Journal Club

Blood factors transfer beneficial effects of exercise on neurogenesis and cognition to the aged brain

Xiangjie Zhao

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RESEARCH ARTICLE

Blood factors transfer beneficial effects of exercise on neurogenesis and cognition to the aged brain

Alana M. Horowitz[1,2,*], Xuelai Fan[1,*], Gregor Bieri[1], Lucas K. Smith[1,2], Cesar I. Sanchez-Diaz[1], Adam B. S...

+ See all authors and affiliations

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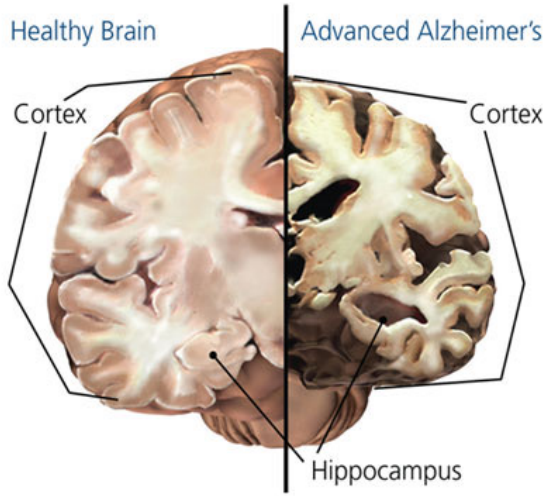
Saul A. Villeda (Corresponding author)
Assistant Professor, Department of Anatomy, UCSF

Cellular and molecular mechanisms
that contribute to brain aging

http://villedalab.ucsf.edu

RATIONALE



1. Exercise could help to reduce the risk of age-related neurodegenerative diseases like dementia

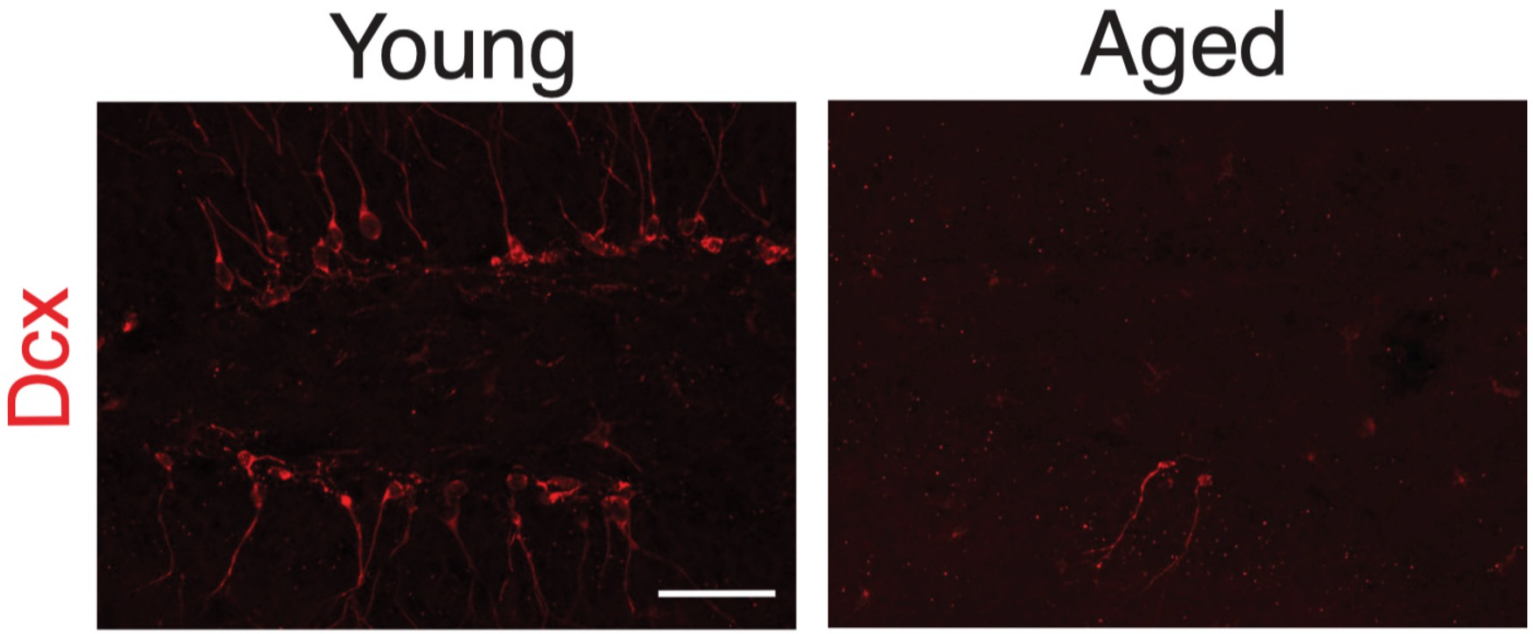
2. But its application is hindered in the elderly, as physical frailty or poor health can decrease a person's ability or willingness to exercise

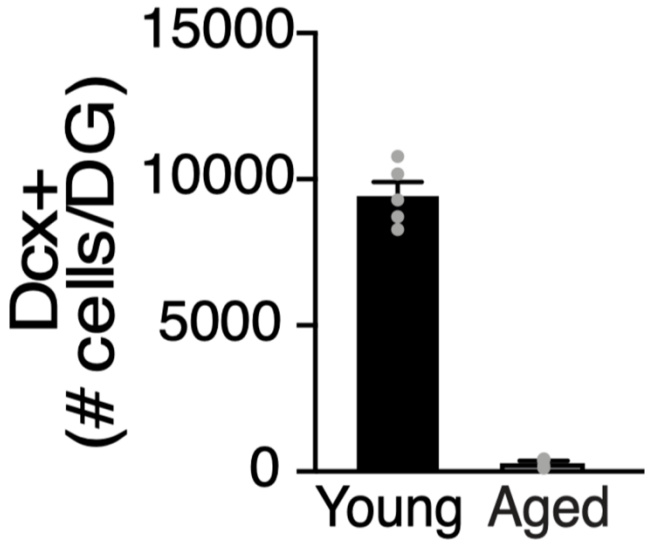
A. Maass et al., Mol. Psychiatry 20, 585–593 (2015)

SCIENTIFIC QUESTION & OBJECTIVE

How to develop approaches transferring the benefits of exercise?

Measurements for age-related impairments --- cellular level

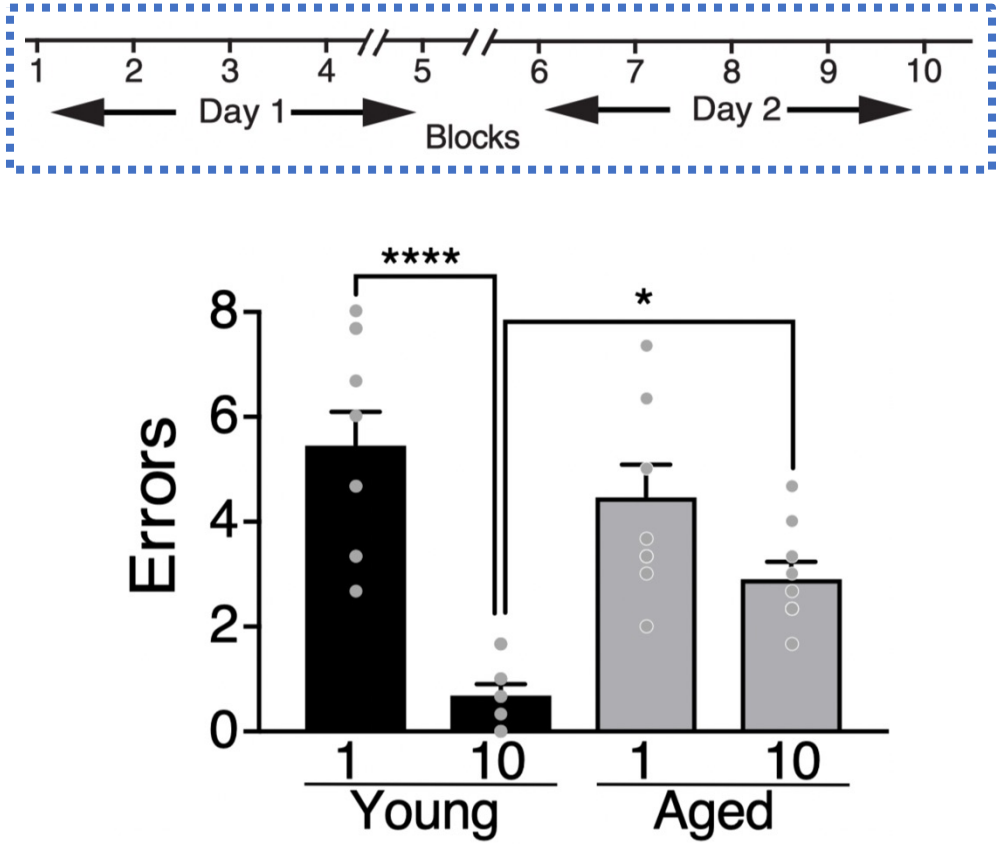




DCX: a marker of neuroblast (immature neuron)

Measurements for age-related impairments --- individual level

Radial arm water maze (RAWM)



Spatial learning and memory are assessed by RAWM as number of entry errors committed during the training and testing phases

https://www.youtube.com/watch?v=dhVPWuVGJuw

Validation of benefits of exercise on aged mice?

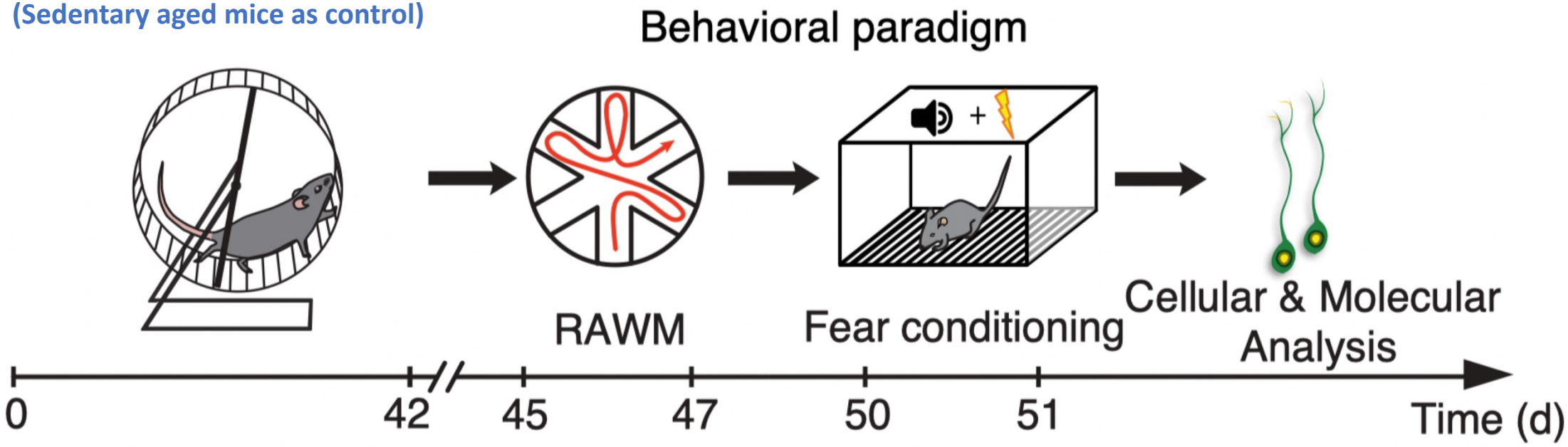
Exercise

?

Aged mice

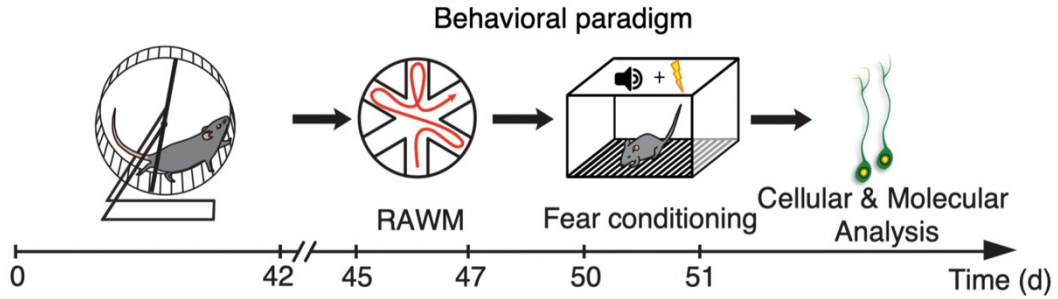
Schematic illustrates chronological order of cognitive testing and cellular and molecular analysis

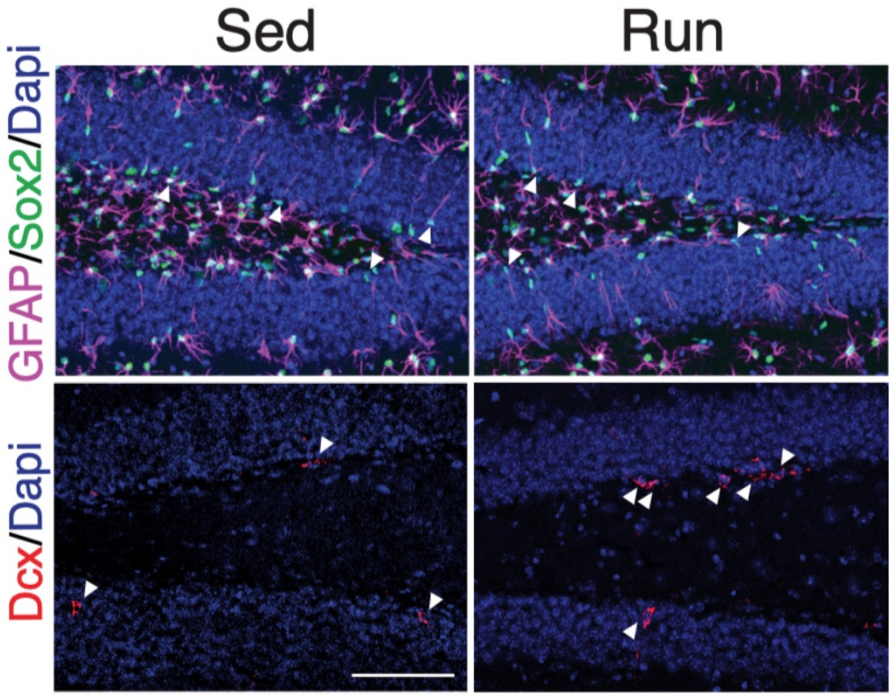
Exercised aged mice
(Sedentary aged mice as control)

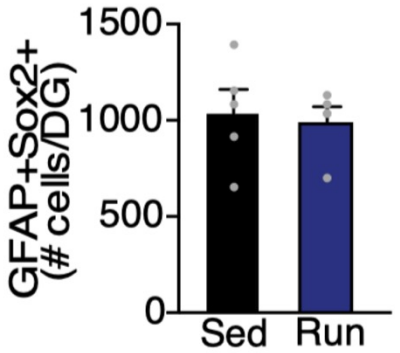


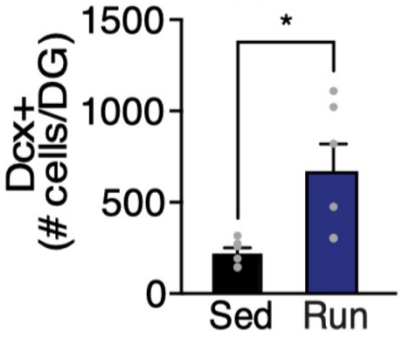
Sedentary = Sed = 不经常活动的

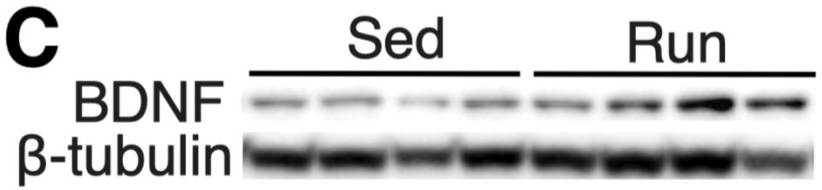
Exercise benefits the aged hippocampus at the cellular level

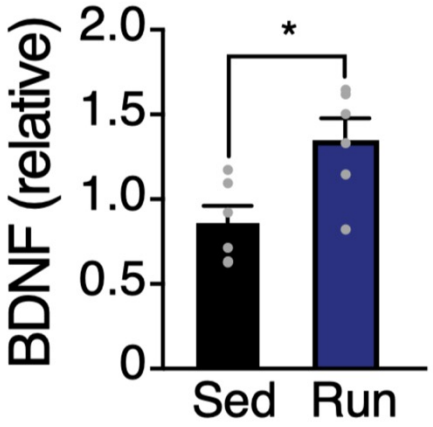








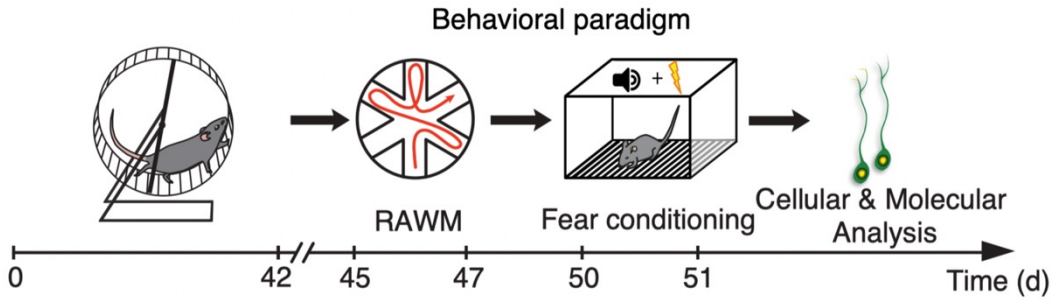


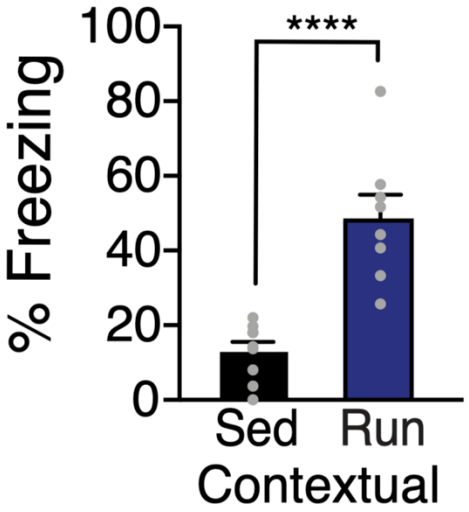


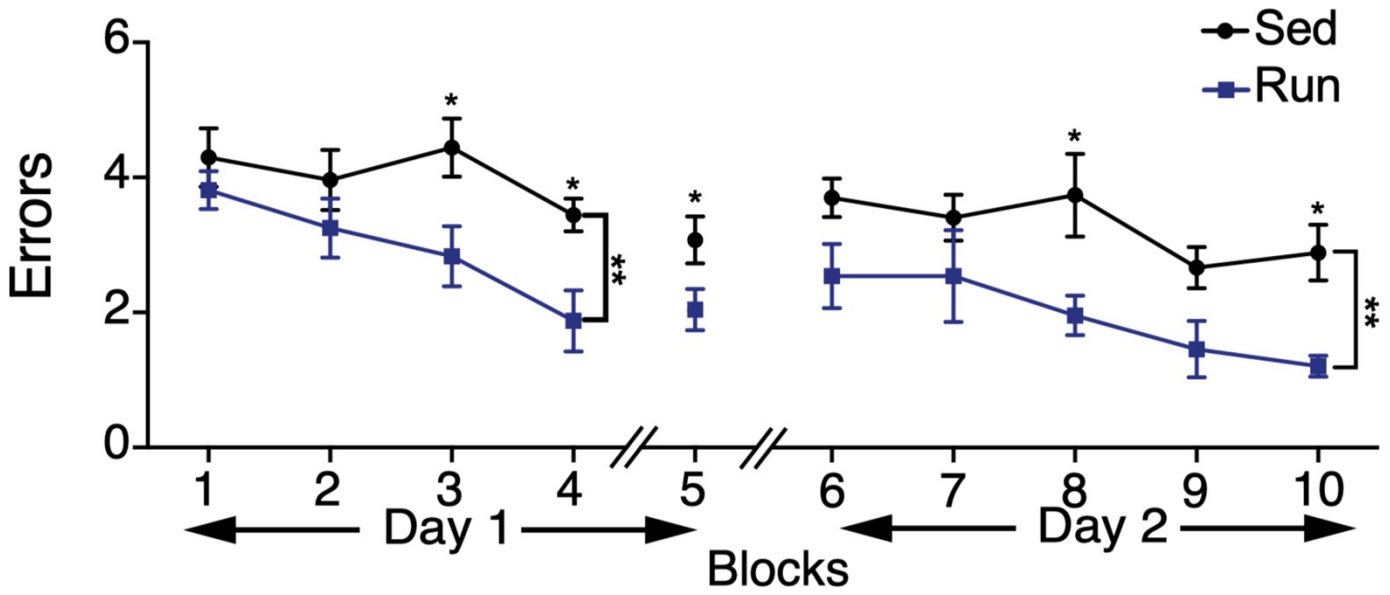
Brain-derived neurotrophic factor (BDNF): BDNF helps to support survival of existing neurons, and encourages growth and differentiation of new neurons and synapses

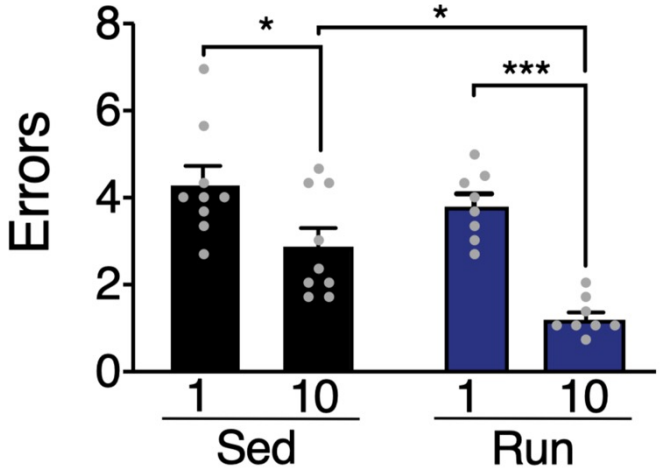
--- Wikipedia

Exercise benefits the aged hippocampus at the cognitive level









Exercise indeed benefits cognitive ability in aged mice

Exercise

✅

Aged mice

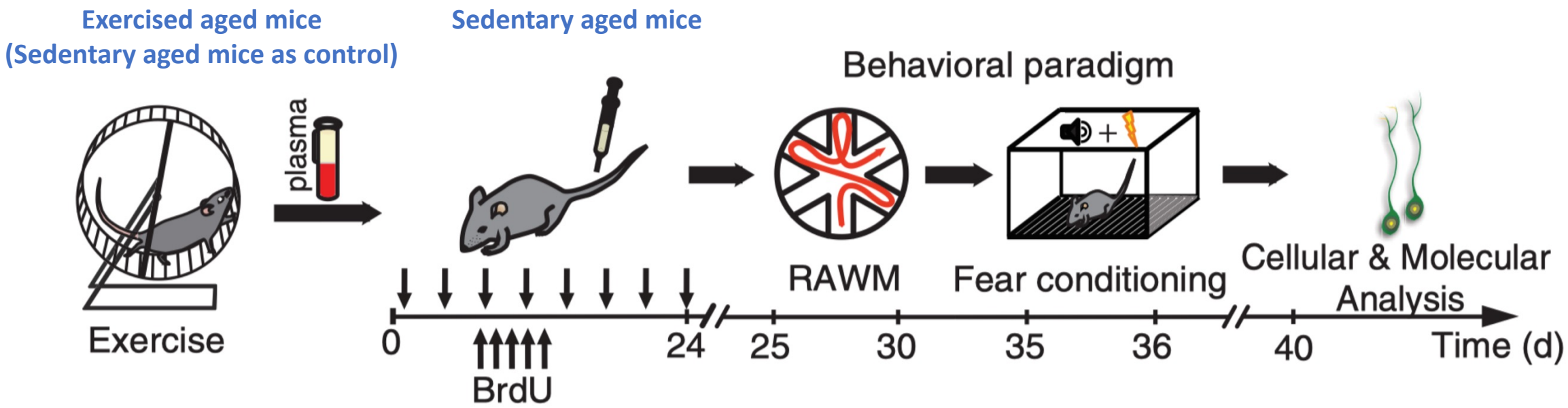
Can plasma transfer the exercise benefits to a sedentary aged mouse?

Exercise ✅ →  Exercised aged mice

? **plasma** →

Sedentary aged mice

Schematic illustrates chronological order of plasma administration from exercised aged mice and cognitive testing

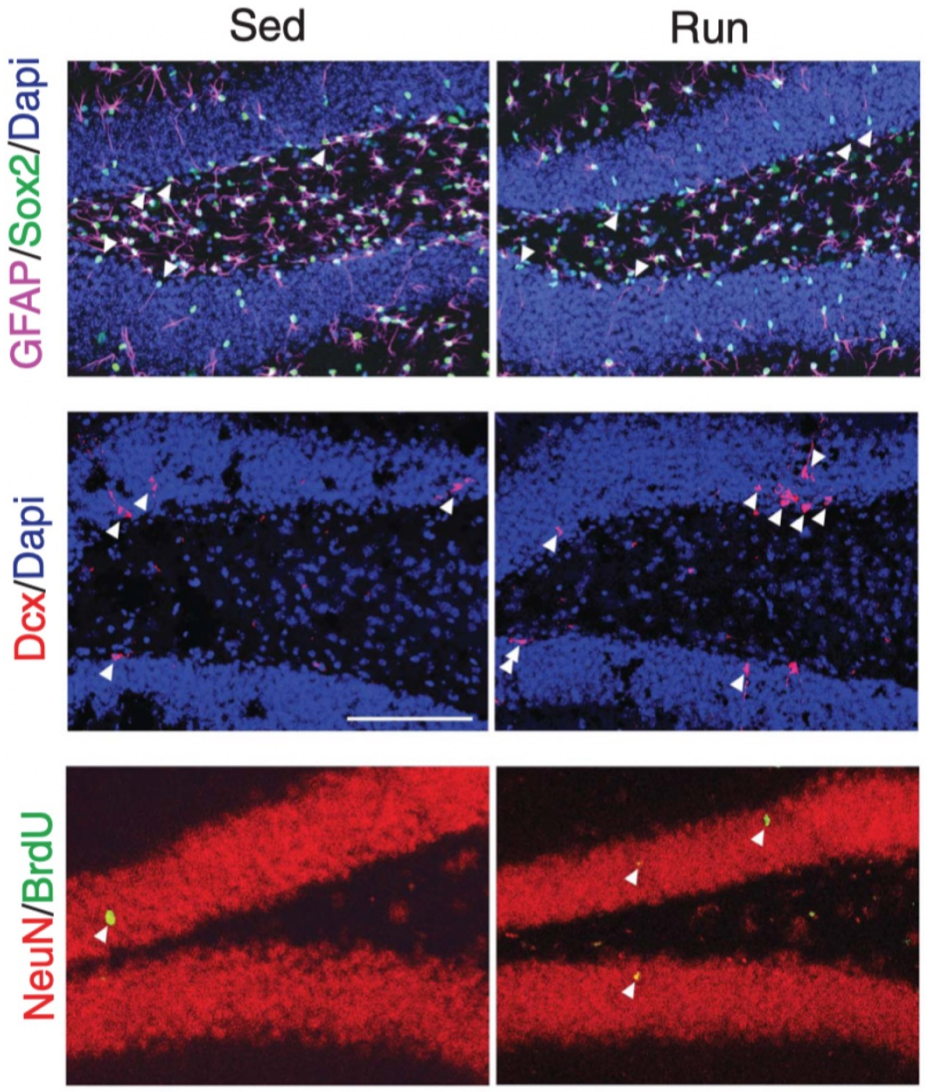


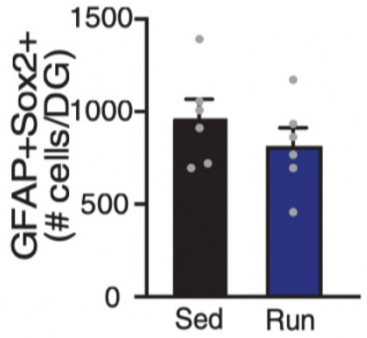
Plasma from exercised mice induces neurogenesis in aged mice

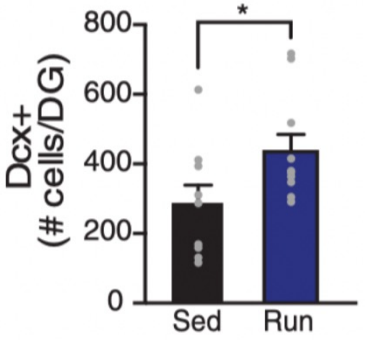
GFAP+SOX2+:
Neural stem cell

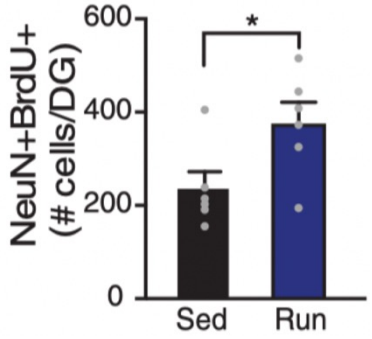
DCX:
Immature neuron

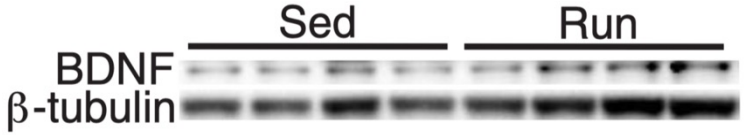
NeuN:
Mature neuron

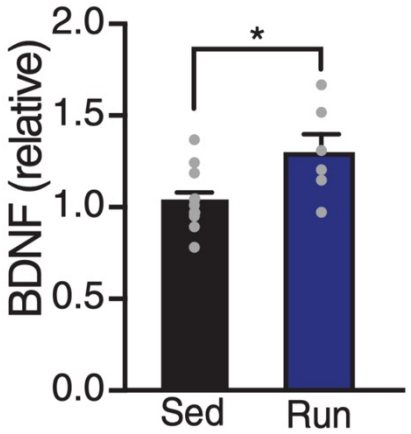




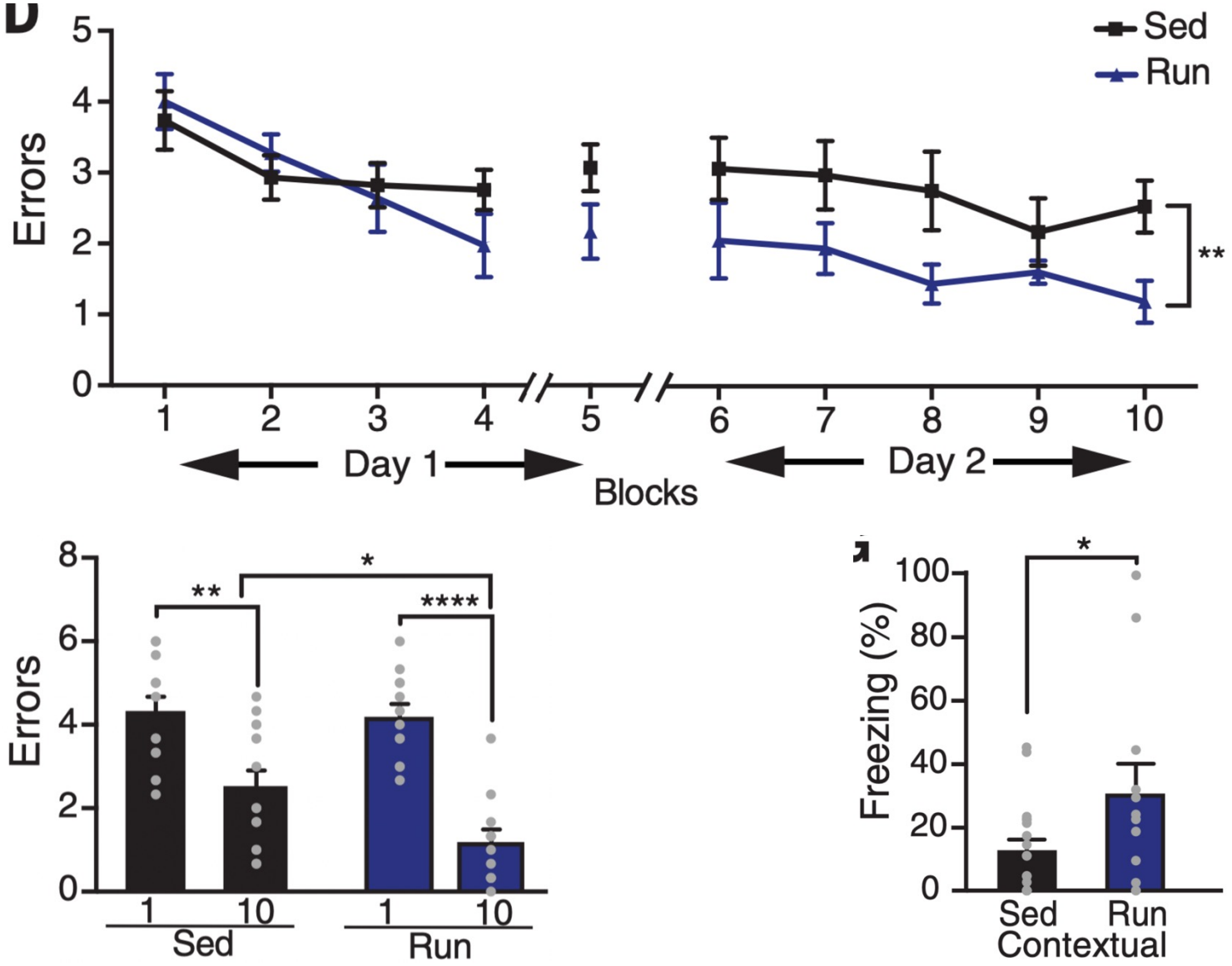








Plasma from exercised mice promotes learning and memory ability in aged mice

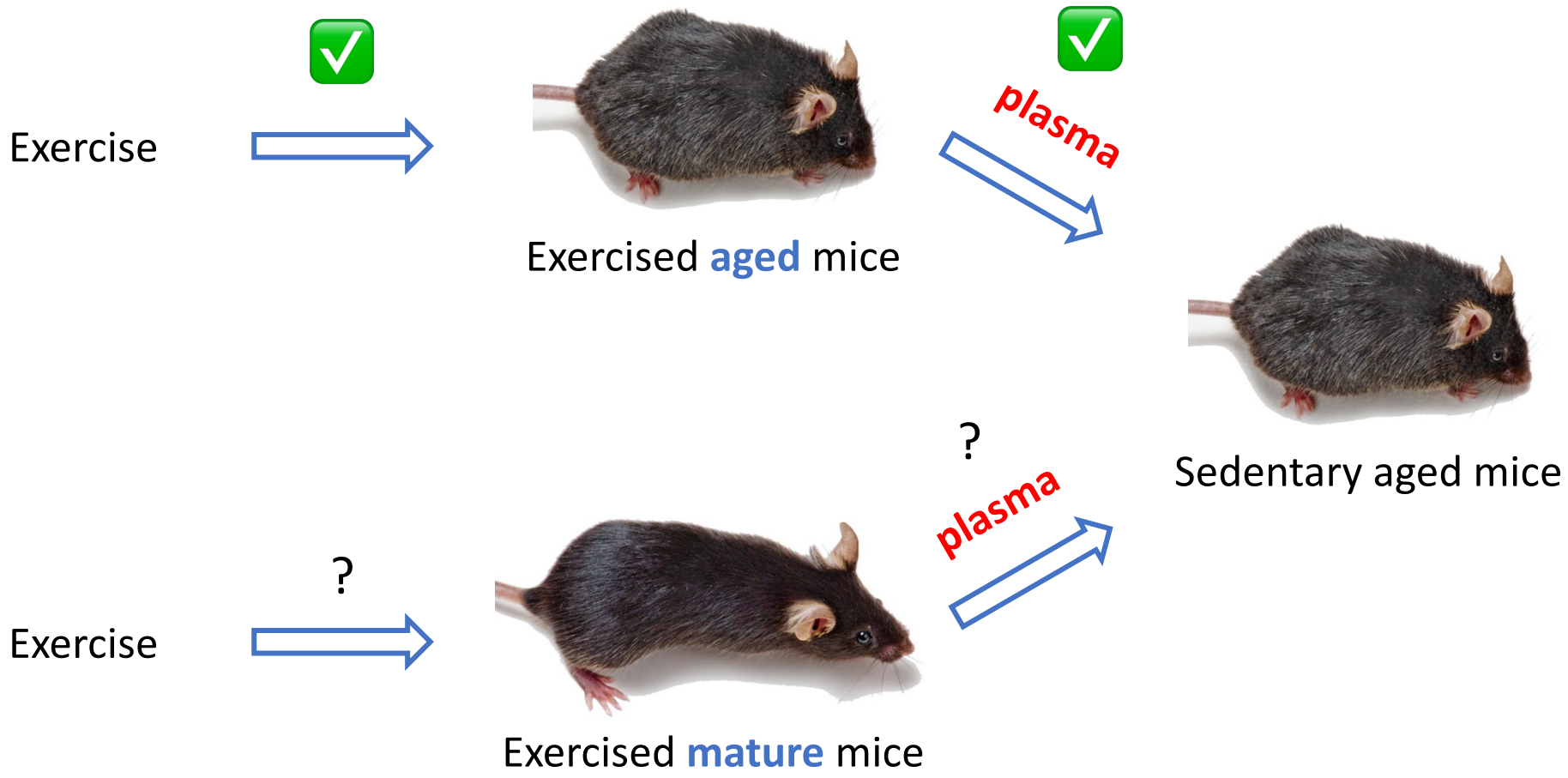


Plasma from aged mouse benefits another sedentary aged mouse

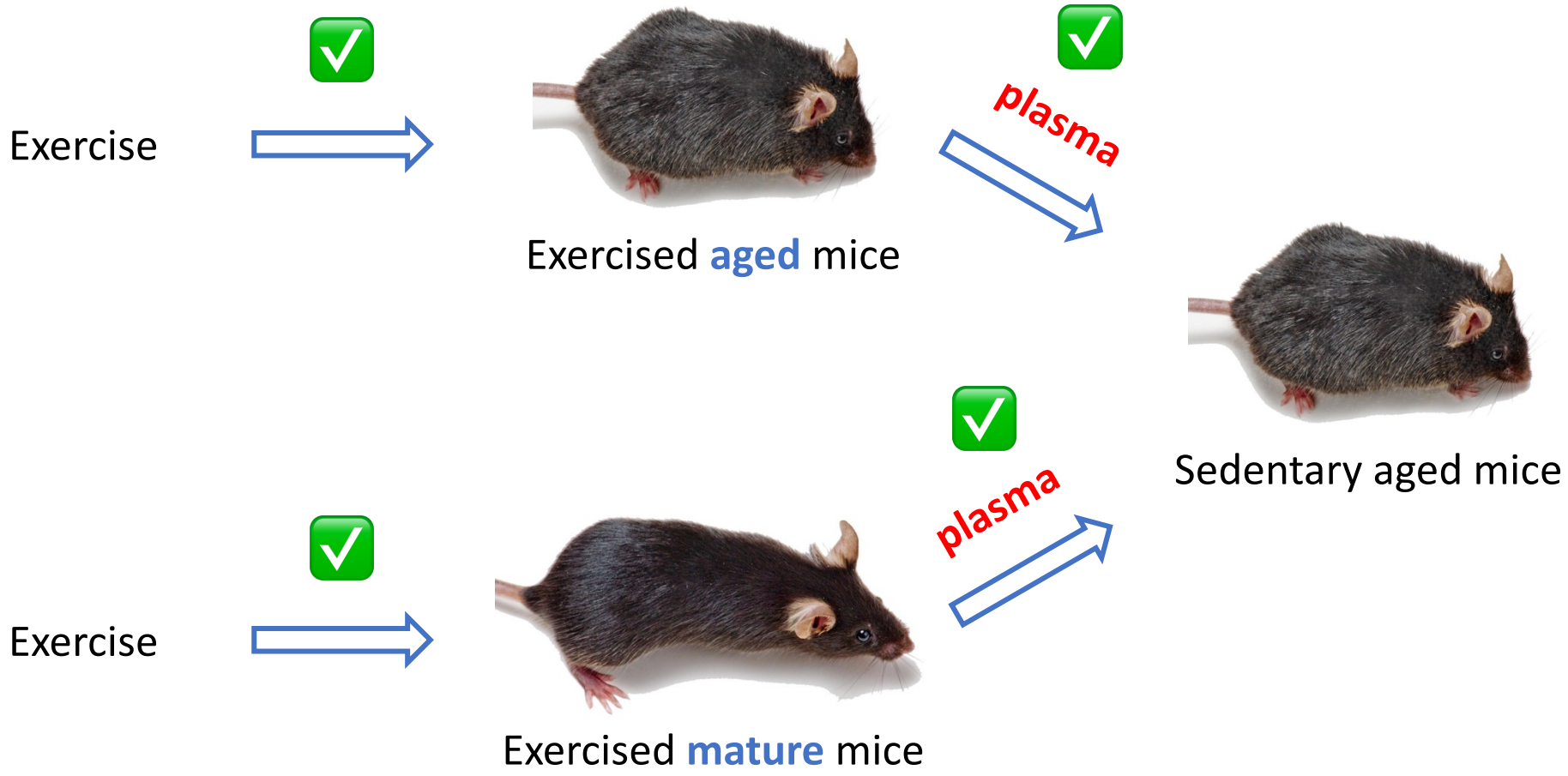
Exercise ✅ →  Exercised aged mice

✅ **plasma** →  Sedentary aged mice

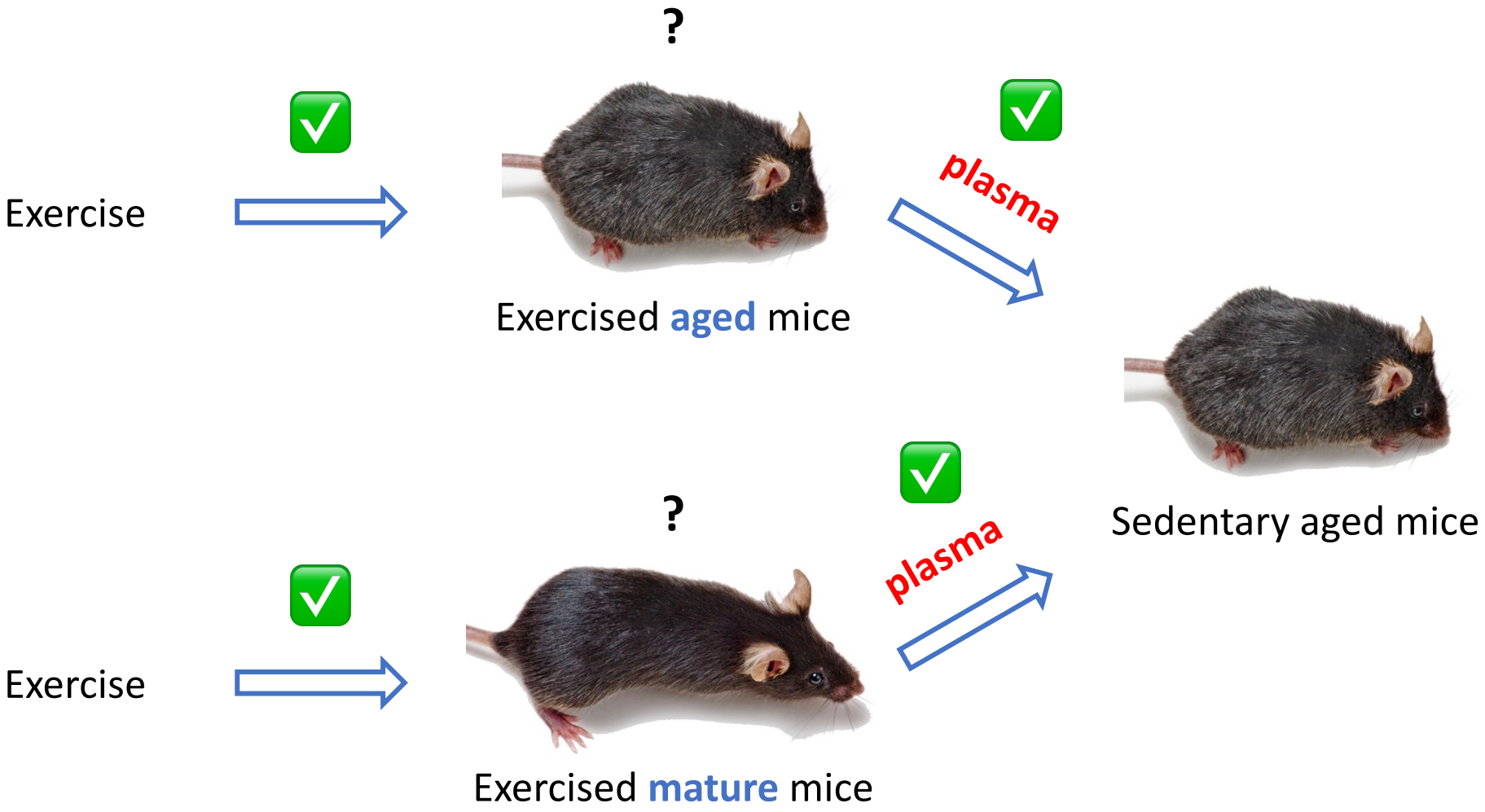
Is there any age limitation for the donor?



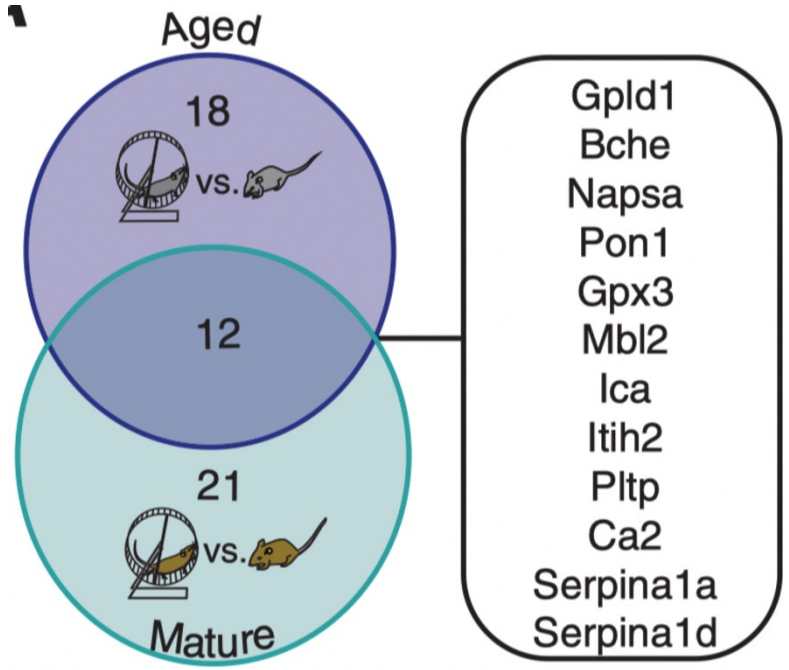
Exercise-induced circulating blood factors across ages can confer the benefits of exercise on the aged hippocampus

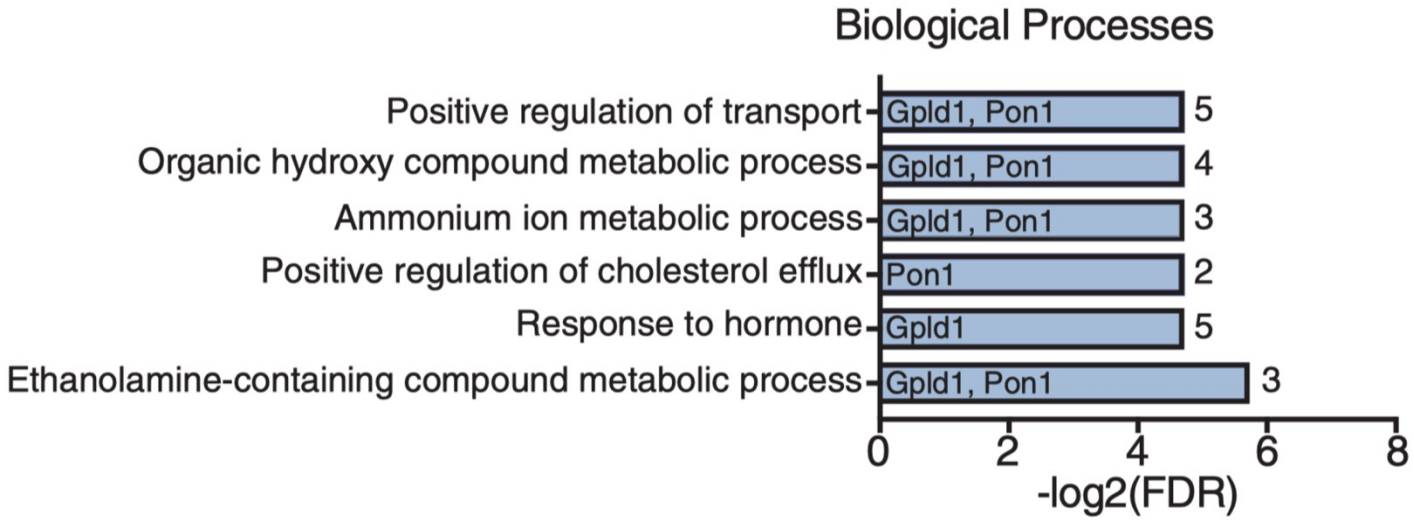


What‘s the specific factor in donor plasma contributing to cognitive benefits?

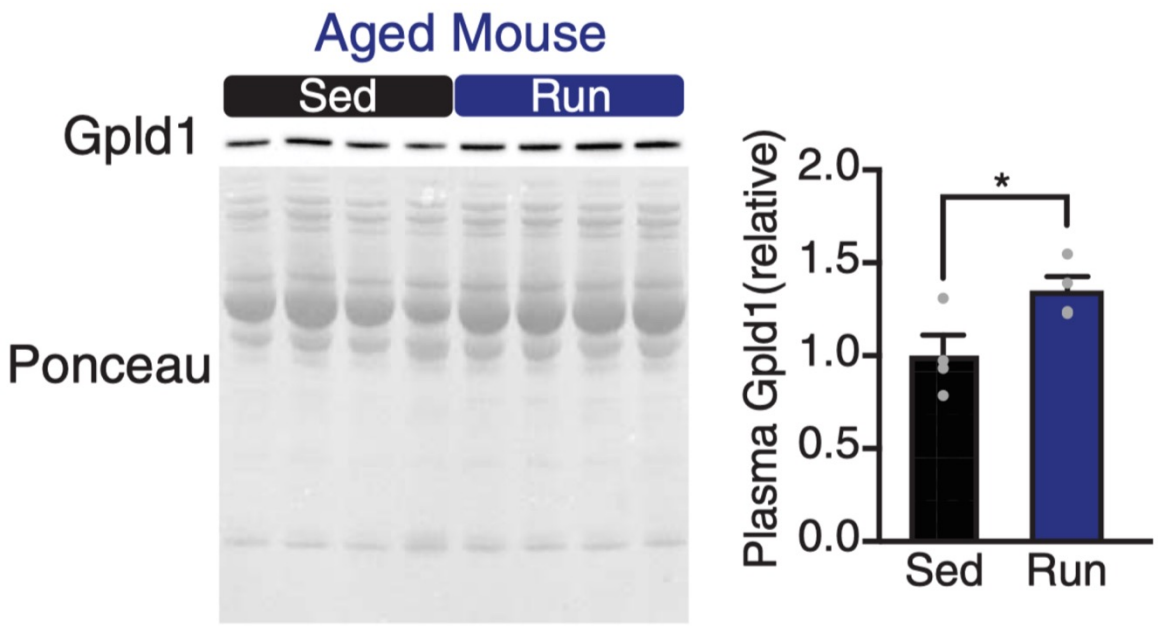


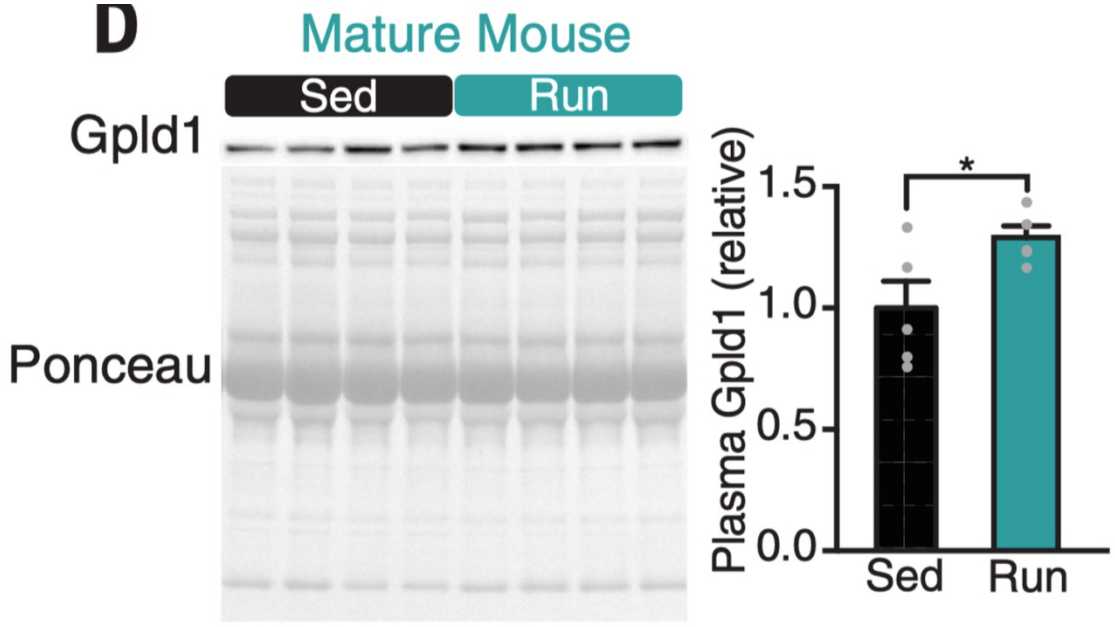
Proteomic analysis of exercise-induced circulating blood factors in mature and aged mice



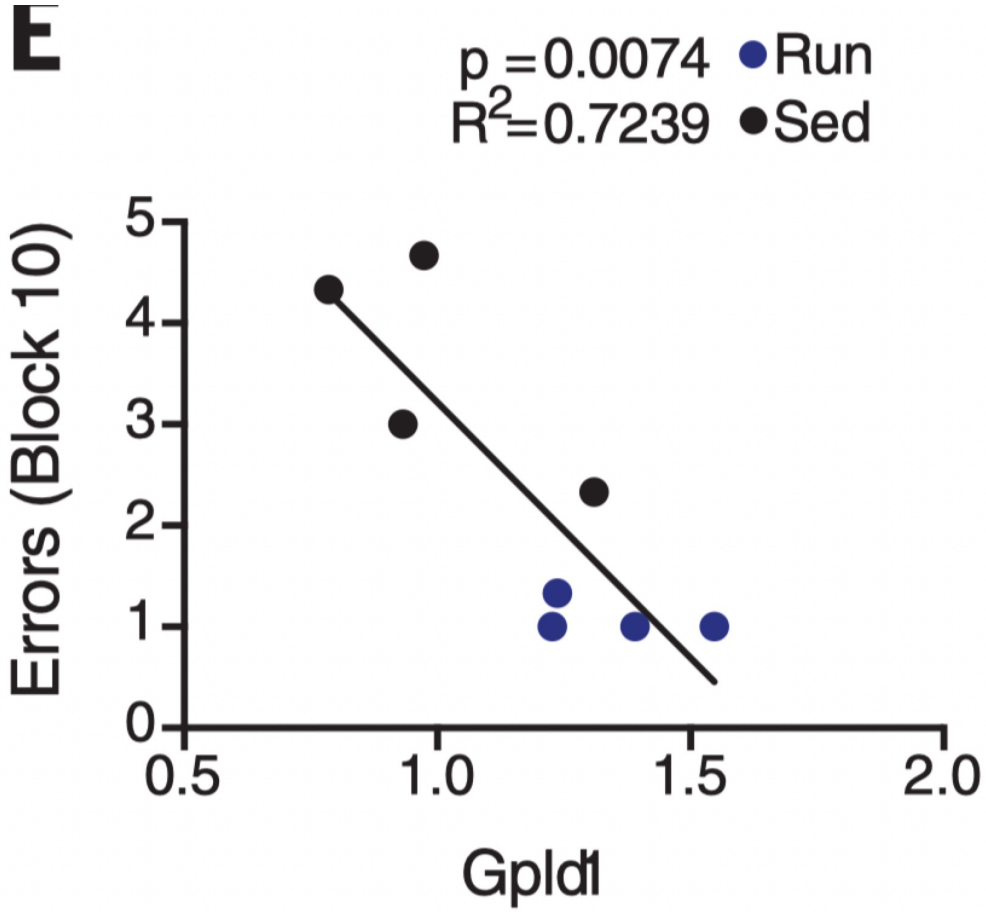


Validation of increased concentrations of Gpld1 in plasma of exercised mice by western blot

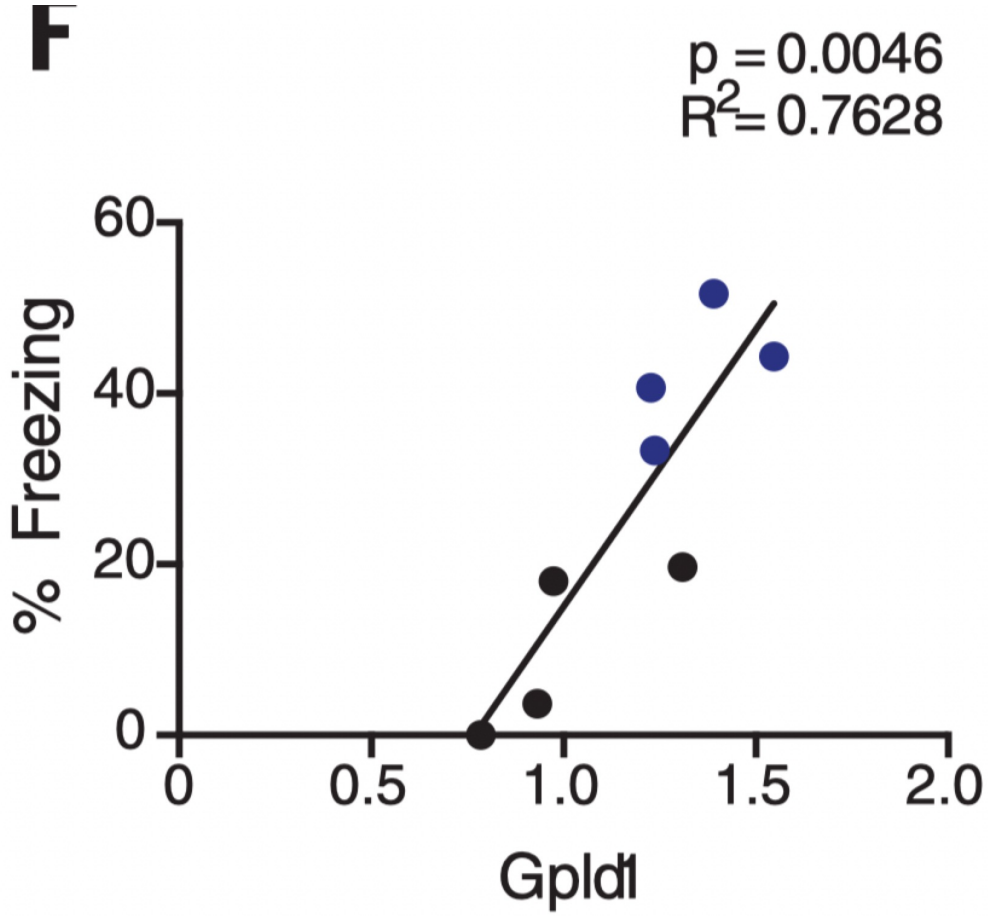




Gpld1 concentrations in plasma is highly positively correlated with cognitive performance

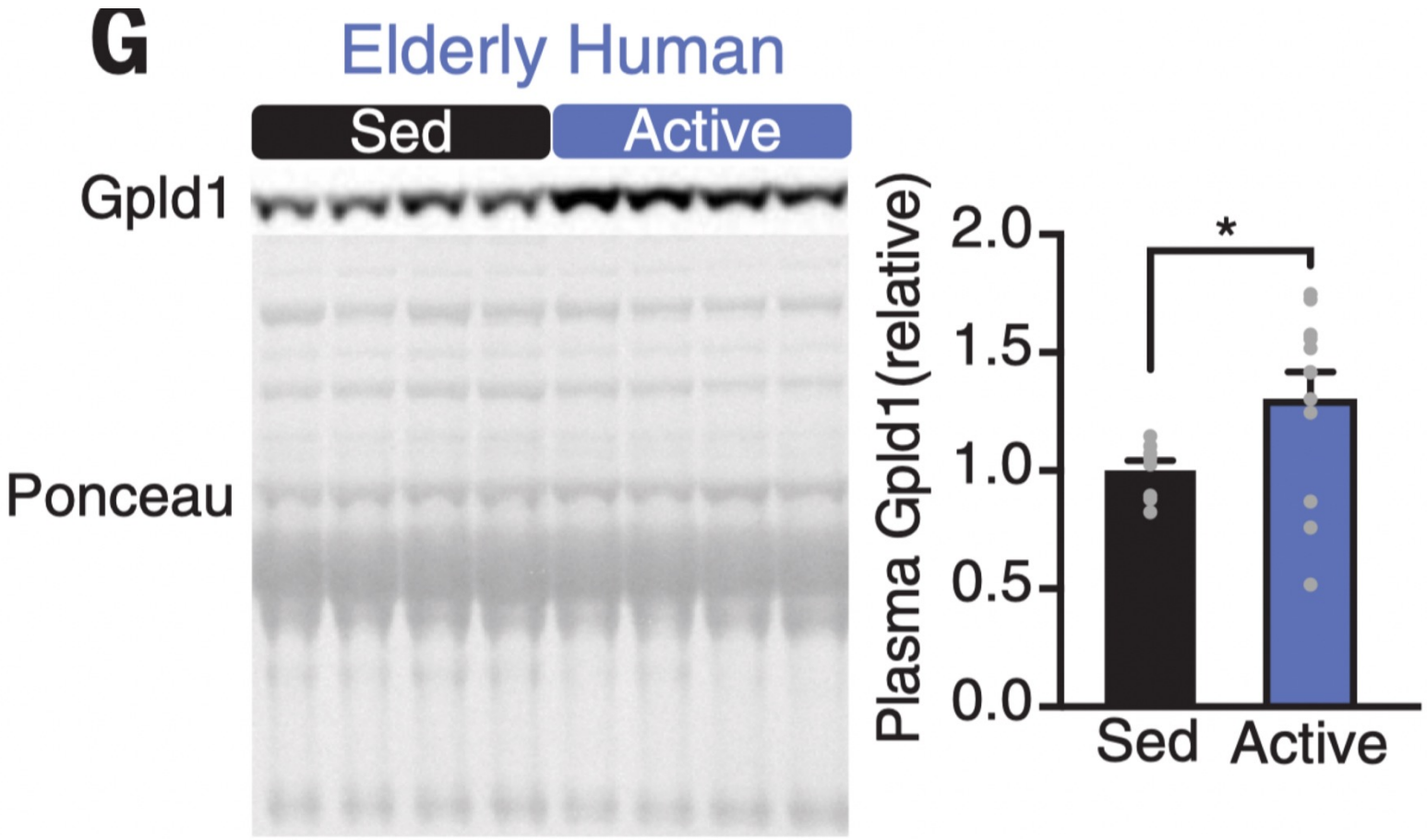


RAWM behavioral test

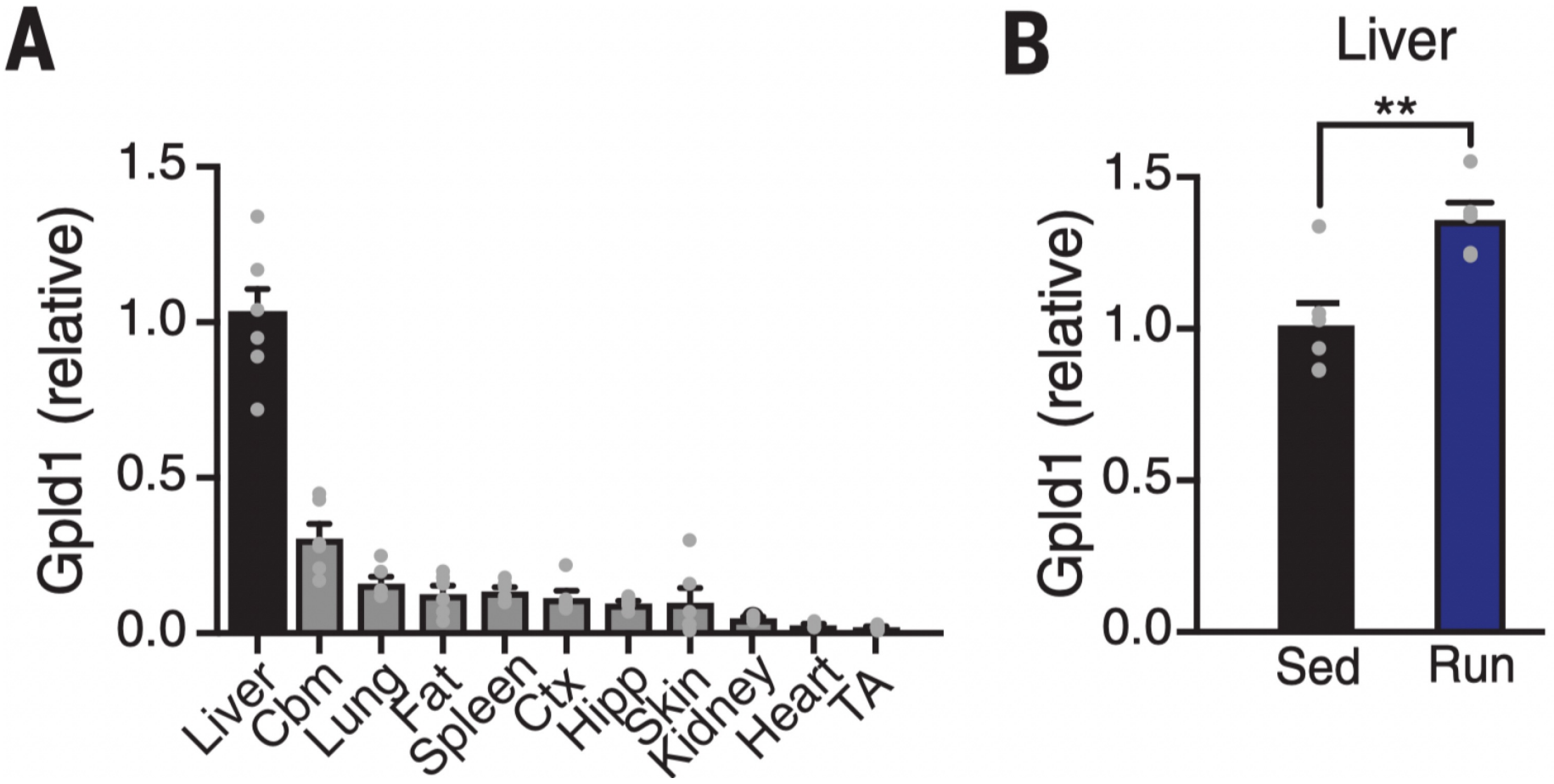


contextual fear conditioning behavioral test

Gpld1 increases in plasma from active, healthy elderly human individuals relative to their sedentary counterparts

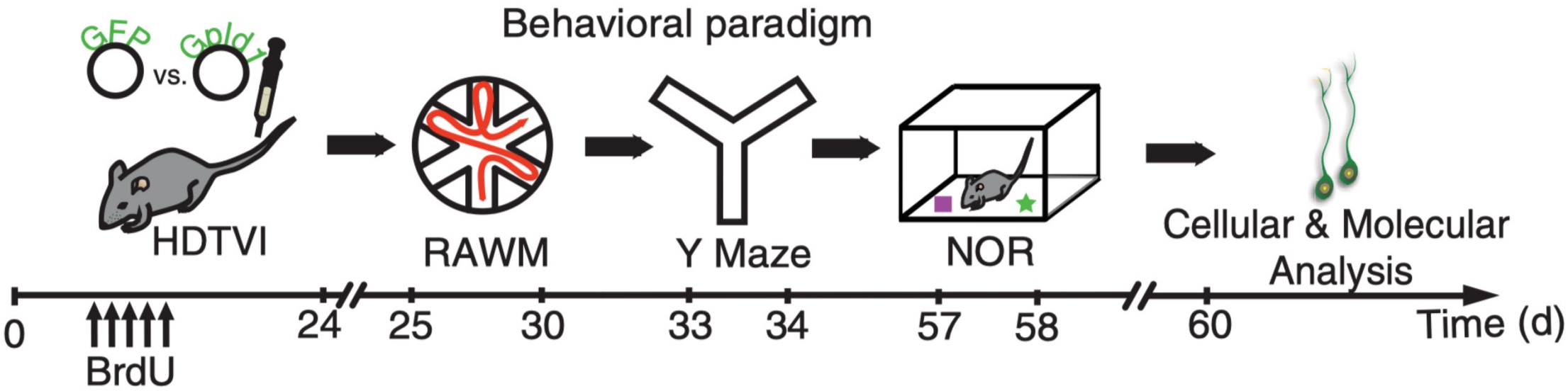


The liver is the primary source of circulating Gpld1



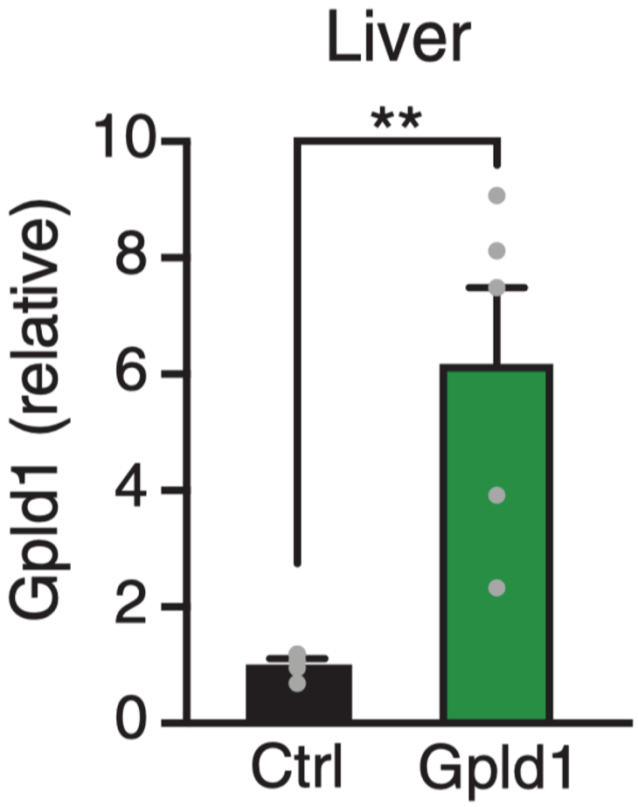
qRT-PCR

Schematic illustrates chronological order of Gpld1 overexpression, cognitive testing, and cellular and molecular analysis

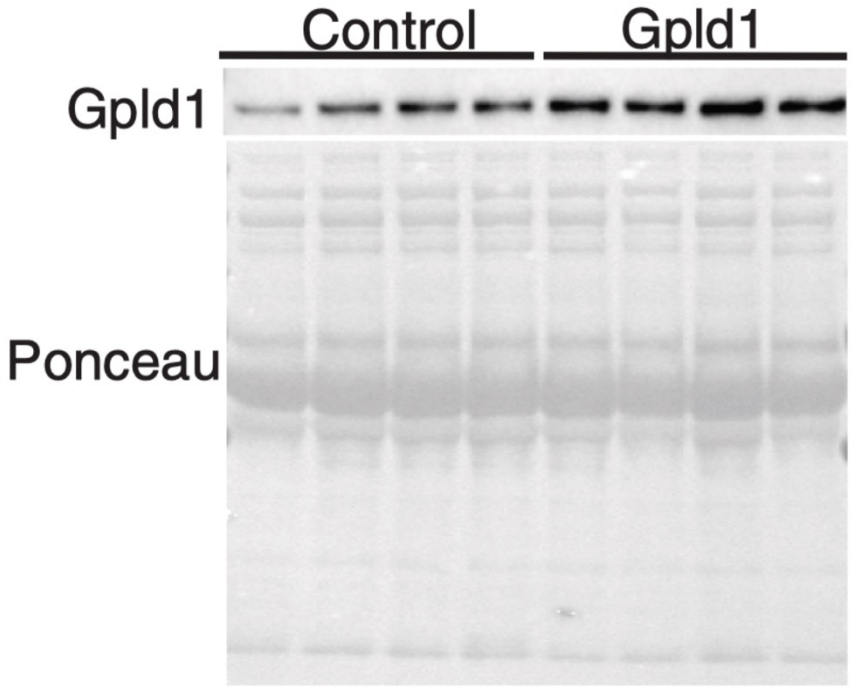


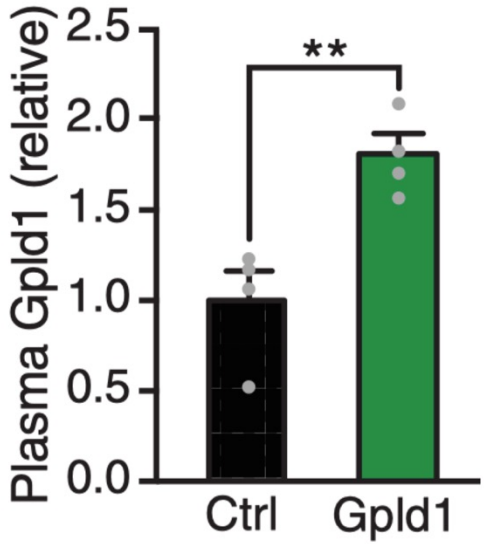
hydrodynamic tail vein injection (HDTVI): 流体动力尾静脉注射

Validation of Gpld1 overexpression



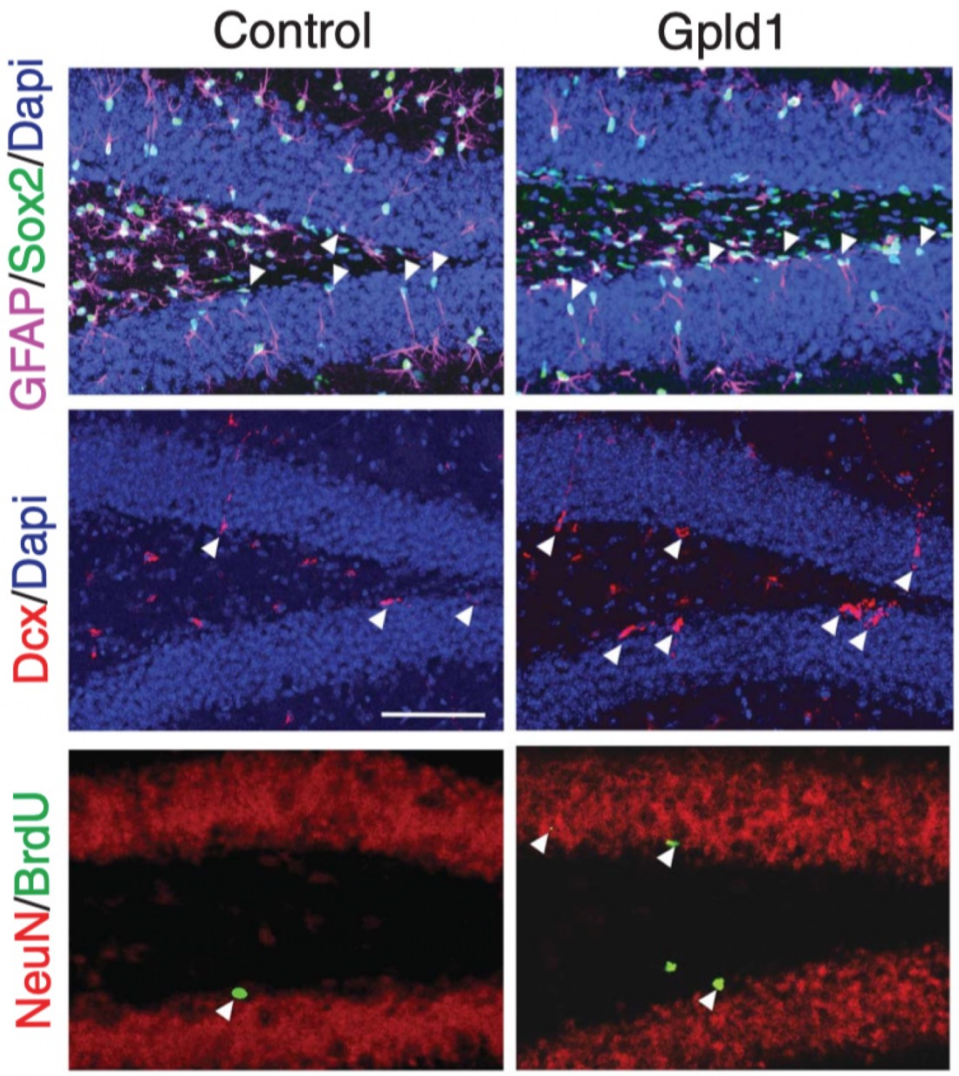
qRT-PCR

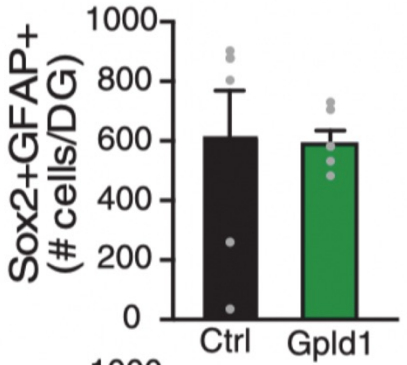


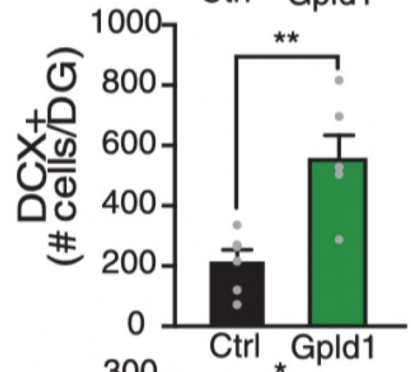


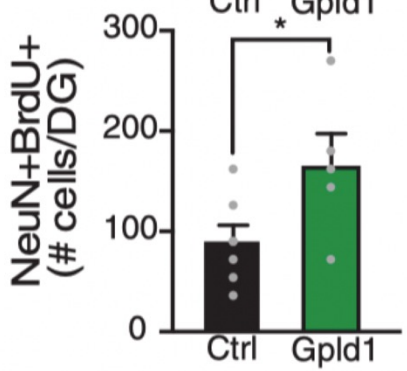
Western blot (plasma)

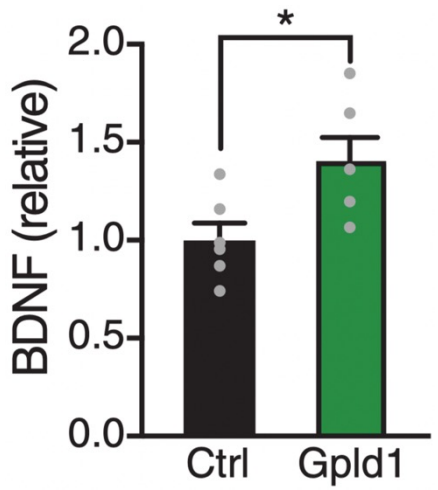
Gpld1 overexpression promotes hippocampus neurogenesis



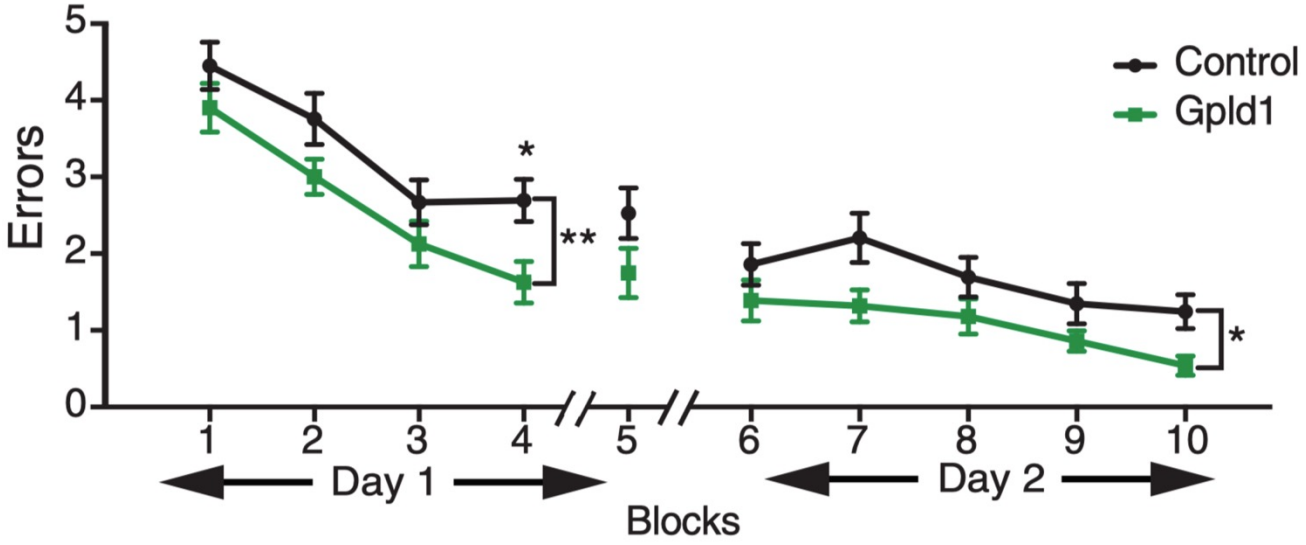


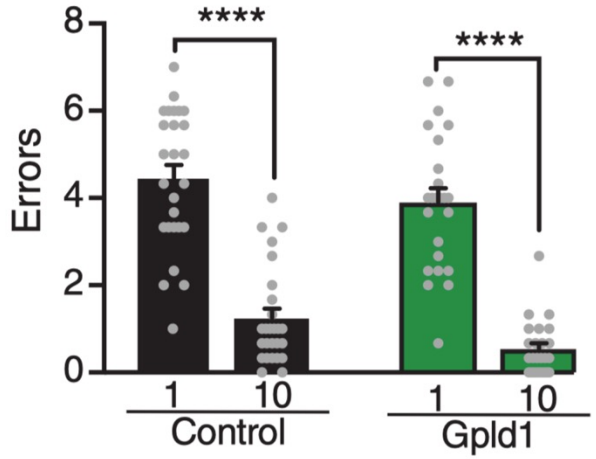


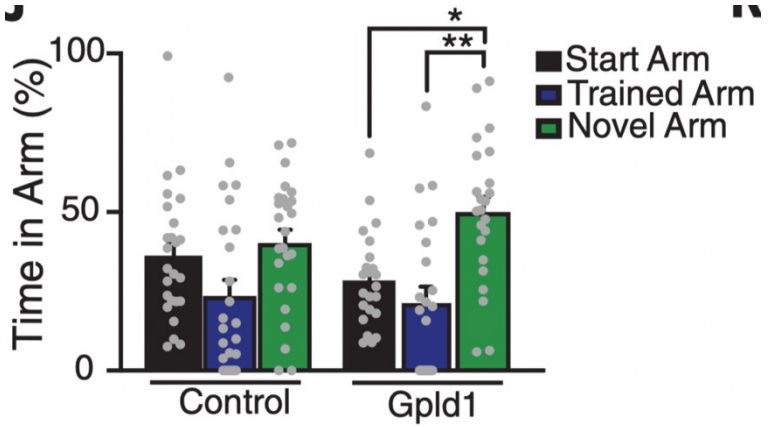


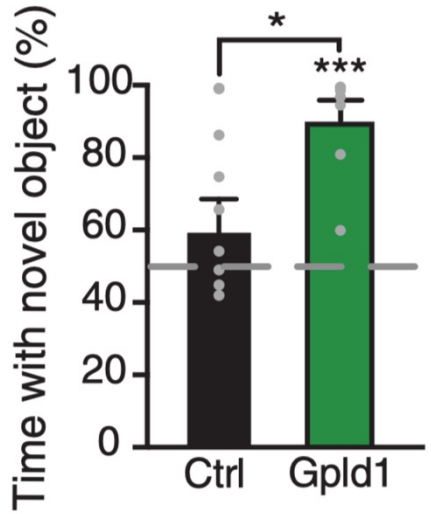


Gpld1 overexpression promotes hippocampal-dependent learning and memory

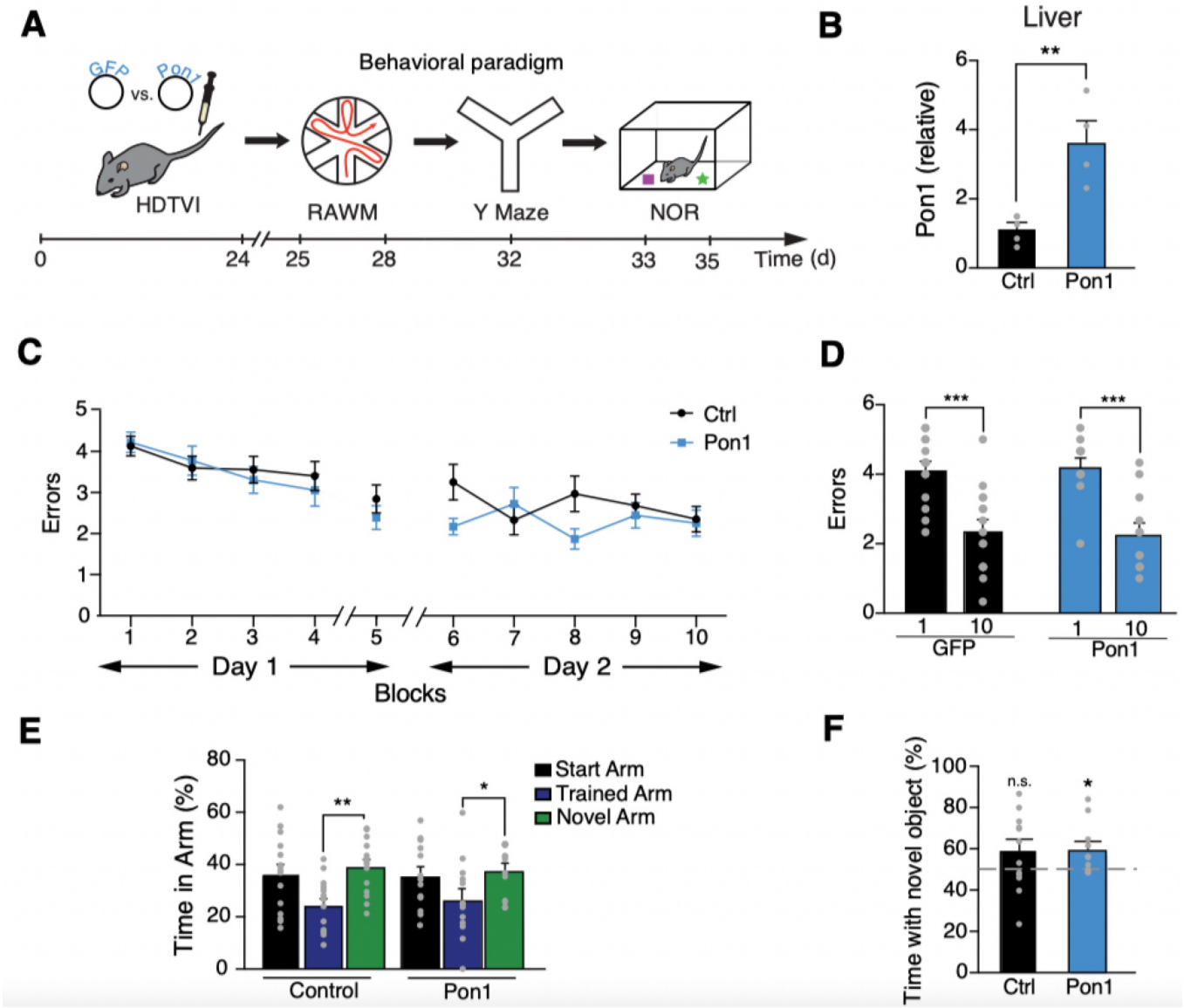




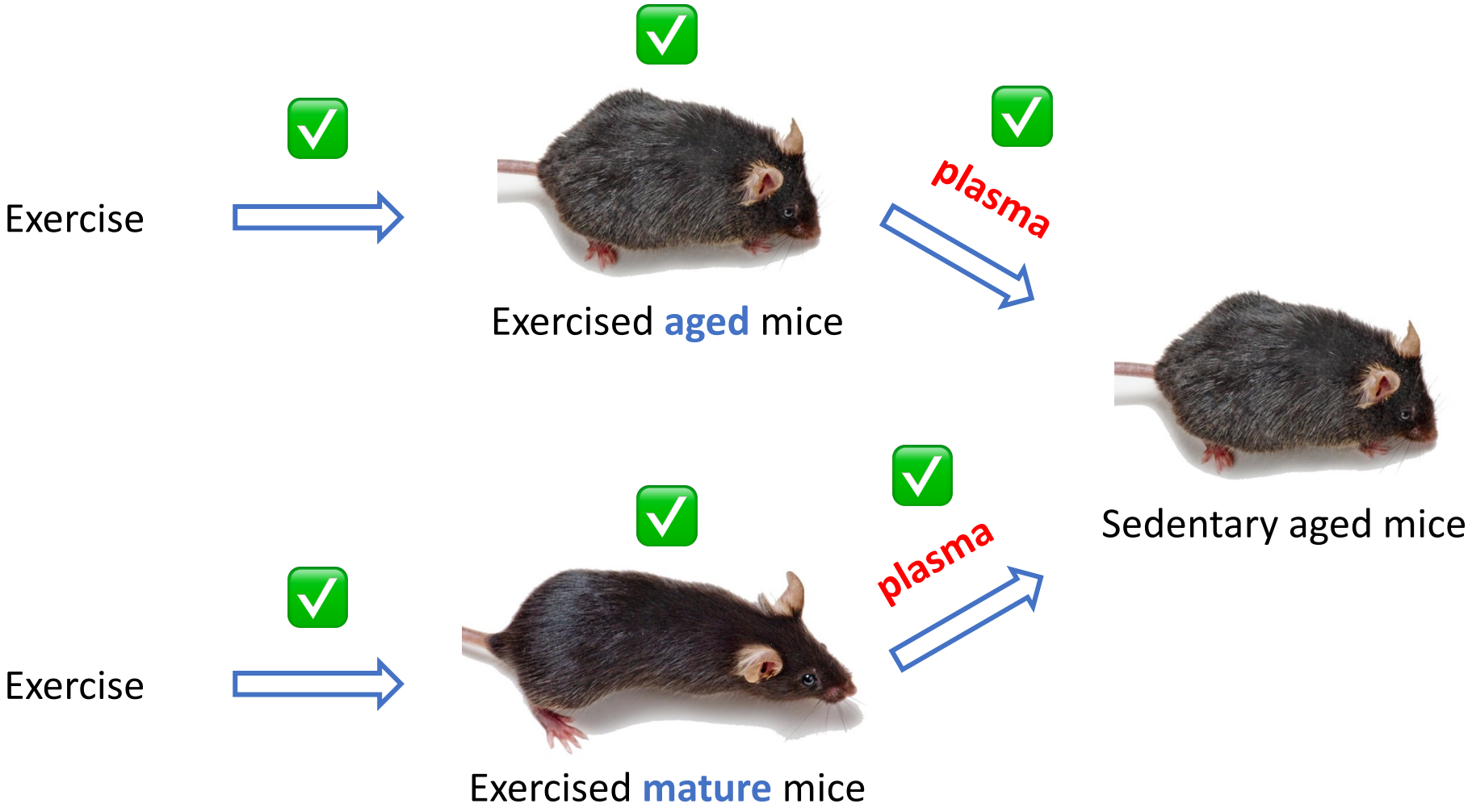




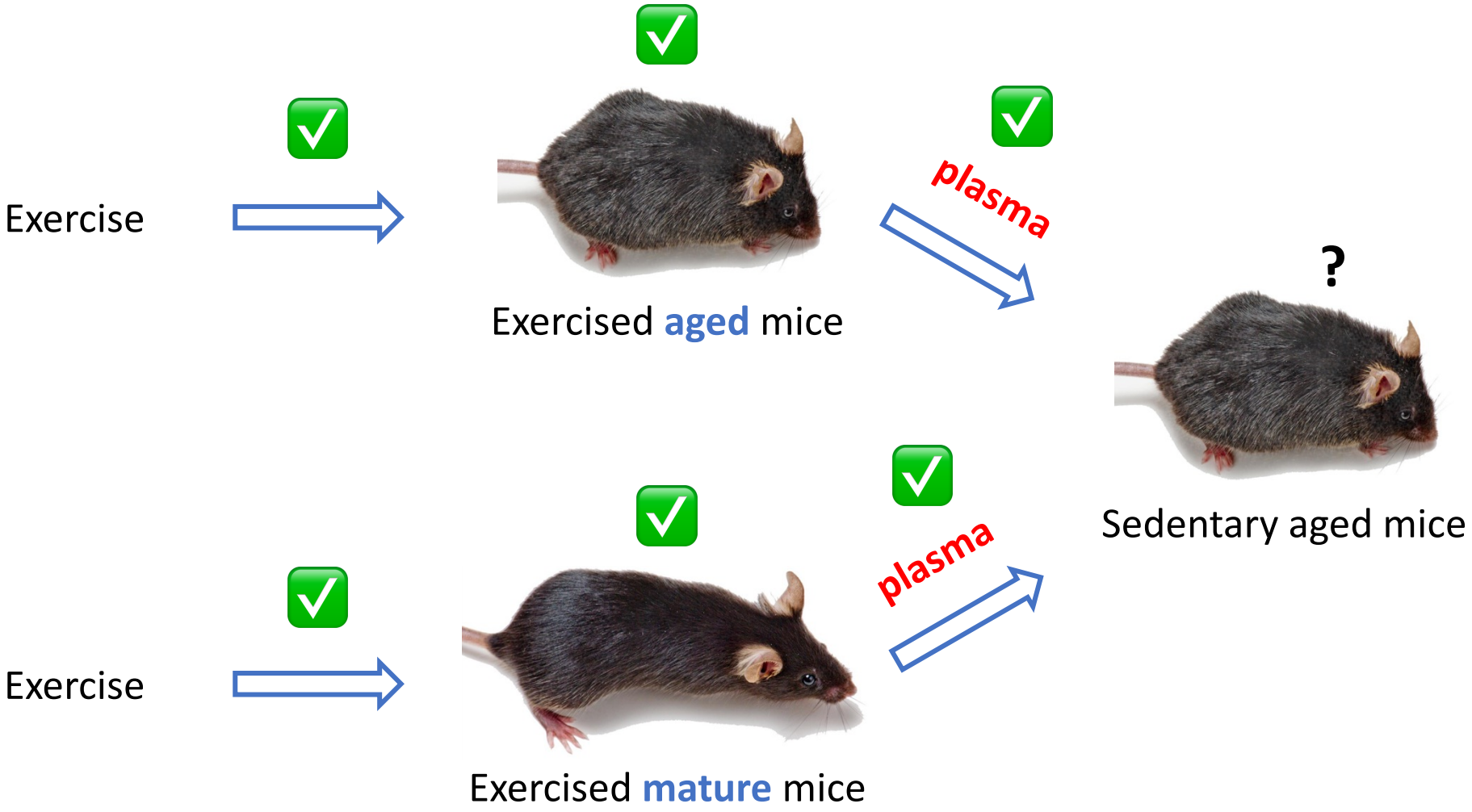
Pon1 overexpression does not improve cognition in the aged hippocampus



Selectively increasing liver-derived concentrations of Gpld1 is sufficient to improve neurogenesis and cognitive function in the aged mice

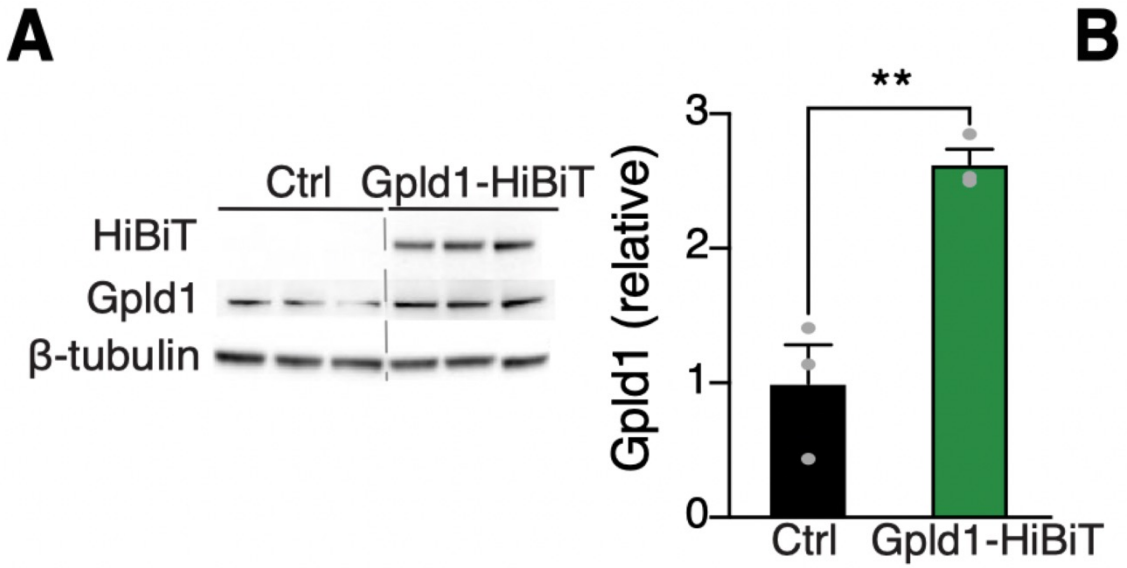


What is the central versus peripheral mechanisms of action of liver-derived Gpld1?



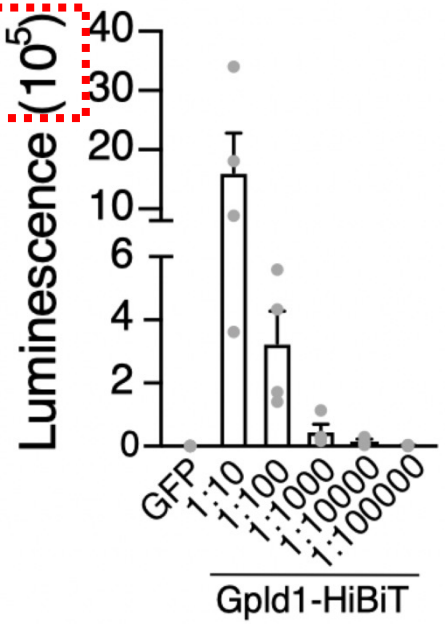
Liver-derived systemic Gpld1 appears not to readily enter the brain

HiBiT tag validation using western blot

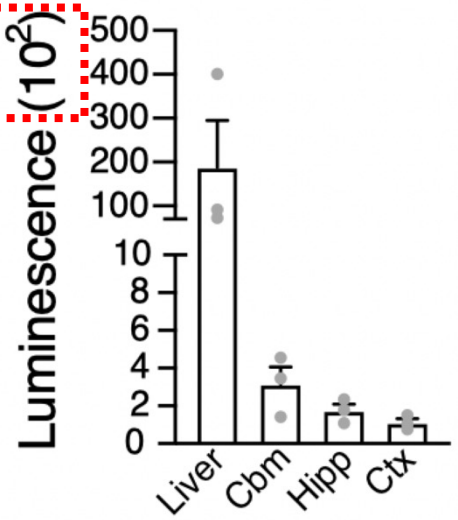


HiBiT: high-affinity nanoluciferase binary technology
Assessment of Gpld1 localization

Blood plasma

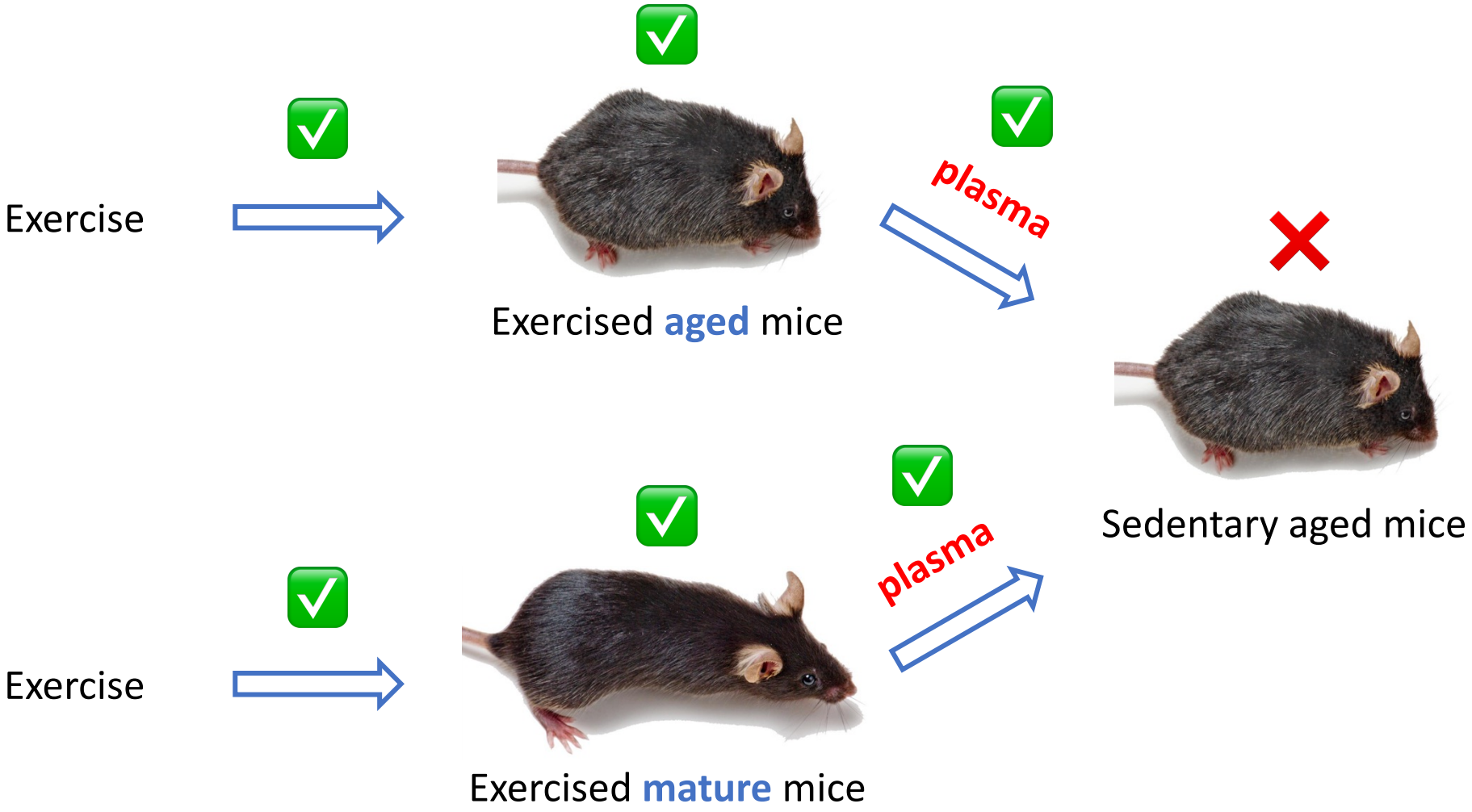


Liver and brain

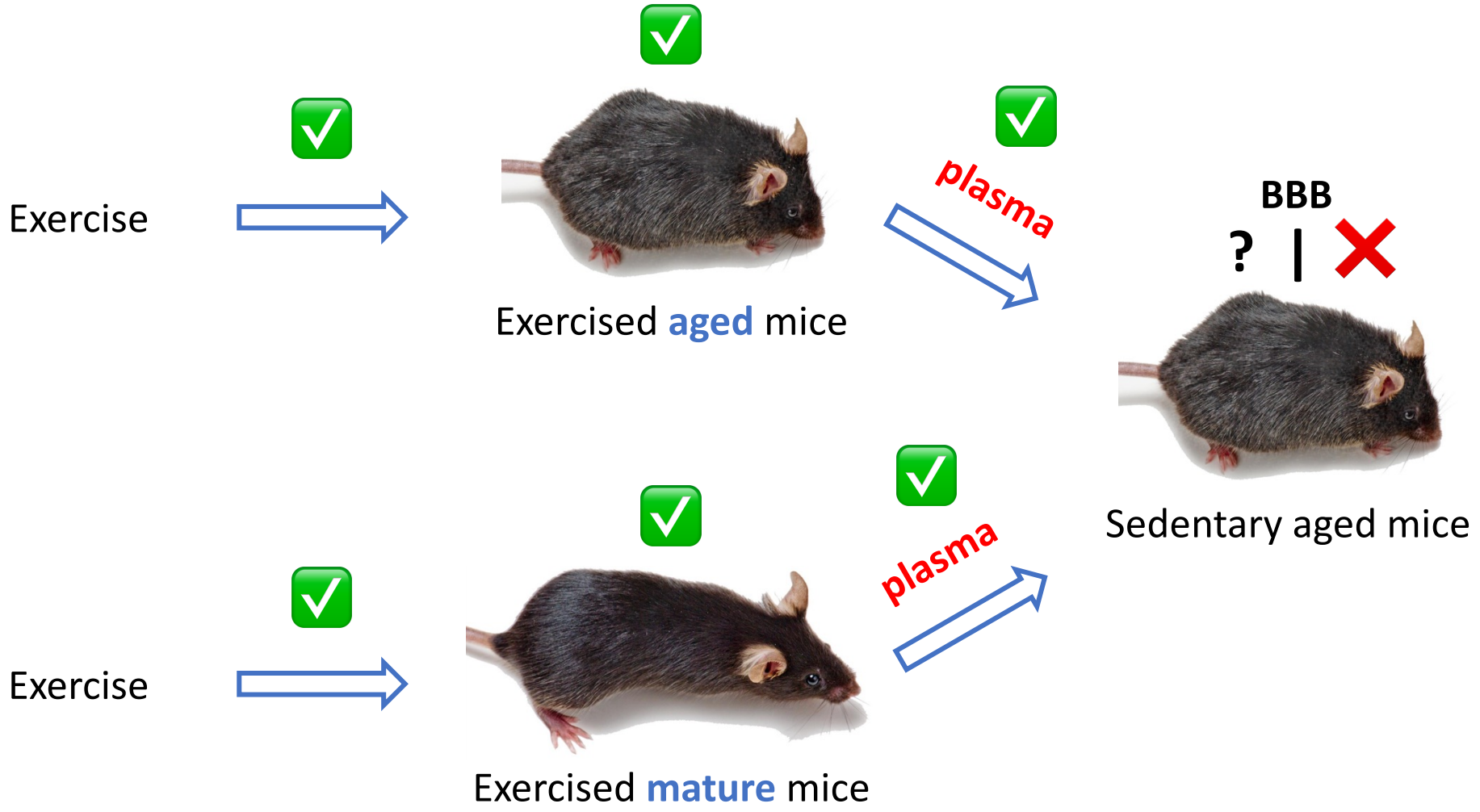


The signal detected in the brain was several orders of magnitude (数量级) lower than that in plasma

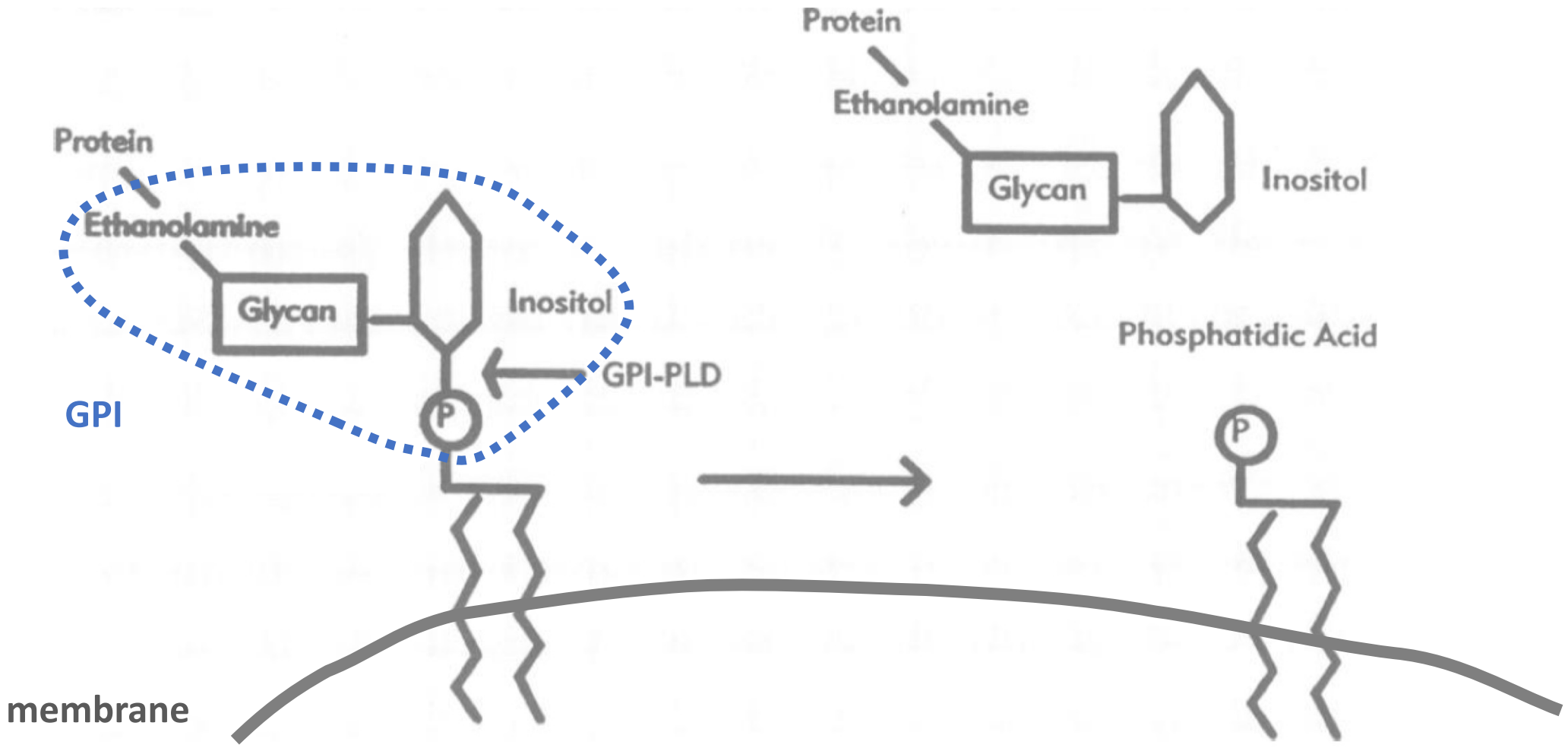
How GPLD1 transfers signals into and interacts with brain are unknown



What happens in the recipient plasma before the signal passes through the blood-brain barrier (BBB)?

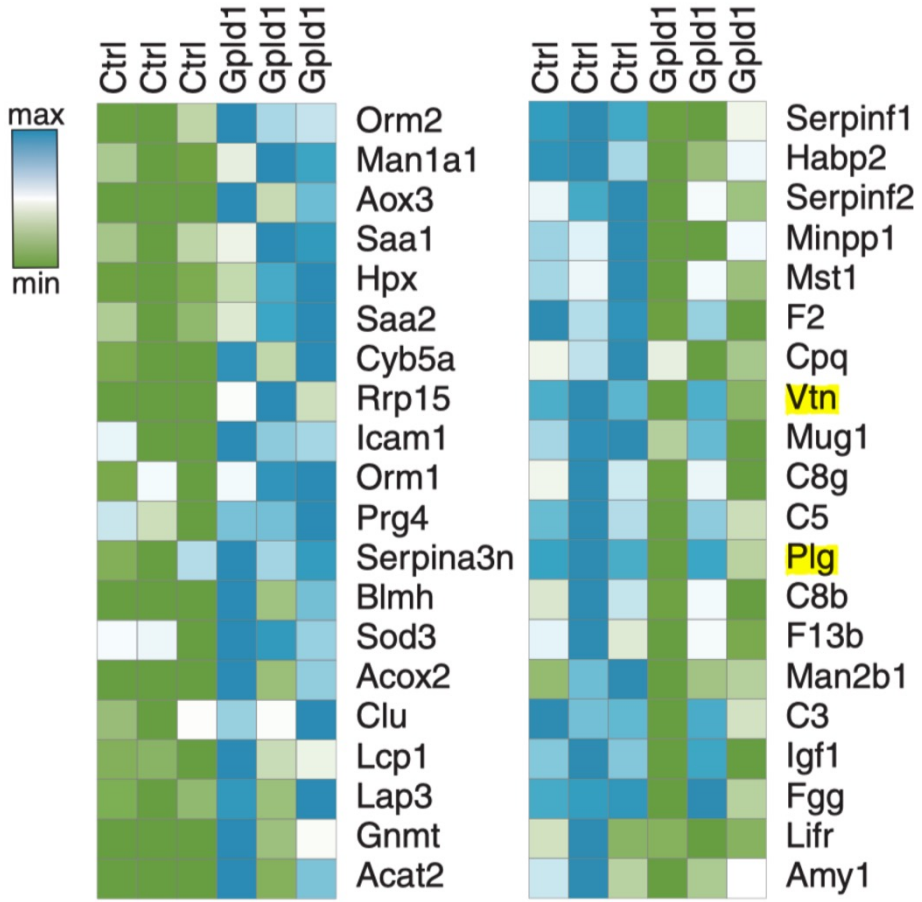


The canonical role of GPLD1 is a GPI-degrading enzyme



Proteomic analysis of blood plasma in Gpld1 overexpression mice

Significantly changed proteins associated with signaling pathways of Gpld1-catalyzed substrates



Up-regulated

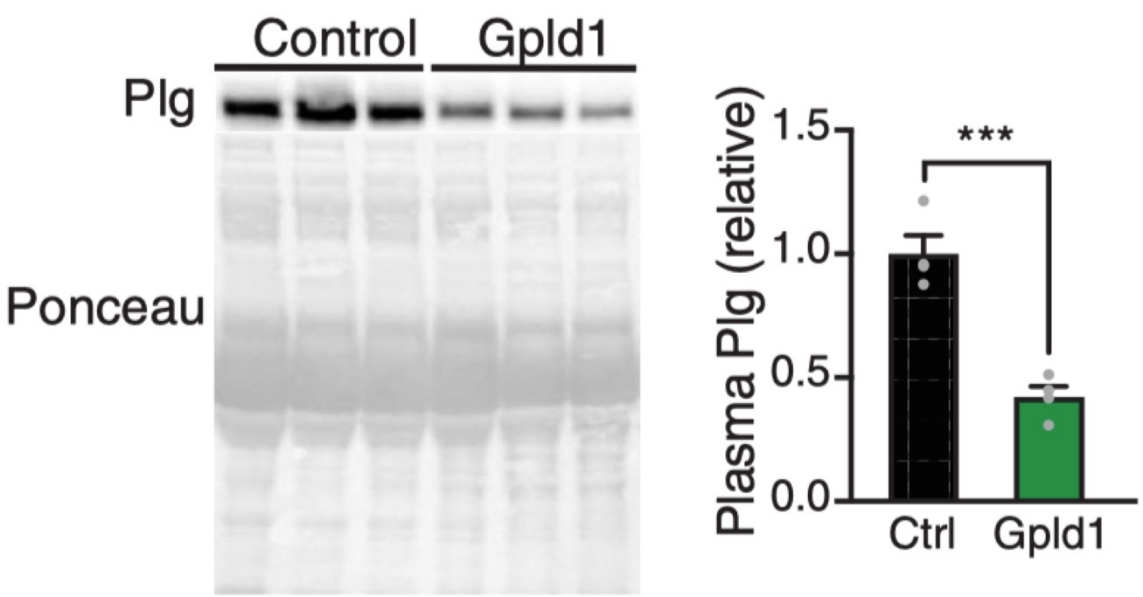
Down-regulated

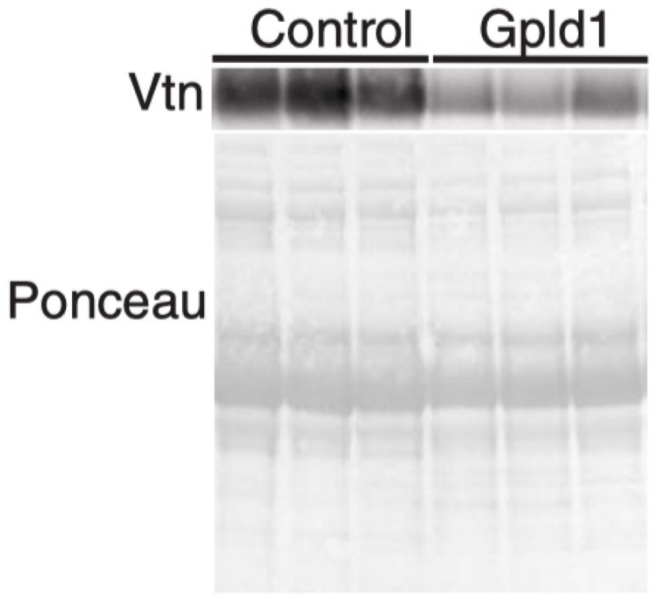
Decrease in Aged + Exercise

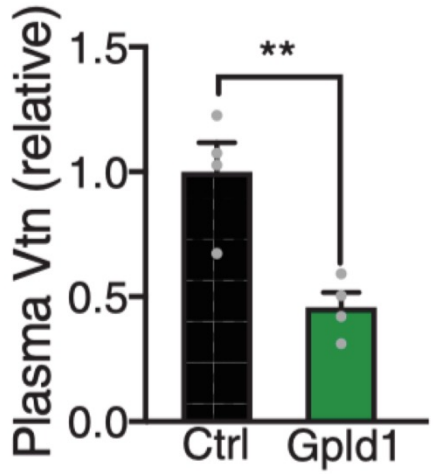
Serpina10	F2	C5	Hpx
Serpind1	Serpinf1	Cfi	Cd5l
Hspa5	Plg	Cfh	Fgb
Apoa4	F9	Itih4	Krt42
Fn1	Azgp1	Fgg	Orm1
Mbl1	Pvalb	Qsox1	Cfp
F13a1	Vcam1	C1sa	C9
Agt	Cp	Fga	Cfb
Gc	Cpb2	Actb	Orm2
Olfm1	C4b	Serpina3n	Saa1
			Hp

Yoshitaka Fujihara and Masahito Ikawa, Journal of Lipid Research (2016)

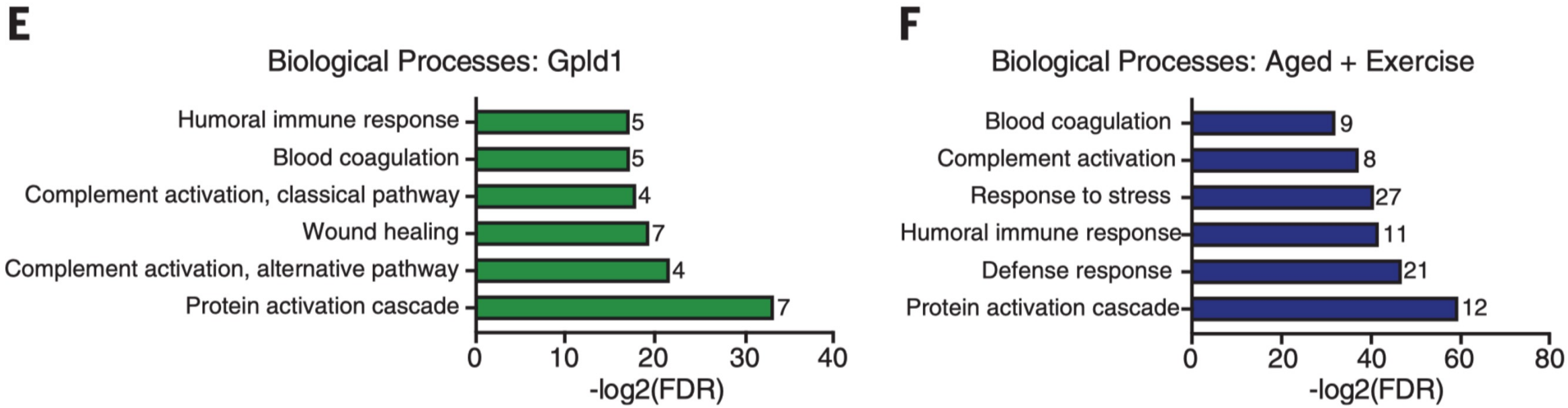
Validation using western blot





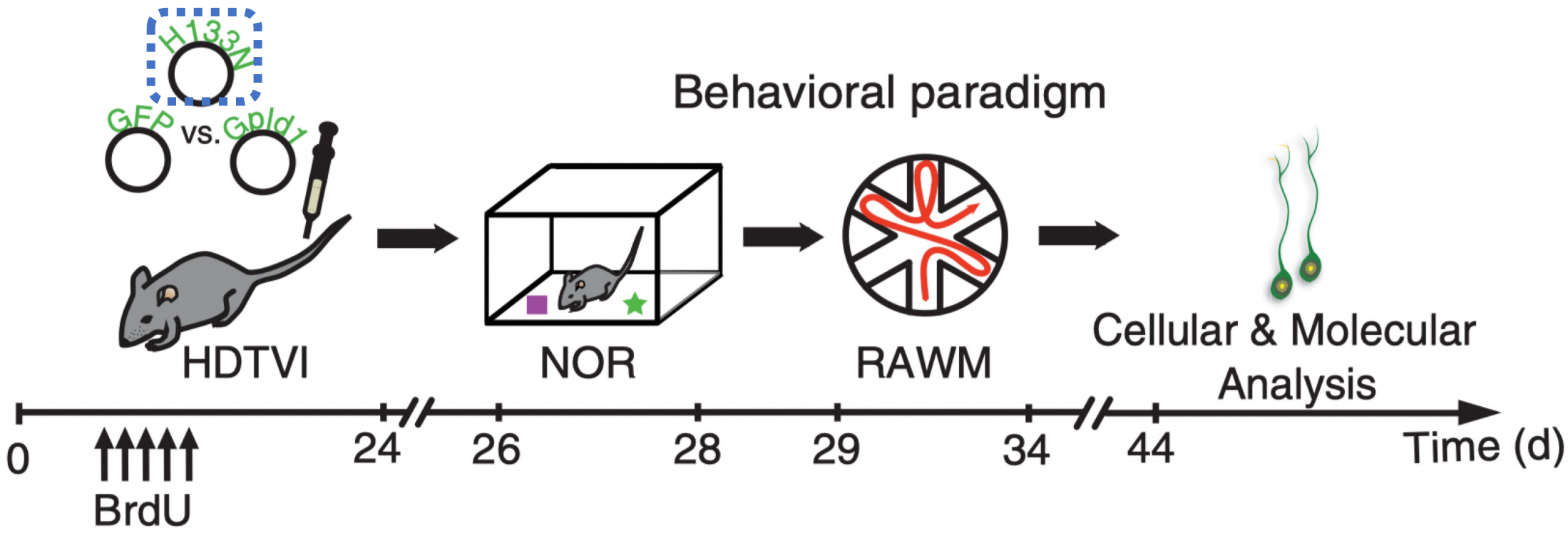


Enrichment analysis of plasma proteins down-regulated with Gpld1 overexpression (left) or exercise (right) in aged mice



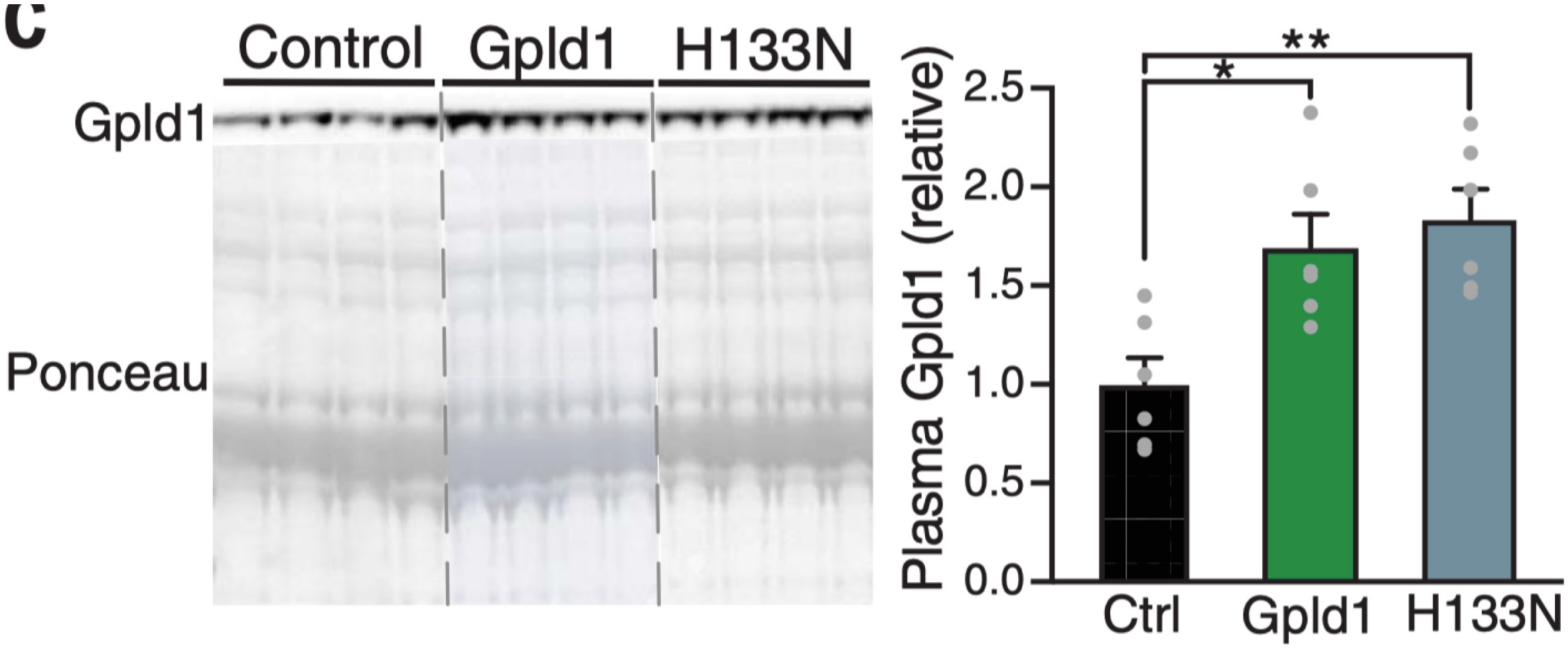
Whether GPI-anchored substrate cleavage is necessary for the effects of Gpld1 on the aged hippocampus?

Schematic illustrates chronological order of HDTVI, cognitive testing, and cellular and molecular analysis

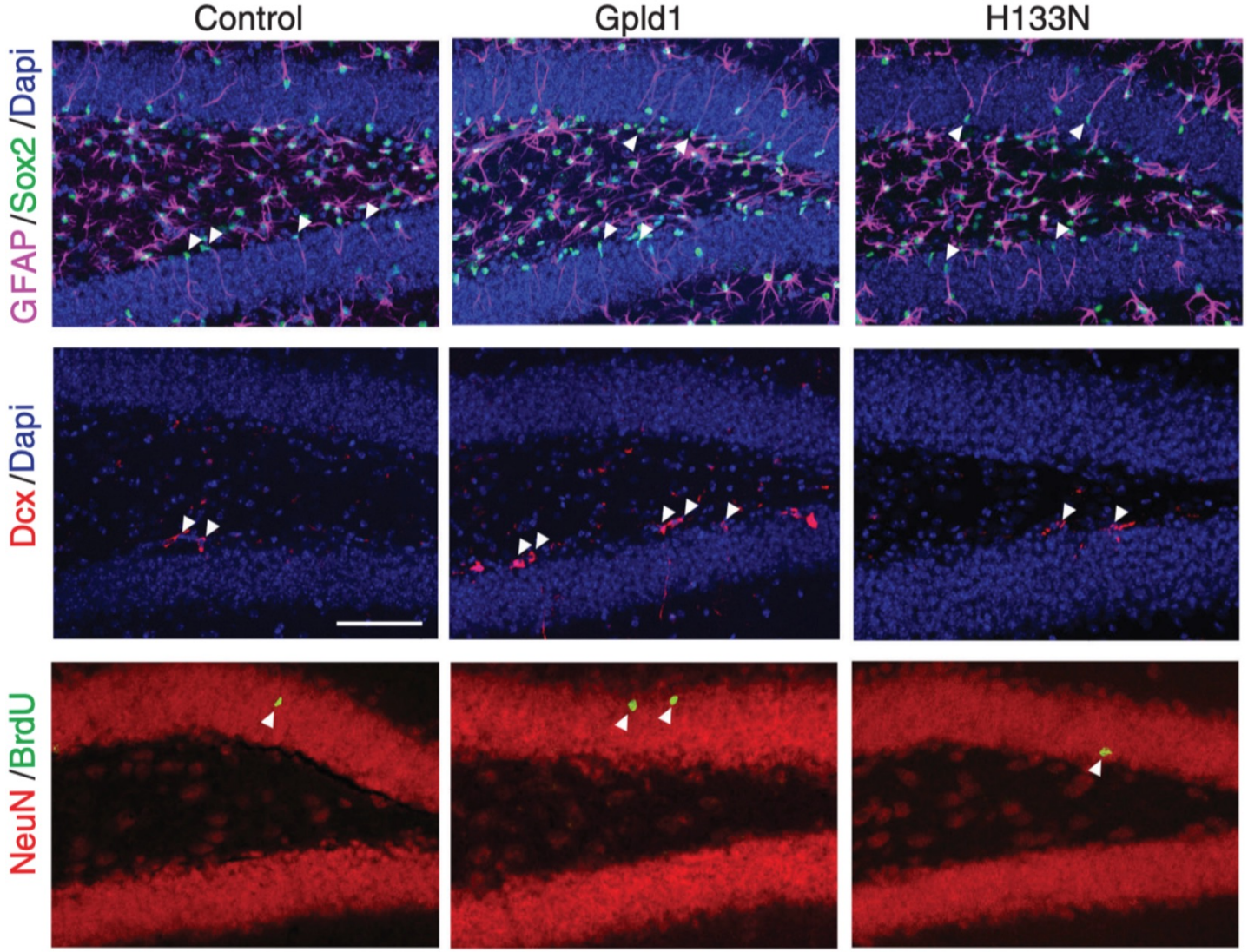


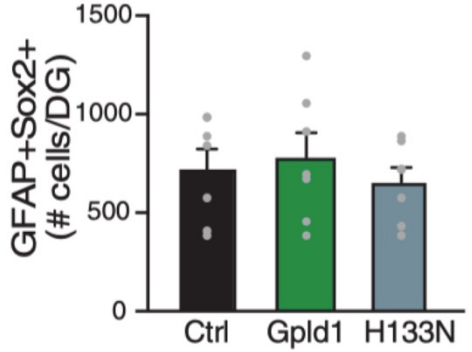
H133N: His^{133} → Asn mutated Gpld1 losing catalytic activity

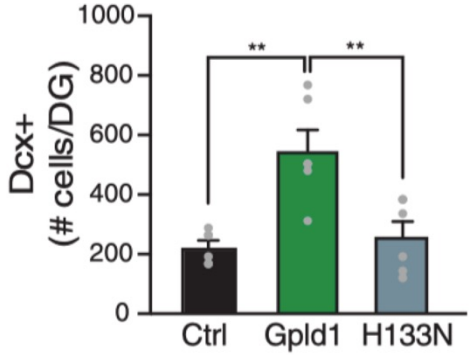
Validation of Gpld1 and its mutation overexpression

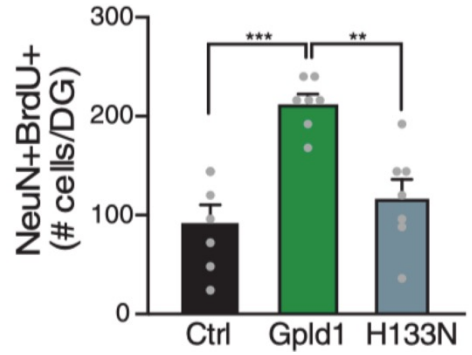


Overexpression of catalytically inactive H133N Gpld1 loses ability to promote hippocampus neurogenesis in aged mice

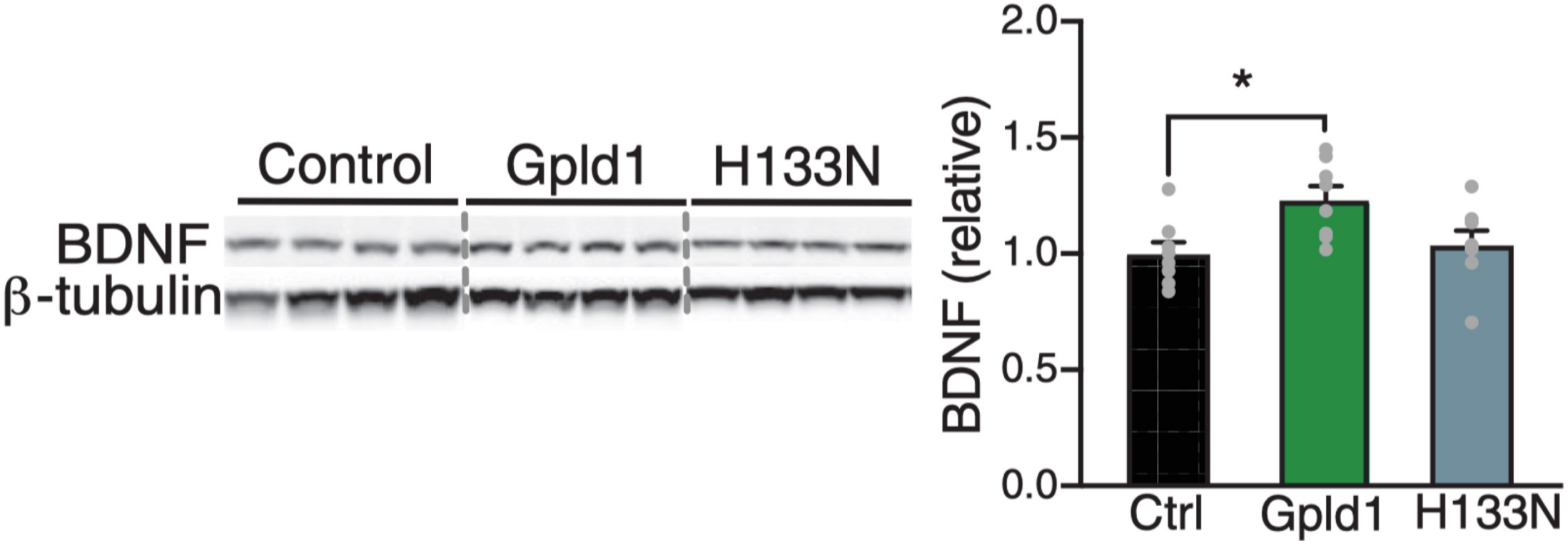




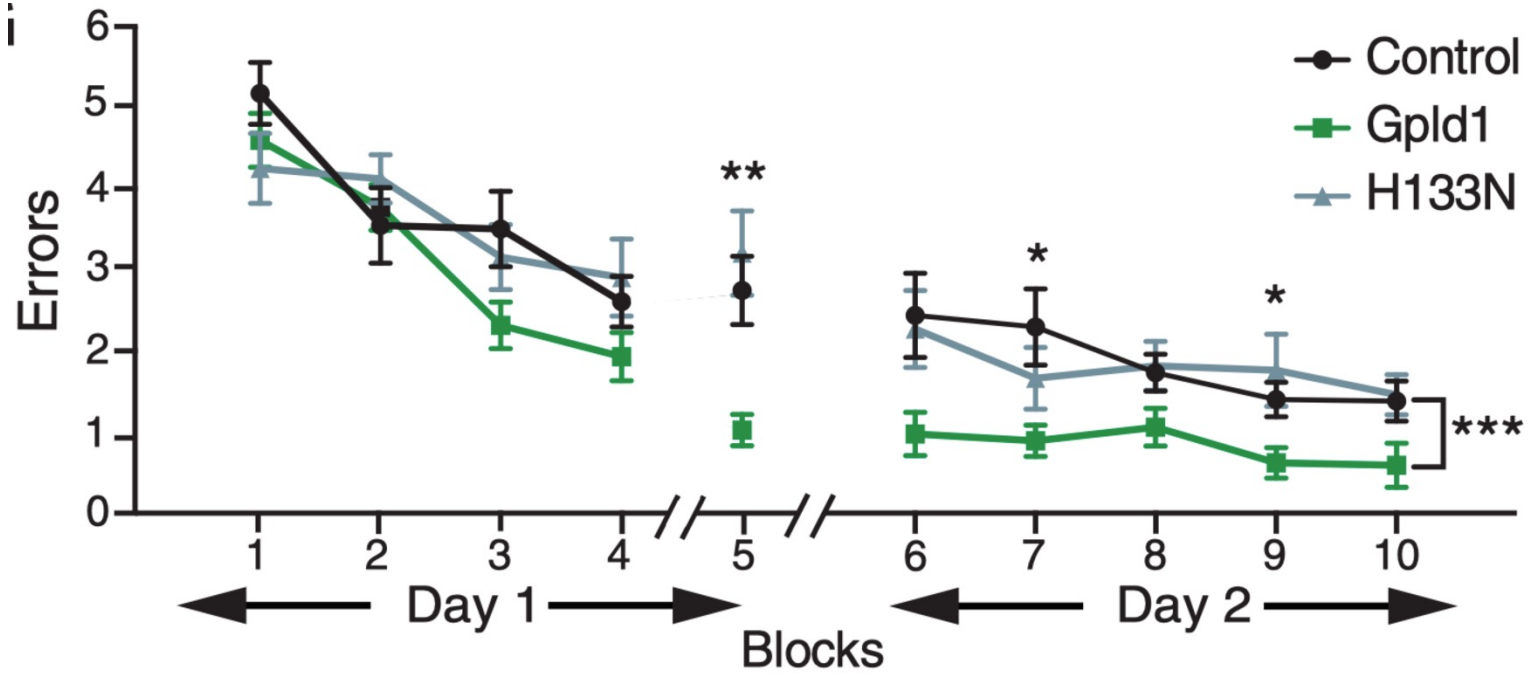


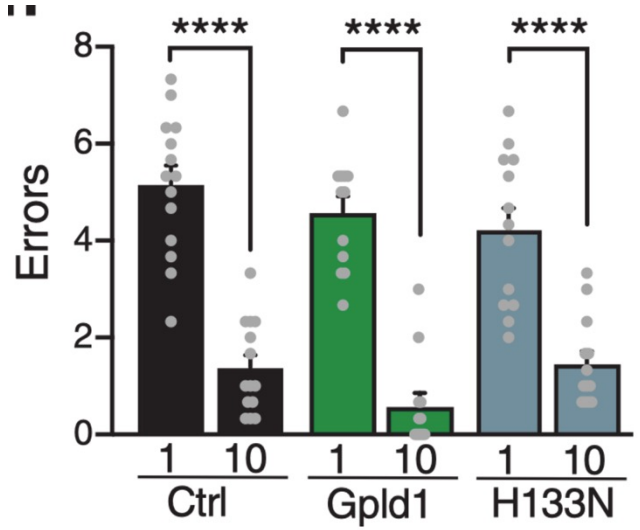


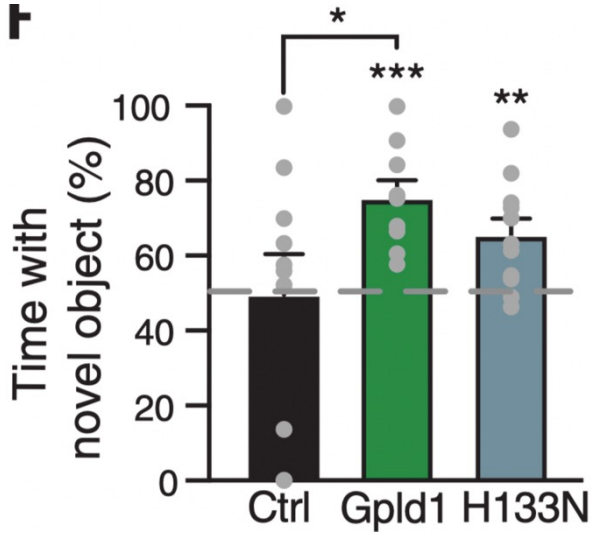
Overexpression of catalytically inactive H133N Gpld1 does not increase level of neurotrophic factor BDNF in aged hippocampus



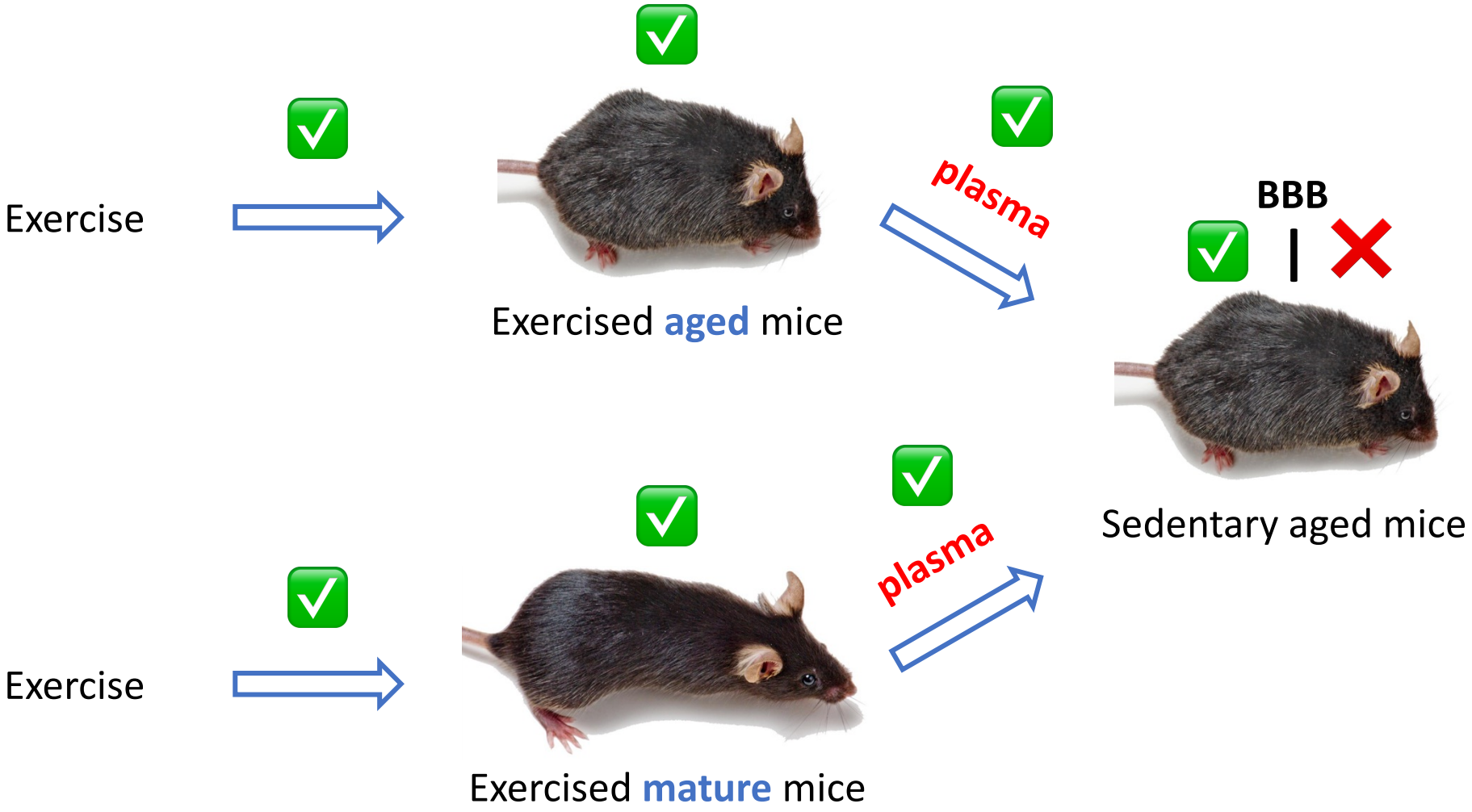
Overexpression of catalytically inactive H133N Gpld1 loses ability to promote cognitive ability in aged mice



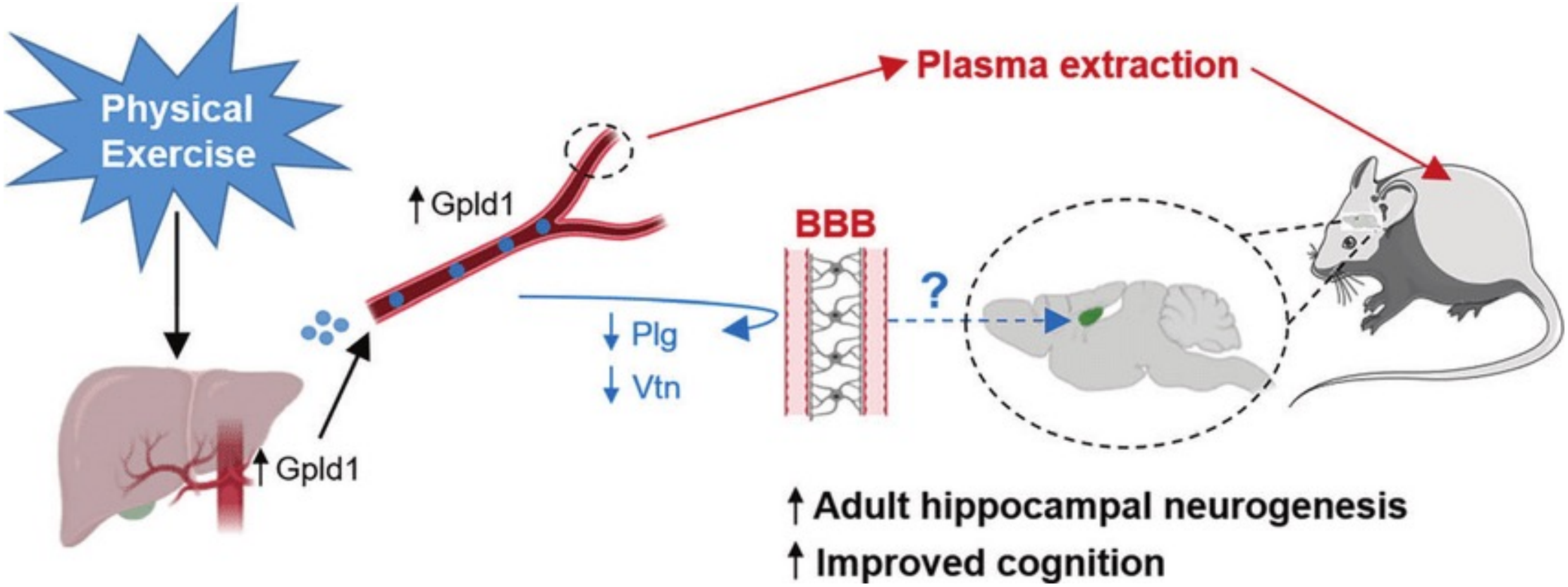




Coagulation and complement signaling cascades are altered in response to Gpld1

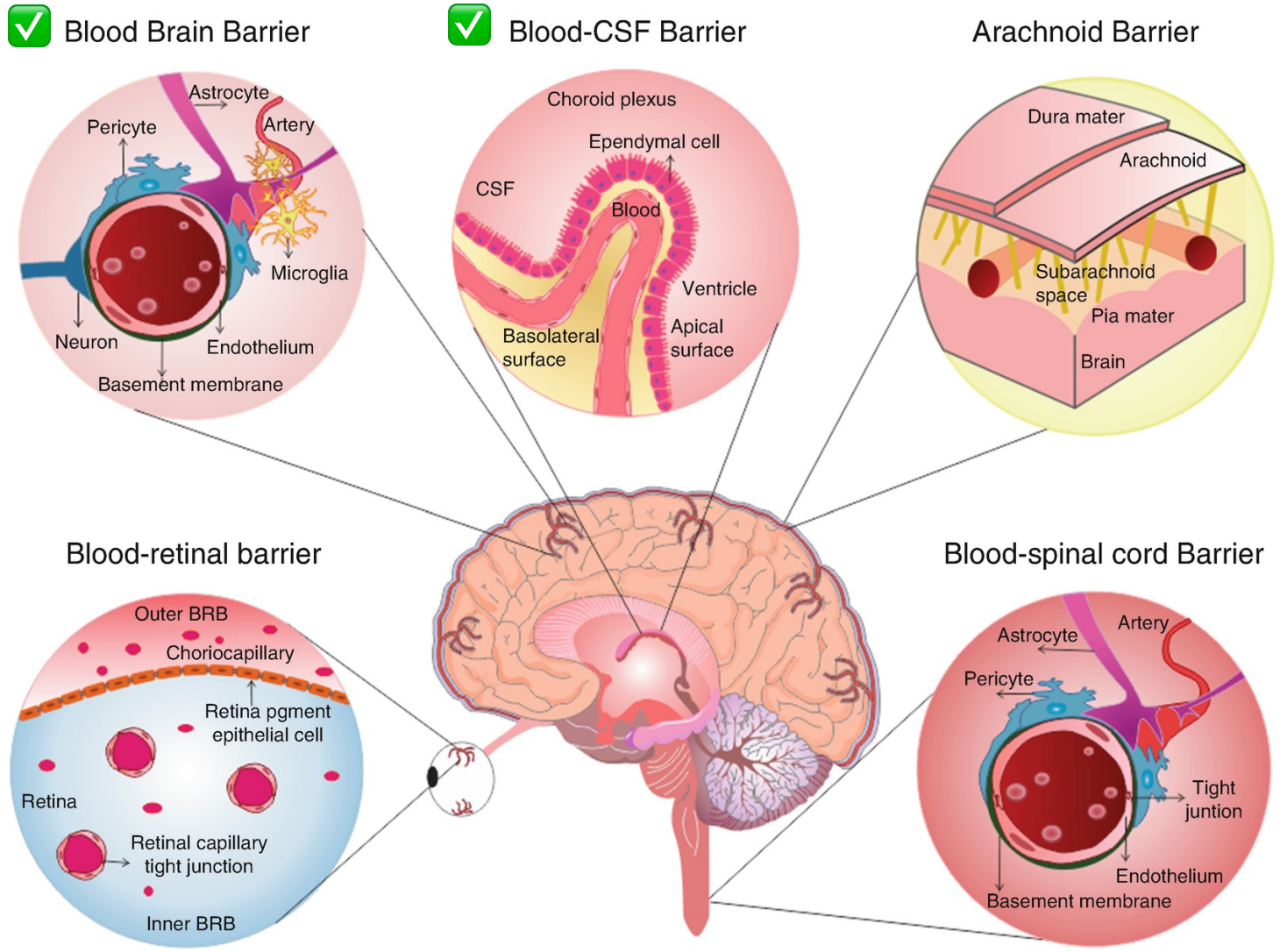


Summary and discussion



https://www.researchgate.net/publication/344105432_A_new_player_in_the_beneficial_effects_of_exercise_on_the_aged_brain

Central nervous system barriers



https://media.springernature.com/original/springer-static/image/chp%3A10.1007%2F978-1-4939-8946-1_1/MediaObjects/421700_1_En_1_Fig1_HTML.png

Thanks for your attention!