Interaction of LRRK2-G2019S with Rab GTPases *in vivo*

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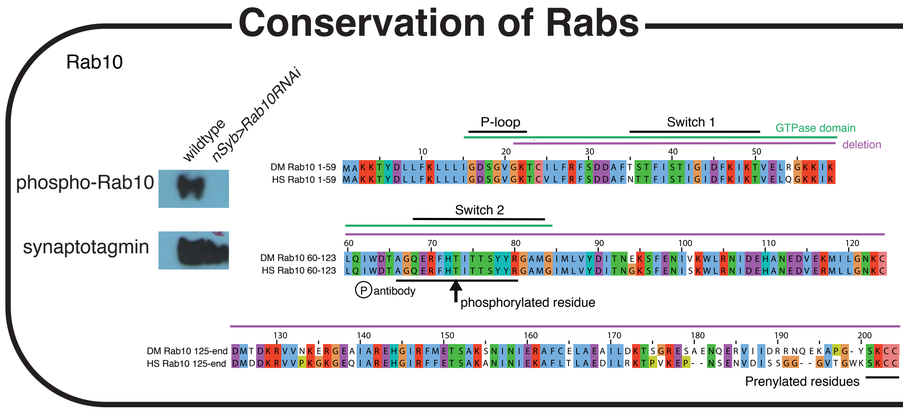
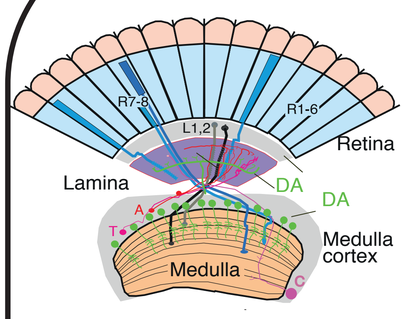
Aim

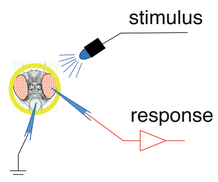
To test if LRRK2-G2019S interacts with any Rab GTPase in dopaminergic neurons, *in vivo.* We use the conservation of Rab sequence, neuronal circuit, easy genetics of the fly to show an interaction with Rab10 in some (but not all) dopaminergic neurons.

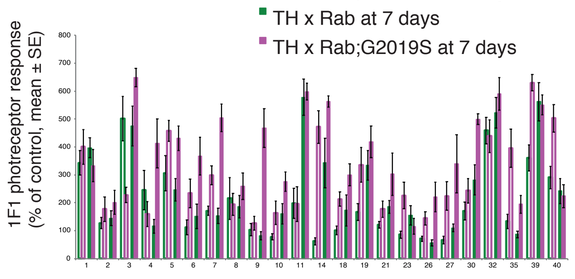
Conservation of Rabs

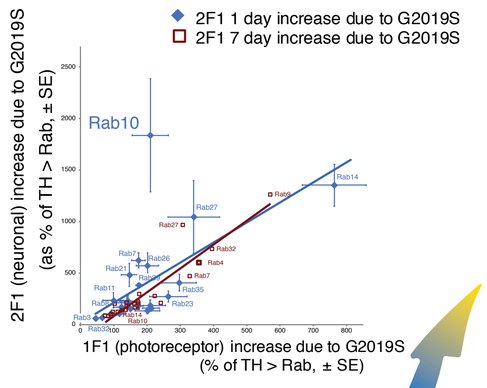


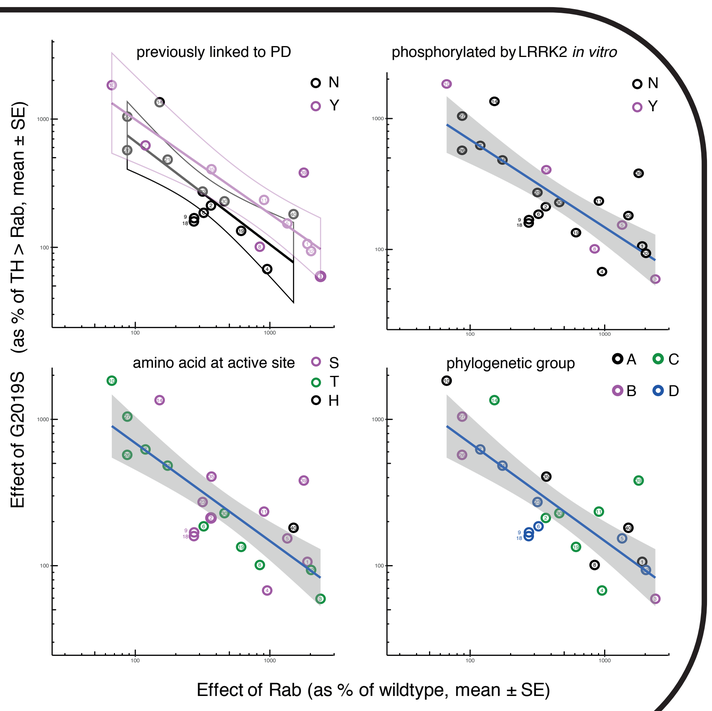
Expression Screen for interaction: Rab10 is top hit and Rab3 the weakest

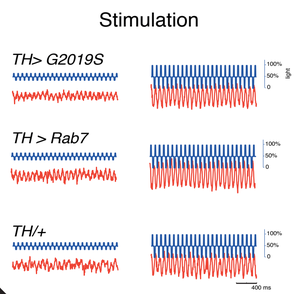


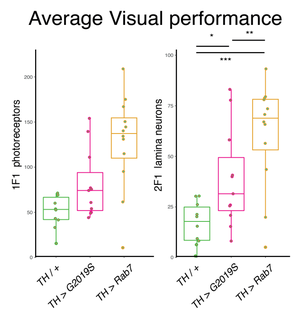


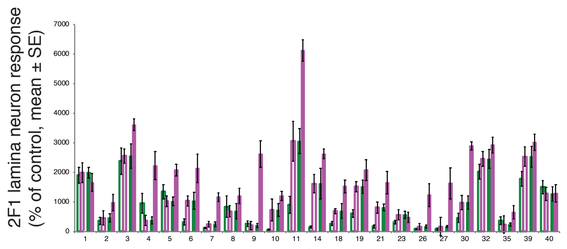


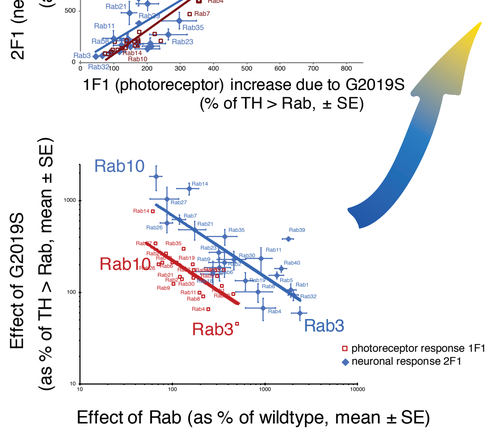






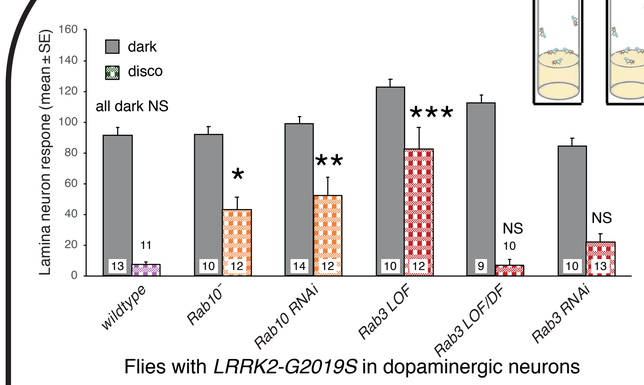


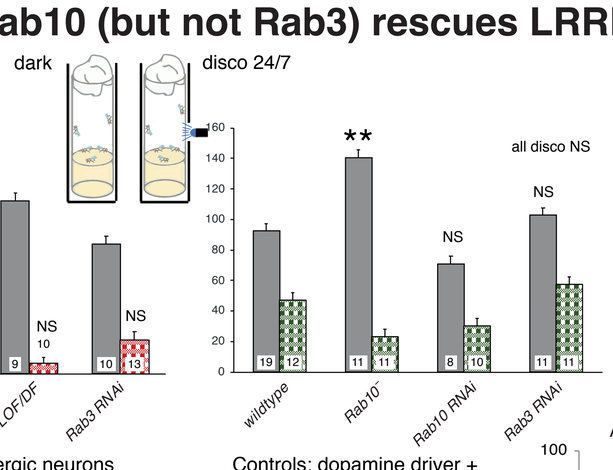




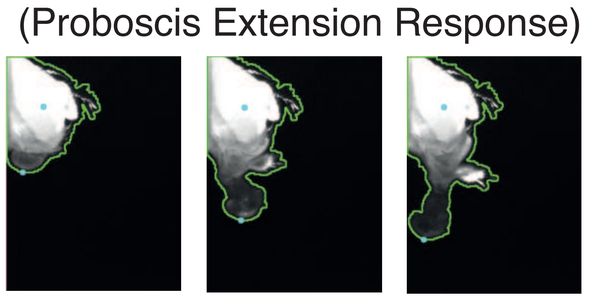
Knockout of Rab10 (but not Rab3) rescues LRRK2-G2019S degeneration

Vision

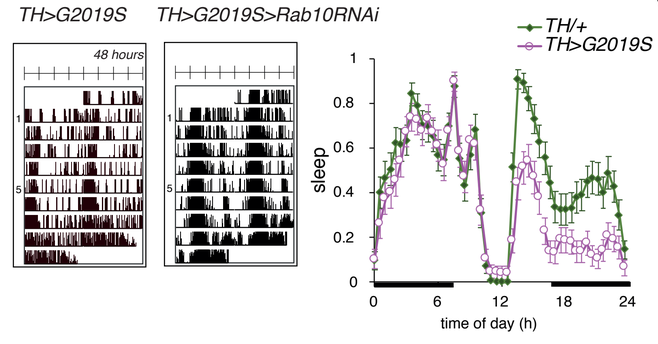




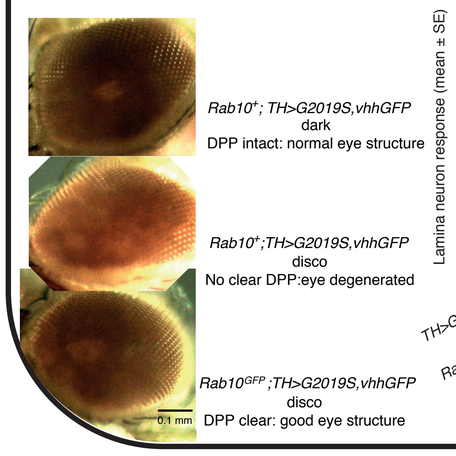
Reaching (Proboscis Extension Response)

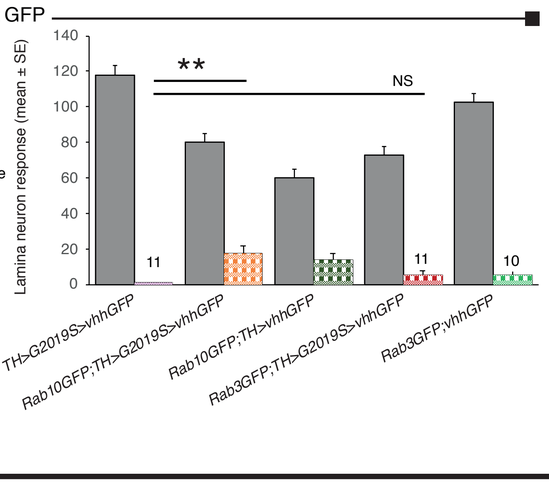


Circadian activity ... and "sleep"

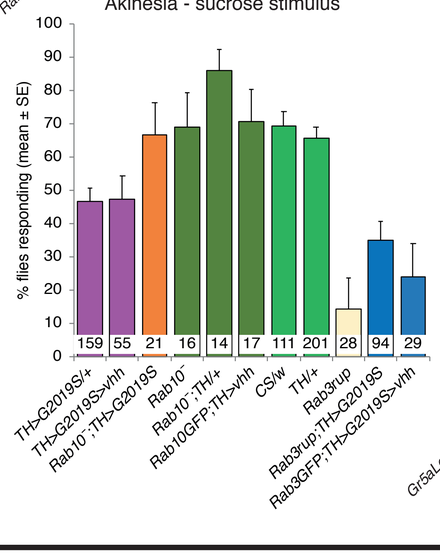


Flies with nanobody targeted at GFP

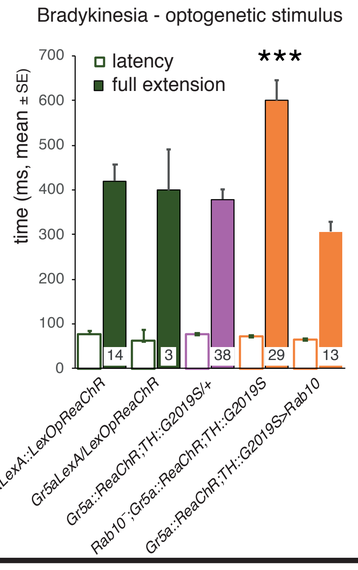


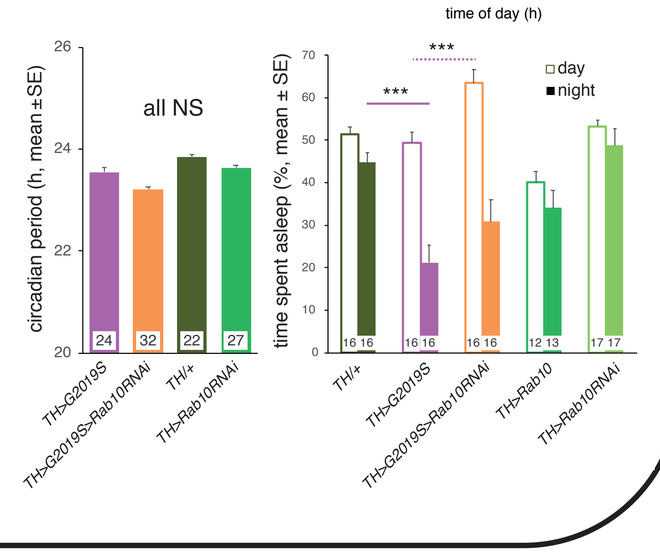


Akinesia - sucrose stimulus



Bradykinesia - optogenetic stimulus

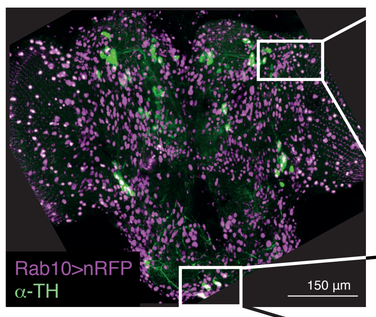




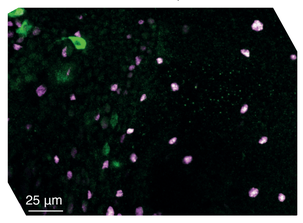
Morphologically - not all dopamine neurons have the same Rabs

Rab10

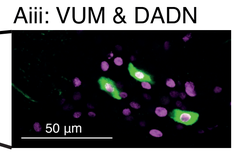
Ai: whole CNS



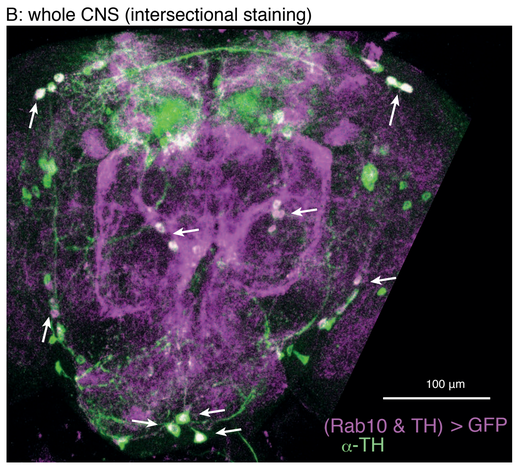
Aii: Visual lobes (MC neurons)



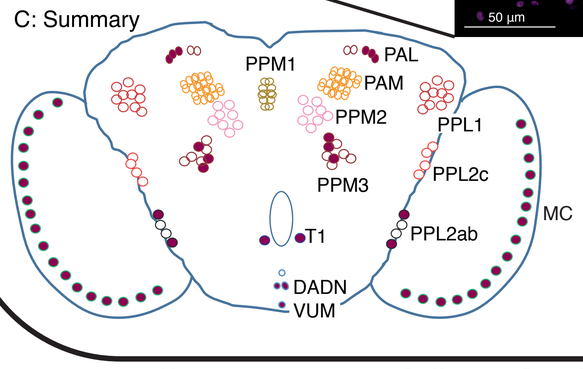
Aiii: VUM & DADN



B: whole CNS (intersectional staining)



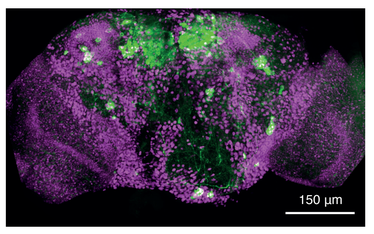
C: Summary



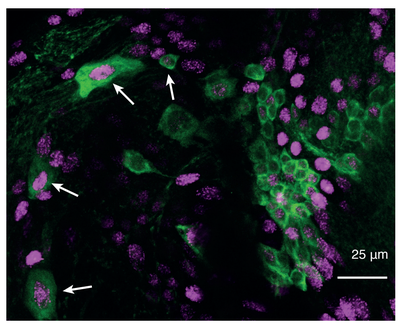
		Rab3	Rab10	
MC	vision	☒	☑	
TH-VUM	proboscis extension	☑	☑	Marella et al (2012)
DADN	leg movement	☑	☑	Tschida & Bhandawat, 2015
PAM	promotes wake	☒	☒	Sitaraman et al (2015)
PPL1	promotes wake	☒	☒	Sitaraman et al (2015)
PPM3	promotes sleep	☒	☑	Potdar & Sheeba (2018)

Rab3

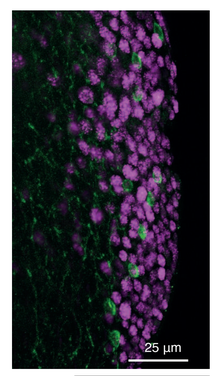
Ai: whole CNS



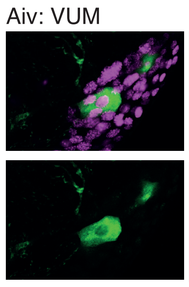
Aii: PAL and PAM



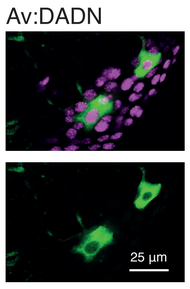
Aiii: MC neurons



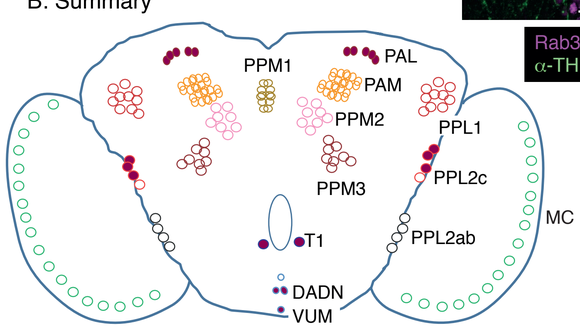
Aiv: VUM



Av:DADN



B: Summary



Summary and Conclusion

In vivo, in dopaminergic neurons Rab10 strongly interacts with LRRK2-G2019S, both in overexpression and knockout experiments.

- Global and dopamine-specific knockouts are equally effective

Not all dopamine neurons have the same palette of Rabs

Novel Hypothesis

We suggest the differences in dopamine neuron death (in different parts of the *substantia nigra* or VTA) may be due to the palette of Rabs contained in dopamine neurons

Acknowledgements

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PARKINSON'S UK
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DFG