect of deep brain stimulation on it.

To shed some light on the ZI's potential function, we used axonal tracing to map its anatomical connections. We placed injections of anterograde and retrograde tracers (4 in the ZI, 14 in the frontal cortex) in 18 non human primates (Macaca mulatta and M. nemestris). We charted connections using light microscopy. We built 3D charts to visualise the topography of different afferent projections to the ZI (we could not study the topography of outputs for technical reasons).

First, we demonstrate that there is a dorsal/ventral division of the ZI similar to the one described in rodents. The ventral ZI receives motor-related inputs, whereas the dorsal ZI receives reward-related inputs. Our injections in the ZI were not precise enough to distinguish between dorsal and ventral ZI outputs.

Second, we show that the ZI receives inputs from major reward/punishment-related regions: the hypothalamus and periacqueductal grey matter (processing of food, sex and pain signals), the prefrontal cortex (processing of secondary reward signals, e.g. money), and the border cells of the pallidum (reward prediction). In turn, it projects to the lateral habenula and the columns of dopaminergic cells in the substantia nigra, the areas involved in the computation of reward prediction error.

In conclusion, we show that the ZI, probably its dorsal component, is at a crossroads in the reward network. It receives convergent inputs from regions encoding reinforcers, and projects to the areas computing to reward prediction error. Thus, the ZI is potentially involved in an intermediate step of reward which will need to be tested with functional experiments.

00186
Testing the causative importance of dichotomous GPe neurons for circuit dynamics and animal behaviour

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Abstract

The external globus pallidus (GPe) contains two major types of GABAergic projection neuron, so-called arkypallidal and prototypic neurons. Arkypallidal neurons innervate striatum, exhibit relatively low firing rates when animals are at rest, and encode movements with increased firing. Prototypic neurons innervate multiple basal ganglia nuclei, exhibit relatively high firing rates when animals are at rest, and often encode movements with decreases in firing. Both arkypallidal and prototypic neurons are positioned - through diverse substrates - to affect other cells in GPe. The causal influences of the activities of these two GPe populations on each other, their extrinsic targets, and animal behaviour remain largely unknown. To begin to address this, we used optogenetics-based manipulations targeted to prototypic GPe neurons in mice, the effects of which were defined in terms of neuronal activity and, in separate experiments, movement. Single-cell recording/labelling in vivo confirmed that brief pulses of light delivered to the GPe were sufficient to rapidly and profoundly suppress the firing of many prototypic neurons expressing the opsin ArchT. However, the same manipulations had little effect on neighbouring GPe neurons that did not express ArchT. In further contrast, the firing of arkypallidal neurons was often increased. Preliminary recordings suggested that the subthalamic nucleus could mediate these responses of arkypallidal neurons. Unilateral delivery of light to the GPe of behaving animals induced ipsiversive turning at short latencies, whereas bilateral delivery appeared to reduce the probability of movement. Open- and closed-loop delivery of light, as based on head-mounted accelerometer data, suggested further effects on movement initiation and on performance of ongoing movements. Altogether, these data argue that the spontaneous firing of prototypic GPeneurons plays important roles in orchestrating basal ganglia activity dynamics and animal behaviour.

00032
AMP-activated protein kinase slows D2 dopamine autoreceptor desensitization in substantia nigra neurons

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Abstract

Dopamine neurons in the substantia nigra zona compacta (SNC) are well known to express D2 receptors. When dopamine is released from somatodendritic sites, activation of D2 autoreceptors suppresses dopamine neuronal activity through activation of G protein-coupled K+ channels. AMP-activated protein kinase (AMPK) is a master enzyme that acts in somatic tissues to suppress energy expenditure and encourage energy production. We hypothesize that AMPK may also conserve energy in central neurons by reducing desensitization of D2 autoreceptors. We used whole-cell patch-clamp recordings to study the effects of AMPK activators and inhibitors on D2 autoreceptor-mediated current in SNC neurons in slices of rat midbrain. Slices were superfused with 100 µM dopamine or 30 µM quinpirole for 25 min, which evoked outward currents that decayed slowly over time. Although the AMPK activators A769662 and ZLN024 significantly slowed rundown of dopamine-evoked current, slowing of quinpirole-evoked current required the presence of a D1-like agonist (SKF38393). Moreover, the D1-like agonist also slowed the rundown of quinpirole-induced current even in the absence of an AMPK activator. Pharmacological antagonist experiments showed that the D1-like agonist effect required activation of either protein kinase A (PKA) or exchange protein directly activated by cAMP 2 (Epac2) pathways. In contrast, the effect of AMPK on rundown of current evoked by quinipirole plus SKF38393 required PKA but not Epac2. Current-clamp recordings showed that an AMPK activator prolonged dopamine-induced hyperpolarization and inhibition of evoked action potentials. We conclude that AMPK slows D2 autoreceptor desensitization by augmenting the effect of D1-like receptors. By reinforcing the inhibitory influence of dopamine, this action of AMPK is consistent with its role to conserve neuronal energy.

00035
The dopamine active transporter: a switcher in striatal plasticity and learning

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Abstract

The acquisition of new skills is an incremental learning process characterized by an initial phase (here called early learning) during which performance is still not optimal and sensitive to interference. Practice progressively leads to behavioural optimization until a plateau performance and full automatism is reached (here called plateau learning). Previous studies suggested that early and plateau learning require the activation of segregated pathways in striatal subregions: D1 receptors (D1Rs)-mediated long-term potentiation (LTP) in the dorsomedial striatum (DMS) and D2 receptors (D2Rs)-mediated long-term depression (LTD) in the dorsolateral striatum (DLS), respectively. How these pathways are differently activated during distinct steps of skill learning remains unknown.

We will present our recent findings showing that early motor learning is stored for more than a week in medium spiny neurons (MSNs) of the DLS as a switch from LTD to LTP. We called this form of LTP, early-learning LTP, as it is no longer evident when animals reach performance plateau. Early-learning LTP requires the dopamine active transporter (DAT) and D1Rs, but not D2Rs, activation; D2Rs activation is instead necessary for plateau learning. Interestingly, we have discovered that early learning leads to increased DAT expression in the striatum, whereas plateau learning decreased it, proposing DAT as a mechanism to control early vs plateau transition during motor learning. The fact that early motor learning activates D1Rs pathway also within the DLS, goes beyond the classical dichotomic view and suggests that plasticity in the DLS possesses a structure for storing motor information during all stages of incremental learning. This novel discovered mechanism of experience-dependent striatal metaplasticity has high translational relevance, as it is impaired in early stages of Parkinson ’s disease.

00038
Interneuron-like role of D2-projection systems in the functional parcellation of striatal plasticity during goal-directed learning

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Abstract

Learning new purposeful behaviours and forgetting about those that are no longer needed is critical to survival in changing environments. While such adaptations are known to depend on the basal ganglia, the way its different subcircuits interact with one another to promote acquisition and extinction of goal-directed action remains unclear. As the primary integrative input to the basal ganglia, the striatum is mainly composed of two intermingled and equally large projection systems based on the expression of two types of dopamine receptors (i.e. D1 and D2) as well as their output targets. Here, we combined instrumental conditioning with high-throughput reconstruction of nuclear signalling activity in large ensembles of neurons to investigate the function D1- and D2- spiny projection neurons (SPNs) at different stages of goal-directed learning. Our results revealed distinctive patterns of D1- and D2-SPN distributions across striatal territories that were predictive of both acquisition and extinction of instrumental learning. Specifically, we demonstrate that D2-SPNs can occupy and suppress D1-SPN territories in a learning-dependent manner, a modulation that appears critical for promoting extinction of previously acquired instrumental behaviours. Consistently, by using new viral approaches based on transneuronal labelling of thousands of neurons, we found that D2-SPNs present a remarkable trans-connectivity towards D1-SPNs, and that former pharmacological stimulation of D2-SPNs can completely prevent the subsequent stimulation of D1-SPNs. Genetic ablation of D2-SPNs in defined striatal territories did not affect acquisition of instrumental behaviour, although significantly delayed its extinction. Our findings suggest that, in a similar way to interneuronal systems, D2-SPNs may exert the function of clearing out obsolete D1-SPN plasticity in the striatum, an extensive parcellation process that allows for efficient shaping of goal-directed learning.

00056
Regulation of adenylyl cyclase 5 enables detection of coincident neuromodulatory signals in the striatum

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Abstract

Adenylyl cyclase (AC) isoforms are differentially distributed in the brain, with the AC5 isoform dominant in the striatum. AC5 is regulated by the stimulatory $G\alpha_{olf}$ and inhibitory $G\alpha_i$ G protein subunits, released when neuromodulators bind to their cognate G-protein-coupled receptors (GPCRs). How AC5 integrates the $G\alpha_{olf}$ and $G\alpha_i$ signals which result from the neuromodulatory signals and control the production of cAMP, is not understood, and answering this question is crucial for understanding learning in the basal ganglia, since cAMP is crucial for long-term potentiation of the corticostriatal synapses. Here we combine several computational tools, from molecular dynamics and Brownian dynamics simulations to bioinformatics approaches, to inform and constrain a kinetic model of the AC5-dependent signaling system. We use this model to show how the molecular properties of AC5 together with the $G\alpha_{olf}$ and $G\alpha_i$ G-proteins support a supralinear/synergistic cAMP production downstream of the receptors. We focus on the D_1 MSNs, but the results are generalizable to the D_2 MSNs, as well. The synergistic interaction is a result of a catalytically inactive ternary complex, $G\alpha_{olf}$-AC5-$G\alpha_i$, which might be forming during AC5 regulation. This results in stronger, nonlinear cAMP responses compared to alternative regulatory interactions. The simulation experiments have implications for understanding the prerequisites for corticostriatal synaptic plasticity under physiological conditions, i.e. that both the dopamine and acetylcholine signals are necessary to potentiate the corticostriatal synapse in D_1 MSNs. Also recent experimental data can be explained by our predictions, and our results furthermore provide insights on the computational capabilities of the different AC isoforms.

00069
Dopamine dysregulation in the nigro-striatal pathway studied in brain slices from DAT-KO rats

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Abstract

Cessation of dopamine (DA) transmission largely depends on reuptake by the DA transporter (DAT) encoded by the Slc6a3 gene. DAT expression/activity is reduced in several neurological disorders and after exposure to drugs of abuse (e.g. cocaine, methylphenidate, amphetamine). Our aim was to characterize behavioral, neurochemical and electrophysiological effects of eliminating DAT activity in a novel DAT knockout rat generated using CRISPR/Cas9. As expected, DAT-KO rats displayed no DAT immunoreactivity in the striatum, increased basal locomotor activity, and paradoxical calming by amphetamine. Fast-scan cyclic voltammetry in brain slices demonstrated a large decrease in the clearance of electrically stimulated DA release in the dorsal striatum and to a lesser extent in the Substantia Nigra *pars compacta* (SNc). Cocaine increased the amplitude of DA release and slowed its clearance in slices from wild-type (WT), but not DAT-KO rats. Basal extracellular DA concentration ($[DA]_{out}$), measured with fast-scan controlled-adsorption voltammetry, was higher in DAT-KO rats compared to WT littermates, and was enhanced by L-DOPA, showing that DA release after L-DOPA is not due to DAT reversal. Baseline firing frequency of SNc neurons and GABAB-mediated inhibition were similar in DAT-KO and WT rats. However, D2-mediated inhibition (by both quinpirole and L-DOPA) was blunted in DAT-KOs, likely due to downregulation of D2 receptors previously reported in DAT-KO mice. Amphetamine increased $[DA]_{out}$ in the dorsal striatum of WT rats, but this effect was strongly attenuated in DAT-KOs. Surprisingly, amphetamine increased $[DA]_{out}$ in the SNc of DAT-KOs, which did not differ to the response seen in WTs. The mechanism of this release is likely through reversal of low-affinity, high capacity uptake-2 transporters. These results not only validate our DAT-KO model, but also provide novel insights into the mechanism of DA releasing agents and form the basis for our future i*n vivo* studies.

00073
Direct comparison of striatal and cortical dopamine release using a genetically-encoded, fluorescent dopamine indicator (dLight) and fast-scan cyclic voltammetry

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Abstract

The recent development of optical sensors based on G protein-coupled receptors (GPCRs) has initiated a thriving line of research. One of these sensors, the genetically encoded fluorescent dopamine biosensor, dLight, has a modified non-signaling dopamine D1 receptor containing a circularly permuted green fluorescent protein (GFP). It binds dopamine causing an increase in GFP fluorescence without activating downstream signaling cascades. We measured dLight fluorescent responses to electrical stimulation in brain slices using photometry that allows for analysis of fast dynamics and regional differences. Here, we provide a detailed characterization of dLight, by directly and simultaneously comparing fluorescent photometric to voltammetric measurements of dopamine in cortical and dorsal striatal brain slices. We found that dLight can detect lower levels of dopamine release compared to voltammetry in the same striatal brain slice recording. Moreover, with low frequency burst stimulations, dLight more faithfully tracks responses to individual stimulai. Interestingly, cocaine increases the decay time of dopamine signals measured simultaneously with dLight and voltammetry but does not affect the peak height of the dLight signal, which could be due to the adsorptive qualities of the voltammetric sensor or the pool of dopamine detected. Similarly, blockade of nicotinic acetylcholine (nACh) receptors produces different readouts across sampling methods. This difference can be due to the fact that dLight is most likely trafficked to synaptic and extra-synaptic sites and can thus reflect both synaptic and non-synaptic

dopamine levels. Anatomical studies to clarify this are underway. We have also assessed dopamine release using dLight in prefrontal cortex (mPFC) and motor cortical regions (M1 and M2) and found different release properties from those of striatal terminals. Importantly, similar stimulation parameters fail to elicit measurable signals with voltammetry in cortex.

00097
The role of striatal spreading depolarization in a Levodopa-induced Dyskinesia 6-OHDA rat model.

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Abstract

Spreading depolarization (SD) is a self-propagating depolarization wave that involves both neurons and glial cells. SD is extensively characterized in the cortex and in the hippocampus, which are involved in migraine and epilepsy. Conversely, SD in the striatum has been poorly investigated. The striatum, a brain structure deeply involved in motor memory, motor control and in Parkinson's Disease (PD), receives dopaminergic fibers from the substantia nigra pars compacta and glutamatergic innervations from the cortex and the thalamus. We explored the involvement of glutamatergic and dopaminergic transmission in the induction of striatal spreading depolarization (SSD) through the variations of intrinsic optical signal (IOS) coupled with amperometric measurements of endogenous dopamine levels and pharmacological, molecular and morphological analyses. The experiments were performed on cortico-striatal brain slices, obtained from control rats, unilaterally 6-OHDA–lesioned rats (a reliable experimental model of PD) and from 6-OHDA rats, which underwent a long-term Levodopa (L-DOPA) treatment inducing abnormal involuntary movements (i.e. dystonic and choreic movements). L-DOPA-induced dykinesia (LID) is triggered by alterations in the activation of the signaling pathway downstream D1 dopamine receptor. We found that SSD requires the concomitant activation of D1-like receptorof DA, but not D2-like, and Nmethyl-D-aspartate receptors (NMDAr) and was reduced in the rodents model of experimental PD. Chronic L-dopa treatment, inducing dyskinesia in the parkinsonian condition, increases the number of episode and speed of propagation of striatal spreading depolarization, which has a direct impact on one of the signaling pathways downstream from the activation of D1 receptors, independently of DA concentration observed.

00098
mTORC signaling inhibition: a therapeutic target in an experimental model of Parkinson's Disease.

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Abstract

Introduction. Levodopa (L-DOPA) is the most efficient therapy for Parkinson's disease. After its prolonged use patients develop involuntary movements known as L-DOPA-induced dyskinesia (LID). LID is related to a sensitization of dopamine D1 receptors located on dorsal striatal medium spiny neurons (MSNs). The emergence of LID can be related to cAMP/PKA/DARPP-32 and ERK1/2 pathway alterations associated to aberrant NMDA receptor subunit composition and altered striatal synaptic plasticity at corticostriatal glutamatergic synapses. ERK1/2 is able to modulate the activity of the mammalian target of rapamycin complex 1 (mTORC1). We investigated the potential role of this pathway in dyskinesia and the existence of a relationship between mTORC1 activation and striatal synaptic plasticity.

Methods. After the unilateral 6-OHDA injection into the medial forebrain bundle, parkinsonian rats were scored for LID using an abnormal involuntary movements (AIMs) rating scale. We used patch-clamp whole cell technique to examine differences in glutamatergic synapses, evaluating the ratio of excitatory postsynaptic currents mediated by NMDA and AMPA receptors in MSNs of dyskinetic animals treated with either L-DOPA or L-DOPA plus Rapamycin (a mTORC1 inhibitor). The high frequency stimulation (HFS) was used as a long term potentiation (LTP)-inducing protocol. Low frequency stimulation (LFS) was applied to depotentiate synaptic strength.

Results. AIMs scoring showed that L-DOPA plus Rapamycin-treated rats displayed a significant dyskinesia decrease and patch-clamp recordings revealed that their MSNs depotentiated after LTP induction repairing the striatal ability to store new motor memories, compared to L-DOPA-treated rats.

Conclusions. This study allows a better understanding of striatal mTORC1-related events underlying LID, pushing for the development of new interventions through inhibitory treatments against L-DOPA side effects to improve motor capabilities of parkinsonian patients.

00099
Controlled neural organoids grafting promotes functional recovery in experimental parkinsonism

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Abstract

A major impetus for research on Parkinson's disease (PD) is centered on cell therapy strategies that aim at replacing the dysfunctional or dying neuronal cell populations and may open a hope for ancure.The availability of patient-specific cell lines associated with the development of highly in vitro efficient protocols to generate specific neuronal cells is an important step in overcoming the ethical and logistical challenges associated with the use of embryonic stem cells. However, mature neuronal transplantation leads to poor survival due to their detachment sensitivity. Similarly, the transplantation of neuronal precursors does not allow in situ tight control of the neuronal identity and carries a tumor risk. We propose that the striatal transplantation of 3D-neural organoids of controlled cell size and cell content "Controlled Neural Organoids" (CNOs) could circumvent the limitations of current cell therapy and thus allow functional recovery in PD.

CNOs are generated through cell capsules technology developed in the lab associated with differentiation protocol of dopaminergic neurons (DN) from human pluripotent stem cells. Following the neuronal transplantation in immunocompromised hemiparkinsonian rats (6-OHDA), motor functions were evaluated by stepping test, cylinder test and amphetamine-induced rotations. CNOs characterization was carried out by immunostaining. In this study, we compared the therapeutical efficacy of 3D-neural organoids versus individual neurons transplantation.

From eight weeks onwards after the transplantation, CNOs allowed functional recovery associated with tyrosine hydroxylase positive neurons into the graft whereas the transplantation of dopaminergic individual neurons did not induce any effect.

Our CNOs constitute more efficient and safer cell therapy products than individual neurons. This innovative cell therapy approach for the treatment of PD could become a real alternative to drug-based symptomatologic treatments.

00104
Thalamus drives corticostriatal plasticity via concurrent STDP and heterosynaptic interplay

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Abstract

The striatum, the primary entrance to basal ganglia, integrates excitatory inputs from both cerebral cortex and thalamus whose activities can be concomitant or delayed. The striatumis a major site of memory formation as the acquisition in the behavioral repertoire has been associated with cortico-striatal (CS) synaptic plasticity. If the vast majority of the studies focused on cortical inputs, howeverless is known about thalamo-striatal (TS) plasticity rules and their interplay with CS plasticity. Here, using a brain slice preparation preserving afferents from both the somatosensory cortex and the parafascicular thalamic nucleus, we investigated at the single neuron level with patch-clamp recordings the CS and TS synaptic long-term plasticity and their interplay. We found bidirectional Hebbian and anti-Hebbian spike-timing-dependent plasticity (STDP) at thalamic and cortical inputs, respectively, driving concurrent changes at striatal synapses. We show that STDP-TS produced heterosynaptic plasticity at non-stimulated CS synapses, and conversely. Via heterosynaptic plasticity, thalamus shapes CS synaptic efficacy changes. We also provide a mathematical model to explore the dynamics of the interaction between STDP-CS and STDP-TS. Finally, based on the model prediction we unveil the existence of LTD areas in the STDP-CS map under the influence of STDP-TS. The existence of concurrent STDP at CS and TS synapses together with potent heterosynaptic plasticity might contribute to homeostasis of the striatal network. Thus, these findings highlight the major impact of precise timing in cortical and thalamic activity for the memory engram at striatal synapses.

Key words:spike-timing-dependent plasticity, thalamus, striatum, heterosynaptic plasticity

00106
BDNF regulates bidirectional endocannabinoid-dependent plasticity at corticostriatal synapses

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Abstract

The dorsal striatum corticostriatal synapses exhibit bidirectional synaptic plasticity, NMDAR- and endocannabinoids-(eCB)-mediated, implicated in the encoding of procedural learning. Corticostriatal plasticity is of crucial importance for shaping striatal functions that can be modulated by several factors. Brain-derived neurotrophic factor (BDNF) and its receptor, the tropomyosine receptor kinase-B (TrkB) controls NMDAR-dependent plasticity the striatum and other brain structures. However, despite the well-known cross-talk between BDNF and eCBs, the role of BDNF in eCB-plasticity in striatum remains unknown. Here, we show that BDNF/TrkB signaling promotes eCB-plasticity (LTD and LTP) induced by rate-based (low-frequency stimulation) or spike-timing-based (spike-timing-dependent plasticity, STDP) paradigm in striatum. We show that TrkB activation is required for the expression and the scaling of both eCB-LTD and eCB-LTP. Using two-photon imaging of dendritic spines combined with patch-clamp recordings, we show that TrkB activation prolongs intracellular calcium transients. That leads to an increase of eCB synthesis and release. We provide a mathematical model for the dynamics of the signaling pathways involved in corticostriatal plasticity. Finally, we show that TrkB activation enlarges the domain of expression of eCB-STDP. Our results reveal a novel role for BDNF/TrkB signaling in governing eCB-plasticity expression in striatum, that can be implicated in the engram of procedural learning.

00108
Thalamus drives corticostriatal plasticity via concurrent STDP and heterosynaptic interplay

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Abstract

The striatum, the primary entrance to basal ganglia, integrates excitatory inputs from both cerebral cortex and thalamus whose activities can be concomitant or delayed. The striatumis a major site of memory formation as the acquisition in the behavioral repertoire has been associated with cortico-striatal (CS) synaptic plasticity. If the vast majority of the studies focused on cortical inputs, howeverless is known about thalamo-striatal (TS) plasticity rules and their interplay with CS plasticity. Here, using a brain slice preparation preserving afferents from both the somatosensory cortex and the parafascicular thalamic nucleus, we investigated at the single neuron level with patch-clamp recordings the CS and TS synaptic long-term plasticity and their interplay. We found bidirectional Hebbian and anti-Hebbian spike-timing-dependent plasticity (STDP) at thalamic and cortical inputs, respectively, driving concurrent changes at striatal synapses. We show that STDP-TS produced heterosynaptic plasticity at non-stimulated CS synapses, and conversely. Via heterosynaptic plasticity, thalamus shapes CS synaptic efficacy changes. We also provide a mathematical model to explore the dynamics of the interaction between STDP-CS and STDP-TS. Finally, based on the model prediction we unveil the existence of LTD areas in the STDP-CS map under the influence of STDP-TS. The existence of concurrent STDP at CS and TS synapses together with potent heterosynaptic plasticity might contribute to homeostasis of the striatal network. Thus, these findings highlight the major impact of precise timing in cortical and thalamic activity for the memory engram at striatal synapses.

Key words:spike-timing-dependent plasticity, thalamus, striatum, heterosynaptic plasticity

00127
Sub-second dopamine measurement in dorsolateral striatum (DLS) during reward-associated behavior: in vivo assessment by the genetically-encoded dopamine sensor (dLight)

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Abstract

Dopaminergic transmission in striatum accompanying phasic and tonic firing patterns of midbrain neurons is critical for the integration of motor control, habit-formation, and reward-associated behaviors. Despite enormous interest, high-resolution in vivo assessment and identification of phasic (hundreds-of-millisecond bursts) dopamine release has been especially difficult in DLS. The measurement challenge arises mainly from two fundamental reasons; 1) the higher density of the dopamine transporter (DAT) in DLS clears the neurotransmitter faster than other regions, severely reducing the possibility for interaction between the chemical and sensor. 2) the temporal and functional sensing resolution of current in vivo assessment technologies (e.g. microdialysis, fast-scan cyclic voltammetry) are limited to measurements of dopamine overflow and may not reliably reflect synaptically confined rapid dopamine signaling by discriminating neuronal subtype or projection target. Recently, the development of the genetically-encoded dopamine sensor - dLight- has helped to overcome these difficulties and increase our ability to interrogate dopamine signaling with unprecedented resolution. In this study, we report sub-second phasic dopamine release in DLS of behaving mice during Pavlovian training for food reward by exploiting the enhanced dLight sensor (version 1.3b) and in vivo fiber photometry using time-correlated single photon counting (TCSPC) technique. The greater dynamic range of dLight sensor and our highly-sensitive TCSPC detection system allows us to measure pronounced phasic dopamine transients in NAc and DMS, preferentially in the early phase of Pavlovian training, and in DLS in the later phase of training. Also, different dopamine dynamics were monitored in NAc, DMS, and DLS during learning and performance of a food reward-driven goal-directed lever-pressing task. Finally, cocaine effects on striatal dopamine release were investigated with in vivo TCSPC measurement.

00139
Dopamine-endocannabinoid interactions mediate spike-timing dependent potentiation in the dorsal striatum

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Abstract

Dopamine modulates striatal synaptic plasticity, a key substrate for action selection and procedural learning. Thus, characterizing the repertoire of activity-dependent plasticity in striatum and its dependence on dopamine is of crucial importance. We recently unraveled a striatal spike-timing-dependentlong-term potentiation (tLTP) mediated by endocannabinoids (eCBs) and induced with few spikes (~5-15).Whether this eCB-tLTP interacts with the dopaminergic system remains to be investigated. Here, we report that eCB-tLTP is impaired in Parkinson's disease and rescued by L-DOPA. Dopamine controls eCB-tLTP by viadopamine type-2 receptors (D2R) located presynaptically in cortical terminals. Combining our experimental results and modeling, we show that dopamine-endocannabinoid interactions via D2Rare required for the emergence of tLTP in response to few coincident pre- and post-synaptic spikes and control eCB-plasticity by modulating the long-term potentiation(LTP)/depression(LTD) 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. Because it is induced by small numbers of pairings, eCB-tLTP may represent a central molecular substrate for the rapid learning of new arbitrary associative memories and behavioral rules characterizing the flexible behavior of mammals or during initial stages of slower habit learnings.

00159
Studying corticostriatal synaptic plasticity at single dendritic spines with two-photon glutamate uncaging

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Abstract

Dopamine plays an important role in motor learning by tempering the information flow between cortical projections and striatal medium spiny neurons (MSNs). It does that in part by modulating plasticity at corticostriatal synapses, which is known to occur during skill learning and goal-directed actions. Electrophysiology studies demonstrated that dopamine is crucial for long term potentiation (LTP) induction at striatonigral MSNs through D1 receptor activation, and favors long term depression at striatopallidal MSNs by binding to D2 receptors. Corticostriatal synapse LTP is also dependent on NMDA receptor activity, while a role for growth factors has been suggested. Few studies, however, have addressed corticostriatal plasticity at the single synapse level. Therefore, it is unknown whether a functional/structural relationship exists and whether plasticity can be evoked at single dendritic spines or needs spine cooperation. We are studying corticostriatal LTP mechanisms at single MSN spines by two-photon glutamate uncaging at individual spines, using mouse brain slices. We monitor spine volume changes of both stimulated and neighboring spines by two-photon microscopy, which have been shown to parallel functional synaptic changes in the hippocampus. Glutamate uncaging at single dendritic spines of striatonigral MSNs evoked a short-term increase in spine volume, in a subset of stimulated spines, when performed in 0 mM Mg2+. We are currently testing how D1 receptor activation affects the outcome and duration of plasticity. We plan to test whether spine enlargement can be used as a proxy for functional LTP at corticostriatal synapses by combining single spine two-photon glutamate uncaging with electrophysiological recordings.

00012
The role of substance P in reinforcement-based sequence learning

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Abstract

Several lines of evidence suggest that the striatum is one of the fundamental structures involved in sequence learning. Substance P is a neuropeptide abundant in the striatum known to interact with dopamine which is, itself, instrumental in producing changes in cortico-striatal synapses as new motor patterns are learned. We sought to investigate substance P role's in sequence learning in an operant conditioning experiment, supplemented with computational modelling. Rats (n = 20) were trained to perform a two action sequence in a Skinner box with two levers, for at least 25 sessions and until they had reached stable behaviour for five consecutive days. Then, half of the rats were switched to learn a new sequence and half were kept doing the same sequence. In the first three days of this second phase, rats were injected (i.p.) with a substance P (neurokinin 1) antagonist (L-733,060: 2mg) or with vehicle. Rats injected with the substance P antagonist learned the new sequence faster and performed the previous sequence less than vehicle rats. The performance of the rats that kept doing the same sequence was not affected by the drug. Using a temporal difference reinforcement learning model with an actor-critic paradigm we were able to replicate the results from both experimental groups by manipulating the state value learning rate of the model. It has been suggested that striatal striosomes represent state values, and it has recently been reported that substance P boosts dopamine transmission only in striosomes. Our results are in line with these findings, since blocking substance P facilitated learning of a new sequence, an outcome replicated by decreasing the state value learning rate in our model. Interestingly, this led to the decay of all previously learned action preferences, resetting the system, which ultimately led to faster learning of new actions. This suggests that striatal substance P plays a role in the perseveration of learned action preferences.

00027
Framework for modelling the effects of motivational state on choice and learning in the basal ganglia

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Abstract

Decision-making relies on adequately evaluating the consequences of actions, a process in which the basal ganglia plays a key role. Neural activity and plasticity in the basal ganglia are modulated by dopaminergic signalling from the midbrain. Physiological factors, such as hunger, scale dopamine levels and the reward prediction error. Consequently, they alter the motivation for taking actions and learning about the consequences of actions. However, to our knowledge, no formal mathematical formulation exists for how a physiological state affects learning and action selection in the basal ganglia. We developed a framework for modelling the effect of motivational state on choice and learning. During action selection, the model evaluates the utility of all available options by weighting the positive and negative consequences of each action according to a physiological state. We defined the value function of the physiological state as a concave function, because it is more important to act when you are in a low physiological state, compared to a near optimal state. We also proposed a mapping of the computation of the utility onto the basal ganglia network, in which the motivation is encoded by dopamine. We defined a state-dependent reward prediction error in which the motivational level scales both the reward and the expected value, because recent data show that after conditioning, the physiological state of the animal modulates the reward prediction error encoded in dopaminergic activity. Such modified definition allows the model to explain a large body of experimental data. In summary, we developed a biologically relevant, mathematical framework for state-dependent choice and learning in which learning models of the basal ganglia and the incentive salience theory are brought together. This work provides mechanistic insight into how certain factors modulate decision-making in the basal ganglia and can serve as a building block for extending this to different contexts.

00048
Striatal low-threshold spiking interneurons regulate goal-directed learning

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Abstract

The dorsomedial striatum is critically involved in motor control and reward processing, yet the specific neural circuit mediators remain poorly understood. Current models implicate both excitatory projection neuron and local interneuron control of striatal spiny neuron populations. Despite recent evidence highlighting the extensive local connectivity of striatal low-threshold spiking interneurons (LTSIs), the in vivo function of this subtype remains largely unexplored. We employed fiber photometry to assess LTSI population calcium activity during a range of DMS-mediated behaviors. While we did not find significant movement or novelty-associated activity, LTSIs were found to strongly responded to reward. Surprisingly, this specific reward-related activity was down-modulated during operant learning. To explore a causal role for LTSI modulation in regulating the early stages of instrumental acquisition, we employed two mechanistically distinct in vivo manipulations (Kir2.1-mediated inhibition and halorhodopsin) to suppress LTSI spiking. We revealed that down-modulation of LTSI activity was critical in regulating the acquisition of novel contingencies, but not modification of previously learned contingencies. In contrast, persistent activation of this population with channelrhodopsin slowed instrumental acquisition. Similar suppression of fast spiking interneurons did not reproduce these effects, suggesting a unique function of LTSIs in these early stages of operant acquisition. Finally, we utilized viral-genetic approaches to specifically reveal a role for the GABAergic functions of LTSIs in learning. Together, our data provide new insights into this subclass of striatal interneurons as important initial gatekeepers of goal-directed instrumental learning.

00050
Dopaminergic modulation controls evoked plasticity in mPFC after aversive learning

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Abstract

The genesis and turnover of excitatory neuronal connections underlie development, learning, and disease. Decades of studies have yielded insights into the processes that regulate the formation, pruning, function, and dysfunction of synapses. Still, making causal inferences about the regulation of synapse birth remains technically challenging within complex circuits. Here, we use multilaser 2-photon microscopy in order to probabilistically induce the de novo growth of dendritic spines and synapses with high spatiotemporal precision on genetically targeted pyramidal neurons of the medial prefrontal cortex (mPFC). Using this approach to causally interrogate structural plasticity in the mPFC in the context of aversive learning, we find that rapidly acting antidepressant drugs, such as ketamine, potently increase the potential for spinogenesis in mPFC pyramidal cells. De novo spinogenesis is enhanced by acute stress, blunted after aversive learning, and recovers with a single low-dose ketamine treatment. Surprisingly, this effect depends on dopaminergic (DA) signaling from the ventral tegmental area (VTA). Low-dimensional optical readout of VTA DA neuron activity is sufficient to predict acute behavioral responses during aversive learning, as well as future sensitivity to ketamine. A single dose of ketamine normalizes DA activity dynamics, recovering normal behavioral responses and glutamate uncaging-evoked plasticity. Ketamine actions on behavior and plasticity of dendritic spines are blocked by chemogenetic inhibition of DA signaling and mimicked by activating VTA DA neurons using optogenetic or chemogenetic approaches. Together, these data demonstrate a causal link between neuromodulatory systems regulating mPFC function, aversive learning, and plasticity enhancements driven by a therapeutically promising NMDA receptor antagonist.

00053
Adaptative reward coding by dopamine neurons is explained by a model of noise-sensitive value learning

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Abstract

Many experiments have established that VTA dopamine neurons respond to unpredicted rewards. According to an influential theory pioneered by Schultz et al., those signals should be interpreted as reward prediction errors (the difference between reward obtained and reward expected) that drive reinforcement learning in the basal ganglia.

However, more recent experimental findings imply that this theory needs to be refined. Notably, Tobler et al. have shown that dopaminergic neurons encode individual rewards relative to previous rewards—the same reward might provoke different responses depending on the statistics of the recent reward history. Such adaptive coding is not compatible with the conventional model of basal ganglia learning, which requires absolute feedback. Tobler's findings, therefore, indicate that the interpretation of dopaminergic signals as reward prediction errors must be updated.

We offer an updated model of learning—noise-sensitive value learning—that reconciles the conventional theory with adaptive reward coding. The model features adaptive prediction errors by design, and thus allows to reinstate the interpretation of dopamine responses as teaching signals that drive reinforcement learning.

The crucial new feature of noise-sensitive learning is that reward variability is tracked and incorporated in the evaluation of newly encountered rewards. Concretely, reward predictions are scaled by the learned reward variability. When rewards are stable, prediction errors are thus magnified and result in strong behavioural adaption. Variable rewards, on the other hand, result in dampened prediction errors and therefore afford more careful adaption in unpredictable environments.

In addition to explaining adaptive prediction errors, our model also explains certain features in behaviour. We review those behavioural signatures of adaptive coding and discuss a biological implementation of noise-sensitive learning in the basal ganglia network.

00083
Sustained dopaminergic bursts and noradrenergic pauses favor exploitative behavioral states

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Abstract

We are constantly faced with the trade-off between exploiting past actions with known outcomes and exploring novel actions whose outcomes may be better. When environmental rewards are stable, it is preferable to perform actions known to be rewarding, but when the environment is changeable, it is adaptive to explore alternatives and revisit actions whose value may have changed. This balance between exploitation and exploration is thought to rely on two interacting systems, namely modulation of corticostriatal circuits by dopaminergic neurons of the substantia nigra pars compacta (SNc), and modulation of anterior cingulate cortex (ACC) processing by noradrenergic neurons of the locus coeruleus (LC). However, little is known about the dynamics of these systems during exploitative and exploratory states. Here, we investigate the ways in which dopaminergic and noradrenergic transmission evolve during exploratory and exploitative behavioral states. We developed a novel behavioral paradigm to capture exploratory and exploitative action selection in which mice explore an environment to discover a rewarded sequence of three nose pokes in order. The entropy of the distribution of sequences performed is initially high, suggesting that mice are exploring a range of possible actions, but entropy falls with training, showing that mice learn to consistently focus on the rewarded sequence. We then imaged the activity in genetically-identified dopaminergic neurons in SNc or noradrenergic neurons in LC during task performance. Exploitative behavioral states were marked by sustained increases in dopaminergic activity and decreases in noradrenergic activity. These effects cannot be accounted for by simple differences in reward rate. Together, these experiments clarify the role of dopaminergic and noradrenergic circuits in modulating behavioral variability, with important implications for coding in downstream circuits of the dorsal striatum and ACC.

00085
Direct but not indirect pathway spiny projection neurons in the posterior dorsomedial striatum are required for goal-directed learning

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Abstract

It is now well accepted that the posterior region of dorsomedial striatum (pDMS) is necessary for learning goal-directed instrumental actions, however the role of pDMS spiny projection neurons (SPN), which project either directly (dSPNs) or indirectly (iSPNs) to basal ganglia output structures, in such learning remains largely unknown. In a series of experiments, we examined the role of dSPNs and iSPNs in the acquisition of goal-directed instrumental actions in rats. Our first experiment used double retrograde labelling in combination with an activity marker (zif-268/EGR1) to measure activity of dSPNs and iSPNs following instrumental or yoked, non-contingent training. Immunofluorescence quantification revealed significantly higher zif-268 expression in the pDMS following instrumental relative to yoked training in dSPNs but not iSPNs. Our next two experiments examined whether dSPNs and iSPNs are functionally required for goal-directed learning. We used a two-virus approach; retrograde AAV-Cre was infused bilaterally into the substantia nigra or globus pallidus external segment, and Cre-dependent hM4Di DREADDs was infused bilaterally into the pDMS to specifically express hM4Di-DREADDs on dSPNs or iSPNs respectively. Rats were trained on an instrumental lever press task, and prior to each training session, SPNs were silenced with a systemic injection of clozapine-n-oxide (CNO; control rats received vehicle). We then conducted a drug-free test of goal-directed learning using an outcome devaluation test with specific satiety. We found that silencing dSPNs but not iSPNs in the pDMS during training decreased rats' sensitivity to outcome devaluation despite restoration of pathway activity on test. Together, these results suggest that activity in dSPNs but not iSPNs in the pDMS is necessary for learning goal-directed instrumental actions. Results will be discussed in terms of the relative involvement of dSPNs and iSPNs in learning and performance of instrumental actions.

00113
Sensitivity of calcium-dependent corticostriatal plasticity to trial-to-trial variability

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Abstract

Corticostriatal plasticity is hypothesized to support goal-directed and habit learning by modifying the weights of synapses from cortical pyramidal neurons to striatal projection neurons (SPNs). Both in vitro and computational experiments support this hypothesis by demonstrating that patterns of cortical stimulation and postsynaptic activity in SPNs can produce either long term potentiation (LTP) or long term depression (LTD), depending on timing and frequency of inputs. Calcium dynamics are critical for corticostriatal plasticity, and synaptic calcium transients are sensitive to spatiotemporal patterns of synaptic input. We have previously shown that a calcium based plasticity rule with dual amplitude- and duration-thresholds can predict LTP and LTD outcomes of several in vitro plasticity experiments (Jędrzejewska-Szmek et al., Eur J Neurosci, 2017). However, it is not clear how corticostriatal plasticity outcomes from in vitro experiments translate to in vivo conditions. Cortical activity in vivo exhibits high trial-to-trial variability, while in vitro plasticity results from precisely timed, repeated stimuli. To address the effect of variability on synaptic plasticity, we extended our biologically realistic, computational model of SPNs, which previously showed that calcium transients encode spatiotemporal patterns of synaptic input with high spatial specificity (Dorman et al., eLife, 2018). We test whether LTP and LTD develop when trials are repeated with variability as observed in vivo. We conducted simulations using inputs constructed from experimentally recorded in vivo cortical spike trains with low, intermediate, or high trial-to-trial variability. Our results show that low or intermediate variability results in stronger plasticity and more potentiated synapses, while fewer synapses develop persistent plasticity for high trial-to-trial variability. These results will enable predictions of plasticity outcomes in vivo based on recorded spike trains.

00117
Experience-dependent changes in the nucleus accumbens underlie acquisition of cued reward-seeking behavior.

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Abstract

Animals learn associations between contextual cues and the natural rewards they predict (e.g., food, water, sex). As a result, reward-predictive cues come to trigger approach to locations where rewards are available. The nucleus accumbens (NAc) in the ventral striatum is implicated in the expression of such cued reward-seeking behaviors. Consistent with this idea, many neurons in the NAc become excited upon presentation of an already-learned reward-predictive cue (e.g. Nicola et al., J Neurophys 2004a). Cue-evoked excitations encode the motivational value of the stimulus and are required for expression of the subsequent approach behavior (e.g., Caref & Nicola, eLife 2018; Du Hoffmann and Nicola, J Neurosci 2014). However, whether and how cue-evoked excitations emerge during learning has not yet been established. In Experiment 1, we recorded the unit firing activity of NAc core neurons as rats learned to approach a reward receptacle upon presentation of a cue. Our results indicate that cue-evoked excitations begin to increase a few trials before cued approach behavior is detected and they continue to escalate as cued reward-seeking responses become more vigorous.

Because infusion of NMDA receptor antagonists into the NAc during training impairs acquisition of similar reward-oriented behaviors (e.g., Di Ciano et al., J Neurosci. 2001), we hypothesized that the emergence of cue-evoked excitations during cued approach learning is due to NMDA receptor-dependent plasticity within the NAc. In Experiment 2, we performed colocalized simultaneous unit recordings and NMDA antagonist microinfusions in the NAc. We found that the potentiation of learning-related cue-evoked signals in the NAc depends on NMDA receptor-dependent plasticity within this structure. Our results link accumbens plasticity, changes in striatal activity and the emergence of conditioned behavior, revealing a neural mechanism via which the NAc participates in associative learning.

00120
Cortex-Basal Ganglia interactions in category learning

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Abstract

Category learning is more than just a simple sensory convergence, but a fundamental characteristic of sophisticated thought that structures the world into meaningful concepts (Seger & Miller, Annual Review of Neuroscience, 2010). Studies suggest that both basal ganglia (BG) and prefrontal cortex (PFC) are involved in category learning (Seger & Miller, Annual Review of Neuroscience, 2010; Antzoulatos & Miller, Neuron, 2011), and here we present a neurocomputational model to study the interplay between these two brain structures in category learning (Villagrasa et al., Journal of Neuroscience, 2018).

In our model, the quickly learning BG teach the slowly learning PFC to acquire category knowledge via inhibiting the cortico-thalamo-cortical loop. Particularly, the BG teaching signal provides the PFC with the BG category response to the presented stimuli. We show that the slow learning in the PFC is key to push the categorization performance of the full model to high levels while the fast learning in the BG is key for the system to quickly adapt to new environments.

As our model replicates key physiological and behavioral data from monkeys (Antzoulatos & Miller, Neuron, 2011), our model gives some confidence in our predictions. We predict that the observed decrease of category selectivity in the striatum of monkeys when dealing with an increased number of stimuli is not due to a striatal disengagement in category learning but to an increase in the variability of the striatum cells response to category information. We confirmed this prediction by re-analyzing previous monkeys' data. This increase in variability occurs because the fast learning in the striatum cells does not allow them to respond to all stimuli of the same category when the number of these stimuli becomes large.

00130
Behavioral flexibility and neuromodulation—an hypothesis of an underlying mechanism

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Abstract

Recent studies indicate that high activity in striatal cholinergic interneurons (ChINs) increases behavioral flexibility. Synchronized ChIN activity, leading to high acetylcholine (ACh) release, has also been shown to directly trigger dopamine (DA) release from dopaminergic terminals in striatum. High DA leads to increased excitability of the direct pathway striatal projection neurons (dSPN). High ACh inhibits the M-current localized at the axon initial segment, which also leads to increased excitability of dSPNs (Shen et al., 2005).

Here we investigate the combined effect of high ACh and DA on dSPN using biophysically detailed models. The models used were derived from a previously published model in the lab (Lindroos et al., 2018) and included non uniform modulatory effects over cellular compartments.

Preliminary results predict that high DA and ACh under in vivo like conditions, with synaptic activation of dendrites, can give rise to complex spiking pattern, resembling the ones seen in hippocampus. In hippocampus these complex spikes are associated with behavioral time scale plasticity and place cell tuning.

Based on this, we propose that complex spikes may also occur in striatum, when the effect of multiple neuromodulators are combined, and that they could signal the need for an updated action selection strategy.

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00150
Acquisition of goal-directed actions potentiates prelimbic projections to direct pathway neurons in the dorsomedial striatum

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Abstract

Learning associations between actions and outcomes in a goal-directed behavioral task requires converging inputs to the posterior dorsomedial striatum (pDMS). Projections on to SPNs undergo plasticity during this learning, however it is unknown what specific inputs change and what the nature of this plasticity is. Areas projecting to the pDMS that are required for goal-directed learning include the basolateral amygdala (BLA) and the prelimbic cortex (PL). We first discovered via behavioral tests that BLA-pDMS projections were not critical for goal-directed learning, whereas BLA-PL projections were. In Drd2-EGFP mice, we then investigated the PL projections to the pDMS, ex vivo, following acquisition of a goal-directed action. Plasticity on to pDMS SPNs was measured using activation of pathway specific fibers. We found significant potentiation (greater AMPA/NMDA ratio) in both ipsilateral and contralateral PL projections to D1 SPNs, but no change to D2 SPNs. Conversely, no learning-related plasticity in BLA-pDMS projections was found, confirming this direct pathway is unrelated to the behavior. Further experiments demonstrated that transient BLA inactivation during learning with DREADD technology abolished the development of learning-related plasticity in the PL-pDMS pathway. These results demonstrate critical pathways that undergo plasticity during goal-directed learning, to encode and enact information via direct pathway SPNs. Additionally, the findings suggest that a role of the BLA in this system is to support PL-pDMS plasticity.

00166
Subthalamic neuromodulation improves short-term motor learning in Parkinson’s disease

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Abstract

The basal ganglia and cerebellum are implicated in both motor learning and Parkinson’s disease (PD). Deep brain stimulation (DBS) is an established treatment for advanced PD that leads to motor and non-motor effects by modulating specific neural pathways. Recently, a disynaptic projection from the subthalamic nucleus (STN) to cerebellar hemispheres was discovered. To investigate the functional significance of this pathway in motor learning, short-term improvement in motor execution in 20 PD patients ON and OFF STN-DBS and 20 age-matched healthy controls was studied in a visuomotor task combined with whole-brain connectomics. Motor learning was impaired in PD OFF stimulation, but was partially restored through DBS. Connectivity between active DBS contacts and a distributed network of brain regions correlated with improvement in motor learning. Region of interest analysis revealed connectivity from active contact to cerebellar hemisphere ipsilateral to hand movement as the strongest predictor for change in motor learning. Peak predictive voxels in the cerebellum localized to Crus II of Lobule VII, which also showed higher STN than motor cortex connectivity, suggestive of a connection surpassing motor cortex. Our findings provide new insight into the circuit nature of PD and the distributed network effects of DBS in motor learning.

00030
Interactions between dopamine and other neuromodulators in the striatum.

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Abstract

The striatum integrates incoming glutamatergic and dopaminergic inputs, directly fed to medium spiny neurons (MSN) but also indirectly through cholinergic, NOergic and other interneurons. While dopamine is primarily integrated through the cAMP/PKA signaling pathway, glutamate, acetylcholine and NO may also affect the same pathway. To study how these neuromodulatory cues interact dynamically in MSNs, we used genetically-encoded biosensors to image the cAMP/PKA pathway with a high spatial and temporal resolution in live striatal brain slices. These data were used to constrain models of intracellular signaling, and simulations were used to test mechanistic hypotheses.

Surprisingly, we observed that the cAMP response to D1 and D2 receptor stimulation was obtained with dopamine concentrations in a similar sub-micromolar range, suggesting that both D1 and D2 receptors can transduce phasic dopamine into a cAMP signal. However, downstream at the PKA level, D2 MSNs were unresponsive to phasic dopamine: simulations suggest they might respond to a pause in dopaminergic input.

We found that D1 MSNs respond non-linearly to transient dopamine, switching on PKA-dependent phosphorylation in an all-or-none manner. We propose that this effect, particularly prominent in the nucleus, may work as a binarizing filter to selectively detect phasic dopamine while rejecting background cAMP “noise”.

Glutamate, through NMDA receptors, was found to activate type 1 phosphodiesterase, which, by degrading cyclic nucleotides, antagonizes striatal LTP. NO, through the cGMP pathway, activates type 2 phosphodiesterase.

Finally, we report that very low levels of acetylcholine, through M4 muscarinic receptors, efficiently prevented D1 response in MSNs, indicating that a pause in acetylcholine release is required for the action of dopamine. Activation of M4 receptors in vivo reversed the effects of chronic hyperdopaminergia, which may constitute a therapeutic strategy to treat hyperactivity.

00031
Broadband entrainment of striatal low-threshold spike interneurons

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Abstract

Neurons firing repetitively respond to input in a frequency dependent manner. The frequency dependence of entrainment, spiking resonance, determines which frequencies will increase the regularity of a neuron's spike pattern. For striatal circuits consisting of both interneurons and spiny projection neurons, the unique spiking resonance of each striatal cell type (Beatty et al. 2015) will set the temporal dynamics for the output to downstream basal ganglia nuclei. We studied the spiking resonance of identified low-threshold spike (LTS) interneurons expressing GFP under the control of the neuropeptide Y promoter. LTS cells were probed using small amplitude sine wave currents or broadband noise input, and their spiking resonance was compared to that of spiny projection neurons. On average, LTS cells were less frequency selective and entrained by a broader range of frequencies, peaking within the beta band (13 - 30 Hz). Spiny neurons were more selective, peaking in a narrower band of frequencies centered on their own firing rates. We measured phase resetting curves (PRCs) for both cells types and used them as a modeling tool to interpret our results. PRCs of LTS cells were nearly twice as large in amplitude but had smaller first harmonics, and their PRCs had greater representation of higher order harmonics. These results simultaneously explain their broad frequency response to sine waves and their greater sensitivity to noise. LTS cells form a much smaller proportion of total cells within any one striatal circuit. Their broad frequency spectrum allows them to be flexible in their response to inputs. Spiny neurons form a much larger proportion of cells, and cluster into groups of narrowly tuned projection neurons.

00039
Specific reorganization of striatal network dynamics during habit formation

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Abstract

Procedural memory, the memory of habits, is formed by the repetition of a given action. The neural substrates underlying this memory are the basal ganglia, long known to be critical for normal motor control, but now also recognized as influencing cognitive and motivational aspects of behavior. The striatum, the input stage of basal ganglia, relays information between the cortex and other subcortical structures, thus insuring the selection and integration of cortical information by forming functional parallel loops (associative, sensory-motor and limbic). The associative loops include the dorsomedial striatum (DMS) and mediate the first phase of procedural learning (goal-directed behavior). The sensorimotor loops include the dorsolateral striatum (DLS) and mediate habit formation. Although the anatomy of the circuits involved in procedural learning has been well described, virtually nothing is known about the dynamics of the striatal networks responsible for the engram of procedural memory.

The goal of our study was to characterize the dynamics of the striatal networks involved in the different phases of procedural learning. Using an accelerated rotarod paradigm, we formed procedural memory in animals with moderate or intensive training to form goal-directed behavior and habit, respectively. We monitored the striatal networks' activity using two-photon calcium imaging and we processed the signal to build functional maps of the networks. We first observed that in naïve animals, DMS and DLS networks have different properties. Then, after training, we observed a re-organization of the networks' activity with different patterns emerging in the two territories.

Altogether, our findings show a rapid and major territory-specific change in the striatal network dynamics during procedural learning.

00052
Input dependent encoding of basal ganglia neurons

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Abstract

The basal ganglia (BG) have an important role in the processing of motor, cognitive and limbic information through their reciprocal connections with the cortex. Abnormal BG activity has been related to a variety of sever disorders, including Parkinson's disease. Characterizing the computational properties of individual BG neurons is crucial for understanding their contribution to normal brain function and its breakdown during different pathologies.

We used a generalized linear model (GLM) to quantify the encoding of individual neurons by incorporating a linear stimulus filter, a spike history filter, and a bias term. The model was generated by fitting parameters to the in-vitro whole-cell responses of the neurons to repeated current injection (frozen noise). These models accurately reproduced the responses of the experimentally recorded cells, however, the GLM parameters were found to be highly sensitive to the internal state of the neurons, such as the dependency on the baseline firing rates. Moreover, the GLMs were not inter-exchangeable, such that there was no single GLM of a neuron that was useful for all of its states. This indicates that the underlying computation performed by the neuron is not independent of its firing rate, and that there is no single "real" encoding of a neuron, but rather an input dependent encoding. We show how different encoding properties are dependent on the baseline firing rate, and their influence on the information processing and the fidelity of the neuron.

As the firing rate of real neurons typically fluctuates over multiple time scales, this finding is crucial for understanding the principles of information transmission, which are dynamic and are dependent on the state of the network. We propose that this input dependent computation may contribute to the deficient in computational capabilities of BG neurons during different disorders, due to the change in baseline firing rates throughout the BG over the course of the disorders.

00054
Uncoupling the roles of firing rates and spike bursts in shaping the beta band oscillations in basal ganglia

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Abstract

One of the most prominent features of Parkinson's disease (PD) is the emergence of pathological epochs of β-band oscillations in the basal ganglia. There has been a strong interest in understanding the mechanisms underlying these oscillations because their suppression alleviates many motor symptoms of PD. Previous work has suggested that the STN-GPe network plays an integral role in emergence of β oscillations in the basal ganglia. These oscillations are also accompanied with change in the average firing rates and increase in spike bursts in STN and GPe neurons. However, it is not well-understood how changes in firing rate and spike bursting may affect β-band oscillations.

Therefore, here we investigated the dynamics of oscillations in a model of STN-GPe network. To isolate the effects of firing rate and spike bursts we used a neuron model in which firing rates and spike bursting can be independently varied. We found that an increase in STN firing rates is crucial to generate β -band oscillations. Surprisingly, oscillations were independent of changes in GPe firing rate if STN firing rate was constant. Next, we found that the effect of spike bursting is contingent on the network activity state. In strong oscillations or completely aperiodic state, spike bursting had no effect on the network activity. Only when the network state was close to the border of oscillatory and non-oscillatory regimes, an increase in GPe bursting enhanced oscillations whereas an optimal proportion of STN bursting quenches these oscillations. However, excessive increase in STN bursting induces long-lasting β-band oscillations. Our results suggest that in this regime the tandem of STN and GPe bursting may provide a mechanism to generate short-lived oscillations (β-bursts) as has been observed in healthy conditions. However, during PD, the network state shifts to the oscillatory regime where this tandem fails and leads to run away pathological oscillations.

00063
Responses of substantia nigra pars reticulata neurons to direct and indirect pathway GABAergic projections depend on intracellular chloride dynamics

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Abstract

The substantia nigra pars reticulata (SNr) is the primary output nucleus of the rodent basal ganglia and receives converging $GABA_A$-receptor mediated synaptic inputs from the direct and indirect pathways. The resulting $GABA_A$ current (I_{GABA}) is typically considered to be inhibitory; however, it may also be shunting, excitatory, or biphasic with inhibitory-to-excitatory responses mediated by intracellular chloride dynamics, which affect the $GABA_A$ reversal potential (E_{GABA}). Direct pathway projections synapse on the distal dendrites whereas indirect pathway projections form basket-like synapses around the somas of SNr neurons. Due to differences in compartment size and the distribution of the Cl extruder KCC2, dendritic and somatic compartments may have different susceptibilities to Cl accumulation and to breakdown of E_{GABA}. We predict that GABAergic signals to SNr will induce the range of atypical responses described above, depending on Cl extrusion capacity, compartment size and input properties. To investigate the contributions of the factors involved in shaping SNr responses to synaptic inputs, we constructed a novel data-driven conductance-based model of an SNr neuron that includes dendritic and somatic compartments. Our simulations show that $GABA_A$- and KCC2-mediated fluctuations in intracellular Cl can explain many aspects of the SNr spiking responses to GABAergic inputs from the direct and indirect pathways. We also explore the predictions of our model relating to SNr activity patterns in functionally relevant settings involving inputs from both pathways. Additionally, we provide a possible explanation for motor rescue in akinetic dopamine-depleted mice during optogenetic stimulation of indirect pathway subpopulations published by the Gittis lab. Integration of $GABA_A$ receptor-mediated synaptic inputs to somatic and dendritic compartments is not unique to SNr neurons; thus, these results may have implications for other brain regions as well.

00064
Dopaminergic transmission rapidly and persistently enhances excitability of D1 receptor-expressing striatal projection neurons

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Abstract

The activity of substantia nigra dopamine neurons has recently been linked to the initiation and invigoration of movement. Dopaminergic modulation of striatal projection neurons (SPNs) is thought to underlie this linkage, although the impact of native transmission on SPN excitability has not been directly studied. Using perforated patch-clamp recording, we found that optogenetic stimulation of nigrostriatal dopaminergic axons rapidly and persistently elevated the intrinsic excitability of dopamine D1 receptor-expressing SPNs (D1-SPNs). The evoked firing of D1-SPNs increased within hundreds of milliseconds of optogenetic stimulation and remained elevated for several minutes thereafter. Consistent with the negative modulation of depolarization- and Ca^{2+}-activated K^{+} currents, dopaminergic transmission accelerated subthreshold depolarization in response to somatic current injection, reduced the latency to fire, and diminished action potential afterhyperpolarization. Together, these data demonstrate that dopaminergic transmission potently increases the excitability of D1-SPNs with a time course that could support both sub-second and sustained behavioral control.

00093
How do subcortical networks shape the dynamics of pathological beta bursts? An in-silico dissection of Parkinsonian brain rhythms.

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Abstract

Parkinsonism and its associated motor impairments have been attributed to an aberrant rhythmicity of large-scale neural dynamics in the basal ganglia. The biophysical origins of this rhythm, occurring at beta frequencies (14-30 Hz), are currently unknown. Multiple hypotheses exist to explain the emergence of pathological oscillations as arising from alterations in the strength of connections in the cortico-basal-ganglia network. In this work we employ a modelling framework by which we test the plausibility of a range of competing computational models' ability to reproduce empirical data. Specifically, we optimize model parameters to match the statistical features (spectral power and directed functional connectivity) of a set of local field potentials experimentally recorded from the cortico-basal ganglia circuit in Parkinsonian rats with 6-OHDA induced dopamine depletion. This approach allows us to go beyond stationarity assumptions underlying frequency domain representations of brain activity and look at the mechanism that shape the intermittencies in rhythms- so called beta bursts, -which have recently become of interest to the field.

Using a formal model comparisons, we demonstrate the importance of: i) hyperdirect (cortico-subthalamic) pathway; and ii) thalamo-cortical relays in reproducing the patterns of observed functional connectivity. Having established the best fitting model we then conduct a systematic in-silico lesion study in order to a) validate our model using findings from empirical lesion experiments; b) determine the origin and propagation of rhythms in the model; and c) analyse the roles of particular pathways in shaping the properties of intermittent beta activity such as burst length and duration, as well as the role of inter-areal pathological synchronization.

00095
Use of a novel, genetically-encoded intensity-based acetylcholine sensing fluorescent reporter (iAChSnFR) to study basal ganglia function

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Abstract

Acetylcholine (ACh) was the first neurotransmitter to be identified and studied. “Vagusstoff”, as it was termed by Otto Loewi due to its release from vagus nerve, could regulate heart rate in isolated frog hearts. Since then, ACh has been found to be critical for alertness, cognition, and action control and has been studied for decades. Recently, microdialysis in combination with sensitive detection methods has allowed for study of ACh release in freely-moving animals. This method, however, is limited by low temporal resolution (typically 10-30-minute bins). Electrode sensors based on enzymatic methods were developed and allow for indirect measurements of ACh release on a faster time scale (tens of seconds), but are limited to a single behavioral session before the degradation of the enzymes impacts sensitivity of the sensor. These limitations have hindered the study of ACh dynamics and the role of ACh in specific behavioral events with any appreciable temporal resolution. Recently, several genetically-encoded fluorescent biosensors have been developed that allow for better study of neurotransmitter release in head-fixed or freely-moving animals. Our lab has validated one of these novel sensors, the iAChSnFR, to study ACh dynamics. We first characterized iAChSnFR ex vivo in striatal and cortical brain slices. We found that we could electrically evoke ACh release and that this release was stimulation duration- and intensity-dependent. We further found that we could dynamically, pharmacologically modulate the ACh signal with acetylcholinesterase inhibitors, a muscarinic receptor agonist, and a D2 dopamine receptor agonist. Importantly, we did not see any responses to electrical simulation in a control sensor. We have also confirmed the detection of a photometry signal in vivo and found tonic and phasic alterations in ACh activity in freely-moving mice treated with drugs of abuse. Finally, we are examining ACh dynamics in the acquisition of a motor skill (rotarod).

00101
Parkinson's disease uncovers an underlying sensitivity of subthalamic nucleus neurons to beta-frequency cortical input

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Abstract

Dynamics of beta-frequency oscillations in the cortex and subthalamic nucleus (STN) have become an important biomarker for akinetic/rigid symptoms in PD. Given the spectrum of different cortical input frequencies to basal ganglia, it is unclear why dopamine depletion specifically leads to an increase in beta-frequency synchronisation and how this relates to single neuron activity. Using microelectrode recordings from Parkinson's patients, we examined the strength of phase-locking of subthalamic nucleus (STN) unit activity to local and cortical oscillations as they varied in amplitude over time. A subset of STN neurons displayed a linear relationship with the instantaneous amplitude of ongoing oscillations, suggesting highly sensitive synchronisation between individual neurons and network oscillations selectively in the beta-frequency range. Using cortical stimulation in healthy and dopamine-depleted anaesthetised rats, we tested whether STN neurons displayed beta-frequency selectivity when driven with constant amplitude input at different frequencies. Beta frequency stimulation selectively reduced variability in spike timing following stimulation pulses. The timing of evoked spikes in relation to the initial multiphasic response suggests that the interval of beta-input provides an optimal window for eliciting the next spike with high fidelity. These findings suggest that cortical inputs to basal ganglia have a selective vulnerability to beta-frequency input that is uncovered when multiple pathways are driven at those frequencies. This beta-frequency specific resonance of STN neurons, and/or the network in which they are embedded, provides a potential mechanism for selective amplification of beta-frequency oscillations in the parkinsonian basal ganglia.

00109
Framework for development and optimisation of two multicompartmental neuron models: Cholinergic and Low-Threshold Spike Interneurons in the Striatum

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Abstract

The mouse striatum has an extensive microcircuit composed of 95% striatal projection neurons (SPNs) and 5% interneurons. Here, we focus on two of the spontaneously active interneuron types (Assous et al., 2018): cholinergic (ChIN) and low-threshold spiking (LTS) interneurons which each represents about 1% of striatal cells (Burke et al., 2017). Despite their rarity, they strongly influence the behavior of the striatum. The pause response in ChINs is important for reinforcement learning (Lim et al., 2014), and LTS provide a GABA-mediated inhibitory control of SPNs (Koós and Tepper, 1999). Additionally, a reciprocal influence exists between these interneurons (Elghaba et al., 2016). We developed detailed multicompartmental models based on reconstructed morphologies and ion channel expression. The neurons were filled with neurobiotin during patch clamp recordings, then stained and reconstructed. The electrophysiological data were analysed and features of interest were extracted using custom code, exploiting the open source library eFEL. We manually constrained the intervals of the conductance values for the optimisation. The optimisations were performed using BluePyOpt and carried out on resources provided by SNIC (PDC center for high performance computing, KTH). The models were validated against electrophysiological features not included in the initial optimisation and known properties, like the pause response in ChINs. Furthermore, the cortical, thalamic and intrastriatal synaptic inputs were modeled using NMDA, AMPA and GABA receptor models. These models will be used in the data driven framework to reconstruct the striatal microcircuits and investigate their function and interactions in the striatum. This study is funded by: Horizon2020 grant agreement 720270 and 785907 (Human Brain Project, SGA1 and SGA2); The Swedish Research Council; Swedish e-Science Research Center.

00115
Real-time in vivo monitoring of striatal GPCR signaling using FRET-based biosensors

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Abstract

Striatal neuromodulators have critical roles in action selection/initiation, decision-making, and reward-related learning. These neuromodulators exert their functions through G-protein-coupled receptors (GPCRs) that activate second messenger intracellular cascades to affect neuronal signaling. The dorsal striatum is a critical basal ganglia region that integrates a variety of neuromodulatory inputs from cortex, thalamus, and midbrain to control action learning and performance. These afferents form synapses onto indirect and direct projecting medium spiny neurons (MSNs). MSNs contain receptors that can oppositely regulate cAMP accumulation and PKA phosphorylation, which in turn can modulate neuronal activity and circuit function. The cAMP-PKA signaling pathway has been shown to be a key synaptic modulator not only in striatum, but throughout the brain. Little is known about real-time intracellular cAMP-PKA signaling following GPCR activation in vivo. We optimized in vivo optical fiber photometry methods to assess intracellular cAMP accumulation and PKA phosphorylation using Förster Resonance Energy Transfer (FRET)-based EPAC (cAMP) and AKAR (PKA) biosensors. These sensors can measure activity-induced changes in cAMP accumulation and PKA activity, respectively. Next, we validated these biosensors using 2-photon fluorescence lifetime microscopy in both lysates and cells. Since both sensors can be virally expressed in striatal neurons, it is now possible to measure real-time intracellular signaling in distinct striatal MSNs in freely moving animals. Fiber photometry was used to measure fluorescence lifetime to quantify FRET. Striatal PKA activity was reduced by general anesthesia, as measured by changes in the AKAR sensor donor lifetime. This finding suggests a tonic level of PKA activity in vivo. Anesthesia also altered cAMP accumulation. Finally, we have observed changes in cAMP mediated PKA activity dynamics in an accelerated rotarod training task.

00123
On how dopamine modulates sensory integration in dorsomedial striatum

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Abstract

Basal ganglia are a highly interconnected group of nuclei involved in sensory-motor, cognitive and emotional functions. The striatum is the input layer of the basal ganglia and receives cortical projections from motor, associative and sensory areas. In mouse, the dorsal striatum has been divided into two different functional areas; the dorsolateral (DLS) or sensory-motor and the dorsomedial (DMS), also called the associative striatum. The Medium Spiny Neurons of the direct (dMSNs) and indirect (iMSNs) pathway receive sensory information in the whole dorsal striatum. Whereas MSNs in the DLS are activated by tactile inputs, single MSNs in the DMS can be activated by inputs from different sensory modalities, or at least by visual and tactile inputs (Reig and Silberberg, 2014). Additionally, the dorsal striatum is densely innervated by dopaminergic axons from the Substantia nigra *pars compacta* (SNc). Dopamine is known to play a role in processes leading to corticostriatal synapses, modulating and inducing changes in neuronal transmission and plasticity, and behaviourally it has been strongly related with reward and attention. Moreover, dopamine depletion modifies the bilateral tactile responses recorded in the DLS (Ketzef et al, 2016). In this study, we explore the impact of dopamine when modulating visual, tactile and multimodal sensory responses in MSNs located in the DMS. To asses our objective, we perform *in vivo* opto-patch clamp recordings in identified MSNs and simultaneous local field potential recordings in primary visual and somatosensory cortex in anesthetized mice. Dopamine is released from the SNc terminals in the DMS by optogenetic or electrical stimulation while presenting visual and tactile contralateral stimuli. Our data suggests that dopamine release modulates differently the integration of visual and tactile inputs and selectively synchronizes multisensory information in a specific subpopulation of MSNs.

00124
Asymetric dynamics in the striatal indirect pathway under arousing psychotimulant drug action

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Abstract

The classical model of basal ganglia suggests that striatal indirect and direct pathways exert opposite action on the thalamo-cortical activation triggering motor control. However, recent studies performed in mice showing conjoint neuronal activities in action initiation or decision-making indicate more complex functions and diverse behavioral encoding, particularly in the indirect pathway. In the present work, we are interested in how the striatum conveys the general arousing effects of psychostimulants, which involve enhanced monoaminergic neurotransmission and cause important molecular changes in striatal projecting spiny neurons (SPNs). The questions of how psychostimulants affect the neuronal activity dynamics of the different pathways and their behavioral correlates remain quite elusive while the striatum plays a central role in controlling and promoting the behavioral activation properties of these drugs. To untangle striatal processing under psychostimulants effects, we employed large-scale *in vivo* calcium imaging (Inscopix) in videotracked freely behaving mice in open field. We show that indirect-pathway SPNs (iSPNs) in the dorsal striatum are divided into functional dynamic ensembles that are oppositely modulated by various psychostimulant drugs. Besides, our results suggest a higher level of heterogeneity underlied by a diverse motor encoding that is differentially reshaped by the drugs psychomotor-activating properties. Together these data show a high degree of functional diversity within iSPNs and highlight a versatile encoding of psychostimulants action by the indirect pathway.

00147
Does GABA co-released from striatal dopamine axons autoregulate dopamine release?

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Abstract

It is now established that striatal dopamine (DA) axons co-release GABA. We tested the hypothesis that this co-released GABA autoregulates DA release via $GABA_A$ receptors on DA axons. We optically stimulated DA axons in dorsal and ventral striatum (dStr and vStr) in *ex vivo* slices from male and female Ai32:DAT-cre mice and monitored evoked increases in extracellular DA concentrations ($[DA]_o$) using fast-scan cyclic voltammetry. We found that application of the $GABA_A$ receptor agonist muscimol (10 µM) inhibited single-pulse (1 p) evoked $[DA]_o$ by 20-30% in both regions and in both sexes, indicating the presence of functional $GABA_A$ receptors on DA axons. Immuno-electron microscopy analysis from 3 mice confirmed that 45 ± 13% of DA axons express α3-$GABA_A$ receptor subunits in dStr and 37 ± 5% in vStr. The $GABA_A$ receptor blocker, picrotoxin (PTX; 100 µM) significantly increased 1 p evoked $[DA]_o$ in dStr [males: 31 ± 7% (5); mean ± SEM, females: 20 ± 7% (6)] and in vStr [males: 23 ± 7 (5); females: 14 ± 4 (5), $P < 0.05$], revealing the presence of a GABA tone in striatal slices. PTX also increased optical pulse-train (10 p, 10 Hz) evoked $[DA]_o$ in both dStr [males: 57 ± 6% (7); females [35 ± 3 (6), $P < 0.05$] and vStr [males: 41 ± 6% (5); females: 46 ± 9 (7), $P < 0.05$]. Comparison of the $[DA]_o$ increase with 10 p *vs*. 1 p in PTX revealed a significantly greater increase in dStr in males and vStr in females ($P < 0.05$), consistent with inhibition of DA release by co-released GABA during subsequent pulses in a train. Moreover, pre-incubation in 4-diethylamino-benzaldehyde (DEAB; 10 µM), a blocker of Aldh1a1-dependent GABA synthesis in DA neurons significantly ($P < 0.05$) attenuated the effect of PTX on 10 p evoked $[DA]_o$ in dStr from males to 30 ± 3 (3), and in vStr from females to 13 ± 6 (4). Thus, our data support autoregulation of DA release by co-released GABA in dStr in males and in vStr in females and introduce α3-$GABA_A$ receptors as novel regulators of striatal DA release.

00149
Evaluation of synaptotagmin7 in the unique properties of somatodendritic dopamine release

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Abstract

Midbrain dopamine (DA) neurons in the substantia nigra pars compacta (SNc) exhibit somatodendritic release of DA. Released DA acts at D2 autoreceptors to regulate neuronal firing patterns that regulate DA release throughout the brain. We reported previously that: 1) the Ca^{2+} dependence of somatodendritic DA release differs from that of axonal release; 2) aspects of molecular organization for somatodendritic DA release are distinct from those for conventional synaptic release. Additional evidence from our group implies that D2 receptors on a given DA neuron are activated primary by DA released from that same cell, literally autoregulation, via exocytosis.

Here we focused on synaptotagmin 7 (Syt7), a high affinity Ca^{2+} sensor required for neurotransmitter release, to test the hypothesis that Syt7 contributes to the unique Ca^{2+} dependence of somatodendritic DA release in the SNc. Immunohistochemical studies confirmed the presence of Syt7 in somata and dendrites of SNc DA neurons. We then evaluated Syt7 function using voltage-clamp recording of SNc DA neurons in acute midbrain slices. Locally evoked D2 DA-dependent inhibitory currents (D2ICs) mediated by D2 receptor G-protein coupled K^+ (GIRK) channels as monitored an index of somatodendritic DA release. Evoked D2IC amplitude was attenuated when an antibody against Syt7 (anti-Syt7) was included in the recording pipette. This attenuation was prevented when the blocking peptide was included with anti-Syt7 in the pipette. Consistent with our previous finding in control recordings, D2ICs persisted in low extracellular Ca^{2+} concentrations ($[Ca^{2+}]_o$) that do not support axonal DA release. However, this Ca^{2+} dependence was lost when anti-Syt7 was applied via the recording pipette. Persistent DA release in low $[Ca^{2+}]_o$ sensitivity of evoked DA release was also lost in heterozygous Syt7 mutant mice. Thus, these data support a key role for Syt7 in SNc DA neurons in the unique Ca^{2+} dependence of somatodendritic DA release.

00153
Simulating striatal interactions during motor tics

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Abstract

A common feature of Tourette Syndrome patients is a stereotyped motor tic. These tics can be induced, and recordings from both monkeys and rats show the striatum receives a large surge of cortical input, causing a secondary surge in the medium spiny neurons (MSNs) and tonically active cholinergic interneurons (TANs). These striatal surges themselves have a characteristic relative timing, with MSNs rising first, followed by TANs. Since TANs are well known to modulate MSN activity particularly through acetylcholine's effect on the M-current, we seek to develop a model which can accurately capture this temporal relationship through cholinergic interactions. MSNs are known to weakly inhibit both each other and TANs, while TANs widely innervate MSNs, recruit MSNs during movement related tasks, and exhibit a long characteristic pause after receding inputs. While a TAN pause is not likely to be capable of completely suppressing an MSN surge, it may reduce the surge enough that other sources of inhibition take over and return MSNs to baseline firing. To test the viability of this hypothesis, we coupled a large network of model MSNs from McCarthy et. al. (Striatal Origin of the Pathologic Beta Oscillators in Parkinson's Disease, PNAS 2011, 108:28, 11620-11625) with random connections, with a novel TAN model which has good qualitative matching under the presence of tetrodotoxin, and under certain parameter settings is capable of achieving the various firing modes TANs exhibit in vivo.

The simulation proceeds as follows: MSNs and TANs receive a large cortical input and begin surging. The TANs release acetylcholine, further enhancing the MSN surge via reduction of the M-current. Through MSN inhibition the TANs are suppressed and begin to pause. Intracellular acetylcholine begins to rapidly decay, restoring the M-current above baseline levels, now dampening the MSN surge. The MSNs, now do not receive enough cortical input to overcome other sources of inhibition.

00157
Striatal dopamine release dynamics are shaped by endogenous dynorphin and kappa opioid receptors in a regional manner

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Abstract

Dynorphins (DYNs) are abundantly expressed throughout the striatal complex primarily in D1 DA receptor containing medium spiny neurons and act primarily at kappa opioid receptors (KORs). However, whether endogenously released DYN plays a role in shaping the dynamics of striatal dopamine (DA) release remains an open question. Here fast-scan cyclic voltammetry was used to monitor DA release regulation by locally released DYN in coronal slices of guinea pig or mouse striatum. Demonstrating that endogenously released DYN inhibits axonal DA release in guinea pig, the selective KOR antagonist nor-binaltorphimine (nor-BNI, 1 μM) markedly enhanced pulse-train (10 Hz) evoked increases in extracellular DA concentration ($[DA]_o$) in the nucleus accumbens (NAc) shell of the ventral striatum, but not in the caudate putamen (CPu) of the dorsal striatum. Moreover, this DYN-dependent DA release modulation in NAc was fast: with an increase in evoked $[DA]_o$ seen within 500 ms. In mouse, nor-BNI also significantly elevated evoked $[DA]_o$ in the NAc, although it was less pronounced. Again, no effect was seen in CPu. Importantly, the lack of effect of nor-BNI in the CPu was not a due to an absence of functional DA release-regulating KORs in this region because the selective KOR agonist BRL-52537 (1 μM), decreased single-pulse evoked $[DA]_o$ in both species. Notably, this decrease persisted when cholinergic modulation of DA release was prevented or with selective optical stimulation of DA axons, thereby confirming a direct action at KORs on DA axons rather than via cholinergic interneurons. Instead, DYN modulation of DA release in the NAc but not CPu is consistent with relatively higher basal expression of proDYN, the precursor of DYN, in ventral *versus* dorsal striatum. Thus, endogenously released DYN acting at KORs on DA axons provides a powerful, yet selective, sub-second suppression of mesolimbic DA signals.

00202
In vivo validation of DREADD-based inhibition of GPe neurons in the non-human primate.

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Abstract

Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) technique can be used as a powerful tool to remotely, reversibly and repeatedly manipulate the neural mechanisms underlying higher brain functions. Although this chemogenetic approach is widely used in rodents, the efficacy/utilization of DREADD technique in non-human primates (NHPs) is still controversial. Here, we aim to test DREADD expression in the NHP external globus pallidus (GPe) and electrophysiologically validate DREADD-based inhibition of GPe neurons in the anesthetized monkey.

To do so, we performed intracranial injections into the left GPe of viral vector expressing hM4Di receptor under a neuron-specific promoter (AAV2-hSyn-hM4Di-mCherry). The hM4Di receptor is a popular muscarinic-based DREADD that specifically inhibits the neuronal firing of the transduced neurons when binding with clozapine-n-oxide (CNO) or CNO analogues. After a 4-week minimum waiting period for allowing vector expression, the animal was re-anesthetized (isoflurane and O2 deep anesthesia) and neuronal activity was recorded in the left transduced GPe (using narylene-coated tungsten microelectrodes) following local intra-GPe microinjection (in the proximity of the electrode tip) of CNO (at a concentration of 1mM) or saline.

In doing so, we reported substantial decreases in the firing rate of the GPe cells/units following local CNO microinjection in the transduced GPe, while local saline microinjection did not change the firing rate of the GPe neurons. Moreover, immunoreactivity of the mCherry reporter protein was carried out to determine the specificity and extent of hM4Di receptor expression in the GPe.

Our preliminary results are encouraging and powerful arguments suggesting that DREADD technique might be efficient in NHPs to explore the causal contribution of brain structures and/or neuronal populations in higher brain functions with minimal invasiveness and maximal control of anatomical coverage.

00021
Role of Striatonigral and Striatopallidal CB1 in the physiology of basal ganglia

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Abstract

Some of the functions of the Basal Ganglia (BG) are: motor control, motor coordination and habit learning. Evidence show that the exogenous administration of cannabinoids affect this function, suggesting a role of the endocannabinoid system. Cannabinoids exert their effects by binding the CB1 receptor, mainly expressed at the presynaptic terminals, therefore leading to a decrease of neurotransmitter release. The CB1 receptor is highly expressed in the BG: at low levels in the corticostriatal terminals and importantly, in both populations of striatal medium spiny neurons, the striatonigral and striatopallidal neurons, where it represents the highest pools of CB1 in the brain. However its function in this cell types is still unknown.

The aim of this project is to study the role of the CB1 in the striatonigral and striatopallidal neurons in the control of locomotor activity, motor coordination and procedural memory. Using a double viral approach in a transgenic mice line we were able to delete CB1 specifically in the striatonigral or striatopallidal neurons.

We observed that the deletion of CB1 in the direct or indirect pathway, alters differently the motor abilities and coordination, tested using an accelerating rotarod. We observed also a different regulation of the locomotor activity following CB1 deletion in direct versus indirect pathway neurons, in basal condition and in amphetamine-induced hyperlocomotion. We also tested striatal dependent-spatial recognition, using a Y maze test, and again we observe a different modulation of this spatial memory mediated by CB1, in the striatonigral and striatopallidal neurons.

From preliminary experiments we observe a role of striatal CB1 in the physiology of BG, but future experiments are previewed, using fiber photometry and conditional mutant mice, to better understanding the impact of the cannabinoid system in the BG functions, and its mechanism in vivo.

00044
Optogenetic modulation of specific striatal pathways elicits abnormal behavior in a Parkinson disease model

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Abstract

Striatal dopamine depletion in Parkinson disease (PD) is the main cause of the cardinal motor features exhibited by PD patients: akinesia, bradykinesia, rigidity and in some cases tremor. This dopamine loss affects both the direct and indirect striatal output pathways, neurons of which exhibit differential changes in excitability, firing activity, spine density, etc… Dopamine replacement therapy (levodopa) remains the treatment of choice in PD, however, despite its broad benefits, it is associated with the development of levodopa-induced dyskinesias (LIDs). In a rat model of PD we previously reported that simultaneous optogenetic activation of the direct and indirect striatal efferent pathways elicited abnormal movements (optodyskinesias) that resemble those evoked by levodopa (Hernandez et al, Mov. Dis., 2017). Here, we present the data obtained from transgenic mice that allowed us to dissect striatal circuitry by optically activating each pathway separately. When both pathways were activated we evoked optodyskinesias in both control (intact) and dopamine depleted animals (different from results obtained in rats). However, when we stimulated each pathway separately, optical activation of direct pathway D1R-expressing neurons evoked the optodyskinesias, while optical activation of indirect pathway D2R-expressing neurons promoted freezing behavior and/or ipsilateral rotations. These experiments show that co-activation of both pathways can elicit abnormal movement, both in dopamine depleted and control animals, but it was stimulation of D1R-expressing neurons that was sufficient to elicit the dyskinetic movements. Finally, we reported the blockage of LIDs by means of activating the indirect pathway, which supports the traditional inhibitory movement role of this pathway and may lead to some potential therapy approaches.

00062
Stimulating SNpr – motor thalamus pathway in a Parkinsonian rat model modulates forelimb movement

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Abstract

Degeneration of midbrain dopaminergic neurons in Parkinson's disease (PD) causes severe movement deficits and altered neuronal activity in basal ganglia networks. Basal ganglia output is sent to motor thalamus nuclei, which innervate cortical motor areas that control voluntary movements. However, the consequences of dysfunctional basal ganglia activity on movements and motor thalamus activity are unclear.

Here, we optogenetically stimulated basal ganglia output (substantia nigra pars reticulata, SNpr) to ventroanterior (VA) motor thalamus in sham and hemi-parkinsonian rats (6-OHDA lesion of medial forebrain bundle) and assessed the impact on reaching performance and VA neuron activity. Stimulating SNpr axons in 6-OHDA lesioned rats with SNpr activity previously recorded from a walking sham rat significantly increased the number of reaches executed by the affected paw. The same number of stimuli applied tonically at 9 Hz significantly impaired reaching in the lesioned group, but did not affect sham rats.

Mean VA neurons firing rate was higher in 6-OHDA lesioned than sham rats. SNpr stimulation modulated VA firing rate; inhibiting 13% and exciting 53% of VA neurons in sham rats. In 6-OHDA lesioned rats, therapeutic SNpr stimulation inhibited significantly more VA neurons (43%), compared to sham rats, and only 19% of cells were excited. Data show that SNpr axon stimulation with an appropriate complex pattern inhibits VA neurons and is associated with improved movements.

Our results highlight trialling complex patterns of electrical deep brain stimulation to treat the motor symptoms of PD.

00102
Information processing in the rat globus pallidus during novel environment exposure

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Abstract

It is well established that the Basal Ganglia (BG) and the globus pallidus (GP) in particular process information regarding many different mental faculties. However, it remains unclear whether and how information regarding those different processes is integrated within the Basal Ganglia. A way to address questions regarding different mental computations is to use a novel environment exposure (NEE) task, in which an animal is transferred between a familiar and an unfamiliar environment. When an animal is exposed to a novel environment it usually initiates 'exploratory behavior' – that is performing rapid movements throughout the environment, in order to familiarize itself with it. In order to execute the exploratory behavior two mental faculties need to be activated: the cognitive distinction between the familiar and the unfamiliar environment, and the planning and execution of the physical locomotion of the exploratory behavior. Previously we have shown that these two mental faculties are encoded in the BG main input structure, the striatum, by two separate subsets of striatal output neurons. Recordings of neuronal activity in the GP during the NEE task enables us to investigate how information regarding these two mental attributes propagates downstream from the striatum and then integrated in the GP.

We chronically recorded single unit activity in the GP of rats performing the NEE task. Our data show that like the striatum, GP neurons encode the environment’s identity and aspects of the animals' motoric activity; however, unlike striatal neurons, single GP units could encode both the environment and the animals' behavior. Our data support the notion that the GP integrates striatal information irrespective of the encoded features rather than extracting feature-based information and conveying it to BG output nuclei.

00132
Neural activity in the internal (GPi) and external globus pallidus (GPe) during proactive motor inhibition

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Abstract

A crucial component of adaptive behavior is response inhibition, the capacity to refrain from reacting to external events or internal urges, which underlies the ability to deliberately select one plan of action from amongst potentially many. In addition to reactive inhibition—initiated when specific stimuli are identified—responses can be inhibited proactively in the absence of explicit stimuli or triggered by particular contexts, acting to gate actions when fast or erroneous actions are undesirable. Cortico-basal ganglia interactions may be important for implementing proactive inhibition, and we recorded neurons in output nucleus of the basal ganglia, the internal segment of the globus pallidus (GPi), while monkeys performed a Go/No-go task. Our preliminary analyses of multi-channel single-unit recordings in GPi, as well as the GPe, indicate that some neurons responded in a manner consistent with encoding proactive inhibition. We used regression analyses to separate effects of movement from response inhibition and reward expectation. Together with planned recordings in the thalamic nuclei receiving direct projections from the GPi, we hope to decipher the type and timing of information transmitted from the basal ganglia to support adaptive motor control.

00151
Transient activity of SNc dopaminergic neurons codes the vigor of contralateral movement sequences

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Abstract

Classical basal ganglia models suggest that dopamine effects on movement and movement vigor are mediated on a slow, tonic timescale. This has led to the hypothesis that the reduction of tonic dopamine activity is the culprit of bradykinesia in Parkinson's Disease (PD).

Inspired by a finger tapping manoeuvre used to assess PD we developed a self-paced operant task, in which mice learn to perform a sequence of fast lever presses with only one forepaw. By design, the task allowed us to assess individual forelimb movements with data on limb position and speed being collected. Healthy mice learned the task, with progressive performance improvement and variability reduction. Unilateral Substantia Nigra compacta (SNc) depletion with 6-OHDA lead to a decrease of movement vigor contralateral to the lesioned side, with slower movements and shorter sequences, suggesting that dopamine activity is related to vigor of contralateral movements.

We next used a miniature epifluorescence microscope to image GCaMP6f in dopaminergic SNc cells while mice performed the task. We identified different populations of SNc neurons specifically modulated before movement sequence initiation versus reward consumption. The majority of units classified as movement-modulated was stable across sessions. Phasic activity of movement-modulated neurons preceded the start of sequences executed with either paw. However, this activity was only related to the vigor of the upcoming contralaterally performed sequences, with higher activity related with faster movements and/or longer sequences.

These data shows that transient increases in a subpopulation of SNc dopamine neurons are related to movement of both limbs, but this activity was specifically correlated with vigor of contralateral movements, consistent with the lesion data and with PD symptoms. These results suggest a role for dopamine supporting movement transitions in general, but only contralateral vigor rather than a general invigoration signal.

00161
Optogenetic manipulation of basal ganglia outflow to the thalamocortical system in macaque monkeys

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Abstract

The basal ganglia (BG) play a crucial role in controlling voluntary movements, and their dysfunction causes severe motor disturbance, such as Parkinson's disease and dystonia. The BG receive information from a wide area of the cerebral cortices, and the internal segment of the globus pallidus (GPi), the output nucleus of the BG, sends GABAergic projections to the thalamocortical neurons and governs the original cortices. To understand how GPi inputs control thalamocortical activity, thalamocortical neurons were identified by the electrical stimulation of the forelimb regions in the primary motor cortex and supplementary motor area, and their response to the electrical stimulation of the GPi was recorded in macaque monkeys. Single-pulse stimulation induced a biphasic response composed of short-latency inhibition and following excitation. Repetitive stimulation evoked a train of biphasic responses. Local injection of gabazine, GABA-A receptor antagonist, into the vicinity of recorded thalamocortical neurons abolished not only inhibition but also following excitation without changes in spontaneous firing rates, suggesting that the excitation is caused by a post-inhibitory rebound mechanism. Next, we expressed halorhodopsin in the axon terminals of GPi-thalamic projections by injection of an adeno-associated virus vector into the GPi. Thalamocortical activity was recorded using an optrode during performance of a hand reaching task, and selectively blocked GPi-thalamic inputs by yellow laser light application in the vicinity of recorded neuron. Inhibitory responses induced by GPi-stimulation were successfully abolished by the light application. Task-related firing increase was enhanced by blockade of GPi-thalamic inputs in the half of thalamocortical neurons, but diminished in the other half. These results suggest that GPi-thalamic inputs modulate thalamocortical activity through both GABAergic inhibition and following rebound excitation, and control voluntary movements.

00164
Monitoring striatal cholinergic cell assemblies in awake behaving mice

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Abstract

Cholinergic interneurons (CINs) make up a tiny fraction of cells in the striatum. However, they are key modulators of the canonical corticostriatal and thalamostriatal circuits and are believed to form synchronous cell assemblies that possibly orchestrate dopamine release. The striatum is widely viewed as essential for the selection of the appropriate motor plan during ongoing behavior. It is, nevertheless, largely accepted that the tonic activity of CINs, as well as the stereotypical pause response that they exhibit, code for the value of the selected action rather than the movement itself. However, experiments supporting this claim were performed on animals that were both head-fixed and over-trained in executing task related movements. Our novel approach allows us to study the collective activity of CINs in the naturalistic setting of a freely-moving mouse.

We express GCaMP6, a genetically encoded calcium indicator (GECI) selectively in CINs and use microendoscopes to visualize the putative CIN assemblies in the dorsal striatum of mice during self-initiated behaviors. The GECI fluorescence signal from the dorsal striatum is composed of signals from individual CIN somata that are engulfed by a wide-spread fluorescent neuropil. Our preliminary results show strong movement related neural activation - background neuropil signals are highly correlated forming a "global mode" that is strongly associated with self-initiated movement. Additionally, bouts of synchronous activation of the cholinergic neuropil, induced by movement onset, reveal a traveling-wave-like pattern of activity that propagates mediolaterally along the dorsal striatum, providing the first empirical evidence for a spatiotemporal structure of recruitment of striatal CINs. This direction of propagation corresponds to the mediolateral anatomical and functional organization exhibited by various neuronal populations in the striatum, and may be related to similar patterns in dopamine release.

00177
Reach-related activity in basal ganglia- and cerebellum-recipient thalamic nuclei

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Abstract

Neurons in the ventrolateral (VL) nucleus of the thalamus serve as critical links by which the basal ganglia (BG) and cerebellum (Cb) communicate with cortical motor areas. In primates, BG and Cb afferents terminate in distinct anterior and posterior parts of VL ("VLa" and "VLp," respectively). Thus, the respective contributions of BG and Cb to motor cortical function should be revealed through comparisons of the task-related activities of neurons in these two nuclei. We studied the single-unit activity of electrophysiologically-identified VLa and VLp neurons (n=184 and 114 respectively) in two non-human primates during the performance of a reaching task. Even though VLa and VLp receive markedly different subcortical afferent inputs, neuronal activity in the two nuclei was surprisingly similar in many respects. Changes in firing rate around the time of reach onset were common in both nuclei and increases were the most common change detected (63% and 65% of changes, respectively). Many other response metrics were also similar between the two nuclei. We did find marked differences, however. Movement-related decreases in firing were more common (32% vs. 23% of neurons) and longer-lasting (491ms vs. 357ms) in VLa than in VLp. Increases in firing generally began earlier in VLp than in VLa whereas the latencies of decreases did not differ between nuclei. Movement-related changes in VLa were largely monophasic whereas those in VLp were often polyphasic (e.g., increase/decrease couplets). Time-resolved linear models found that neurons in VLp encoded the direction of movement earlier and more strongly (i.e., higher R2 values) than did neurons in VLa. VLa neurons, in contrast, more often encoded concurrent reaction time or the duration of the previously elapsed delay period. Overall, these results suggest that VLp contributes to specific parameters of movement whereas VLa may relay motivation-related information.

00180
Subthalamic Nucleus Activity Encodes Aspects of Speech Production

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Abstract

Deep brain stimulation (DBS) is the only setting in which basal ganglia recordings can be obtained while a person speaks. Simultaneous recordings of subthalamic nucleus (STN) units, STN local field potentials (LFPs), electrocorticography (ECoG), and spoken utterances were obtained in 14 subjects with PD, during DBS lead implantation. At different recording depths in the STN, subjects read aloud 3-phoneme words and pseudowords presented on a computer screen. The initial consonant of the stimuli involved articulation primarily with the tongue or the lips. We examined the relationship of 1) STN unit firing to speech cue and onset, 2) STN LFPs to articulation with lips vs. tongue, and 3) STN LFPs to the formant ratio, an indirect acoustic measure of gain in speech articulation.Half of 79 STN unit recordings exhibited firing rate modulation. Trial-to-trial timing of changes revealed that locking to cue presentation was associated with decreases in firing rate, while locking to speech onset was associated with increases in firing rate. Speech-related increases in high gamma activity were found in most of the 88 STN LFP-recording locations, ~1/3 of which exhibited a significant effect of articulator type. The greatest changes in gamma power occurred more dorsally, but without exhibiting articulator type topography. In addition, both cortical and STN alpha power positively predicted the magnitude of the formant ratio during speech. In summary, we discovered that STN neuron activity is dynamic during the production of speech, reflecting temporally-dependent inhibition and excitation of separate populations of neurons. STN population activity also is involved in speech production at the level of articulatory features, including contributions to gain adjustment of articulatory movements. Overall, these studies are the first to establish a role for subthalamic encoding during speech production.

00188
Projection pathways in ventrolateral striatum modulate operant control of licking

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Abstract

Ventrolateral striatum (VLS) neurons receive input mainly from orofacial sensory-motor regions, and respond to orofacial movements, suggesting that VLS could be involved in the control of orofacial movements. However, the role of this region in goal-directed licking behavior, and particularly the interplay between direct- and indirect- pathways during licking remain largely unknown. In a first set of experiments we found that optogenetic stimulation of direct pathway neurons induced licking while stimulation of indirect pathway did not affect ongoing movements of freely moving mice. To further investigate the role of VLS direct and indirect pathways in operant licking under different motivational conditions, we developed a head-fixed olfactory-guided operant task in which mice were trained to modulate licking differently in response to four different odors (go/nogo/wait/neutral). Calcium imaging during task performance showed that both direct and indirect pathways contain subpopulations that are differently modulated by salient events, such as odor, licking initiation, termination and reward. Optogenetic manipulation experiments showed that direct pathway activity is sufficient and necessary for licking, while indirect pathway activity is sufficient and necessary for suppression of licking during task execution.

00189
GABAergic inhibition of midbrain dopamine neurons by the pedunculopontine nucleus: Implications for motor behavior

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Abstract

Midbrain dopamine (DA) neurons play a critical role in modulating goal directed actions and reinforcement learning and are essential for normal motor function, the lack thereof causing deficits such as those observed in Parkinson's disease. DA activity encodes positive and negative reward prediction error, guiding this way purposeful actions. Movement itself is heterogeneously represented in DA neurons. Essential for understanding how DA-dependent motor behavior is shaped is the understanding of the excitatory and inhibitory modulation that the DA midbrain receives from a wide variety of sources. Anterograde labeling of GABAergic axons originated in the pedunculopontine nucleus (PPN) were observed to innervate the dopaminergic midbrain, predominantly the substantia nigra pars compacta (SNc). We next identified the presence of putative synapses in the SNc, as determined by the immunolabeling of the postsynaptic protein gephyrin apposed to PPN-transduced axons, and further supported by appositions between synaptophysin-positive varicosities and tyrosine hydroxilase processes. Whole-cell recordings of SNc DA neurons revealed an inhibitory effect by PPN GABAergic axons dependent on GABA-A receptors. Given the prominence of this novel GABAergic input to DA neurons, we aimed to identify the behavioral consequences of the activation of PPN axons. VGAT-cre mice were transduced with ChR2 in the PPN and received optogenetic stimulation in the SNc through chronically implanted optic fibers. Mice underwent a battery of behavioral paradigms using different parameters of stimulation. Optogenetic activation of GABAergic axons consistently stopped spontaneous locomotion while preserving other motor behaviors intact. Our results support the existence of an inhibitory input to DA neurons which selectively affects spontaneous locomotion. Ongoing experiments will aim to understand the full impact of PPN contribution to motor behavior.

00197
Direct- and indirect-pathway striatal projection neurons and the control of locomotion

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Abstract

It is generally believed that the basal ganglia (BG) are critical for the control of well-learned actions. The dorsolateral striatum has been implicated in such function but its exact contribution is still debated. Striatal projection neurons (SPN) form two relatively separated pathways depending on their target. Direct pathway forming SPN (dSPN) project directly to the output nuclei of the BG while indirect-pathway forming SPN (iSPN) targets relay nuclei before modulated BG output. The classical pro/anti-kinetic model suggests that the activity ratio between dSPN and iSPN controls the amount of behavioral activity. In this model, prominent dSPN activity facilitates movements while prominent iSPN activity inhibits movements. Recent studies showing co-activation of dSPN and iSPN during action initiation have challenged the kinetic model and suggested that dSPN activity is crucial to select the action that must be executed while concurrent iSPN activity repress competing unwanted motor programs.

To better understand the role of theses two pathways , we developed a task in which head-fixed mice, were trained to run continuously for a fixed distance to get a reward and then stay immobile for a few seconds to start a new trial. We performed optogenetic-based manipulation of dSPN and iSPN using a close-loop paradigm, allowing to alter neuronal activity at different phases of the task, during running or immobility. Preliminary results are neither compatible with the classical kinetic model nor the action selection models.

00199
Investigating the Role of the Striatum in Motor Learning and Execution

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Abstract

Many of our daily motor behaviors are shaped through extensive repetition and trial-and-error adjustments, such as driving a car and brushing our teeth. The striatum, the main input structure of the basal ganglia, is assumed to contribute to trial-and-error motor learning. It is widely believed that the dorsomedial striatum (DMS) contributes to the early phase of motor learning whereas the dorsolateral striatum (DLS) is implicated in the execution of learned motor programs, however their exact roles still remain debated.
Here, we designed a time-estimation task wherein rats running on a powered treadmill learn, by trial-and-error, to maximize a reward/punishment ratio. All the animals progressively converge toward a common embodied strategy: they perform a stereotyped back-and-forth sequence on the treadmill whose duration approximates the time they need to estimate. We examined the function of the DMS and DLS in learning and execution of this motor routine by performing striatal lesions of various size and location.
Interestingly, both DMS and DLS lesioned animals demonstrate similar results. Naive animals manage to learn the task and trained animals execute the motor sequence successfully. Furthermore, lesion of the entire dorsal striatum does not prevent execution of the motor program. Another common trait among lesioned animals is a prominent decrease in running speed. This effect on speed is correlated with the size of the lesion, but not its location. Altogether, these results provide new insights into the function of the striatum in motor learning and execution

00072
Hierarchical organization of multiple basal ganglia loops: a neuro-computational study.

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Abstract

We introduce here a set of three novel key concepts, tested and evaluated by means of a neurocomputational model, that bring together current ideas regarding the hierarchical organization of the basal ganglia. According to key concept one, each loop learns to select an intermediate objective at a different abstraction level, moving from goals in the ventral striatum to motor in the putamen. Key concept two proposes that the cortex integrates the basal ganglia's selection with environmental information regarding the achieved objective. Key concept three proposes shortcuts between loops.

We have tested a neuro-computational implementation of our concepts comprising of two loops and tested it on two cognitive tasks used to measure the development of habitual behavior (Smith and Graybiel, Neuron, 2013; Packard and McGaugh, Neurobiol. Learn. Mem. 1996). Our numerical simulations show that the model can account for the effects of devaluation in the task of Smith and Graybiel (2013) and for the effect of lesions to the caudate nucleus in the experiments of Packard and McGaugh (1996).

As a way to test the core predictions of our hierarchical approach we propose to add a relearning protocol to the task of Smith and Graybiel (2013). The model predicts that changes in the outcome of actions mainly alters the connectivity in the dorsolateral loop while changes in the location of the rewards mainly alters the connectivity in the dorsomedial loop. Such changes could be detected by measuring transitions in the selectivity of striatal cells: after relearning, dorsomedial striatal cells switch their action selectivity while dorsolateral cells switch their goal selectivity.

In summary, our approach proposes a new concept of cortex-BG loop interactions and with respect to habitual learning, shortcuts between loops explain habitual responses, differently than the dual controller approach of parallel BG loops.

00077
Chemogenetic Inactivation Using Double Virus Vector Infection Reveals the Inhibitory Function of the Prefronto-striatal Pathway in the Macaque Brain

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Abstract

The interaction between the prefrontal cortex and the basal ganglia underlies our value-based decision making. Among subareas of the prefrontal cortex, the lateral part (LPFC) strongly project especially to the caudate nucleus (Cd) in the striatum. Several human fMRI studies assigned different functions to this LPFC-Cd pathway. So far, however, mainly due to technological constraint, no study directly elucidates what role this pathway plays on the value-based decision making.

In this study, we used a chemogenetic technique that can reversibly modulate the activity of specific projection neurons by expressing the Designer Receptors Exclusively Activated by the Designer Drugs (DREADDs) through the double virus vector infection and by administering its extrinsic ligand, Clozapine-N-Oxide (CNO). This technique was applied to the bilateral LPFC-Cd pathway in the macaque brain. The monkey was trained one-direction reward (1DR) saccade task, which is a version of the memory-guided saccade task with asymmetric reward schedule.

After administering CNO to a doubly-infected monkey, task performance gradually deteriorated. This effect was stronger for small reward trials than large reward trials. Moreover, saccade latency became shorter and peak saccade velocity became

faster during choice period. These results are consistent with the inhibitory control hypothesis on the function of the LPFC-Cd pathway.

Spike activities and local-field potentials (LFP) were recorded simultaneously from the LPFC and the Cd. Firing rates of LPFC neurons were decreased after CNO administration. We calculated coherence between the LPFC and the Cd based on LFP signals and found that cue-induced elevation of coherence around beta-band was decreased after CNO administration. The effect was observed only in small reward trials, which may explain increased error especially in small reward trials after CNO administration.

00119
Impairment of cortical dopaminergic neurotransmission and executive functions in a mouse model of n-3 long chain polyunsaturated fatty acids deficiency

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Abstract

Reward related dysfunctions and cognitive alterations represent the first cause of therapy discontinuation in patients with major depression disorders and schizophrenia, and pharmacological interventions employed to treat these symptoms are often limited by the poor tolerability in the long-term period. In the last years, several clinical evidence have highlighted a link between a reduced level of n-3 long-chain polyunsaturated fatty acids (n-3 PUFAs) and the aforementioned psychiatric conditions. However, the implication of these lipids in the etiology of cognitive and reward-related dysfunctions has still to be clarified. A major neurobiological mechanism that is considered to be critical in the origin of these symptoms is an impaired dopaminergic neurotransmission at both cortical and striatal levels. In order to assess whether the n-3 PUFA deficiency entailed some perturbations of dopaminergic activity in these regions, we performed multi-site microdialysis to measure basal and stimulated release of dopamine in the Nucleus Accumbens (NAc) and Prefrontal Cortex (PFC) of n-3 PUFA deficient mice. We found that, while the n-3 PUFA deficiency does not impair dopaminergic neurotransmission in the NAc, it profoundly affects that of the PFC, with blunted amphetamine-stimulated release of dopamine and altered turnover. Furthermore, since cortical dopaminergic hypofunction is considered to play a major role in the expression of cognitive dysfunctions in many psychiatric conditions, we evaluated whether n-3 PUFA deficient mice displayed comparable behavioral alterations. Using a specific satiety outcome-devaluation paradigm we showed that n-3 PUFA deficient mice are compromised in their ability to perform goal-directed actions.

00131
GPe Arky cells transmit a stop signal in a spiking network implementation of the “pause-then-cancel” model

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Abstract

The basal ganglia are strongly implicated in the suppression of inappropriate actions (Aron & Poldrack, J Neurosci 2006). A common test of response inhibition is the “stop-signal-task” (SST), and behavioral performance in this task is generally well matched by a theoretical “race” model in which separate “Go” and “Stop” processes compete (Schmidt et al., Nat Neurosci 2013, Schmidt & Berke, Phil. Trans. R. Soc. B 2017). Based on recent experimental observations, Schmidt et al. (2013) have proposed that the “Stop” process may involve two separate phases: First, a rapid “pause” phase, followed by a slower “cancellation” phase. Further, (Mallet et al., Neuron 2016) have presented evidence that Arky cells, a recently identified subpopulation of the GPe, show a temporal activity pattern consistent with a role in stopping ongoing actions.

Based on these observations, we have adapted our previous spiking network model of the basal ganglia (Baladron et al., Eur J Neurosci 2017) to solve the stop-signal-task, in a manner inspired by the “pause-then-cancel” model. Key features of the proposed model are: (1) STN activity related to a rapid “pause” signal is triggered by the presence of a “Stop” cue, and (2) GPe Arky cell activity is triggered by a slightly slower “cancellation” signal, causing inhibition of striatal D1 neurons, effectively interrupting ongoing actions.
Model simulations show that ongoing actions can be reliably inhibited if a Stop cue is presented. Our results highlight that successful stopping depends on the appropriate timing of pause-related STN activity and cancellation-related GPe Arky cell activity.

00134
Task contingency and context selectivity in single unit and synchronous activity of striatal and prefrontal neurons in rats

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Abstract

We recorded multiple single neuronal activity and local field potentials simultaneously in areas including dorsomedial and ventral striatum (STR) and prefrontal cortex (PFC) as rat performed at criterion levels in Visual (VD) and Spatial (SD) Discrimination tasks in the same automated T-maze. STR and PFC cell activities were behaviorally correlated and discriminated between first and second repetition of the VD task with an intervening SD epoch in the same session. A Support Vector Machine successfully distinguished between tasks on the basis of STR and PFC population activities respectively.

With a PCA-ICA based method, 74 groups of synchronously co-active neurons were detected in 16 recording sessions. These groups could include dorsomedial and/or ventral STR neurons (n=32), or dorsal and/or ventral medial prefrontal neurons (n=9). Interestingly, 35 included both PFC and STR neurons. Co-active groups appeared with 150 ms bins, but over 70% persisted even with 10 ms bin widths. Co-active groups were also behaviorally modulated and task or task/order selective. Co-active groups were reactivated more during post-task than pre-task sleep, consistent with memory consolidation.

Interestingly, 25% of STR neurons and 30% of co-active groups were phase locked to 4 and/or 8 Hz PFc oscillations. Moreover, in pooled data, PFC and STR gamma oscillations (30-50 Hz, 50-70 Hz, 70-100 Hz) were modulated by PFC 4 and 8 Hz oscillations. The co-active groups tended to have the same preferred 4 Hz phase as high gamma (70-100 Hz). This suggest possible mechanisms of synchronization. Furthermore, PFC and STR LFPs were coherent in the 4 and 8 Hz bands. Thus widespread networks of STR and PFC neurons cooperate, are behaviorally correlated, and reflect previous and current action-outcome contingencies.

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00140

Neuronal encoding of temporal information in the primate striatum: contribution of presumed cholinergic interneurons and GABAergic projection neurons

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Abstract

Theoretical and experimental studies emphasize the role of the striatum in time perception. However, we lack information about how temporal representations are achieved at the level of distinct components of the striatal circuitry. To investigate this issue, we recorded from phasically active neurons (PANs) and tonically active neurons (TANs), thought to be GABAergic projection neurons and cholinergic interneurons in the striatum, respectively, in two macaque monkeys trained to wait for a specified time interval before initiating a movement leading to reward. We used two visually cued interval timing tasks with short and long intervals (1.0 to 2.3 s): (1) a duration estimation task (DET) in which the movement is triggered by an internal decision process based on the estimation of elapsed time from cue onset; (2) a temporal prediction task (TPT) in which the movement is triggered by an external stimulus after interval end. Of 202 PANs recorded in the DET and TPT, 11% showed activations that reached maximal firing during the 0.5-s period immediately after the onset of the timing cue. Among these early activated PANs, 36% were modulated by interval duration, 23% by task condition, and 14% by both variables. During the same initial period of time intervals, 36% of 182 TANs recorded in both conditions showed brief decreases in firing ("pauses") in response to the timing cue. There was no significant effect of task condition on the magnitude of pauses, whereas at least one monkey showed an effect of interval duration, the response being stronger with a short rather than a long interval. These results suggest distinct temporal information processing by the two populations of striatal neurons: TANs act as detectors of the beginning of the time interval. Their responses would be necessary to time upcoming events and to shape output neurons (PANs) that encode more detailed information about action and other task components, including the time elapsed since the TAN signal.

00152
Exploring Correlates of Value in Striatal Neuron Populations

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Abstract

As neuroeconomic approaches to decision-making have flourished, there is increasing interest in the cellular and circuit-level neural mechanisms supporting value-based action selection. The striatum has been shown to play a critical role in regulating voluntary motor output and goal-directed decision-making via a combination of targeted lesion studies, anatomical dissections and pharmacology. Here, we detail a novel paradigm allowing us to investigate decision-making with a focus on how benefits and costs are integrated to modulate action selection. We developed global and individual trial measures to assess the choice patterns and behavioral flexibility of mice in response to differing “choice benefits” (modeled as varying reward magnitude ratios) and different modalities of “choice cost” (modeled as increasing repetitive motor output to obtain reward). We demonstrate that mouse choice is highly sensitive to the relative benefit of outcomes and that choice costs are heavily discounted in environments with large discrepancies in relative reward. We then used this behavioral framework as a foundation to analyze cell-type specific population activity of direct and indirect pathway spiny projection neurons in the dorsomedial striatum of awake-behaving mice. Here we probe whether these sub-populations mediate dissociable aspects of value-encoding, with benefits and costs segregated according to direct and indirect pathway SPNs, respectively. We find that while coordinated ramping activity prior to the onset of an action sequence is correlated with the benefit of that action for both cell types, the D2 population, alone, alters its activity pattern in response to differential effort requirements.

00165
Working memory along the primate cortico-basal ganglia-thalamo-cortical loop

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Abstract

Working memory is fundamental for goal-directed behavior but its neurophysiological correlates remain unclear. It has been suggested that working memory is supported by a network of cortical and subcortical brain structures including the basal ganglia and the thalamus. However, evidence for this notion from large-scale invasive studies is still largely missing. To close this gap, we simultaneously recorded neural activity from frontal and parietal cortices as well as associated basal ganglia and thalamic structures in macaque monkeys during feature and spatial working memory. We found differential encoding of task, memory content and choices across all stages of this network. Temporal dynamics of information varied across areas in a task- and performance-dependent manner. Furthermore, we found strong frequency-dependent coupling between all areas, most notably in the beta band. In sum, our results provide critical novel evidence suggesting that working memory depends on large-scale interactions along the cortico-basal ganglia-thalamo-cortical loop.

00184
Cannabidiol acts via FAAH inhibition and cannabinoid and TRPV-1 activation to reduce experimental parkinsonism-induced nociception

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Abstract

Besides originally described as motor disease, Parkinson´s disease (PD) patients suffers from a variety of non-motor symptoms, such as pain. This symptomatology is not completely understood and dopaminergic and non-dopaminergic mechanisms may have a role in the appearance/maintenance of these pain symptoms. Endocannabinoid system has emerged as a promising therapeutic potential in the modulation of pain, besides having a neuroprotective effect on neurodegenerative diseases. Our hypothesis is that Cannabidiol (CBD) has an anti-nociceptive effect in a model of intrastriatal 6-hidroxidopamine (6-OHDA)-induced pain, upregulating anandamide levels and TRPV-1 receptors activation. Male adult C57⁄BL6 mice (USP, Brazil; 20– 25g) were used in this study (Animal Committee # 2017.1.369.58.4). Nociceptive behavior tests (Hot Plate, Tail Flick, Von Frey and Acetone-induced cold allodynia) were performed prior to the 6-OHDA lesion (-1) and after 1, 7, 14 and 21 days of the surgery. Then, CBD (10, 30, 100 mg/kg) effects were tested on these hyperalgesia and allodynia responses compared to Celecoxibe (CXB), Morphine (MOR) and Saline. To investigate the involvement of the Fatty Acid Amide Hydrolase (FAAH), cannabinoid receptor 1 (CB1) and transient receptor potential vanilloid type 1 (TRPV-1) on antinociception effect of CBD, pre-treatment with URB, AM and CPZ was tested. We showed that: (i) experimental parkinsonism increased the thermal and mechanical nociception; (ii) different doses of CBD prevented hyperalgesia and allodynia 6-OHDA-induced; (iii) the highest CBD dose exhibited similar effectiveness to morphine. (iv) The inverse agonist of CB1 receptor prevented the antinociceptive effect of CBD while ineffective doses of either FAAH inhibitor or TRPV-1 antagonist improve the CBD antinociception effect. These results imply that CBD can be a useful drug to reduce the parkinsonism-induced nociception, increasing endogenous anandamide and activating CB1 and TRPV-1 receptors.

00016
Efficacy and safety of deep brain stimulation in the treatment of Parkinson's disease: a systematic review and meta-analysis of randomized controlled trials

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Abstract

Background: Deep brain stimulation (DBS) is a neurosurgical procedure indicated for patients with advanced Parkinson's disease (PD). Whether similar benefits may be realized by patients with early PD, however, is currently unclear, especially given the potential risks of the procedure. This systematic review and meta-analysis aimed to investigate the relative efficacy and safety of DBS in comparison to best medical therapy (BMT) in the treatment of PD. It also aimed to compare the efficacy of DBS between patients with early and advanced PD.

Methods: A systematic search was performed in MEDLINE, EMBASE, and CENTRAL. Randomized controlled trials (RCTs) comparing DBS to BMT in PD patients were included. Outcome measures were impairment/disability (UPDRS), quality of life (QoL) (PDQ-39), levodopa equivalent dose (LED) reduction and rates of serious adverse events (SAE).

Results: 8 eligible RCTs (n=1189) were included in the meta-analysis, 2 of which recruited early PD patients. Regarding efficacy outcomes, there were significant improvements in UPDRS, PDQ-39 and LED scores in favour of DBS (P<0.00001). There was a significantly greater reduction of LED in patients with early PD (P<0.00001), but no other differences between early and advanced PD patients were found. The risk of a patient experiencing a SAE was significantly higher in the DBS group (P=0.005), as was the total number of SAE (P<0.00188).

Conclusions: Overall, DBS was superior to BMT at
improving impairment/disability, QoL and reducing medication doses, but these benefits need to be weighed against the higher risk of SAE. There was insufficient evidence to determine the impact of PD stage on the efficacy of DBS.

Keywords: Deep brain stimulation, Parkinson’s disease, randomized controlled trials, systematic review, meta-analysis

00017
Bilateral Sensory Integration in the Striatum of awake mice

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Abstract

Integrating sensory information to produce the appropriate motor output is crucial for the survival of living beings. Responses to sensory input are modulated by the state of the animal (for example alertness) and its activity (i.e. locomotion) all of which are integrated to form the measured response. Previous studies have shown that striatal projection neurons (MSNs) of anesthetized mice integrate sensory inputs from both sides of the body and from different sensory modalities. However, it is not clear how these sensory responses are modulated by different brain-states, specifically by the slow oscillations induced by anesthesia. To address this question, we obtained in vivo whole-cell recordings in the dorsolateral striatum of awake, head-fixed mice. We used the optopatcher to identify direct and indirect pathway MSNs (dMSNs and iMSNs, respectively) in real time during recordings using focal optogenetic stimulation through the patch pipette. We found that both dMSN and iMSN exhibit sensory responses to whisker deflection from both sides of the body. Similarly to anesthetized mice, MSNs of awake animals encode the laterality of sensory inputs with larger and earlier responses to contralateral than ipsilateral whisker deflection. However, during wakefulness responses are briefer and smaller in amplitude compared to responses of anesthetized mice. Our results show that laterality coding in MSNs is maintained in both anesthetized and awake animals, further suggesting that, as seen in anesthetized mice, it would be impaired in the dopamine-depleted striatum.

Keywords: In-vivo, Awake, Parkinson, Sensory Impairment, Lateral Coding.

00019
Aberrant beta synchronous oscillations during sleep in the basal ganglia predict the degree of Parkinsonian sleep fragmentation

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Abstract

Sleep fragmentation and insomnia stand among the most prevalent and debilitating non-motor symptoms of Parkinson's disease (PD). Nevertheless, the neuronal mechanisms responsible for these sleep disturbances have remained un-known. We recorded basal ganglia (BG) spiking activity and local field potentials in non-human primates during normal sleep and after MPTP-induced Parkinsonism. In this systematic analysis of BG neuronal activity during sleep in the normal and Parkinsonian monkey, we first show that during normal slow wave sleep (SWS), most basal ganglia nuclei manifest high-amplitude slow-oscillatory (~0.5 Hz) activity in firing rate. However, in sharp contrast to any neural substrate explored thus far during sleep, the slow oscillations in all BG structures were completely desynchronized between individual neurons. Analyzing Parkinsonian sleep, we demonstrate that similarly to PD, MPTP intoxication induced a profound fragmentation of sleep, an increase in wakefulness after sleep onset and a decrease in SWS. During SWS in the Parkinsonian monkey, the BG slow oscillatory activity decreased and synchronous beta (10-17 Hz) activity emerged in the LFP and spiking level. In contrast to waking beta activity, which is widely acknowledged and studied, aberrant beta activity in the BG during sleep has received surprisingly little attention so far. We show that this aberrant BG beta oscillation was coherent with scalp EEG beta activity that replaced normal slow oscillatory activity. Strikingly, the degree of BG beta activity was strongly correlated with the severity of the Parkinsonian sleep symptoms. Thus, we characterize the neural correlates of normal and Parkinsonian sleep in the BG and suggest that the degree of aberrant BG beta activity may predict the severity of sleep fragmentation in PD.

(This presentation would be ideally presented in a 30 minute time frame)

Keywords: Sleep, Slow Wave Sleep, Parkinson's Disease, Non-motor Symptoms, Beta Activity

00025
STN-DBS in Parkinson’s disease: pitfalls and limitations of rodent’s models

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Abstract

Three decades of stereotactic neurosurgery in Parkinson’s disease (PD) have changed dramatically our understanding of circuitry and our therapeutic armamentarium. Experimental “toxic PD” in non-human primates under MPTP and rodents (6-OHDA) inspired the clinical boldness of stereotactic pioneers impinging the subthalamic nucleus (STN).

For neuroscientists, deep brain stimulation (DBS) represented, in fact, a paradigmatic example of an efficient and bidirectional cross-talk between bench and bedside. Of note, both models and clinical evidence shared some neurophysiological hallmarks of the Parkinsonian state such as the exuberance of high-beta band and its critical cortical-basal ganglia (BG) synchronization (counterpart of akinesia). This synergy is promoting new developments, such as on-demand loop stimulation and big-data multi-centre acquisitions.

Nevertheless, critical divergences did emerge, mostly considering the experience in rodent models, whose capability to recapitulate PD pathophysiology is modest. Here a brief summary:

In patients, it was demonstrated negligible the DBS-mediated suppression of glutamate.
A tonic release of dopamine, as inferred in rodents, was not replicated in humans.
Further, there are conspicuous pitfall in rodent’s approximate models. They a) do not mimic the full spectrum of motor and non-motor disabilities experienced in humans; b) reproduce an extremely advance neurodegeneration and may fail to provide a progressive assessment of the discrete changes correlated to different stages of a

progressive disease; c) describe a “pure” dopamine depletion (not affecting other systems notoriously critical in some parkinsonian phenotypes, i.e. noradrenergic and cholinergic brain-stem deficits).

Here, we examine these limitations, to endeavour where to shift the tiller of DBS-oriented research.

00028
GABA transporter activity governs tonic GABA inhibition of striatal dopamine release and is dysfunctional in prodromal parkinsonian mice

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Abstract

Dopamine (DA) release in the striatum is integral to motivated behaviours and motor control. DA release is gated locally and powerfully by numerous presynaptic mechanisms at its axonal release sites. The striatum is one of the most GABA-rich nuclei in the mammalian brain, and unsurprisingly then, we demonstrated recently that DA release is under tonic inhibition by a striatal GABA source. Given the paucity of GABAergic axoaxonic synapses on DA axons, we propose that this striatal GABA tone arises from ambient GABA levels, which are well-documented to tonically inhibit other striatal neurons. Ambient GABA tone in striatum is determined by the activity of plasma membrane GABA transporters (GAT). However, whether striatal GATs set the level of DA output is unknown. We reveal that GAT-1 and GAT-3 strongly regulate DA release in mouse striatum by limiting the GABA tone on DA axons, specifically in dorsal striatum, but not ventral striatum. We find correspondingly greater GAT-1 and GAT-3 levels in dorsal versus ventral striatum. Further, we demonstrate that GAT-1 and GAT-3 on astrocytes are key regulators in limiting GABA inhibition of DA release, as astrocyte inactivation prevented the effects of GAT inhibition. Moreover, in a human alpha-synuclein-overexpressing mouse model of prodromal Parkinson’s disease, we find that tonic inhibition of DA release by GABA is augmented in the dorsal but not ventral striatum, as a consequence of decreased GAT-1 and GAT-3 levels. Altogether, these data indicate that GAT-1 and GAT-3 critically determine the level of GABA inhibition of DA release in a region-specific manner and are dysfunctional in Parkinson’s disease. These findings might offer novel targets for the treatment of Parkinson’s disease and other disorders associated with DA dysfunction.

00036
Buspirone modulates the activity of the entopeduncular nucleus only when the nigrostriatal integrity is assured

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Abstract

The pathophysiology of Parkinson's disease (PD) and of L-DOPA-induced dyskinesia (LID) is associated with dysfunctional neuronal activity and abnormal oscillatory and synchronization patterns in several nuclei of the basal ganglia (BG). Serotonin-based therapies are promising candidates for treating PD and LID, such as buspirone, a partial agonist of 5-HT1A receptors. This drug has demonstrated antidyskinetic properties but the mechanisms involved in this therapeutic effect are not fully understood. Here, we aimed at further investigating the effect of buspirone on the neuronal activity of the entopenduncular nucleus (EP), one of the output nuclei of the BG. Single-unit extracellular recordings were performed under urethane anaesthesia in sham, parkinsonian (6-hydroxydopamine lesioned) and dyskinetic rats. Neuronal activity parameters, oscillatory activity and synchronization between this nucleus and motor cortex were analyzed. Systemic administration of buspirone inhibited EP firing rate in sham but not in parkinsonian or dyskinetic rats. By contrast, the local administration consistently reduced the firing frequency in all groups. In addition, buspirone did not affect synchronization and low-frequency oscillatory activity in the EP or in the motor cortex in sham, parkinsonian or dyskinetic rats. To further elucidate the mechanism of buspirone, using optogenetic tools, we observed that photoactivation of the STN increased EP firing frequency, but this increase was significantly higher under buspirone effect. These results suggest that buspirone may enhance the STN-EP excitatory input. Altogether, these results indicate that buspirone produces an inhibitory effect mediated by a complex mechanism that involves DA system integrity.

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Keywords: 6-hydroxydopamine, L-DOPA, buspirone, low frequency oscillations

00037
Buspirone differentially modulates the cortico-entopeduncular and the cortico-nigral information transmission through the direct pathway in a rat model of Parkinson´s Disease

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Abstract

Cortical information is transferred to the entopeduncular nucleus (EP) and the substantia nigra pars reticulata (SNr), the output structures of the basal ganglia (BG), through three different pathways, the hyperdirect trans-subthalamic and the direct and indirect trans-striatal pathways. Functional alterations of these pathways have been associated with Parkinson's disease. On the other hand, the activity of these pathways may be modulated by serotonin (5-HT) since 5-HT receptors are present all along the BG. Here we aimed to investigate how buspirone, a 5-HT1A receptor partial agonist, modulates the cortico-entopeduncular and cortico-nigral information transmission through the sensorimotor (SM) circuits of the BG in control and PD conditions. To do that, electrical stimulation of SM cortex and simultaneous single-unit extracellular recordings of EP and SNr neurons were carried out in urethane anaesthetized sham and unilaterally 6-hydroxydopamine (6-OHDA) lesioned rats. In both nuclei, SM stimulation evoked a triphasic response consisted of an early excitation (activation of the hyperdirect pathway), an inhibition (activation of the direct pathway), and a late excitation (activation of the indirect pathway). No changes were observed after the lesion. In the EP, systemic injection of buspirone (0.6125 mg/kg) enhanced the duration of the inhibition in both sham and 6-OHDA lesioned rats. By contrast, in the SNr, buspirone enlarged the duration of the inhibition only in the sham group. These effects were reversed by the 5-HT1A receptor antagonist, WAY-101635 (0.5 mg/kg). These results suggest that buspirone modulates transmission mainly by potentiating the direct pathway, which contributes to understand the involvement of 5-HT1A receptors in SM circuitry functionality.

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No conflict of interest.Keywords: 5-HT1A, basal ganglia, single-unit recording

00041
Effect of dopaminergic degeneration on the locus coeruleus neurons and cortical activity

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Abstract

The locus coeruleus (LC), the main noradrenergic nucleus of the brain, is altered in neurodegenerative disorders as Parkinson's disease (PD). The interaction between this nucleus and its projections to cortical areas, as somatosensory and medial prefrontal cortex (mPFC), is likely involved in pain, anxiety or cognitive problems, which are common non-motor symptoms in the disease. Here, the aim of the study was to investigate the oscillatory activity of LC noradrenergic neurons and cortical areas, together with the synchronization between both regions in sham and hemiparkinsonian (6-hydroxydopamine lesioned) rats. To do that, single-unit activity and local field potentials (LFP) recordings were performed in the LC under chloral hydrate anaesthesia. Electrocorticogram (ECoG) signals from the mPFC and somatosensory cortex were also analyzed. In the LC, dopaminergic denervation reduced basal spontaneous activity and did not modify the proportion of oscillatory cells. LFP from the LC and ECoG from mPFC and somatosensory cortex showed low frequency oscillations (1-5 Hz) that were enhanced after dopaminergic denervation only in the somatosensory cortex. Coherence analysis showed significant synchronization between LFP from the LC and mPFC or somatosensory cortex that was similar in both groups. In addition, we studied the effect of systemic administration of L-DOPA, which did not modify the tonic activity of LC neurons nor the synchronization and low-frequency oscillatory activity. Altogether, our results indicate that dopaminergic degeneration induces modifications in the noradrenergic system, accompanied by enhanced somatosensory cortical activity.

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Keywords: Locus coeruleus, Somatosensory Cortex, Prefrontal cortex, oscillatory activity, 6-OHDA

00060
Local field potentials in the subthalamic nucleus during repetitive fist opening/closing in Parkinson's disease patients

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Abstract

Beta band oscillation in the subthalamic nucleus (STN) has been proposed as a pathophysiological feature of Parkinson's disease (PD). Many studies in which the local field potentials (LFPs) were recorded via deep brain stimulation (DBS) electrode have showed that oscillatory activity at the beta band frequency was frequently detected in PD patients and the levodopa therapy and DBS therapy suppress this oscillation. The aim of this study was to investigate the significance of neuronal oscillatory activity in PD patients.

At the electrophysiological targeting during DBS surgery, both multiunit neuronal activity (micro-recording) and local field potentials were studied in 28 PD patients. Their mean score of the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part III was 43.2±10.7 (mean±SD) in the OFF state. In the STN that was identified according to the micro-recording, the LFPs during active repetitive fist opening/closing, which is prescribed in the MDS-UPDRS as an example of activation maneuver for inducing rigidity, was also recorded. Power-spectra of LFPs were analyzed for the frequency range from 8 to 50 Hz.

In all subjects, the power-spectra analysis of LFPs in the STN showed a distinct peak in the power within the low beta band [14.1±2.2 (mean±SD) Hz]. The repetitive fist opening/closing induced a significant increase in the peak power both on the contra-lateral side (176 % increase, $p<0.05$) and ipsi-lateral side (40 % increase, $p<0.05$). Eighteen among 28 patients showed not only the low beta peak but also another peak at the high beta range [27.0±2.9 (mean±SD) Hz], and many of them (67%) easily exhibited dyskinesia with an intravenous drip of levodopa. However, among the rest without high beta peak, only 2 patients showed the levodopa-induced dyskinesia.

These results suggest that abnormally synchronized neuronal activity in the STN reflects some of the parkinsonian symptoms such as rigidity and levodopa-induced dyskinesia.

00075
Contrasting changes in DARPP-32 and calbindin immunoreactivity in striatal medium spiny neurons in Parkinson's disease

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Abstract

While the substantia nigra is widely implicated in Parkinson's disease, the amount of degeneration of the striatum and medium spiny neurons (MSNs) is still unclear in Parkinson's disease. Our previous work has indicated that DARPP-32 (dopamine and cAMP-regulated neuronal phosphoprotein) can be used to identify a subset of MSNs, and that DARPP-32 MSNs partially colabel with calbindin, the traditional MSN marker. The mammalian striatum (composed of the caudate nucleus, putamen and ventral striatum) is heterogeneously organized into neurochemically distinct compartments, called striosomes and matrix. Furthermore, preliminary qualitative investigations showed that the great majority of DARPP-32 positive cells in the dorsal striatum were localised in the striosomes whereas scattered DARPP-32 positive cells were localised to the matrix. This study utilised human post-mortem striatal sections from neurologically normal and Parkinson's disease cases, in order to investigate whether DARPP-32 and calbindin are altered in Parkinson's disease. Morphometric analysis using Metamorph® image analysis software revealed that overall calbindin-positive integrated density within each striatal compartment showed no major difference from control to Parkinson's disease, DARPP-32 integrated density in Parkinson's disease striatal regions was decreased overall in comparison to control DARPP-32 integrated density. In particular, significant decreases were found in the putamen striosomes ($p = 0.0197$, 50% decrease), putamen matrix ($p = 0.0079$, 59% decrease), ventral striatal patches ($p = 0.0087$, 65% decrease) and ventral striatal matrix ($p = 0.0036$, 62% decrease). Histological examination also revealed weaker immunoreactivity of DARPP-32 positive MSNs with morphological and dendritic changes, particularly in the putamen. This study shows that in the striatum, the putamen and ventral striatum show selective loss of DARPP-32 immunoreactivity in Parkinson's disease.

00090
Suboptimal multisensory integration in Parkinson's disease: visual dominance despite impaired visual self-motion perception

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Abstract

Introduction: Parkinson's disease (PD) is prototypically a movement disorder. However, motor and perceptual functions are highly interdependent. Yet, much less is known about perceptual deficits in PD. These are less observable, important to understand in and of themselves, and may be related to motor impairments. Posture, gait, balance and other motor functions impaired in PD, rely on veridical perception of self-motion.

Methods: We directly tested visual and vestibular self-motion perception, and visual-vestibular cue integration in 19 (non-demented, independently walking) PD participants, 23 healthy age-matched adults and 20 healthy young adults. Participants experienced vestibular (motion platform), visual (optic flow) and combined visual-vestibular self-motion stimuli, and reported the direction of their perceived heading. PD participants (and age-matched controls) repeated the same experiment twice – PD on and off medication.

Results: PD participants had significantly impaired visual self-motion perception compared to age-matched controls ($p<10^{-4}$) irrespective of medication status, but their vestibular performance was unimpaired (comparable to both control groups). Moreover, the PD deficit in visual self-motion perception correlated with clinical disease severity ($r=0.7$, $p=0.002$). Strikingly, despite impaired visual self-motion perception, PD participants significantly over-weighted visual cues in the multisensory condition ($p<0.01$), reflecting sub-optimal visual-vestibular integration. No significant differences were seen between age-matched and young healthy controls

Discussion and Conclusions: Here we found that PD patients have impaired visual self-motion perception. Furthermore, they integrate visual and vestibular cues sub-optimally. These impairments may contribute to impaired mobility and motor function in PD. PD may be marked by a general deficit in multisensory integration.

Conflict of interests: No conflict of interest

00107
Theta-Alpha Oscillations Characterize Emotional Sub-region in the Human Ventral Subthalamic nucleus

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Abstract

Therapeutic outcomes of subthalamic nucleus deep brain stimulation for movement and psychiatric disorders depend to a large extent on electrode location within the subthalamic nucleus. Beta band oscillatory activity is the electrophysiological signature of the dorsal sensorimotor subthalamic nucleus, the stimulation target in movement disorders. However, a reliable marker of the subthalamic nucleus emotional sub-region, the stimulation target in psychiatric disorders, is still missing.

Here, we analyzed ventral subthalamic nucleus multi-unit activity in Parkinson's patients (n=303 patients, 933 trajectories) undergoing deep brain stimulation surgery. We divided ventral subthalamic nucleus according to relative position within the trajectory and studied location dependency of electrophysiological properties and functional correlations. We found high theta-alpha (6-13 Hz) oscillations at ventral subthalamic nucleus most ventral quartile. Theta-alpha power within this area was correlated with depression severity score in Parkinson’s disease patients (Beck Depression Inventory test, n=41 patients).

We suggest that theta-alpha oscillations can serve as an electrophysiological marker of ventral subthalamic nucleus emotional sub-region. Therefore, theta-alpha oscillations can guide optimal electrode placement in neuropsychiatric deep brain stimulation procedures. Theta-alpha oscillations might also provide a reliable emotional biomarker input for future closed-loop deep brain stimulation device.

00111
Nociceptive processing in the basal ganglia and parabrachial nucleus of Parkinson's disease rat models.

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Abstract

Parkinson's disease (PD) is associated with pain symptoms described by patients as bizarre transitory painful sensations such as painful burning, stabbing, aching, itching or tingling sensations. The origin of these pain symptoms is still poorly understood. A classic hypothesis in PD suggests that GABA neurons in substantia nigra reticulata (SNr) are hyperactive, possibly increasing their inhibitory influence on SNr targets. The parabrachial nucleus (PBN), a key structure in nociceptive processing from the midbrain, is under the direct influence of SNr. Therefore, PBN may present alterations that could explain some of PD pain symptoms. However, the functional state of this structure has never been evaluated in the context of PD. Using a technique of extracellular electrophysiology in anesthetized rats, we recorded nociceptive responses in the PBN and SNr following nociceptive footshocks, as well as in the subthalamic nucleus receiving a direct projection from PBN (Pautrat et al., 2018). We tested control and PD rats with either a partial or total dopamine lesion (6-hydroxydopamine).

We have shown that STN and SNr present a hyperactivity and hypersensitivity to the nociceptive stimuli in PD rat models. However, only animals with a total DA lesion presented reduced pain responses in PBN, and abnormal nociceptive responses, behaviorally evaluated with the hot plate test. Our results show that the normal PBN nociceptive processing in the partial DA lesion group, despite SNr hyperactivity could be caused by an efficient compensatory neuroplasticity. SNr activity has been recently hypothesized to be "leaky" (Terao, 2013), relieving transiently its inhibitory influence over its target structures. This leaky activity from the SNr, combined with a neuroplasticity in PBN could shortly release this structure from its pathological inhibitory influence and lead to painful sensations.

00135
Effects of external globus pallidus photostimulation on motor behavior in normal and hemi-parkinson mice

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Abstract

The basal ganglia (BG) are a set of interconnected subcortical nuclei involved in voluntary motor control. External globus pallidus (GPe) is located centrally in the BG, but its precise contribution to BG function is not fully understood. GPe has long been regarded as a simple relay nucleus within the BG, but recent evidence suggest that it may act as an integrative hub for shaping motor and non-motor aspects of behavior. Here, we used an optogenetic approach to investigate the contribution of GPe neurons to motor behavior in normal and Parkinson's disease (PD) mice. Global GPe photostimulation and selective photostimulation of parvalbumin (PV)-expressing neurons were achieved by expressing channelrhodopsin-2 variants using respectively AAV5-HSyn-ChR2(H134R)-eYFP vector in BL6 mice and AAV2-EF1a-DIO-ChR2(E123T/T159C)-eYFP vector in PV-Cre mice. Optical stimulation of GPe with laser-generated green light pulses produced a contralateral circling in normal BL6 mice. Similar locomotor asymmetry was elicited by selective stimulation of PV-expressing neurons. In both cases, the locomotor asymmetry effects were reversible and dependent on the stimulation parameters (light intensity/frequency). We next studied the effects of GPe photostimulation on motor deficits induced by unilateral 6-hydroxydopamine (6-OHDA) lesion of the substantia nigra. As expected, hemi-Parkinson mice displayed a range of motor deficits, spontaneous ipsilateral circling, forelimb akinesia and locomotor hypoactivity. GPe stimulations improved the various motor deficits in lesioned mice. These beneficial effects were reversible and observed with stimulation parameters ineffective in sham mice, thus supporting the view that reduced GPe activity contributes to the development of parkinsonian motor impairments. Together, these findings suggest that GPe stimulation may represent a potential therapeutic target for PD. This work was funded by H2020-EU (Grant agreement ID: 767092).

00136
Involvement of striatal dopamine and cholinergic interneurons in behavioral flexibility

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Abstract

Degeneration of nigrostriatal dopamine (DA) neurons in Parkinson's disease (PD) leads to motor and non-motor symptoms including loss of behavioral flexibility. Cholinergic interneurons (CINs) of the striatum are also known to play a critical role in behavioral flexibility, although the nature of their implication may vary upon studies. Here, we used an optogenetic approach to inactivate CINs activity in behaving mice and addressed their involvement in flexibility and inhibition processes. In transgenic mice (RosaeNpHR/+ ::ChATcre/+) specifically expressing halorhodopsin (eNpHR) in CINs, we investigated the effects of cholinergic interneurons photoinhibition or striatal DA depletion in a reversal learning task. In operant chambers equipped with three nosepokes, mice were trained to nose poke in a central hole then respond either in a left or right adjacent holes, to be rewarded by a sucrose pellet. When a baseline level of 70% correct responses was reached, the reinforced contingency was switched. Striatal DA-depletion or CINs photoinhibition differently impaired reversal learning. DA depletion increased perseverative responses in the previously reinforced hole after change of contingency and premature responding, while CINs inactivation produced only a dramatic effect on premature responding. This later effect, that may reveal deficits of inhibitory control, was further tested in a signaled nose poke task providing independent measures of associative learning and motor impulsivity. CINs inactivation induced an increase of impulsive behavior, showing that flexibility disorders could be closely related to impulse control deficits. Activity of striatal CINs appears to facilitate behavioral flexibility and regulate different aspects of behavioral inhibition. On-going studies aim to determine whether striatal DA depletion impairs behavioral flexibility by a direct interaction with striatal CINs.

00142
Thalamic dopamine changes in parkinsonism: insight into novel pathogenic mechanisms?

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Abstract

It is relevant to learn about changes in the parkinsonian brain beyond the mesostriatal system in order to understand a series of ill-defined pathogenic mechanisms and clinical manifestations. Dopamine loss in Parkinson's disease (PD) affects most intensely the striatum but is also present in other brain regions. We hypothesized that dopamine deficit in the thalamus may be a relevant unraveled mechanism in the parkinsonian brain. Indeed, the thalamus in primates is densely innervated with dopaminergic axons that express the dopamine transporter (DAT).

The toxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) was administered to adult macaque monkeys using a slow intoxication protocol. The intoxicated monkeys were classified into four groups by motor tests: asymptomatic, recovered, mild parkinsonian and severe parkinsonian. Dopaminergic innervation was studied by immunohistochemistry against DAT. The total length and length density of DAT-ir axons were estimated with stereology using a 3D fractionator. We also generated maps of the distribution of the DAT-ir axons.

Compared to control animals, parkinsonian monkeys exhibited less DAT-ir axonal length density in the mediodorsal (MD) and centromedian-parafascicular (CnMd-Pf) nuclei. In MD the dopamine denervation was present early, that is in monkeys asymptomatic at the time of sacrifice and with moderate substantia nigra cell loss (40-60%). In the reticular (R) nucleus, DAT-ir axonal length density exhibited an inverse pattern, with a progressive increase up to a maximum density in parkinsonian animals. DAT-ir axonal length density in the ventral thalamic nuclei did not show differences between groups. These results show a diverse reaction to MPTP of the dopaminergic axons innervating the thalamus. This may result in dysfunction of thalamocortical, thalamostriatal and intrathalamic transmission, and may contribute to motor and non-motor manifestations of PD, in particular attention and sleep disturbances.

00144
Alpha and beta oscillations in rest and during voluntary movements in STN of Parkinsonian patients

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Abstract

Oscillatory activity in subthalamic nucleus (STN) is under extensive study as it may contribute to both normal motor control in basal ganglia and in it's pathophysiological impairment in Parkinson's disease (PD). However, the particular borders of beta oscillatory range that is considered to be pathological are chosen arbitrarily. They may vary from 8 to 15 Hz for the lower limit, thus capturing occasionally a part or the whole alpha range into consideration. Here we studied the features of local field potential (LFP) rhythmic activity in alpha (8-12 Hz), low (12-20 Hz) and high (20-30 Hz) beta ranges at rest and during voluntary movements using novel algorithm for automatic parameterization of neural power spectral densities as a combination of the aperiodic signal and putative periodic oscillations (Voitek et al. 2015). This approach allows to estimate aperiodic "background" 1/f component from the slope of the LFP spectras which may reflect excitation/inhibition ratio in neuronal population.

31 patients with PD undergoing DBS surgery were included in the study. LFPs were recorded during rest and motor tests (patient were asked to contract fist and/or move foot contralateral to the hemisphere recorded).

At rest oscillations in both low and high beta range were significantly higher in dorsal part of STN, whereas alpha oscillations were stronger more ventrally. Motor tests led to the significant decrease in the spectral slope and the increase in low beta range. The most pronounced changes in the slope and in the low beta oscillation scores were found in dorsal part of STN. At the same time, alpha and high beta ranges during voluntary movements remained substantially unaffected. We believe that alpha, low and high beta ranges must be considered separately in neurophisiological research of basal ganglia.

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00156
STN and GPi stimulation effects on reactive and proactive inhibitory control: a behavioural and EEG study

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Abstract

Multiple cortical and subcortical regions are involved in controlling motor inhibition during adaptive behaviour. STN is thought to have a central role in ‘reactive’ inhibition, relaying a fast and global cortical stop signal during ongoing action. The network readiness to elicit a stop signal, so called ‘proactive’ inhibition, is probably modulated by STN tonic activity but also by GPi through the indirect pathway. The precise relative contribution of the STN and GPi in both types of inhibitory control remains largely unresolved.

We addressed this question by investigating the behavioral and electrophysiological effects of STN and GPi deep brain stimulation on reactive and proactive inhibition in patients with Parkinson’s Disease.

EEG was recorded while 29 PD patients (12 STN, 7 GPi, 10 non-operated) performed a cued go-no-go (GNG) task with or without DBS. The cue enabled to modulate the involvement of proactive and reactive inhibitory control by predicting the likelihood of a following no-go signal (‘certainly go’; ‘maybe stop’, ‘likely stop’).

‘Likely stop’ cues increased reaction times (RTs) in all groups, confirming the capacity of the task to modulate proactive inhibition. In the STN but not GPi group, the DBS shortened RTs in all conditions. We found no effect of DBS target on reactive or proactive components of inhibition (false alarms, error rate), neither in the STN nor GPi group.

Preliminary topographic ERP analyses revealed an increase in the N2 ERP component amplitude by the DBS in the GPi but not STN group, suggesting an involvement of the GPi in the detection of the conflict between response tendencies and task demands for inhibition.

Our collective results indicate that although not captured by behavioural measures, GPi stimulation interferes with proactive inhibitory mechanisms at the cortical level. The anticipation and decision in conflicting situation might thus be improved by GPi-DBS.

00168
Reproducing subthalamic nucleus beta burst dynamics ON and OFF Levodopa in Parkinson's disease with a simple excitatory/inhibitory population model

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Abstract

It has been shown that motor impairment in Parkinson's disease is positively correlated with the proportion of longer bursts of activity in the beta band of subthalamic nucleus (STN) local field potentials (LFP) OFF medication [1]. It is hypothesised that shorter bursts are more likely to be physiological, whereas longer burst are more likely to be pathological. STN oscillations have been previously studied through computational modelling of coupled excitatory and inhibitory populations with a Wilson-Cowan (WC) model [2]. Here, we investigate whether such a simple model can reproduce both pathological and physiological STN beta bursting dynamics. We study STN beta burst features of 7 patients ON and OFF Levodopa [3], with ON bursts giving an approximation to the physiological state. Burst duration across thresholds is identified as the feature most suited to distinguish between burst dynamics in the ON and OFF states. We select patients that have significant differences in beta burst duration between the ON and OFF state, and fit a stochastic WC model to these patients. Our model is able to reproduce both pathological and physiological bursting features, suggesting that simple neural circuits may be sufficient to replicate these burst temporal dynamics. We conclude by studying the difference in model parameters between the ON and OFF states across patients to understand how the transition between long and short burst can occur in the modelled network.

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00171
Role of Motor Thalamus in Levodopa Therapy for Parkinsonism

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Abstract

Levodopa is the most widely used pharmacotherapy for motor symptom treatment in Parkinson's Disease (PD). Despite decades of widespread clinical use, the neural circuit mechanisms through which levodopa exerts its clinical effects in PD remain unclear. Longstanding models of PD pathophysiology suggest that normalization of motor thalamic neuronal activity should be a critical factor in levodopa's therapeutic efficacy. However, such normalization of motor thalamic neuronal activity has never been directly demonstrated, and alternative hypotheses of levodopa action are tenable. To test this longstanding hypothesis of levodopa action, we are measuring the activity patterns of single neurons in the motor thalamus of nonhuman primates, both healthy and Parkinsonian (MPTP-treated), treated or untreated with a sympotom-alleviating dose of levodopa. Datasets of neuronal firing patterns across treatment conditions are being compared to determine their consistency with traditional models of levodopa action. Here, we describe preliminary results from one subject. Results of this study will shed light on the possible role of motor thalamus in levodopa-mediated symptom relief.

00172
Decreased daytime sleepiness by deep brain stimulation of the pedunculopontine nucleus area in healthy non-human primate

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Abstract

Experiments performed in small mammals reported that pedunculopontine nucleus (PPN) area, which is a component of the reticular activating system, plays a key role in controlling wakefulness. This role has also been recently suggested in humans suffering from Parkinson's disease, in whom, in addition to treat gait disturbances, deep brain stimulation of PPN area also enhanced wakefulness. This clinical observation led us to explore the role of the PPN in the control of wakefulness in primates.

One healthy non-human primate was implanted in the region of the PPN with a quadrupole electrode connected to a stimulator and with a polysomnographic telemetry equipment recording simultaneously electroencephalogram, electrooculogram and electromyogram signals. Those signals, correlated with the videotaped primate behavior, were analyzed to differentiate the different sleep/wake stages. Daytime sleepiness was evaluated by a multiple sleep latency test performed 10 times in baseline condition and 10 times during stimulation of PPN area, 5 at low frequency (LFS) and 5 at high frequency (HFS). Mean sleep latency (min) and mean time spent in the different sleep/wake stages (min) were assessed and compared using a non-parametric ANOVA.

The analyzed naps were exclusively composed of light sleep. During LFS of PPN area, the occurrence of these naps was carried out with a longer latency time compare to the baseline tests (13.5 ± 0.9 min baseline vs 18.5 ± 0.5 min LFS) and a shorter sleep time (5.1 ± 0.7 min baseline vs 1.1 ± 0.4 min LFS). The HFS of the

PPN area did not produce a significant variation of the sleep parameters compare to baseline.

These results show that LFS of the PPN area induces an increase in daytime awakening in healthy primates and offer new perspectives in the comprehension and the treatment of excessive daytime sleep disorders.

00185
Cognitive profile of LRRK2 carriers in preclinical stages: a potential insight into compensatory mechanisms in PD

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Abstract

Background: In Parkinson's disease (PD), neurodegeneration occurs several years before onset of symptoms and compensatory mechanisms might modulate clinical manifestations. Few is known about such mechanisms but the comprehension of their pathophysiology represents a potential target for future development of therapeutics. Non affected carriers of monogenic forms of PD represent a model of preclinical PD. Here, we evaluated whether neuropsychological testing could detect differences in non-affected carriers of LRRK2 mutation (LRRK2+) in the preclinical stages, with the hypothesis that subclinical cognitive modifications might precede the onset of manifest motor symptoms.

Methods: Longitudinal study comparing LRRK2+ PD patients to non-affected relatives at three time points (mean interval: 2.5 years). A neuropsychological battery was administered assessing executive functions, verbal memory, and general cognitive abilities. Neurological examination (MDS-UPDRS) and genetic testing were also performed. Neuropsychological performances were compared at first evaluation and longitudinally: respectively univariate ANOVAs and mixed linear model analyses were performed by correcting for age and educational level.

Results: 10 PD Patients LRRK2+ (PD LRRK+), 5 non-affected LRRK2+ relatives (Non-PD, LRRK2+) and 6 non-affected wild type relatives (Non-PD, LRRK2-) were included. Despite a tendency for reduced accuracy in affected as compared to non-affected participants, no statistical differences were detected with the exception of a sub-score of frontal battery assessing inhibition behavior (PD LRRK2: mean: 19,1/20 SD:1,37; Non-PD LRRK2+: 20/20; Non-PD LRRK2- :20/20; p <0,032 at first evaluation).

Discussion: We could not detect significant differences in the cognitive profile of LRRK2+ Non-PD participants when compared to LRRK2+ PD and LRRK2- Non-PD in this limited dataset. Further analyses of longitudinal data are currently ongoing.

00190
Emergence and propagation of increased oscillatory activity in the cortico-striato-nigral network: is the striatum a key player?

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Abstract

Although exaggerated oscillatory activity has been observed in basal ganglia (BG) nuclei in Parkinson's disease (PD), it is still unclear how it emerges and whether it engages the striatum, the primary input nucleus to the BG and most directly affected by dopamine loss. In this study, we analyzed the time course of emergence of these pathologic activities and compared how they propagate through the cortico-BG circuit under decreased (PD) and increased (L-dopa induced dyskinesia, LID) dopamine levels in hemiparkinsonian rats.

Simultaneous local field potential and spike recordings were performed in motor cortex (MCx), dorsal medial and dorsal lateral striatum, and substantia nigra pars reticulata (SNr) of rats during circular treadmill walking. Recordings were done before and two weeks following lesion by 6-OHDA injection through an implanted cannula, and during LID after L-dopa treatment. We then applied information theory models to compare the capacity of the striatal neurons to represent information at the various dopamine levels.

It has been hypothesized that this excessively synchronized activity in BG-thalamocortical circuits is responsible for the motor impairments seen in PD patients. Our study suggests that, on the contrary, they might play a compensatory role. Results show that a continuous increase in power in the beta range in MCx, striatum and SNr after dopamine lesion, correlates with a continuous recovery of motor performance and capacity of striatal neurons to represent information. Also, while the striatum received excessive oscillatory cortical input during bradykinetic and dyskinetic states, the striatal projection neurons did not entrain to the beta nor high gamma oscillations in PD and LID, respectively. This finding supports the view that the excessive oscillatory activity does not propagate from MCx to downstream BG through the striatum. It remains clear, however, that local spiking activity is affected by the alterations in striatal input.

00191
STN DBS restores the contextual regulation of perceptual decisions

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Abstract

Perceptual decision-making can be described as a process by which sensory evidence is accumulated until a decision threshold (DT) is reached. This DT is adaptively tuned to its context, such as the probabilistic regularities of the environment. Here we use the log odds ratio of the upcoming event (LOR) to quantify contextual information. This study aims at specifying how patients suffering from Parkinson's disorder (PD patients) adjust their DT to contextual information. compared to healthy matched controls (HC) and how does levodopa (L-DOPA) treatment affect this adjustment compared to deep-brain stimulation of the subthalamic nucleus (STN-DBS). 14 PD patients performed a simple perceptual decision-making task under 4 pseudo-randomly ordered conditions: ON or OFF L-DOPA and ON or OFF STN-DBS. 31 HC subjects also performed the task. Subjects had to press a button to match a shape presented on screen. Transitions between shapes were controlled to systematically manipulate contextual information. L-DOPA reduced both PD patient's RTs and performance, suggesting a shift in the speed-accuracy trade-off. This deleterious effect was significantly limited with STN-DBS, both in RTs and performances. RTs in HC decreased linearly as LOR increased. Preliminary results indicate that there was no significant effect of LOR on RTs of untreated patients. The effect was entirely restored when patients were OFF L-DOPA + ON STN-DBS and there was no significant difference in the effects compared to HCs. These preliminary behavioural results suggest that L-DOPA treatment has a deleterious effect on simple perceptual decisions causing a shift of the speed-accuracy trade-off toward impulsivity, which is somewhat rectified by STN-DBS. Moreover, the use of contextual information is deteriorated in untreated PD patients but this impairment is fully rectified through STN-DBS. More analyses are required to better understand these effects and the effect of L-DOPA on the DT contextual regulation.

00198
Doxycycline modulates L-DOPA-induced dyskinesia via mechanism independent of the antibiotic activity

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Abstract

Background:Inflammatory mechanisms are proposed to play a role in L-DOPA-induced dyskinesia in Parkinson's disease. Herein we characterize the effect of the semi-synthetic second-generation tetracyclines doxycycline, minocycline and the non-antibiotic tetracycline COL-3 (incyclinide)in parkinsonian rats presenting L-DOPA-induced-dyskinesia. Methods:Rats sustained unilateral injections of 6-hydroxydopamine into the medial forebrain bundle were treated chronically with L-DOPA. To evaluate how the drugs affect the dyskinesia, L-DOPA primed rats (15 days of L-DOPA) received acute i.p. injection of doxycycline or minocycline and intracerebroventricularly COL-3 (inciclydine). Another group of parkinsonian rats were chronically treated with L-DOPA concomitantly with either doxycycline or minocycline. ResultsAcutely administered doxycycline, minocycline and COL-3 attenuated established dyskinesia. The co-treatment with doxycycline or minocycline and L-DOPA suppressed the development of dyskinesia without compromising the motor benefits of L-DOPA. The anti-dyskinetic effect of doxycycline is associated with a decreased expression of astrocyte, microglia, cyclooxygenase-2, matrix metalloproteinase and the production of reactive oxygen species. The anti-dyskinesia outline was accompanied by a serum decrease of PGE-2 and NOx. Regression analysis revealed that MMP2/MMP9 gelatinolytic activity, MMP3, reactive oxigen species, NOx and PGE2 were factors with a strong linear correlation between L-DOPA-induced-dyskinesiaintensity and doxycycline treatment. ConclusionThis study revealed a notable anti-dyskinetic effect of the tetracycline derivatives modifying the behavioral and molecular consequences of L-DOPA treatment of hemiparkinsonian rats. Based on tetracycline excellent safety profiles in humans from their use for over 50 years as antibiotics, we propose the repurposing of the tetracycline derivatives as an adjunctive therapy to treatL-DOPA-induced dyskinesia.

00146
Hand and neck movement related pallidal single-unit activity in isolated cervical dystonia

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Abstract

Cervical dystonia (CD), the most common form of focal dystonia is characterized by abnormal head posture combined with jerky or tremulous movements. The mechanistic underpinning of this common disorder remains unclear. One of the theories suggests increased activity through cortico-striato-pallidal “direct” and “indirect” pathway as a cause of dystonia. Reduced pallidal output, changes in firing pattern and long-lasting inhibition induced by cortical stimulation was previously described. The aim of our study was to characterize evoked single-unit activity in response to voluntary movement of affected (dystonic) neck muscles and compare it with unaffected (clinically normal) hand movement. We used microelectrode recording from 12 CD subjects undergoing deep brain stimulation (DBS) surgery under local anesthesia. We analyzed 45 neck and 21 hand movement sensitive neurons, recorded from GPi and GPe. Comparison of single-unit response with electromyography (EMG) revealed either lead or lag in neural response. Some neurons responded by short-term phasic activation (or inhibition) as a rule initiating movement and other cells characterized by long-term tonic responses. Some neurons responded with both lead and lag excitatory-inhibitory components accompanied by low frequency (1-5 Hz) oscillations. Comparison between hand and neck movement showed several differences. About 50% of neck sensitive cells responded with prolonged inhibition while most hand movements responded by excitation. Wherein in contrast to hand responses, all neck responses had an exponential decay with comparable to EMG decay time constant. Such decay in neuronal response was characterized by the time constant comparable to the one explained by previously described abnormal head neural integrator controlling head position.

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00162
eIF2alpha Translational Tone Determines the Sign of Dopamine Modulation of Striatal Cholinergic Interneurons

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Abstract

Pathways that regulate protein synthesis are known for roles in cell stress homeostasis and in the brain, in inducing long-term forms of synaptic plasticity. One such pathway, the integrated stress response, is activated by phosphorylation of the translation initiation factor, eIF2alpha. eIF2alpha phosphorylation is also required for mGluR5-LTD in the hippocampus (DiPrisco et al., Nat Neurosci 2014) and striatum (Rittiner et al., Neuron 2016). Here we report that a subset of cells in the striatum have an unexpectedly high basal tone of Pi-eIF2alpha and that these neurons are not sporadic, but coincide with ChAT+ interneurons. Functionally, we find that steady-state p-eif2a signaling in striatal cholingeric interneurons (SCIs) influences how dopamine (through type 2 receptors, D2Rs) modulates tonic SCI firing. Manipulations that reduce phospho-eIF2alpha in SCIs cause D2R agonism to now increase, rather than decrease, SCI firing. These effects are independent of synaptic activity. This non-synaptic, steady-state role for Pi-eIF2alpha activity in cholinergic interneurons significantly broadens the roles associated with the EIF2alpha pathway in the brain. Our findings also raise the possibility that striatal cholinergic interneurons may be a site for selective vulnerability to eIF2alpha signaling impairments that may arise through environmental or genetic susceptibilities

Recent work by our laboratory identified impairment of the phospho-eif2alpha protein translation pathway as a mechanism for dystonia, so we decided to investigate if in an animal model of dystonia (which show dysregulation of SCIs firing in which D2Rs increase rather than decrease firing) the EIF2alpha pathway has an impact on SCIs. In fact, manipulations that augment eIF2alpha phosphorylation restore D2R-induced SCI pausing in dystonia mouse models.

00163
Lateralized differences in pallidal excitation/inhibition balance in patients with cervical dystonia

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Abstract

Lateralized differences in pallidal outflow is assumed to be linked with asymmetric pathological tension of the neck muscles in cervical dystonia (CD) patients. At the population level the interhemispheric asymmetry was usually studied regarding the estimation of the spectral power in specified frequency bands, without taking in consideration the broadband spectral features. Nowadays, it was showed that the 1/f broadband activity is a neurophysiological indicator of excitation/inhibition ratio (Gao et al., 2017).

In view of these concerns, we recorded pallidal LFPs bilaterally in seven CD patients with combined latero- and torticollis and examined how lateralized asymmetry impacts on the 1/f broadband activity. LFPs was recorded intraoperatively during DBS surgery. All patients showed a trend towards an asymmetric difference in the 1/f broadband activity. Ipsilateral 1/f slope was greater in both GPi and GPe than contralateral, along with the prominent correlation between GPi and GPe slopes. We found that torticollis and the interaction between torti- and laterocollis had a strong impact on the 1/f broadband asymmetry, while only laterocollis had almost no significant influence.

Our findings emphasize the importance of mainstreaming a broadband activity in the estimation of LFP spectral features and provide further evidence for the pallidal asymmetry in CD patients.

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Keywords: dystonia, LFP, globus pallidus

1) Gao, R., Peterson, E.J., Voytek, B., 2017. Inferring synaptic excitation/inhibition balance from field potentials. NeuroImage 158, 70–78

00187
New Characteristics of Oscillations in Globus Pallidus Internus in Dystonia

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Abstract

Deep brain stimulation (DBS) of globus pallidus internus (GPi) has been used to treat primary dystonia for many years. However, dystonia patients' responses to DBS are not immediate but progressive over months to even years. Multiple characteristics of neural oscillation in GPi are essential for understanding, which may better predict DBS outcome and investigate neurobiological markers of dystonia for adaptive-DBS treatment regimen than one-dimensional of oscillations. The aim of this study is to investigate new characteristics of oscillations in GPi correlated with stable long-term (twelve months at least) outcome of DBS in primary dystonia. By calculating the oscillation power spectral density across 3-90Hz frequency bands, power ratio of two frequencies among 18 primary dystonia patients to represent the balance of frequencies. Oscillations and balance of different frequencies among 3-90Hz during rest and dystonic state were obtained and correlated with long-term post-operation clinical scores. The results showed that all cases had power spectra peak in theta and alpha band (3-10Hz). Power spectral density over 9-20Hz was correlated with long-term outcome of DBS ($p<0.01$). Balance between high beta and low beta had significantly negative correlation with post-operation scores, while the balance between alpha and theta had positive correlation with post-operation scores ($p<0.001$), both in rest and dystonic state. The balance of frequencies in dystonic state between high beta and low beta was significantly higher than rest state ($p<0.01$). The balance of frequencies in dystonic state between alpha and theta was significantly lower than rest state ($p<0.01$). This study show that the balance of the oscillations play an important role in the symptom of dystonia, which was able to predict long-term stable outcome of DBS in primary dystonia, such new characteristics maybe new biomarker of dystonia.

00201
Role of striatal cholinergic system in the pathophysiology of dystonia: An experimental model in non-human primate

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Abstract

Dystonia is defined as a syndrome of sustained muscular cocontractions leading to repetitive movements and abnormal postures. Studies in humans emphasize the crucial role of basal ganglia in the pathophysiology of dystonia. Recent data in rodents suggest the involvement of a disorder in the striatal cholinergic transmission. But these genetic or pharmacological rodent models do not always express the phenotype of dystonia. Therefore, it was important to propose a primate study to test whether an increase of cholinergic transmission within the putamen is able to induce a clinical phenotype of dystonia similar to that seen in humans.

To verify our hypothesis, we chronically infused non-selective muscarinic agonist (Oxotremorine) in the sensory-motor striatum in non-human primates. Dystonic clinical symptoms induced by this drug were assessed using the Burke-Fahn-Marsden (BFM) scale adapted to animals. We used electromyographic approach to characterize muscular activity linked to clinical symptoms, and we recorded Multi-Unit and Single-Unit neuronal activity in basal ganglia to establish electro-clinical correlations.

The infusions of Oxotremorine allowed us to observe: (i) abnormal postures and movements similar to the dystonic movements encountered in human pathology; (ii) an abnormally low neuronal firing frequency in the GPi (13.5Hz) and a bursty firing pattern mainly when the symptoms where severe; (iii) oscillatory activity (28-30Hz) within the putamen, GPe and GPi; (iv) the lack of coherence of the oscillatory activity between these structures; (v) that the GPi is the only structure to present a coherence of the oscillatory activity.

We have demonstrated for the first time that a model of chronic dystonia can be obtained in non-human primates by increasing cholinergic tone in the putamen. This work validates the hypothesis of an involvement of cholinergic interneurons and striatal acetylcholine levels in the pathophysiology of dystonia.

00020
Production of astrocyte-derived TNF-α in the striatum of dyskinetic mice is elicited by glutamate.

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Abstract

We addressed the hypothesis that L-DOPA-induced dyskinesia (LID) could be favored by the pro-inflammatory environment of the denervated striatum in parkinsonian mice. To this aim, we used 6-OHDA-lesioned C57BL/6 mice treated with L-DOPA (25 mg/kg + benserazide 10 mg/kg i.p.) for 21 days, analyzed dyskinetic behaviors and quantified concomitantly striatal inflammatory markers. Hemiparkinsonian mice developed axial, limb, locomotor and orofacial abnormal involuntary movements. L-DOPA treatment also resulted in the activation of astrocytes and microglial cells in the dorsolateral striatum and caused an elevation of TNF-α, IL-1β and IL-6 in the same region of interest. Interestingly, a treatment with cannabidiol (CBD) and capsazepine (CPZ) (30 mg/kg, 5 mg/kg, i.p.), which provides anti-dyskinetic effects, partially reduced TNF-α production in L-DOPA-treated mice while having no effect on IL-1β and IL-6 levels, indicating TNF-α may play a role in LID induction. Using glial cell cultures, we tested the possible role of glutamate in the induction of neuroinflammatory events in dyskinesia. Whereas glutamate failed to stimulate cytokine production in pure microglial cultures up to 500µM, it increased the expression of the astrocytic marker GFAP and the production of TNF-α in astrocytic cultures at concentrations above 50µM. Neither IL-1β nor IL-6 was induced, however, in these conditions. Most interestingly, a treatment combining CBD and CPZ abolished the increase in GFAP expression and the production of TNF-α triggered by glutamate in astrocyte cultures. Finally, we chronically stimulated cultured cortical neurons with TNF-α (50 ng/ml) and observed that the release of glutamate was increased. Our results indicate LID may result indirectly from the glutamate-dependent production of TNF-α by astroglial cells which, in turn, boost the release of glutamate by cortical neurons, creating a vicious circle that might colaborate with LID permanence.

00046
The perils of movement Initiation: a behavioral and circuit analysis of a mouse model of stuttering

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Abstract

The Perils of Movement Initiation: A Behavioral and Circuit Analysis of a Mouse Model of Stuttering

To learn more about the mechanistic basis of stuttering, we analyzed a mouse engineered to carry a lysosomal enzyme targeting pathway (LETP) gene mutation associated with stuttering in humans. Mice emit ultrasonic vocalizations (USVs) at frequencies in the range of 40-100 KHz in a variety of situations. These LETP mutation mice vocalized abnormally compared to wild type littermates. We show that LETP mutations affect mouse calls and human speech in similar ways, suggesting that both species share a commonly disrupted pathway. Utilizing a variety of methods, we are now discovering brain regions that are involved in this phenotype. In addition, we show preliminary data demonstrating the effects of dopamine on the vocalizations of wild type mice and mice with a mutation in the LETP pathway. Finally, we analyze the possible link between stuttering and Parkinson's disease.

00047
The neural mechanism underlying motor tic reduction during sleep

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Abstract

Motor tics, the hallmark symptom of Tourette syndrome (TS), typically wax-and-wane over multiple timescales and are modulated by behavioral factors. Specifically, tics are greatly reduced in rate and amplitude during sleep.

Experimental and theoretical findings have associated TS with abnormal striatal inhibition. These results were supported by the experimental induction of transient tics by focal injections of $GABA_A$ antagonists into the motor parts of the striatum, leading to temporary disinhibition.

Here, I will present a novel experimental model of chronic motor tics which extends the period of tic expression from tens of minutes to multiple days. This model utilizes a mini-osmotic pump implanted subcutaneously in the rat's back which infuses bicuculline into the striatum in a fixed rate.

During wakefulness, the behavioral and neuronal correlates of tics were similar to the ones observed in the acute striatal disinhibition model: Tic expression was stable and maintained similar kinematic properties and was accompanied by tic-related local field potential spikes (LFP spikes) and individual neuron activity changes that remained stable throughout the infusion period. During sleep, tics were reduced in both amplitude and frequency and eventually ceased. The LFP spikes continued to appear despite tic reduction, and simultaneous changes in the activity of individual striatal neurons occurred.

Our results support the hypothesis of dissociation between LFP spikes and tic expression. Thus, the coordinated neuronal activity expressed as the LFP spikes encodes the potential of tic generation. However, the behavioral expression of tics requires local neural activity entrained to the LFP spike leading to the propagation of the activity to downstream targets. These findings highlight a potential mechanism for reduction of tic expression in TS patients during sleep and potentially during other behavioral states.

00068
Discharge pattern of subthalamic nucleus in Tourette syndrome correlates with optimal DBS target site

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Abstract

Tourette syndrome (TS) is a neurodevelopmental disorder characterized by both multiple motor and phonic tics that tend to wax and wane in severity and frequency. A common treatment is anesthetized neurosurgical procedure, especially deep brain stimulation (DBS) in cortico-basal ganglia areas. DBS relies mostly on the phenomenological outputs interpreted by the doctors; to design more effective therapy we need more knowledge concerning TS neural mechanisms. On that note, we compared the neuronal activity at different depths of the subthalamic nucleus (STN), using microelectrodes for single-unit recordings, during anesthetized functional stereotactic surgery in TS patients and in patients suffering from Parkinson's disease (PD). By applying statistical spike-sorting methods, we were able to isolate 130 single-unity activities (SUAs) in TS and 54 in PD groups. We characterized the discharge patterns and the intrinsic oscillations by means of the mean firing rate (MFR), ISI-characteristics and the power spectral density for each SUA. We found a non-significant MFR difference between TS and PD STN neurons (TS: 11.72 ± 6.1 Hz vs. PD: 12.23 ± 7.3, p = .72). Data showed a significant difference between the population distribution relative to the temporal structure – burst-like vs. non-bursting – of subthalamic spiking activity in TS and PD (TS: 32% vs. 68% of units, PD: 7% vs, 93% of units, p <.001). Furthermore, we evidenced a non-homogeneous spatial relative proportion of discharge activity in TS with a maximum of burst-like SUAs presence (>50%) at the conventional DBS's stimulation target position. Finally, our results suggest that the temporal structure of the STN activity is the keystone to understanding the different mechanisms underlying movement disorders involving the same brain areas and that DBS optimal locations are usually located near the maximum presence of low-frequency burst-like SUAs.

00155
Activity patterns of striatal projection neurons in a mouse model of Parkinson's disease and dyskinesia

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Abstract

L-DOPA is the reference treatment of Parkinson's disease (PD). However, its chronic administration induces abnormal involuntary movements termed L-DOPA-induced dyskinesia (LID). The striatum has a pivotal role in generating PD and LID. PD is related to overactivity of the striatal projection neurons of the "indirect pathway" (iSPN) over the "direct pathway" neurons (dSPN). Conversely, LID is associated to a predominant role of dSPN over iSPN. However, little is known on the population dynamics of both SPNs to the generation of these movement disorders.

Using in vivo calcium imaging in freely-moving mice, we aimed to identify patterns of striatal SPN activities coding for akinesia and dyskinesia in a mouse model of PD and LID. We used D1-Cre and A2a-Cre transgenic mice to express the calcium indicator GCamp6f in dSPN and iSPN, respectively. Mice were implanted with accelerometer devices to record motor activity while imaging striatal activity in vivo in an open field. We measured motor and neural activity in intact and hemiparkinsonian mice at baseline and after administration of dopamine agonists as D1- and D2-agonits and L-DOPA.

Preliminary data show that calcium activity of both SPNs increases with movement in intact and hemiparkinsonian mice. We found a significant correlation between body acceleration and calcium signal activity, that was lost after administration of the dopamine agonists. Differences in the number, amplitude of calcium events and number of active neurons were observed after the different treatments between intact and hemiparkinsonian mice in both SPNs.

These preliminary results show that both SPNs are modulated by movement in healthy and parkinsonian conditions, and that administration of dopamine agonists alters the association between striatal neural activity and movement.

00200
Epileptic seizures induced by focal striatal disinhibition in non-human primates

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Abstract

Background: Although a number of experimental and clinical studies have pointed out participation or an even more prominent role of basal ganglia in focal seizures, the fact that the BG and especially the striatum may be involved in focal seizures, is still an open question. Previous experiments showed that microinjections of GABAergic antagonists of the sensorimotor striatum could induce choreic movements or myoclonic tics. In the present study, we performed microinjections of GABAergic antagonist in the sensorimotor striatum and correlate the induced behavioural modifications to cortical and subcortical activity.

Material and method: Experiments were performed on three fascicularis monkeys. Acute bicuculine injections were performed within the sensorimotor part of the striatum. Behavioural modifications were recorded and scored according to a modified Racine's scale. Electromyography, electroencephalography, basal ganglia local field potentials were recorded during each experiment. A backaveraging analysis was performed for each recorded session.

Results: over the 39 Bicuculline injections, 29 (74.3%) produced dramatic reproducible behavioural changes characterised by repetitive and pseudo-periodic myoclonic jerks with generalised tonic-clonic seizures. Myoclonic jerks were clearly detectable on the EMG signal as short stereotypical EMG burst concomitant from abnormal epileptic spikes recorded on EEG. Back averaging analysis from EMG myoclonia showed that electrophysiological activity started significantly earlier in the striatum ($p < 0.0001$), the GPe ($p < 0.0003$) and the GPi ($p < 0.0086$) than in the cortex.

Conclusion: These changes in striatal activity might be part of an endogenous mechanism controlling the duration of abnormal oscillations within the striato-thalamo-cortical loop. GABAergic interneurones might play a crucial role synchronising the cortico-striato-thalamic network and a drastic GABAergic modification of the striatum can induce focal seizures.

00007
Ultraestructural and functional changes of dopaminergic synapsis in a rat model of progressive parkinsonism

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Abstract

Although aggregation of α-synuclein (α-syn) is a key pathological feature of Parkinson´s disease (PD), it is not entirely clear the temporal sequence of ultrastuctural and functional changes induced by α-syn on neurodegeneration. Recent studies provide evidence that synaptic and axonal abnormalities as well as failure of synaptic mitochondria, occur before the degenerative loss of neuronal cell bodies and synaptic networks in PD, and could be attributed to synaptic accumulation of α-syn. Thus, our aim was to study the temporal sequence of ultrastructural and functional changes in dopaminergic striatal terminals associated with α-syn overexpression. For that purpose, ultrastructural changes by electron microscopy in TH+ striatal terminals and mitochondrial function in isolated striatal synaptosomes, have been assessed at different time points after bilateral inoculation in the SNc of adeno-associated viral vectors (AAV) encoding for A53T mutated human α-syn. We observed reduced TH+ density at the striatal level at 2 weeks post-inoculation (p.i., $p<0.05$) and in the SNc at 4 weeks p.i. ($p<0.05$) as well as robust and persistent expression of α-syn in the nigrostriatal pathway. Ultrastructural examination of striatal tissue also revealed signs of neurodegeneration such as

dystrophic and swollen morphology of dopaminergic axons at 4 weeks ($p<0.05$). We also observed higher number of electroclear vesicles within the dopaminergic terminals at 2 weeks p.i. ($p<0.05$), being more pronounced at 4 weeks p.i. ($p<0.01$) along with an increase in their size. Regarding synaptic functionality, significant reduction of mitochondrial respiration has been observed in striatal synaptosomes at 1 week p.i. (basal respiration, $p<0.01$; proton leak, $p<0.05$; ATP production, $p<0.01$). Our results indicate that pathological α-syn in dopaminergic striatal terminals seems to induce functional synaptic changes that precede axonal pathology and the onset of dopaminergic degeneration. (PI14/00763)

00042
Glucocerebrosidase gene therapy induces alpha-synuclein clearance and slows-down disease progression

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Abstract

Mutations in the GBA1 gene coding for the lysosomal enzyme glucocerebrosidase (GCase) are related to increased incidence of synucleinopathies such as Parkinson's disease (PD) and dementia with Lewy bodies (DLB). The identification of reduced GCase lysosomal activity as a common feature sustaining the neuropathological findings underlying PD and DLB -even when considering sporadic forms of these synucleinopathies- has recently attracted strong interest in the field. Here we have performed bilateral injections of a neurospecific recombinant adeno-associated viral vector serotype 9 coding for the mutated form of human alpha-synuclein (rAAV9-SynA53T) for disease modeling purposes, both in mice as well as in non-human primates (NHPs), further inducing a progressive neuronal death in the substantia nigra pars compacta (SNc). Next, another rAAV9 coding for the GBA1 gene under the control of the constitutive promoter GusB (rAAV9-GBA1) was unilaterally delivered in the SNc of mice and NHPs one month after initial insult with rAAV9-SynA53T, together with the contralateral delivery of an empty-null rAAV9 for control purposes. Obtained results showed that rAAV-mediated enhancement of GCase activity induced a marked reduction in alpha-synuclein burden, leading to improved survival of dopaminergic neurons. The conducted unbiased stereological estimation of tyrosine-positive (TH+) neuronal densities showed 45% of neuronal death in the rodent SNc without GCase enhancement, contrasting with a 24% of neuronal death in the treated side. In NHPs, roughly 40% of neuronal death was observed in the untreated side 3 months post-rAAV9-SynA53T administration (e.g. two months post-delivery of rAAV9-GBA1), compared to a 15% of cell death in the SNc injected with rAAV9-GBA1. Data reported here support the use of glucocerebrosidase gene therapy as a disease-modifying treatment for PD and related synucleinopathies, also including sporadic forms of these disorders.

00055
Metabolic characterization of different phases of Parkinson's disease

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Abstract

Parkinson's disease (PD) is the most common neurodegenerative disorder after Alzheimer's disease, affecting almost 1% of the population beyond the age of 60. Currently, its diagnosis relies on the expression of the well-known motor symptoms which appear in the late stage of the disease. Detecting the disease earlier represents a key step to develop curative treatments which are so far only symptomatic. Long considered as a purely motor disease, PD is nevertheless also characterized by neuropsychiatric disorders that can develop as soon as the early stages of the disease.

In this context, our aim is to find specific molecular markers of early phases of PD, when only the neuropsychiatric symptoms are expressed. Proton NMR-based metabolomics (Nuclear Magnetic Resonance) was applied to serum samples and brain tissues of a rodent model allowing investigation of different phases of PD.

This animal model is based on a specific, partial, bilateral 6-OHDA-induced lesion in dopaminergic neurons. For each rat, motor functions and apathetic-like behaviors were assessed using suitable behavioral tests and striatal dopaminergic denervation was quantified. For more precise evaluation, a scale integrating all these parameters was developed and allow to assign a score to each animal.Serum samples were analyzed by liquid NMR at 950 MHz (IBS Grenoble) and intact tissue by HRMAS-NMR (High Resolution Magic Angle Spinning) at 500 MHz (CEA Grenoble). Data were submitted to multivariate statistics in order to investigate whether behavioral and histological data can be predicted from metabolomics.

In our animal cohort we observed a gradation in the symptoms, from neuropsychiatric only to the expression of neuropsychiatric associated with motor symptoms, which is well in line with PD progression from early to late phases of the disease. In both samples, analysis showed a good correlation between metabolic profiles and score gradation, i.e. with the different phases of PD.

00066
Small conductance calcium-activated (SK3) potassium channel overexpression are involved in L-DOPA induced-dyskinesia and Parkinson's disease

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Abstract

The most effective treatment for Parkinson's Disease (PD) motor symptoms is through administration of L-DOPA. However, the chronicity of this treatment leads to the development L-DOPA-induced dyskinesia (LID). Recent data showed that SK3 (small-conductance calcium-activated K+channel 3) modulates electrophysiological properties of dopaminergic cells of the substantia nigra compacta. Alterations of potassium channel expression and function in the basal ganglia have been linked to the pathogenesis of PD. Our aim is to determine the impact of SK3 channels in neurodegenerative responses in mice model of PD and LID. First, in order to determine SK3 channel expression related to dopaminergic system in naive SK3 overexpressing (T/T) mice, we performed immunohistochemistry analysis of double labelling of Tyrosine Hydroxylase (TH) and SK3 channel in the substantia nigra (SN). Compared to WT, we found SK3-staining increased in SN reticulata and decreased in the SN compacta. Then, SK3 T/T, SK3 knockout (KO) and wild type (WT) male mice received unilateral infusion of 6-OHDA in the striatum to induce degeneration of nigrostriatal dopaminergic pathway. The mice were tested for spontaneous forelimb use in the cylinder test where they showed similar asymmetry (30% of contralateral paw use). Chronic treatment with L-DOPA (25mg/kg; i.p) was able to induce abnormal involuntary movements in both KO and WT groups since the first day of treatment but it was absent in T/T mice. Further analysis with immunohistochemistry for TH will confirm the extension of the lesion and the presence of neuroinflammatory markers. These findings can indicate that ion channels may represent a new pathway to try to unveil the molecular mechanisms responsible for complex central nervous system diseases.

00078
TFEB-driven expression prevents neurodegeneration in a multiple system atrophy mouse model

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Abstract

Synucleinopathies are neurodegenerative diseases characterized by the presence of α-synuclein-positive intracytoplasmic inclusions into the central nervous system. Increasing evidence indicates that impairment of lysosomal function may contribute to the pathogenesis of the synucleinopathies, including Parkinson's Disease (PD) and Multiple system atrophy (MSA). The transcription factor EB (TFEB) coordinates the expression of lysosomal genes leading to an induction of autophagy. It has been demonstrated that overexpressing TFEB in a rat parkinsonian model triggers the restauration of the lysosomal machinery which leads to an enhancement in the clearance of α-synuclein, finally leading to neuroprotective effects. We used a transgenic mouse model of MSA which overexpresses the human wild-type-α-synuclein in oligodendrocytes under the mouse myelin proteolipid protein promoter. By combining a viral-based approach to overexpress TFEB under a neuronal or an oligodendroglial promoter, we investigated the effects of cell-specific targeting TFEB overexpression on neurodegeneration, α-synuclein clearance and lysosomal machinery using both histochemical and biochemical approaches five months following intranigral injection in this mouse model of MSA. We provide evidence that only specific oligodendroglial overexpression of TFEB leads to neuroprotective effects associated with an increased clearance of the protein α-synuclein into the oligodendrocytes after autophagic machinery recovery with increased lysosome biogenesis and lysosomal activity. In addition, we observed defects in TFEB expression levels in MSA patient brains, pointing TFEB as an attractive therapeutic target for MSA. These results reinforce the ability of using viral-mediated TFEB gene expression to regulate lysosomal biogenesis and activity as a powerful therapeutic approach in synucleinopathies such as PD and MSA by targeting its expression specifically into damaged cellular types according to the pathology.

00103
TP53INP1 deficiency exacerbates age-related and alpha-synuclein-induced degeneration of nigral dopaminergic neurons in mice

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Abstract

Parkinson's disease (PD) is characterized by the progressive degeneration of nigrostriatal dopaminergic (DA) neurons. These neurons are also more prone to degeneration during normal ageing, which remains the biggest risk factor for developing idiopathic PD. The stress response protein TP53INP1 acts as a molecular nexus at the crossroad of metabolic pathways essential for reversing stress-induced alterations in cellular homeostasis. Its deficiency has been linked with metabolic syndrome via mechanisms common to those involved in neurodegenerative diseases, including neuroinflammation, oxidative stress and mitochondrial dysfunction. Here we investigated the unexplored role of TP53INP1 in the brain under stress conditions, by focusing on DA neurons in the context of age and PD-related neurodegeneration. We performed comparative regional analysis of mesencephalic DA neuron loss by TH immunostaining and behavioral testing in WT and Trp53inp1-KO mice at different ages and in a PD model based on viral vector-mediated overexpression of human α-synuclein. In the nigra, the age-related DA neuron loss predominates in the rostral part in WT mice and it is worsened specifically in the caudal part in KO mice. In the PD model, DA neuron loss predominates in the rostral nigra and is worsened in both rostral and caudal nigral parts by TP53INP1 deficiency. IBA1 immunostaining suggests increased microglial reaction at early degeneration stages in KO mice. The stronger neurodegeneration is accompanied by aggravated motor deficits. In both conditions, the calbindin-positive subpopulation of nigral DA neurons appears to be the most affected. In the ventral tegmental area, age and PD-related DA neuron loss does not differ between WT and KO mice. These data provide the first evidence for a neuroprotective role for TP53INP1 and emphasize the heterogeneity of responses to cellular stress among DA neurons. Supported by CNRS, Aix-Marseille Univ and Fédération pour la Recherche sur le Cerveau.

00126
Implication of vitamin A in survival of dopaminergic neurons in a rat model of Parkinson's disease

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Abstract

Parkinson's disease (PD) is a brain disease caused by a loss of dopaminergic neurons in the substantia nigra pars compacta (SNc), leading to strong motor impairments. Vitamin A, through the action of its active metabolite retinoic acid (RA), is involved in the development, differentiation and protection of SNc dopaminergic neurons. However, the bioavailability of retinoic acid in the brain decreases with aging. Prior reports suggest that altered vitamin A signaling is implicated in the etiology of Parkinson's disease, though the mechanisms are poorly understood. Here we hypothesize that nutritional supplementation with vitamin A may reduce dopaminergic cells loss by increasing RA levels in the brain, thus delaying the progression of the disease.

We showed that rats deprived of vitamin A became progressively impaired in their motor functions and were unable to perform correctly the rotarod test after thirteen weeks of deprivation. However, locomotor functions were improved after just three weeks of vitamin A supplementation. To assess the effect of vitamin A supplementation, we modeled Parkinson's disease in rat. Dopaminergic neurons were selectively deleted with unilateral injection of 6-hydroxydopamine (6-OHDA) toxin into rat's striatum. Rats fed a vitamin A supplemented diet (20UI/g) for five weeks prior to the toxin injection exhibited an improvement in rotarod test compared to rats fed with control diet (5UI/g). Degeneration of dopaminergic terminals was assessed with stereological analysis of tyrosine hydroxylase staining in the striatum. Finally, dopamine levels in striatum were measured with HPLC.

These preliminary data established the link between dietary vitamin A and dopaminergic system in PD. Future work will focus on establishing its underlying mechanisms and molecular basis.

Key words: Parkinson's disease, vitamin A, nutritional supplementation, animal models

00133
Role of the serotoninergic system in Parkinson's Disease: a morphological study in Tph2 mouse model.

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Abstract

Parkinson's disease (PD) is a neurodegenerative disorder, which principal hallmark is represented by the loss of the dopaminergic neurons in the Substantia Nigra pars compacta (SNpc), with consequent reduction of dopamine levels in the striatum and the appearance of motor symptoms, typical of the disease, such as tremors, bradykinesia, rigidity, and postural instability. Besides the nigrostriatal pathway, other systems are affected and involved in PD. Among these, serotoninergic system seems to play an important role. Serotonin (5-hydroxy-tryptamine, 5-HT), is a neurotransmitter widely distributed in the brain, involved in the regulation of several physiological functions (developmental processes, synaptic plasticity, neuroendocrine function, sleep) as well as in neurodevelopmental and neuropsychiatric disorders of the brain. Moreover, serotonin is involved in the altered processes causing motor and non-motor symptoms of PD, but, in particular, it seems to be responsible for the L-Dopa-induced dyskinesias (LIDs) in 6-hydroxydopamine (6-OHDA)-lesioned rats. To investigate the possible role of the serotonergic system in the mechanisms altered in PD and LID, we used the transgenic mouse model Tph2 concomitantly displaying lack of 5-HT synthesis and an intact serotonergic innervation. Our electrophysiological data (unpublished data not shown) suggest that the serotonergic system is necessary for intact striatal function, confirming its role in corticostriatal plasticity. Then, to deepen this data, we have evaluated loss of dopaminergic neurons (TH+) and their progenitors (Pitx3+), GAD67 alteration and neuroinflammation markers in SN and VTA brain regions, by immunofluorescence and immunohistochemistry techniques, in Tph2 mice, 6-OHDA lesioned, with normal content of 5-HT (Wt), partial (Het) or total absence of 5-HT (KO).

00141
Neuroprotective effect of Cannabidiol in an experimental model of Parkinson's Disease

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Abstract

Parkinson's disease is a progressive and untreatable neurodegenerative condition. The administration of 6-hydroxydopamine (6-OHDA) into the striatum produces selective damage in the dopaminergic neurons of basal ganglia, microglial cell activation, and Parkinsonian-like symptoms. Cannabidiol (CBD) is the main no-psychotropic agent of Cannabis. CBD has demonstrated neuroprotective properties in different studies and models. Thus, we suggest that CBD could be a promising drug to interfere with PD evolution. We used C57BL/6 mice submitted to the unilateral lesion of the nigrostriatal pathway through 6-OHDA injection into the striatum. We treat the animals with different doses of CBD (10, 30 or 60 mg/kg) intraperitoneally for 5 days, starting soon after 6-OHDA injection into the striatum. Our results have shown that the doses of 10 and 60 mg/kg did not alter the dopaminergic loss in the nigrostriatal pathway. However, 30mg/kg of CBD reduced loss of dopaminergic neuronal terminals in the striatum and the number of dopaminergic cells in the substantia nigra pars compacta (SNpc). Microglial cell expression was reduced while astrocyte expression increased in the striatum, but reduced in the substantia nigra reticulata. Moreover, CBD increased CB1 receptor expression in the striatum while reduced FAAH expression in the SNpc. Furthermore, CBD increased the ambulation of animals in the actimeter test, the number of touches with the right paw in the cylinder test, and, in the tail-suspension test, CBD decreased the immobility time and increased the number of oscillations to the right side of the animal's body. In the object recognition test, CBD 30mg/kg improved long-term memory. Therefore, CBD protected the dopaminergic neurons of the nigrostriatal pathway and improved the motor deficits and cognitive decline in a preclinical neurotoxic model of the PD.

00086
An aversive output from the ventral pallidum is selectively potentiated after withdrawal from cocaine

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Abstract

The ventral pallidum (VP) is a central structure in the reward system strongly implicated in reward and addiction. This is attributed to the activity of its main neuronal population, GABAergic neurons. Recent studies revealed a novel glutamatergic neuronal population in the VP (VPvGluT2), whose activation generates aversion. Withdrawal from drugs is often accompanied by aversive feelings, but how these aversive feelings are enhanced after withdrawal is still under investigation. In this work we propose that VPvGluT2 neurons play a crucial role in enhancing aversive feelings after withdrawal. We show, using patch-clamp electrophysiology and optogenetics, that VPvGluT2 neurons preferentially contact aversion-related neurons, such as lateral habenula and ventral tegmental area (VTA) GABAergic neurons, with minor input to reward-related neurons like VTA dopamine and VP GABA neurons. Moreover, after withdrawal from cocaine the VPvGluT2 input to the aversive structures is potentiated while the input to the reward-related structures is depressed. Thus, after withdrawal from cocaine the glutamatergic output of the VP to aversive structures is enhanced selectively. Note that the VPvGluT2 neurons are located upstream of the lateral habenula and the VTAGABA neurons. This places VPvGluT2 neurons as potential master drivers of aversion after withdrawal.

00091
Requirement of Maged1 in glutamatergic cells for locomotor and reinforcing effects of cocaine

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Abstract

Melanoma antigen genes (Mage) were first described as oncogenic markers. However, some subtypes of Mage are also expressed in healthy cells where their functions remain poorly understood. Our group described an unexpected role for one of these genes, Maged1, in the control of drug addiction related behaviours. We provided evidence that mice constitutively lacking Maged1 exhibit a complete failure to display cocaine-induced responses such as dopamine (DA) release, locomotion, place preference and self-administration. Using region specific knockouts we attempt to identify which brain structures are involved in the phenotype and showed that deletions in the prefrontal cortex (PFC), the amygdala or in the ventral subiculum exhibit robust partial recapitulation of the full knockout phenotype, whereas the selective deletion of Maged1 in the striatal, GABAergic or DA neurons does not. We are now working on re-expressing Maged1 either in the PFC or in the amygdala in mice lacking Maged1 to test its sufficiency in these specific regions. To further demonstrate the glutamatergic identity of the cells where Maged1 is necessary for a normal drug-related behaviour we are inactivating Maged1 specifically in different cell types using mouse lines targeting glutamatergic neurons subtypes. To unravel the gene network under influence of Maged1, we are performing transcriptomic analysis after stereotaxic inactivation of Maged1 in the PFC and in the amygdala. Our preliminary results indentify Maged1 as a crucial molecule involved in features of cocaine addiction.

00148
Chemogenetic inhibition of prelimbic cortex reduces habitual methamphetamine self-administration.

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Abstract

An imbalance in activity between that patch and matrix systems of striatum is thought to underlie inflexible and repetitive behaviors, such as psychostimulant-induced stereotypy. Habitual drug abuse is also inflexible, suggesting that addiction is may be mediated by the patch-matrix system. Previous work also indicates that the patch system carries information regarding reward, which could also contribute to the development of habitual drug use. However, whether enhanced activation of the patch compartment underlies the development of habitual behaviors, particularly habitual drug use is not known. Our experiment analyzed the role of the patch compartment in the development of habitual methamphetamine (METH) use by using a designer receptor (DREADD) to inhibit the neurons of the patch compartment prior to METH self-administration. Rats were bilaterally infused in the prelimbic cortex, which selectively projects to the patch compartment, with a GiDREADD and allowed to recover for 6 weeks. The rats were then implanted with jugular catheters and trained to self-administer METH using a random interval paradigm known to generate habitual behaviors. Activation of GiDREADDs in the neurons of the prelimbic cortex with clozapine-N-oxide prior to each self-administration session was used to inhibit the activation of patch compartment neurons. The rats were then trained to associate METH with a negative stimulus, after which they were reintroduced to the operant chambers and given the opportunity to self-administer METH. Our preliminary studies show that activation of GiDREADDs in the prelimbic cortex reduced METH self-administration upon reintroduction to the operant chamber in animals that had learned to pair METH with a negative stimulus, indicating that habitual drug use may have been attenuated in these animals. These preliminary data suggest that the patch compartment could be necessary for the development of habitual METH self-administration.

00167
Egr2 expression in D1R SPNs of the ventrolateral striatum mediates cocaine reward

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Abstract

Gene transcription induced in the brain by salient experiences is necessary for the formation of memories and enables experience-dependent behavioral plasticity. We utilize the information embedded in unbiased gene transcription to dissect mechanisms of neuroplasticity associated with the presentation of cocaine reward. The results describe transcription dynamics induced in multiple brain nuclei in the meso-cortico-limbic dopaminergic pathway at different stages during the development of cocaine sensitization. We resolve the gene expression signatures corresponding to experiences of acute, repeated and challenge cocaine (re-exposure after abstinence). Notably, the tissue- specific induction pattern of a single gene- Egr2 (Early Growth Response gene 2) was sufficient to uniquely cluster and segregate the cocaine experiences of individual mice with greater than 90% efficiency. Therefore, Egr2 expression was used as a marker to dissect the transcriptionally recruited substructures in the brain following exposure to cocaine. We observed that Egr2 was highly induced in D1R-expressing neurons of the ventrolateral (VLS) striatum, a substructure in the dorsal striatum, whose function in context of cocaine reward is unexplored. We report that chemogenetic inhibition of the VLS- Egr2 expressing ensembles during training had no effect on locomotor behavior but attenuated expression of place preference (CPP) for cocaine. Furthermore, CPP was also blocked by the conditional disruption of Egr2 activity in VLS (D1R-expressing) direct pathway SPNs. Thus, our results demonstrate that cocaine reward is mediated by Egr2 expression in VLS D1R-SPNs.

00170
Principles of neuronal ensemble engagement identify the ventrolateral striatum as a novel hub in cocaine reward

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Abstract

During the development of drug addiction, behavior shifts from goal-directed to habitual control. The identification of neural ensembles and plastic processes they undergo to promote pathological compulsive behavior is an important development in this field. Here, we focus on striatal engagement by acute, repeated or challenge cocaine (cocaine after abstinence). We utilize multiplex smFISH to study principles of neural ensemble definition by immediate-early gene (IEG) expression (Egr2, Nr4A1 & Arc). We find that acute cocaine induced coherent expression of IEGs in striatal spiny projection neurons (SPNs) preferentially localized to the ventrolateral (VLS) and medial (MS) striatum. Strikingly, within the VLS, IEG-defined ensembles were selective to D1R expressing-SPNs, while in the MS both D1R and D2R SPNs were recruited to a similar extent. Our results reveal further meso-scale organization, whereby D1R- and D2R- expressing SPNs preferentially localized within small homotypic clusters. Intriguingly, IEG-expressing ensembles were found to associate in large clusters, with the extent of IEG expression correlating to the size of the cluster. We further observed dynamic shifts in the definition of striatal ensembles following consecutive (chronic & challenge) exposure to cocaine. To probe the role of the VLS neurons in cocaine reward, we chemogenetically inhibited the activity of VLS D1R SPNs, and observed an inhibition in conditioned place preference (CPP) for cocaine. Thus, our results reveal underlying principles of striatal ensemble recruitment by cocaine experience, and highlight the ventrolateral striatum as a novel hub dynamically engaged throughout the recurrence of cocaine experience.

00001
Macroautophagy controls striatal projection neuron activity and motor learning.

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Abstract

Macroautophagy (hereafter referred to as autophagy) is classically understood to be a cellular process through which cytosolic proteins and organelles are degraded. This process has recently been implicated in the development of neurodevelopmental disorders such as autism. Here, we demonstrate that developmental loss of autophagy leads to striatal dysfunction and hyperexcitability. Autophagy is required in the indirect pathway spiny projection neuron (SPN) specifically for the degradation and proper function of inwardly rectifying potassium channels. In direct pathway SPNs, autophagy is required for proper synaptogenesis and plasticity. Loss of autophagy in either pathway leads to motor performance and learning deficits and mice exhibit reptitive behaviors and stereotypies. Thus, autophagy may represent a critical cellular pathway required for proper circuit assembly and maintenance in the basal ganglia.

00013
Non-invasive, receptor-specific, millimeter-precision manipulation of brain circuits

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Abstract

Current treatment for brain disorders are either not sufficiently specific in local molecular targets (such as TMS, DBS, Focused Ultrasound (FUS)), are not spatially specific (systemic drugs), or are invasive (such as FUS-based Blood-Brain Barrier (BBB) opening or DBS). Non-invasive, receptor-specific, focal modulation of different brain circuits in a controlled, reliable manner could lead to breakthroughs in future treatments of brain disorders. To achieve this, we systemically deliver engineered ultrasound-controllable therapeutic drug carriers. We apply a two-component ultrasound pulse sequence; the first sequence concentrates the drug carriers with millimeter precision by orders of magnitude. The second sequence uncages the carrier's cargo into the blood stream locally to achieve high target specificity and low off-target effects. Upon release from the carriers, the drugs locally cross the intact BBB. We show circuit-specific manipulation of sensory information flow to motor cortex of rats by locally concentrating and releasing a GABAA agonist from ultrasound-sensitive carriers. This approach uses orders of magnitude lower amount of drug than it is otherwise required by systemic injection. Our approach requires very low ultrasound powers (20-fold below FDA limits for diagnostic ultrasound imaging). We show that BBB remains intact using MRI-contrast agents and, importantly, sensitive fluorescent dye extravasation. This approach enables the most precise type of non-invasive circuit manipulation by combining molecular/receptor specificity of existing small molecules with a spatially-targeted delivery technique.

00057
Vulnerability of the nucleus accumbens neuronal network to developmental n-3 PUFA deficiency: consequences on the reward and motivation system

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Abstract

Various, though distinct psychiatric disorders, such as Schizophrenia, bipolar disorder or major depression are associated with a dysfunction of the reward system linked to an alteration of dopamine transmission. Furthermore, these pathologies are also accompanied by changes in lipid metabolism and in particular a decrease in the brain content n-3 polyunsaturated fatty acid (PUFA) in the nervous system. However, the implication of brain lipid composition in the etiology of psychiatric endophenotypes has been overlooked. The aim of this study was to investigate a potential causal link between n-3 PUFA deficiency and deficits in reward processing.

Using operant conditioning tasks in mice, we showed that developmental n-3 PUFA deficiency leads to a selective motivational deficit at adulthood that is reversed by n-3 PUFA supplementation starting at birth. In parallel, we showed that n-3 PUFA deficiency leads to alterations in electrophysiological properties of medium spiny neurons (MSNs) in the nucleus accumbens, main actors for motivational processes. MSNs from the direct pathway (dMSNs) displayed a decrease in excitability paralleled with an increase of inhibitory input onto these neurons. Using pharmacogenetic and transgenic approaches, we showed that 1) alterations in dMSNs directly results from increased inhibitory input from MSNs of the indirect pathway (iMSNs), called lateral inhibition and 2) rescuing appropriate PUFA levels in D2R-expressing neurons selectively (including iMSNs), was sufficient to reverse both alterations in electrophysiological properties of dMSNs and motivational deficit observed in n-3 PUFA deficient mice.

This study demonstrates the existence of a causal link between modifications in PUFA levels in a discrete neuronal population and behavioral alterations. Overall, it suggests that altered PUFA levels, observed in some psychiatric disorders, could directly participate in the development of symptoms such as avolition or apathy.

00059
Implication of microRNAs in impulsive disorders associated with Parkinson's disease: experimental approaches in rodents

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Abstract

Parkinson's disease (PD) has long been considered as a pure motor disorder. However, a plethora of non-motor symptoms may occur, ranging from apathy to impulse control disorders (ICDs), and are considered as disabling as the motor ones. These neuropsychiatric disorders are two major comorbid syndromes of PD, and dopamine replacement therapy used to treat the motor symptoms is often associated with ICDs, that include pathological gambling, hypersexuality and compulsive shopping. Unfortunately, the mechanisms underlying this behavioral impairment remain elusive and thereby, relevant and efficient management of this syndrome is lacking.

Recently, several studies have linked dysregulations of microRNAs with PD or psychiatric disorders. These molecules are small non coding RNA playing a pivotal role in the translation of RNA messenger into proteins. However, no one has investigated yet the implication of these molecules in the neuropsychiatric symptoms associated with PD. We therefore investigate the potential implication of microRNAs in the development of ICDs.

We used a behavioral approach with a delay discounting task, a task that allow to assess a form of impulsivity tightly linked to ICDs, and looked at microRNAs expression profile with high-throughput microRNA sequencing from tissues of selected brain regions and blood from rats. We identified a specific microRNA profile associated with impulsivity traits and modified by a dopaminergic treatment, pramipexole, known to induce ICDs in PD patients and impulsivity in our model. A

causal validation is ongoing to disentangle the implication of these microRNAs in the development of impulsivity.

These findings may lead to the identification of potential new biomarkers that could be useful for the identification of patients under medication and vulnerable to ICDs. Also, the microRNAs identified will be good candidates for the development of innovative therapeutic strategies, leading to a better caretaking of these patients.

00089
Neurophysiologic characteristics of the medial geniculate body of the thalamus and metabolic alterations in the noise-trauma induced tinnitus animal model.

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Abstract

Introduction: The pathophysiological mechanisms underlying tinnitus are not fully understood. Alterations in neuronal activity are found within auditory and non-auditory structures. Proposed mechanisms underlying these changes are maladaptive gating and increase in central gain. The Medial Geniculate Body (MGB), is one of the key structures in this tinnitus network. Up to date, only few studies evaluated neurophysiological hallmarks of MGB neurons in tinnitus. Hence, we aimed to investigate the neurophysiologic characteristics in the MGB and changes in metabolic activity in the auditory pathway.

Methods: Fourteen male Sprague Dawley rats were included and divided in two groups: tinnitus (n = 9), or control (n = 5). Animal in the tinnitus group were exposed to a unilateral 16 kHz octave-band noise at 115 dB for 90 minutes. Tinnitus was assessed using Gap Prepulse Inhibition of Acoustic Startles. Four to five weeks after noise-exposure, single unit responses were recorded in contralateral MGB. Search stimuli were presented to identify responsive MGB units. Besides recording of spontaneous firing, a standardized sound paradigm was used to determine units' characteristic frequency and minimum threshold and response type. To evaluate metabolic activity in auditory brain structures, a cytochrome C oxidase staining was performed.

Results: After acoustic over-exposure, increased gap:no-gap ratios were found at 16 kHz background sound. In total, 145 responsive MGB neurons were recorded and analyzed. Neuronal properties are described. A significant downregulation of oxidative energy metabolism in auditory cortex was found. No differences were found in MGB, dorsal cochlear nucleus and inferior colliculus.

Conclusion: This experiment shows pathophysiological hallmarks in a noise-exposed tinnitus animal model by describing the neuronal changes in MGB and changes in metabolic activity. These findings support current hypothesis on increase in central gain.

00110
The Behavioural and Ecological Automatized operant Box (BEATBox): a flexible and low-cost system for high-throughput behavioural data acquisition

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Abstract

Behavioural neurosciences is aiming at understanding the complexity of behaviours as well as their underlying neurobiological processes in normal and pathological conditions. To this aim, the use of rodent models has become essential to monitor, map or manipulate their neural activity while they are performing behavioural tasks. Yet, the interpretation of the data collected with conventional behavioural procedures are biased by several conditions imposed by the experimenter. For example, daily manipulation of the animals, often under food or water deprivation, are perturbing their natural circadian rhythm, motivational state and anxiety level. Moreover, these procedures can be long to train the animals in complex tasks, limiting the range of behaviours that can be studied.

Improving behavioural protocols and setups is thus crucial to improve the quality of the data obtained by better considering the animal's natural behaviours. In this respect, we have developed the Behavioural and Ecological Automatized operant Box (BEATBox) where the animals are living during the entire behavioural procedure, with barely no interaction with the experimenter. Their engagement in the task is self-paced according to their needs and can last for weeks, allowing to perform complex behavioural procedures and acquire massive number of data. Thanks to our system, we can design complex behavioural tasks, refine the behavioural protocols and reduce the numbers of animals needed by increasing the number of data per animal.

Importantly, the entire hardware design and associated software are open-source, making the BEATBox easily adaptable and improvable by the scientific community at a much lower cost than commercial alternatives.

00129
Characterization of cortico-striatal myelination in the context of pathological Repetitive Behaviours

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Abstract

Several neuropsychiatric conditions are characterized by repetitive behaviours such as simple tics or ritualized sequences of complex behaviour. Although different types of repetitive behaviours are likely emerging from different aetiologies, a wide array of both clinical and preclinical evidence suggests that these behaviours are imprinted in dysfunctions within the cortico-striatal-thalamic-cortical (CSTC) circuitry. Numerous published studies have demonstrated white matter abnormalities mainly in frontal/prefrontal cortical areas (which project across the corpus callosum into striatum) in patients suffering from excessive repetitive behaviours, such as Obsessive-Compulsive Disorder. Considering the fact that minor alterations in myelin thickness, the main component of white matter, or axonal coverage patterns can provide significant changes in conduction speed, we believed that aberrant myelination of cortico-striatal pathways might participate to dysfunctional cortico-striatal circuits and the emergence of repetitive behaviours.

In order to address these questions, we assessed myelin-related differences between wild-type mice and a well-characterized model for repetitive behaviours, the Sapap3-KO mouse. We performed immunohistochemical analysis for the quantification of oligodendroglial cells, and complemented our results with the measurement of myelin thickness and density of myelinated axons.

We observed a slight, but non-significant, tendency towards a reduced number of mature oligodendrocytes in striatal regions. Additionally, performing a detailed

analysis on the results acquired with electron microscopy, we could verify that the thickness of the myelin sheet was not different between the two groups. Conversely, the striking result we observed in the dorsal striatum was that the axon calibre of putative projecting cortical neurons was significantly diminished in the Sapap3-KO group.

00138
Motivational control of decision making in wildtype mice and a mouse model for compulsive-like behaviours

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Abstract

Anticipated costs and benefits of cognitive control are predicted to be strategically balanced during decision-making. In this context, an impulsive or compulsive decision can be defined as a decision in which too few or too many mental resources are invested, respectively. The expected value of control, a measurement of worthiness of investing executive resources in a decision, has been suggested to be computed by the anterior cingulate cortex (ACC). This assumption is supported by several studies showing abnormal ACC activity in patients suffering of impulsive and compulsive behaviours.

Here, we study the motivational control of decision making in mice, using an automated operant chambers (BEATBox), during which task difficulty and reward amounts vary. Our data obtained from wildtype mice (n=23) showed that task performance decreases with increasing difficulty levels and is elevated in high compared to low reward trials. These results confirmed the hypothesis that cognitive control is in fact the outcome of a specific motivational arbitrage, which weighs the expected benefits of resource allocation against its costs. To assess the potential implication of this process in pathological compulsive behaviours, we compared in the same task the performance of a mouse model of OCD, the Sapap3-KO mice, to wildtype controls. We will now apply in vivo electrophysiological recordings and chemogenetic modulation of the ACC to test our working hypothesis that costs of decision making is encoded by active, prefrontal cortical inhibition of premature selection in basal ganglia.

00169
Prediction and prevention of compulsive behaviors by closed-loop optogenetic recruitment of striatal interneurons

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Abstract

Efficiency in our everyday behavior depends on automatic repetitive behaviors and routines. However, excessive repetitive behaviors are associated with neuropsychiatric symptoms, such as compulsions in obsessive-compulsive disorder. Understanding the neurobiology of the regulation of repetitive behaviors has then an immediate interest for clinical and fundamental research. The pathophysiology of compulsive behaviors points towards cortico-striatal circuits which have a major role in regulating the execution of motor sequences. Compulsive behaviors have been associated with abnormal hyperactivity in the striatum, but the dysfunctional mechanisms at the microcircuit level are still not well understood. In this perspective we are interested in the role of parvalbumin (PV)-immunoreactive striatal interneurons which exert powerful control over medium spiny neurons, thereby are a key element that regulates striatal output. To investigate the potential role of PV interneurons in regulating compulsive behaviors we used the Sapap3-knockout mutant mice, which exhibit excessive self-grooming. Using optogenetics to selectively activate PV interneurons in the dorsomedial striatum, we were able to reduce compulsive behavior to normality. Interestingly, this continuous optogenetic stimulation significantly reduced the number of grooming sequences rather than their duration, suggesting that the recruitment of PV interneurons is particularly necessary at the initiation of the compulsive event. To test this hypothesis we wanted to predict the occurrence of compulsive grooming to optogenetically interfere in a closed-loop design. Using a combination of extracellular signal acquisition, online data processing and optogenetics manipulation, we were able to predict grooming onset and provide closed-loop stimulation of striatal PV interneurons. Using this strategy, we were able to reduce, as much as with continuous stimulation, the compulsive behaviors to a normal level.

00173
Region Specific Dysregulation of Dopaminergic Signaling in Mice Displaying Excessive Grooming

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Abstract

Converging clinical and preclinical data suggest that striatal circuitry plays a key role in modulating repetitive behaviors and indicate that aberrant signaling in specific striatal pathways may represent a common mechanistic underpinning of numerous diseases including autism spectrum disorders and obsessive compulsive disorder (OCD). Imaging studies have found reduced striatal dopamine (DA) receptor binding in OCD patients compared to healthy controls, an indication that DA signaling may be hyperactive in these individuals. Consistent with this hypothesis, administration of atypical antipsychotics can effectively treat some OCD patients that are refractory to serotonin selective reuptake inhibitors (SSRIs). However, the precise role of DA is regulating repetitive behaviors is poorly understood. Here, we report studies using fast-scan cyclic voltammetry (FSCV) in mouse models to determine if DA signaling is altered in mice displaying abnormal repetitive behaviors. As previously reported, mice lacking the postsynaptic protein SAP90/PSD95-associated protein (SAPAP3 KO mice) spent more total time grooming than control littermates. DA transients evoked by a single electrical pulse in slices from SAPAP3 KO mice were not significantly different from those observed in slices from control littermates in any of the regions tested. However, when four electrical pulses were applied at a frequency of 10Hz to mimic DA neuron bursting, the magnitude of DA transients observed in the DMS and NAcc of SAPAP3 mice were greater than those evoked in control littermates. These exciting findings suggest that DA signaling in SAPAP3KO mice is dysregulated in a very precise manner that is sub-region specific as well as dependent on the pattern of stimulation. These results suggest that targeted therapies that can modulate these specific modes of DA signaling in these distinct striatal sub-regions could provide improved efficacy in OCD patients that are resistant to SSRI treatment.

00179
Implications of the striatal inhibitory networks in repetitive behaviors

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Abstract

Compulsion and tics are repetitive behaviors (RB) respectively expressed in obsessive compulsive disorders (OCD) and Tourette syndrome, two neuropsychiatric disorders that are often comorbid. The emergence of RB could result from a loss of control in the execution of isolated motor bout execution (tics) and/or over-expression of complex behavioral sequences (compulsions).

The pathophysiology of these excessive RB points to abnormalities in cortico-striatal loops. The striatum is organized in functional territories that are involved in the execution of processes ranging from motor to cognitive aspects. Interestingly neuroimaging studies have highlighted the importance of these segregated functional cortico-striatal loops for the etiology of tics and compulsions. In Tourette patients suffering of tics, cortical motor areas and dorsal striatum were affected; whereas in OCD patients suffering of compulsions, dysfunctional activity was observed in associative and limbic cortico-basal ganglia loops. However, the dysfunctional regulatory mechanisms at the striatal microcircuit level in these pathological states are still not well understood. In this perspective we are interested by the role of parvalbumin (PVI) and cholinergic (ChAT) striatal interneurons which exert a powerful control over medium spiny neurons, thereby are a key element that regulates striatal output.

Here, we used SAPAP3-KO mouse, a model suffering of pathological repetitive behaviors to investigate this hypothesis. In particular, we performed multiple correlative analysis between number of interneurons and pathological behaviors to assess whether the intrinsic nature of compulsions and tics lie in the anatomo-functional specificity of the striatal areas affected.

00182
Anatomical characterization of the cortico-striatal circuits in SAPAP3-KO mice by high definition fiber tractography

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Abstract

Compulsive behaviors are core symptoms of neuropsychiatric conditions such as obsessive-compulsive disorders (OCD). The pathophysiology of these related pathologies points to abnormalities in cortico-striatal loops, which are known to be essential to regulate action execution. Several human studies have shown white matter abnormalities in cortico-striatal circuits, suggesting that anatomical integrity of these pathways could be affected and responsible for the emergence of compulsive behaviors. To explore this hypothesis, we performed diffusion tractography imaging (DTI) in SAPAP3-KO mouse model suffering of repetitive grooming behaviors to investigate their circuits' integrity.

We used 11.7T MRI to get T1-weighted sequences with a 150 µm definition. This high field MRI allowed us to get precise anatomy of the mice brain and to improve the definitions of the regions of interest (ROI) we were interested in. The ROI were defined to be part of the motor, associative and limbic cortico-striatal loops. We thus defined primary motor cortex, supplementary motor cortex, anterior cingulate cortex, orbital frontal cortex and striatum as ROIs. For the DTI weighted imaging, we used a field of 3T with a b-value defined at 4000 s/mm², TR at 6000 ms and TE at 24 ms. To study the anatomic connectivity between those ROIs, we used Anatomist and Connectomist softwares (developed by Fabrice Poupon and Cyril Poupon). These procedures were performed on post-mortem mice brains, and we compared the results between Sapap3-KO (n=4) and their wildtypes littermates (n=5) to collect some first evidence of anatomical connectivity deficits in these mice model suffering of compulsive behaviors.

00192
Stop me if you can! Closed-loop optogenetic regulation of compulsive behaviors.

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Abstract

Increasing evidence points towards abnormalities in cortico-basal ganglia circuitry in the pathophysiology of disorders characterized by excessive repetitive behaviors. In particular, compulsive symptoms reflect a loss of control of motor and cognitive processes. This lack of regulation may lie in mechanistic properties of cortico-striatal circuits that can be investigate in mouse models suffering of compulsive behaviors, such as the SAPAP3-KO mice which display an over-grooming phenotype. In these mice we identified a striatal hyperactivity that could be dampen, as well as their compulsive behaviors, by a selective stimulation of the orbitofronto-striatal pathway. At the cellular level, we observed that excitation of cortical inputs reduced medium spiny neurons activity, potentially through a feed-forward inhibition mechanism driven by PV-interneurons. Thus, to better characterize the potential role of striatal PV-interneurons in the regulation of compulsive behaviors, we designed a closed-loop protocol using a combination of extracellular signal acquisition, online data processing and optogenetics manipulation. We first identify a neurophysiological event that could predict compulsive grooming about 2 seconds before its onset. We then performed real-time detection of this biomarker to instantaneously stimulate striatal PV-interneurons. Using this closed-loop design, we showed that temporal recruitment of PV-interneurons at the onset of a compulsive event can reduce its expression by regulating striatal activity to normal level.

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