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## Optogenetic manipulations of cortico-pallidal pathway impact specific aspects of motor behaviour in mice.

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### Topic & Theme selection

**Main Topic:** D.10.d: Basal ganglia

### Abstract Body

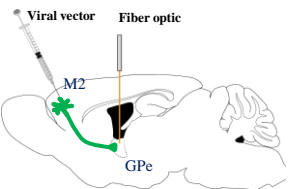
**Abstract body:** The classical model of basal ganglia (BG) network emphasizes a functional organization centered around the striatum and subthalamic nucleus as the main receiving areas of excitatory cortical inputs. However, recent anatomical studies revealed direct input projections from the cortex to the external globus pallidus (GPe) in many species including humans, suggesting that GPe also provides an entry for cortical information to the BG. When and how top-down cortical control of GPe takes place to support motor and cognitive functions remain an open question. Using an optogenetic approach, we first explored the behavioural effects of the cortico-pallidal pathway activation in normal BL6j mice. The excitatory channelrhodopsin-2 variant, ChR2(H134), was expressed in the secondary motor cortex (M2) area, the predominant source of cortical innervation to GPe. Mice expressing the fluorescent protein alone were used as controls. Unilateral photostimulation of cortical axon terminals in the GPe triggered contralateral circling while bilateral photostimulations improved acoustic sensorimotor gating (pre-attentive information filtering mechanism) and increased locomotor activity. The inhibitory chloride-conducting channelrhodopsin, iC<sup>++</sup>, was then expressed in M2 cortex to verify whether cortico-pallidal pathway is recruited in physiological conditions. Photoinhibition of cortico-pallidal axon terminals in GPe produced no change of spontaneous locomotor behaviour mice. By contrast, it reduced directed exploration assessed by spontaneous nose-poking behaviour in the operant chambers and delayed motor learning in the rotarod task. Similar behavioural effects were produced by optogenetic GPe modulations. Collectively, these findings provide the first evidence implicating the cortico-pallidal pathway in the modulation of specific aspects of motor function.

## INTRODUCTION

The classical model of the basal ganglia (BG) emphasizes a functional organization centred around the striatum and subthalamic nucleus as the main receiving areas of excitatory cortical inputs. Direct inputs from neocortex areas (motor cortex, cingulate area and lateral orbitofrontal area) to external globus pallidus (GPe) were recently revealed in many species including humans, suggesting that GPe also provides an entry for cortical information to the BG. When and how top-down cortical control of GPe takes place to support motor and cognitive behavior remain an open question. We used an optogenetic approach to selectively control the activity of cortico-pallidal projections from secondary motor cortex area (M2), the predominant source of cortical innervation to GPe, and study its impact on a range behavioral tasks (pre-attentive sensory gating, spontaneous motor behavior, motor coordination/learning and contextual learning) in mice

## METHODS & RESULTS

BL6 mice



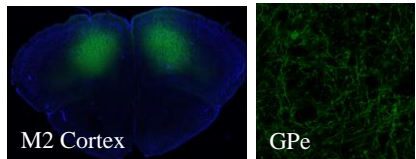
**Optical stimulation**

AAV5-hSyn-ChR2(H134R)-eYFP vector : ChR2  
AAV5-hSyn-eYFP vector : TAG

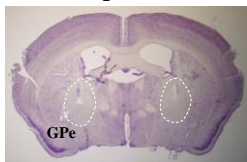
**Optical Inhibition**

AAV5-CamKII-IC++-eYFP vector : IC++  
AAV5-CamKII-eYFP vector : TAG

**Opsine-eYFP expression**

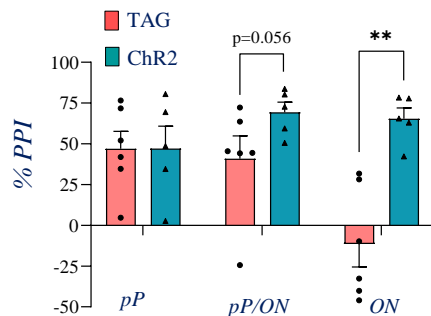
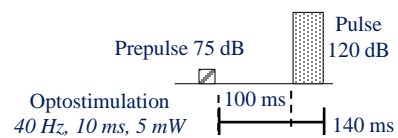


**Fiber optic trace**

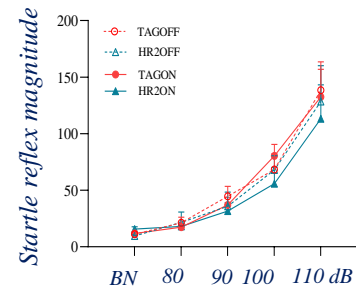
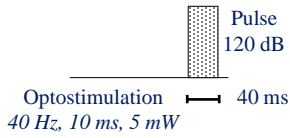


### Optical stimulation

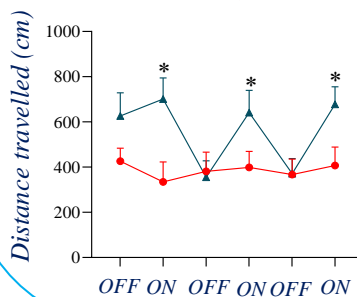
**Sensorimotor gating**



**Startle reflex**



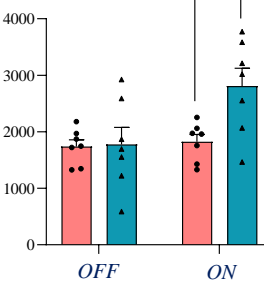
**Locomotor activity**



Optostimulation  
30 Hz, 5 ms, 2 mW

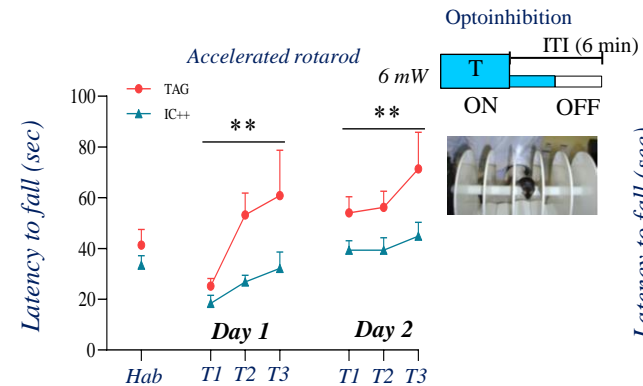


Global scores (cm)

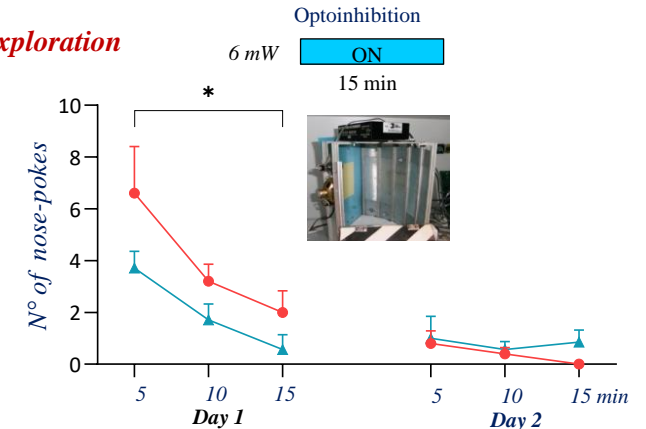


### Optical inhibition

**Motor coordination and learning**



**Directed exploration**



## CONCLUSION

- Photostimulations of cortico-pallidal terminals improve acoustic prepulse inhibition (pre-attentive sensory gating) and enhance locomotor activity in mice
- Photoinhibition of cortico-pallidal terminals impairs motor skill learning and reduce directed exploration of spatial cues, but have no effect on spontaneous locomotion (like global GPe inhibition, Di Bisceglie Caballero et al. 2023, Int. J. Mol. Sci. 24, 7935)

Top-down cortical control of GPe takes place in specific behavioral tasks to support implementation of motor programs/responses engaged by cortico-striatal circuits