BraiNY Journal Club Presents:

Acute Cannabinoids Impair Working Memory through Astroglial CB1 Receptor Modulation of Hippocampal LTD

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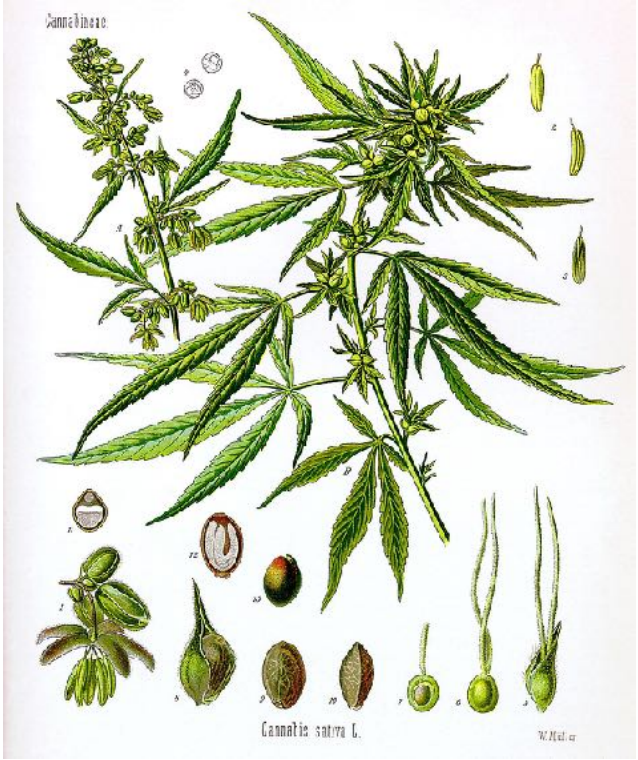
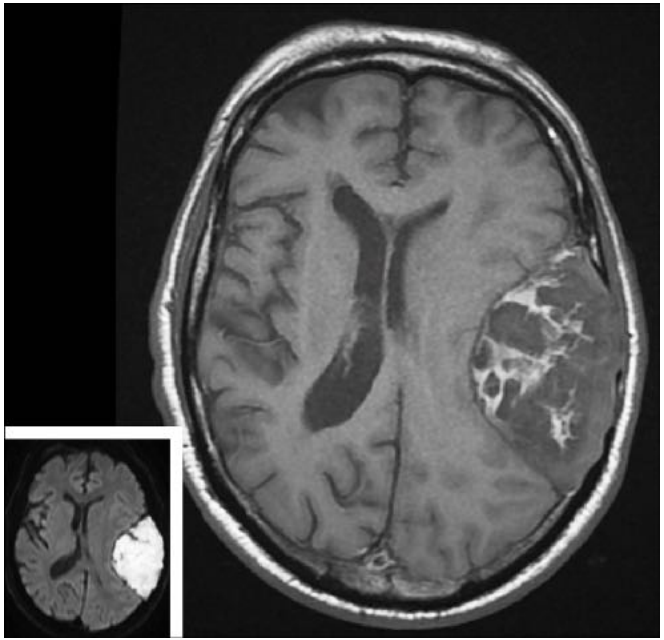
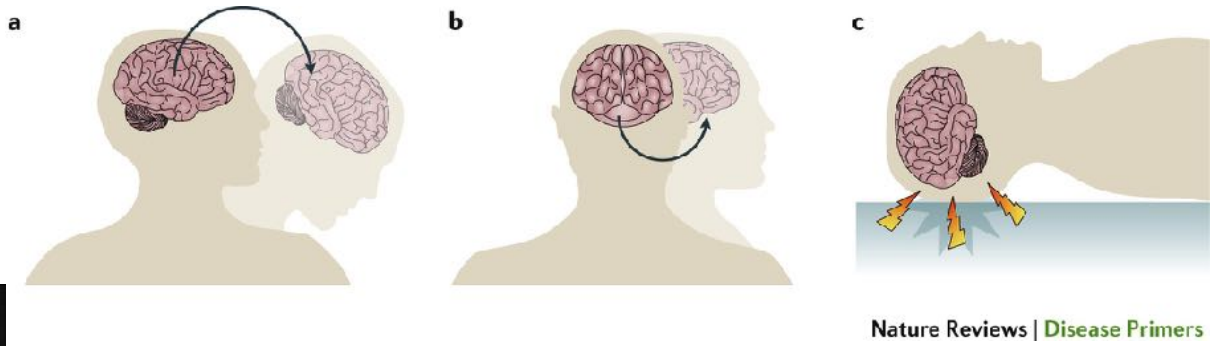
Presented by: Yerram Pooja Chowdary & Siddhartha Mitra

Introduction

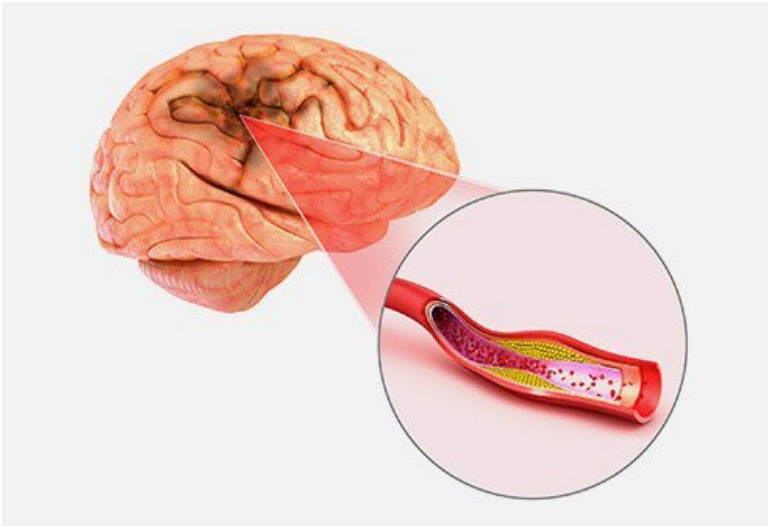


Pros

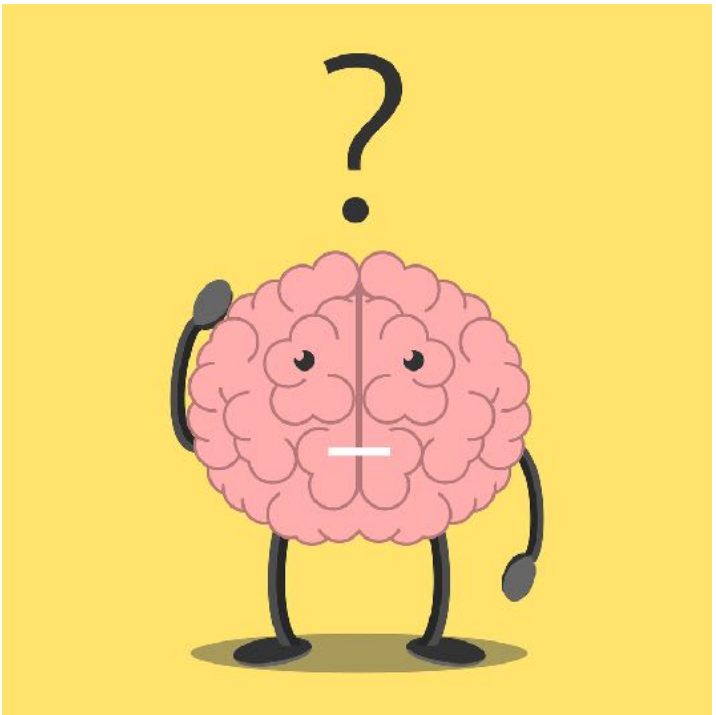




Nature Reviews | Disease Primers



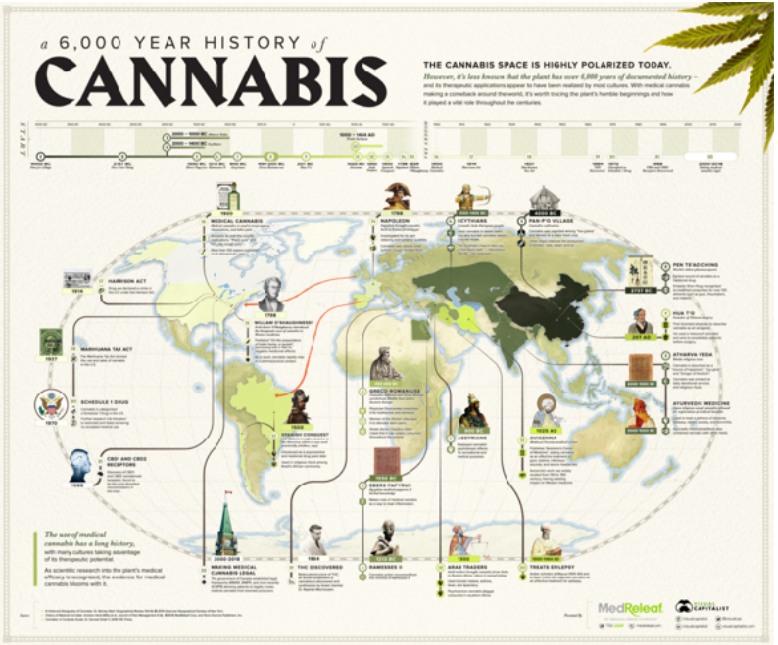
Cons



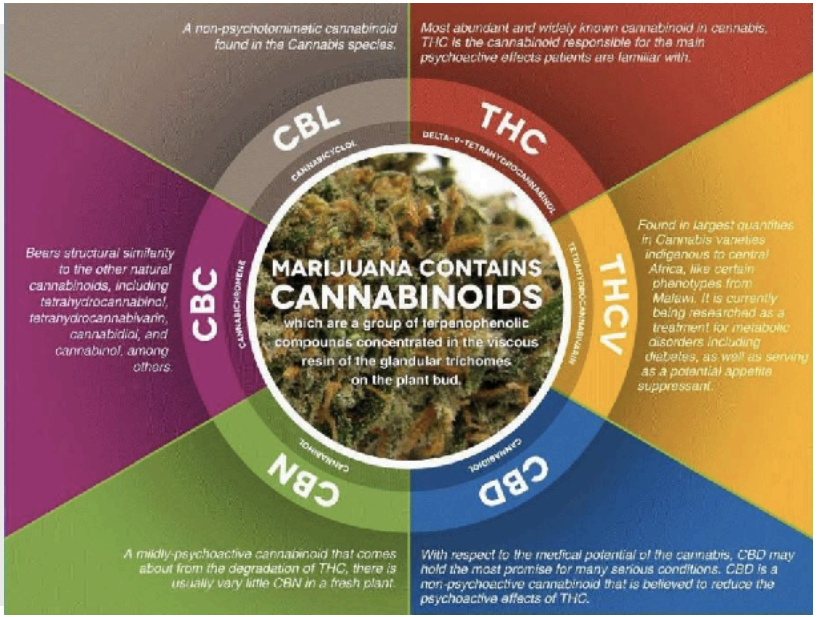
Background

- Marijuana is being legalised in many states
- Medical marijuana
- How does marijuana affect the body?
- What are the health impacts of recreational use?
- Should this be a cause of concern?

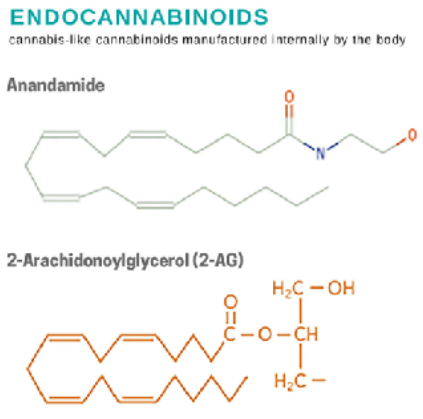
Historical use of marijuana

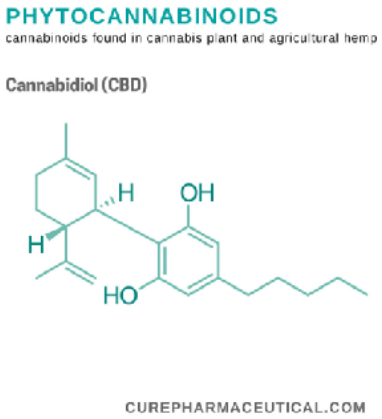


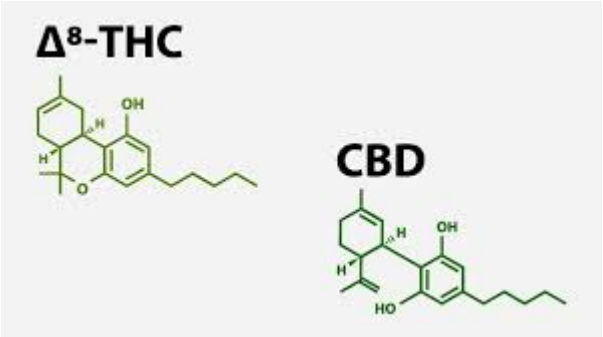
Cannabinoids in the marijuana plant



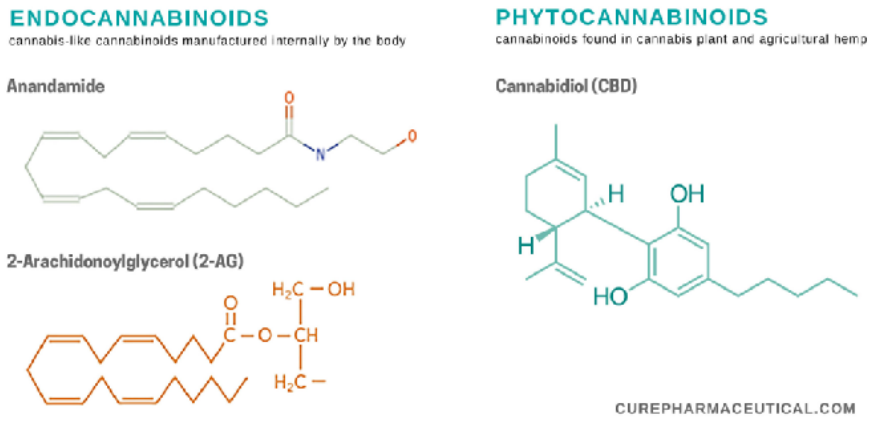
Endocannabinoids

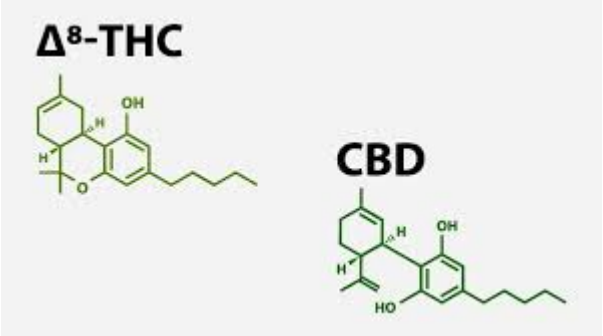




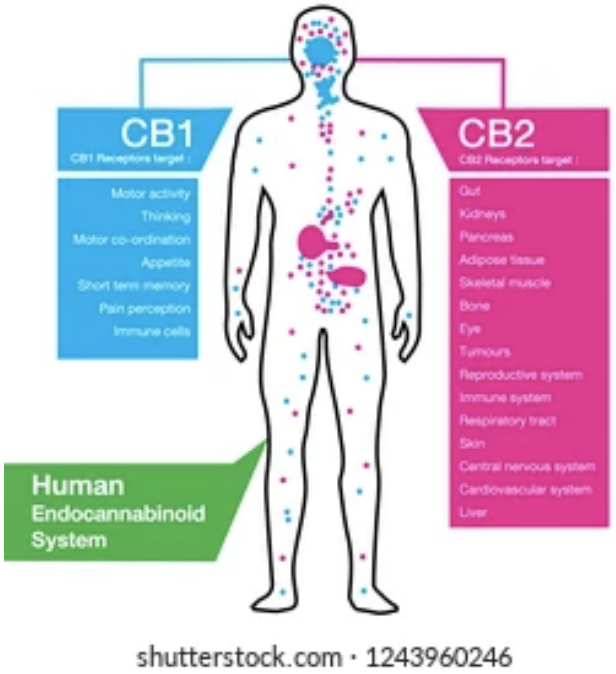


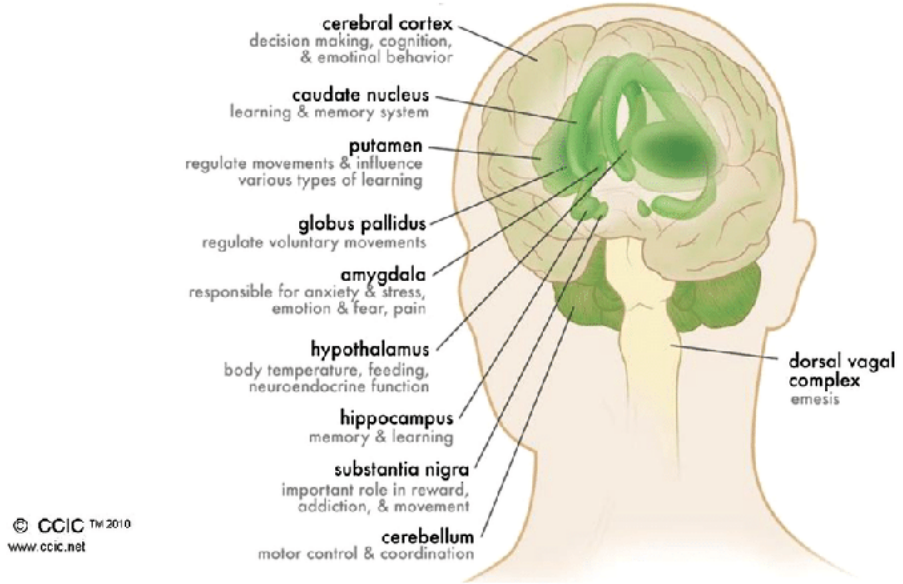
How does it work



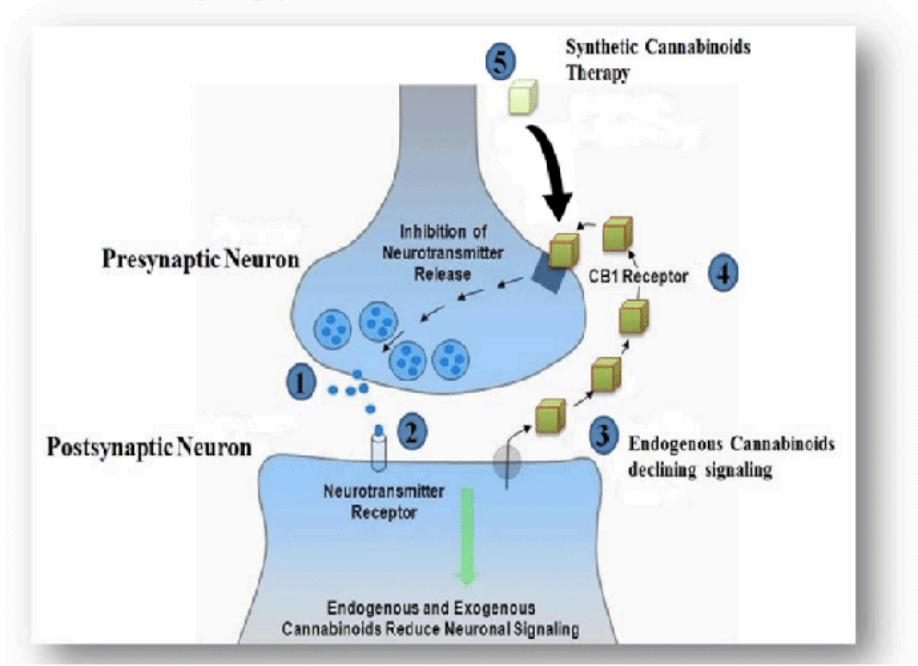


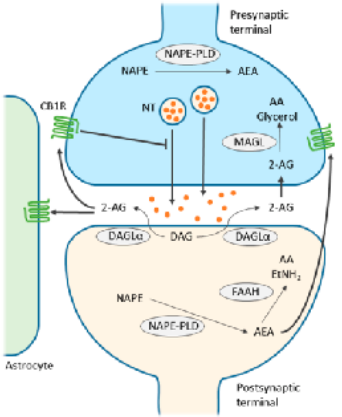
Endocannabinoid system CB1R distribution

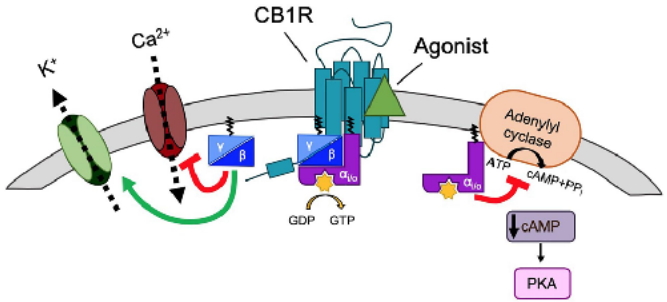




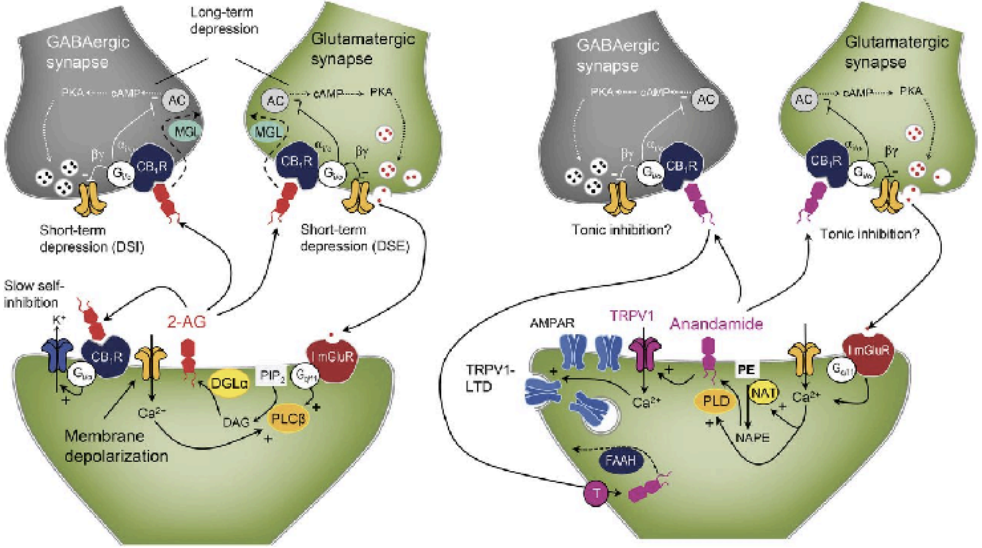
Endocannabinoid system

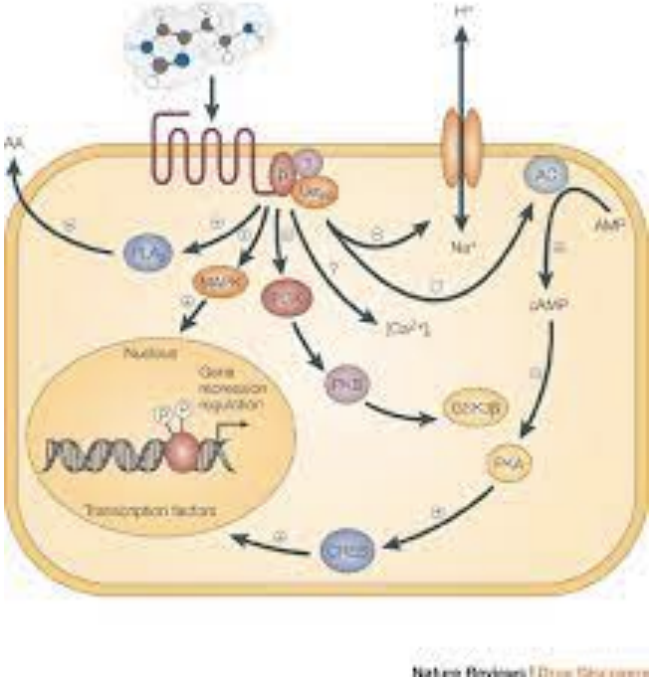




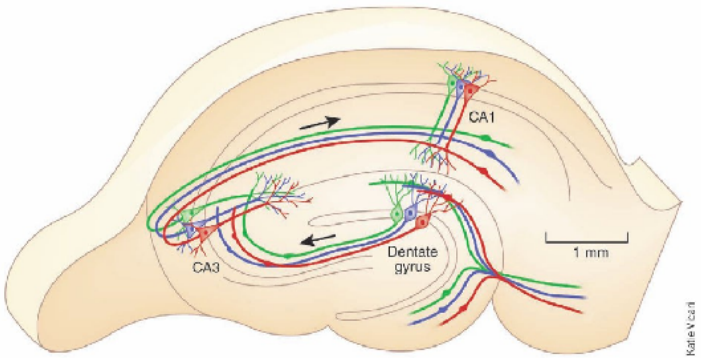


Endocannabinoid system

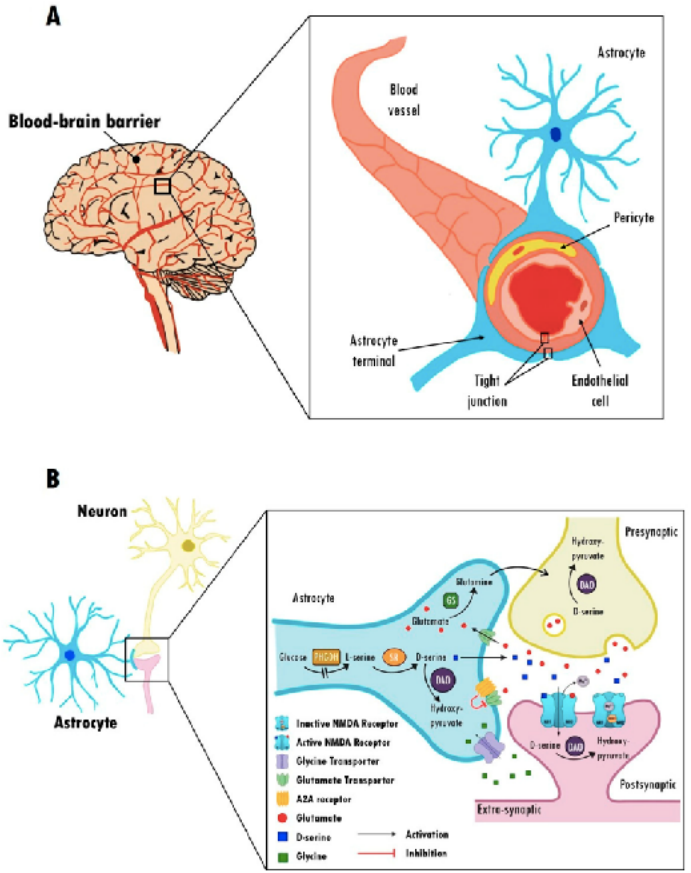




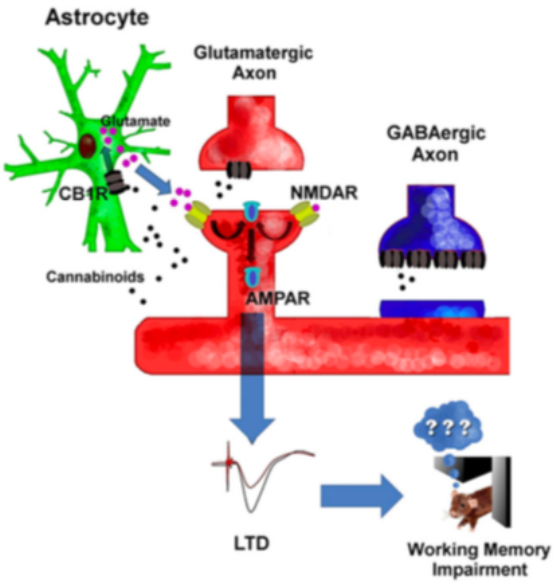
Hippocampus

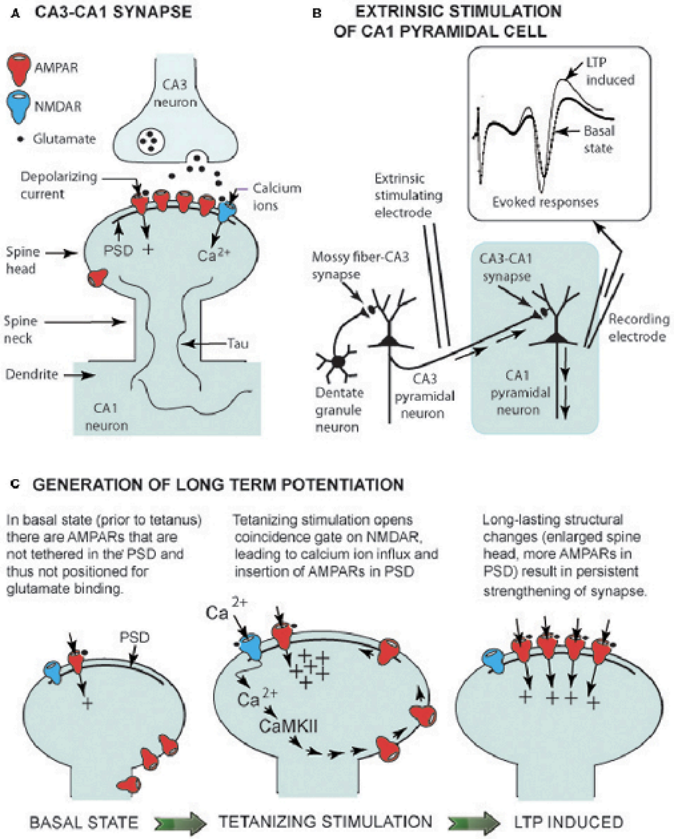


Katie Vicari

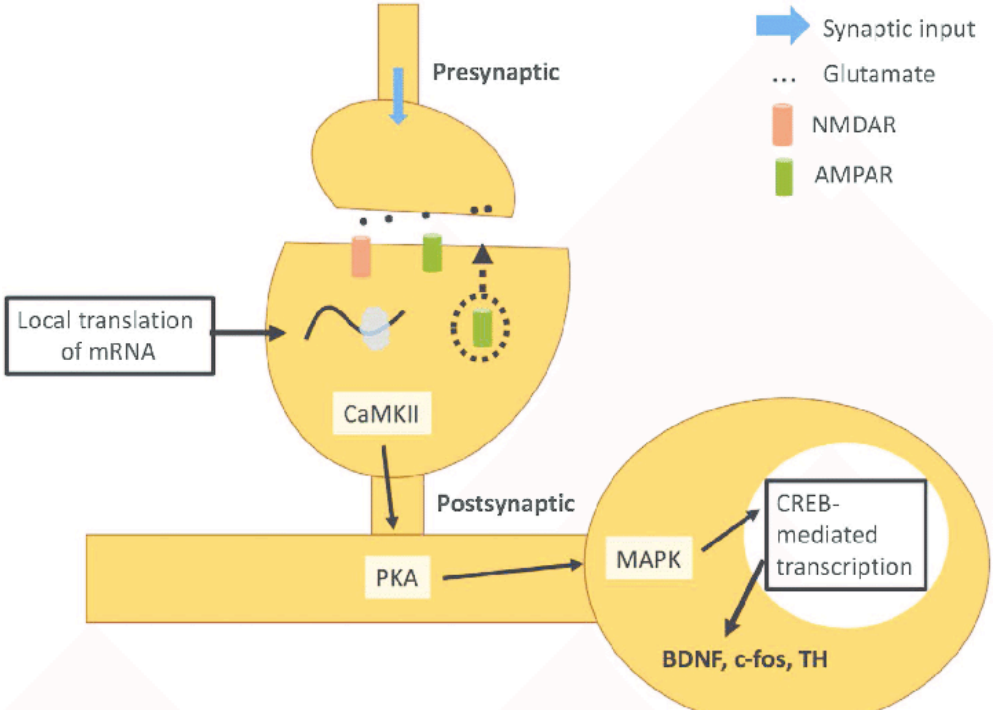


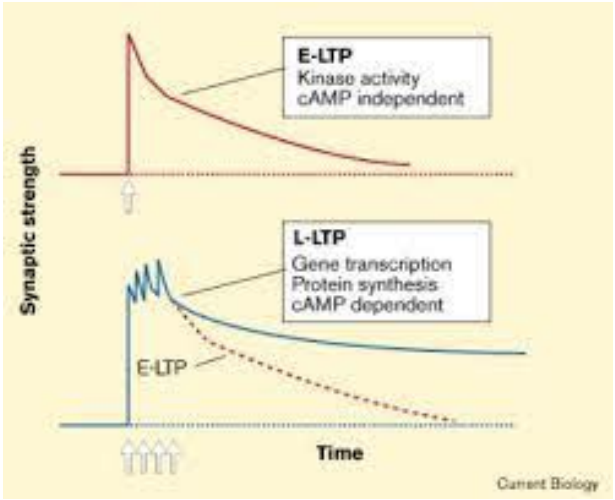
Hippocampus



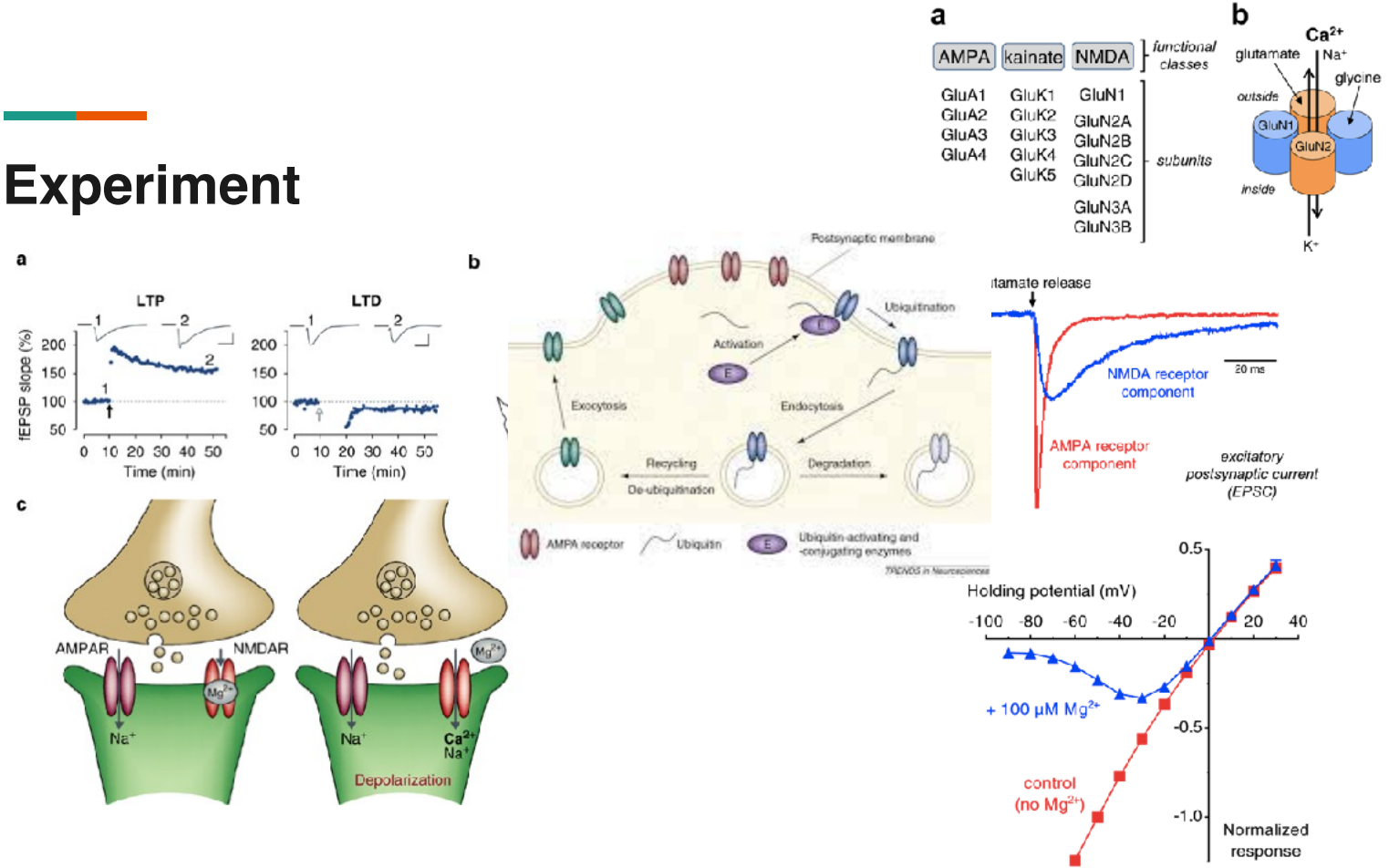


Early and late LTP





Experiment

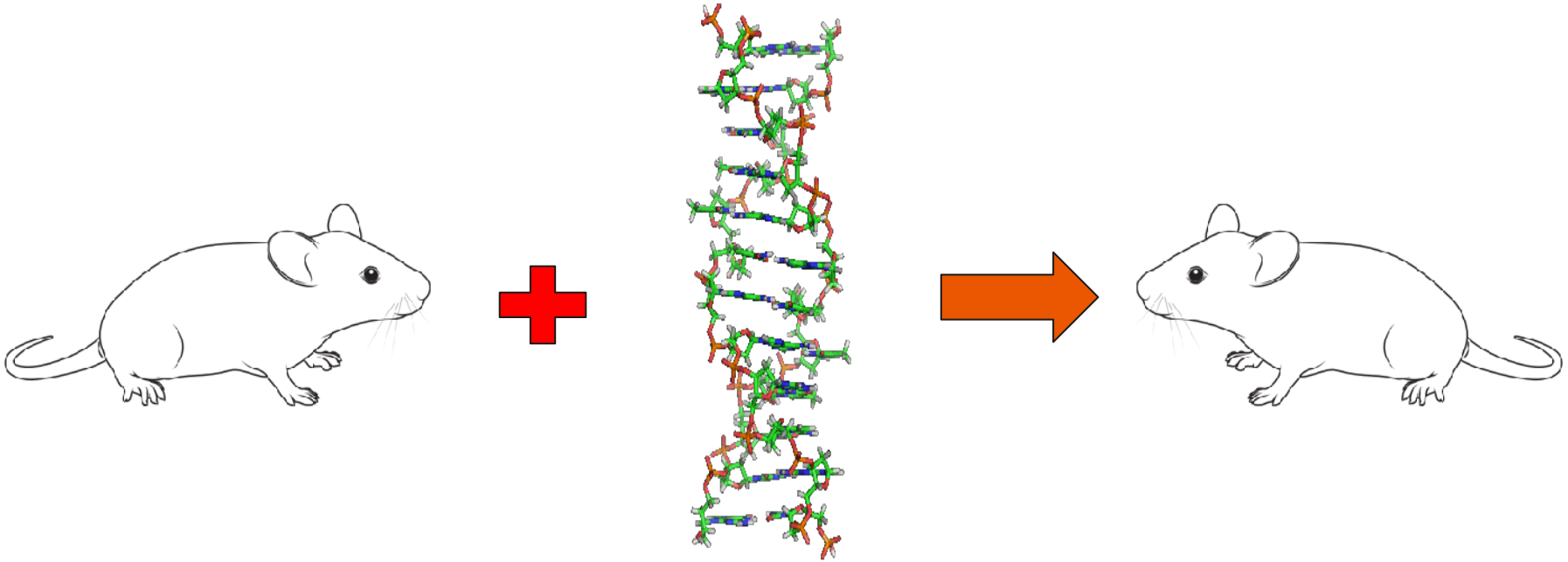

a
AMPA
kainate
NMDA
functional classes
GluA1
GluA2
GluA3
GluA4
GluK1
GluK2
GluK3
GluK4
GluK5
GluN1
GluN2A
GluN2B
GluN2C
GluN2D
GluN3A
GluN3B
subunits
b
Ca2+
glutamate
Na+
glycine
outside
GluN1
GluN2
inside
K+
a
LTP
LTD
fEPSP slope (%)
200
150
100
50
0 10 20 30 40 50
Time (min)
b
Postsynaptic membrane
Ubiquitination
Activation
Exocytosis
Endocytosis
Recycling
De-ubiquitination
Degradation
AMPA receptor
Ubiquitin
Ubiquitin-activating and -conjugating enzymes
TRENDS in Neurosciences
itamate release
20 ms
NMDA receptor component
AMPA receptor component
excitatory postsynaptic current (EPSC)
c
AMPAR
NMDAR
Mg2+
Na+
Ca2+
Depolarization
0.5
Holding potential (mV)
-100 -80 -60 -40 -20 20 40
+ 100 µM Mg2+
-0.5
control (no Mg2+)
-1.0
Normalized response

Approaches in experiment

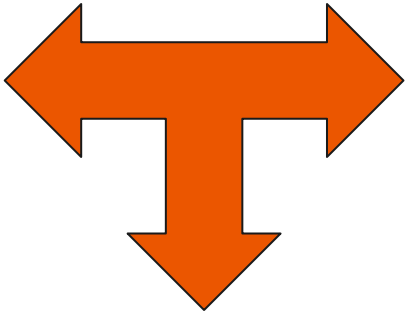
- Does application of **synthetic cannabinoids / THC** reduce LTP - as measured by *in vivo* fEPSP (field excitatory post-synaptic potential)
- Is this occurring because of the **action on the CB1R** on the *pyramidal* cell or the *glial* cell?
- **Measure fEPSP**, create **mutant mice** and conduct **behavioural tests** to answer this question

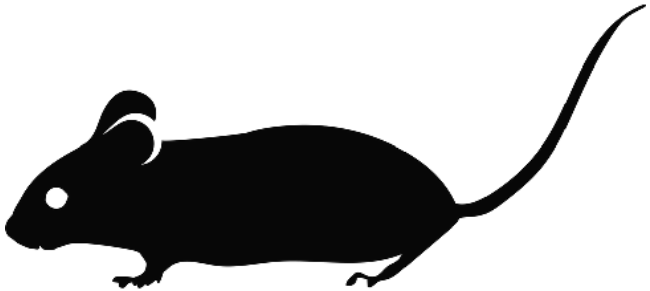
Experimental Procedures

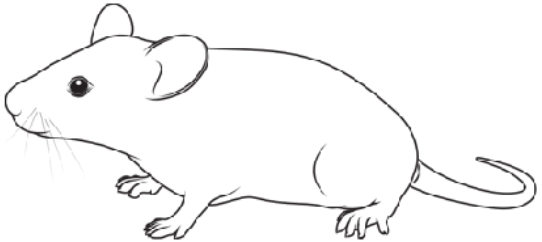
Generation of mutant mice



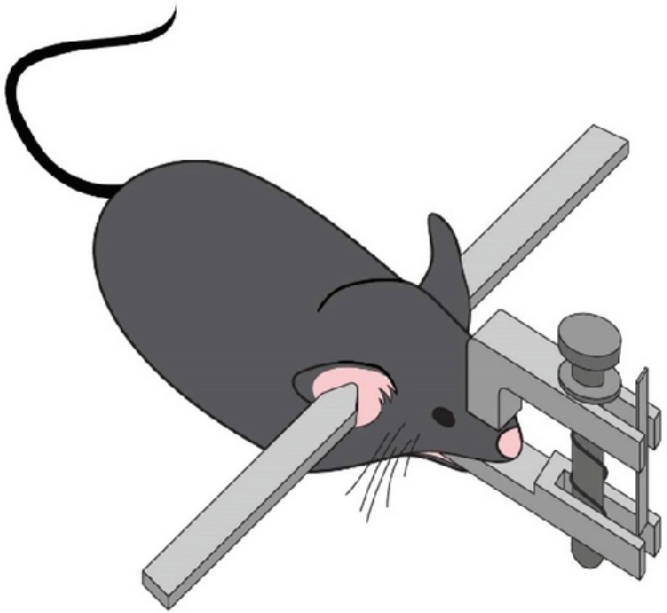
Backcrossing

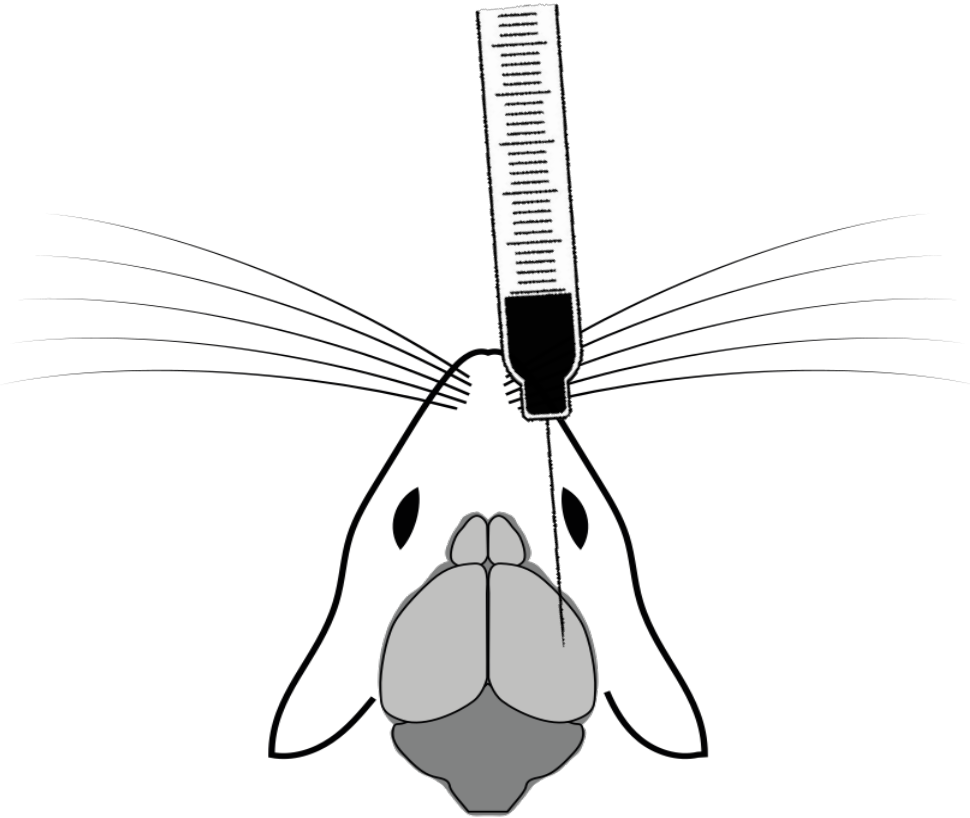


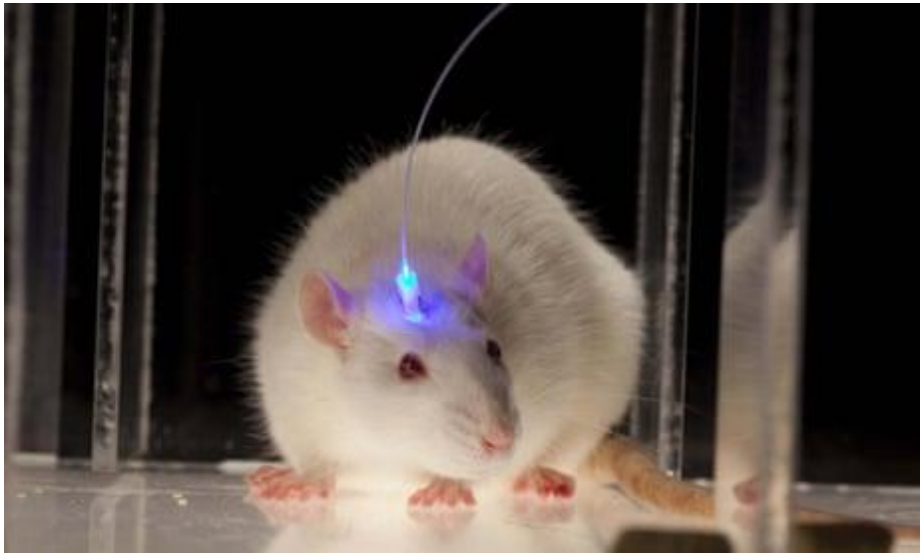




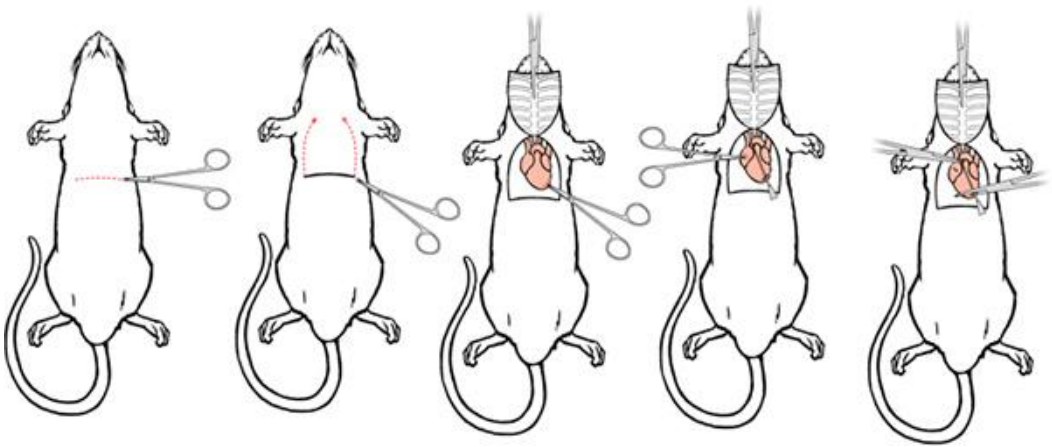
Electrophysiology Analysis

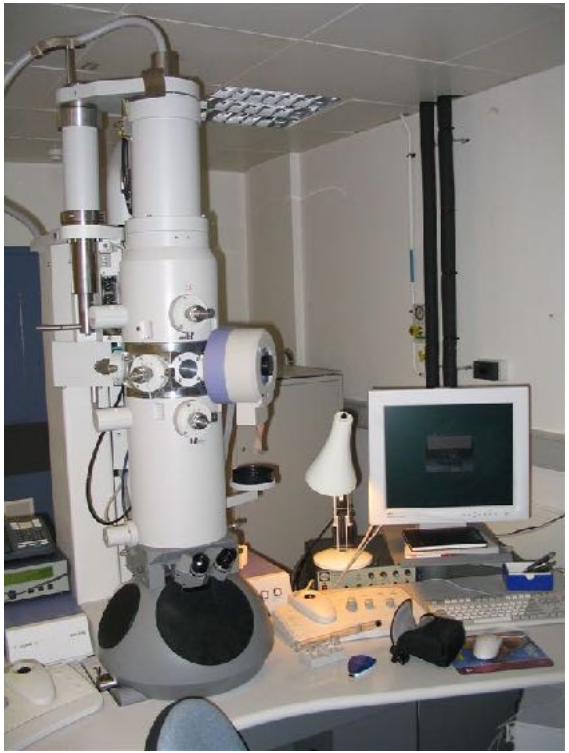




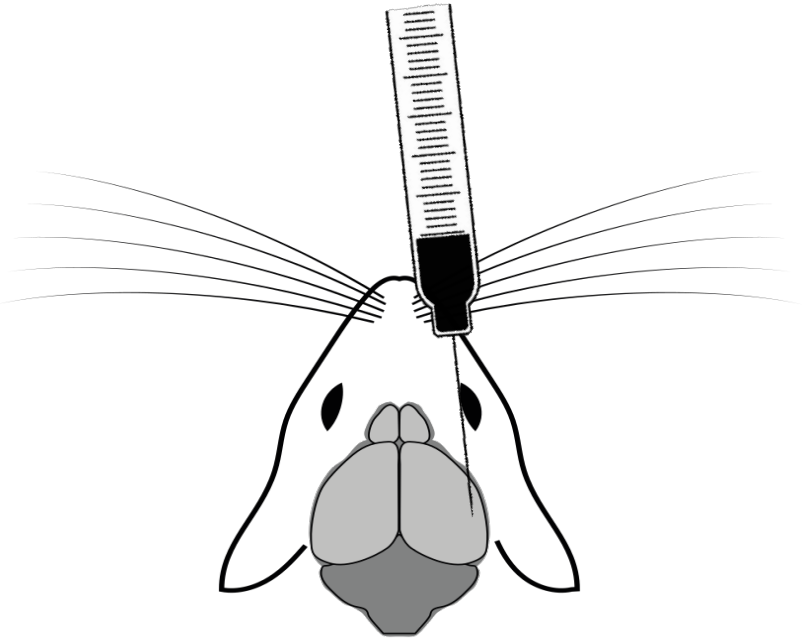


Immunohistochemistry for electron microscopy:



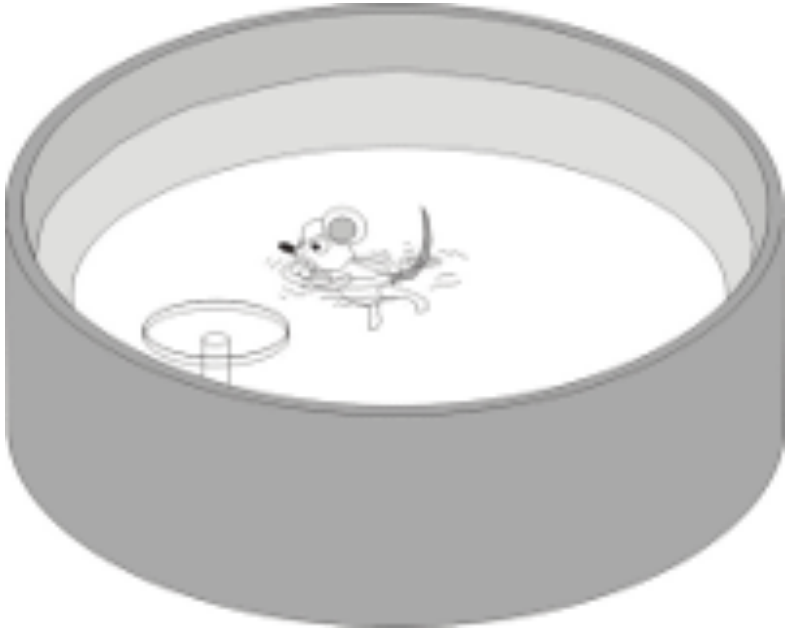


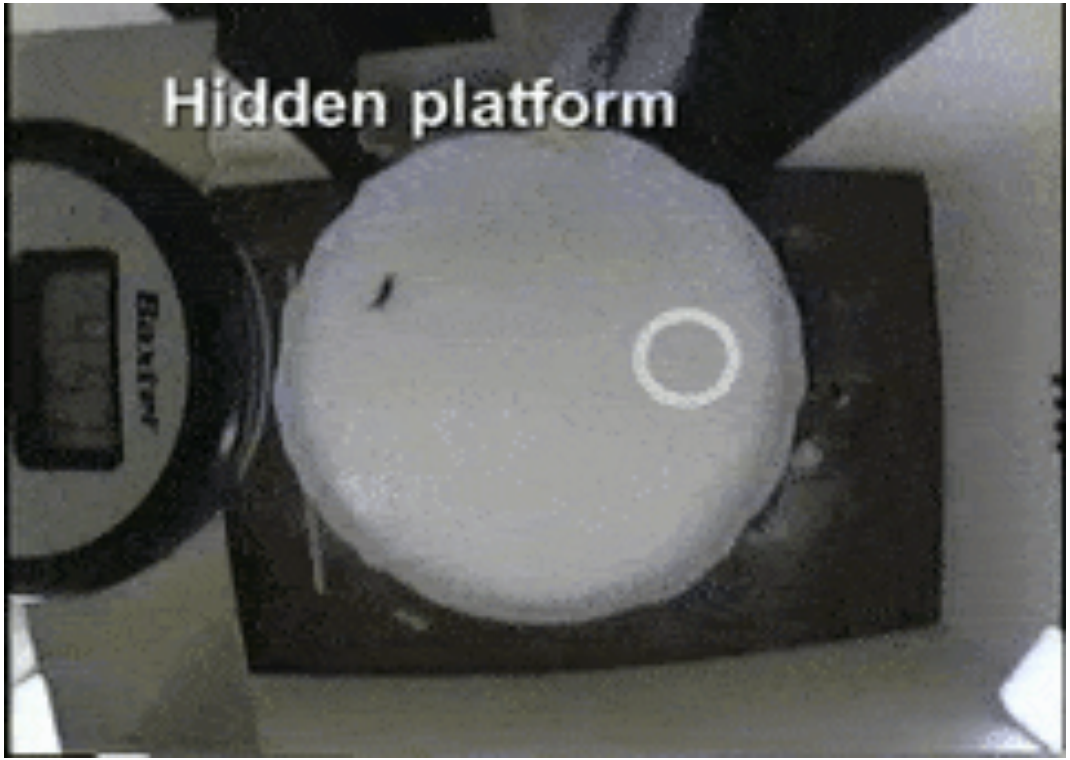
Adenovirus preparation and administration

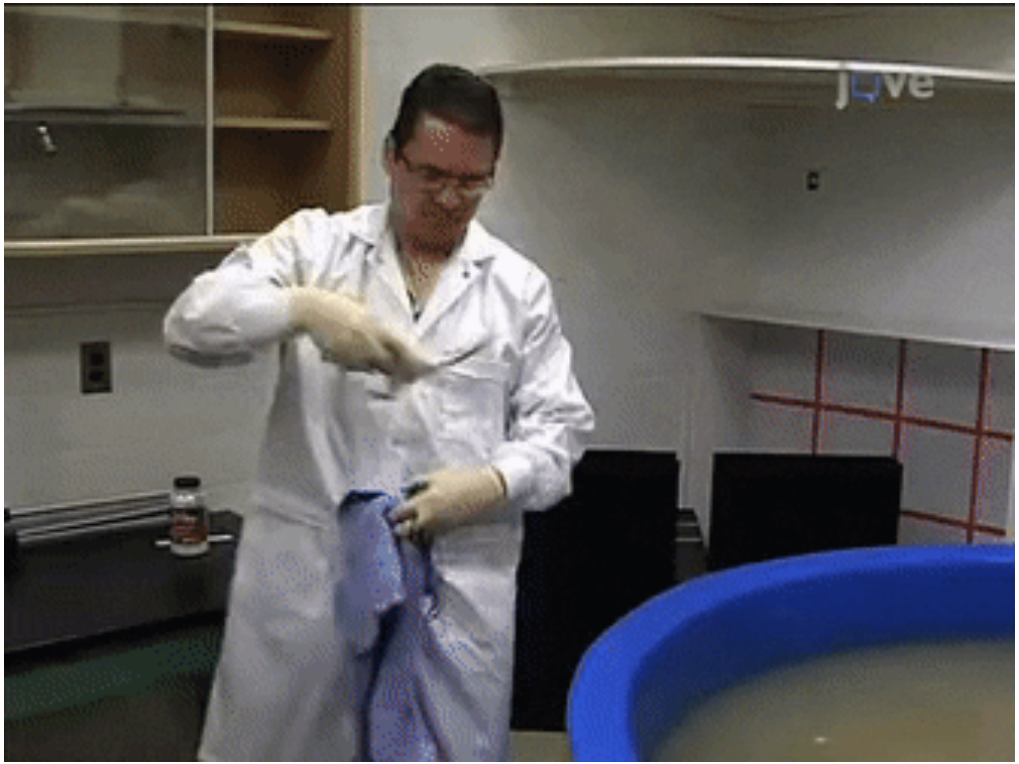


Behavioural tests

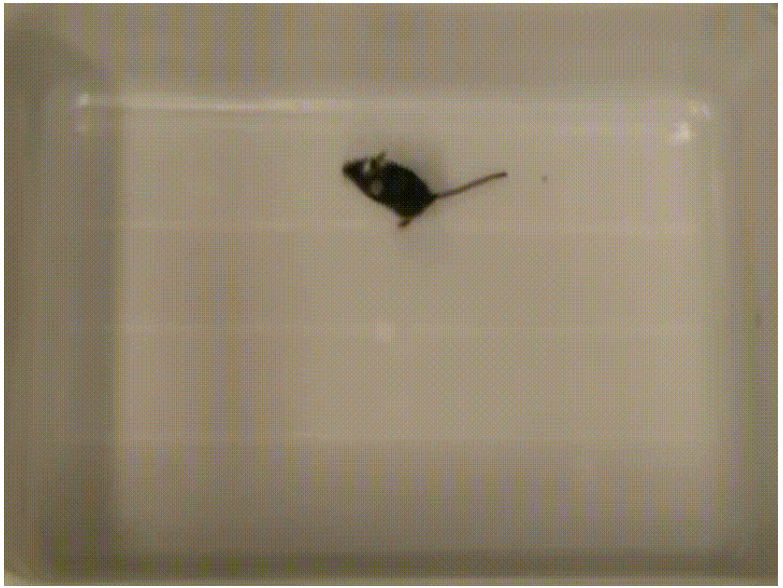
Water Maze test



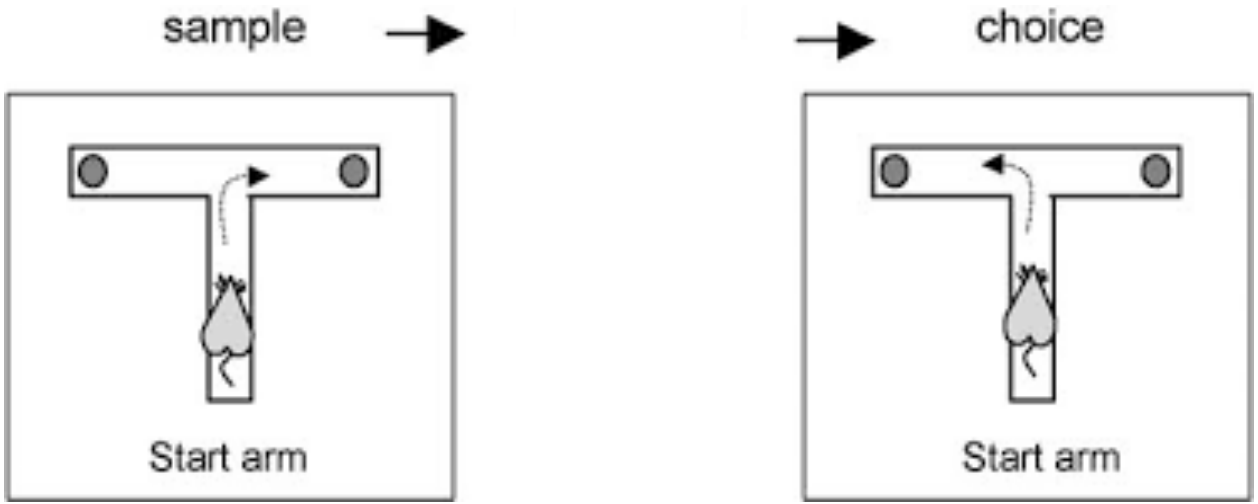

Hidden platform


JoVe

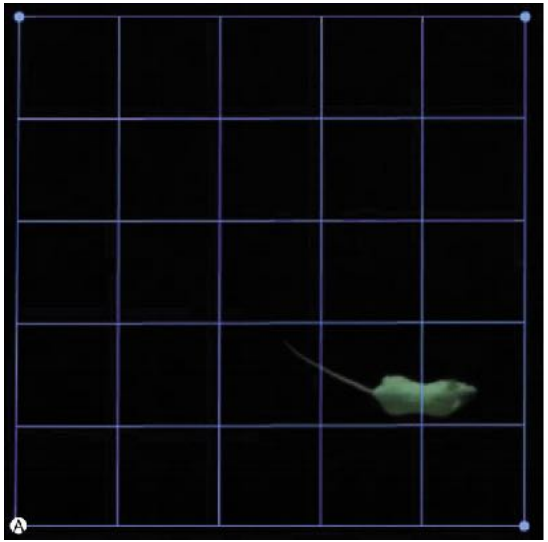
Other behavioural tests:

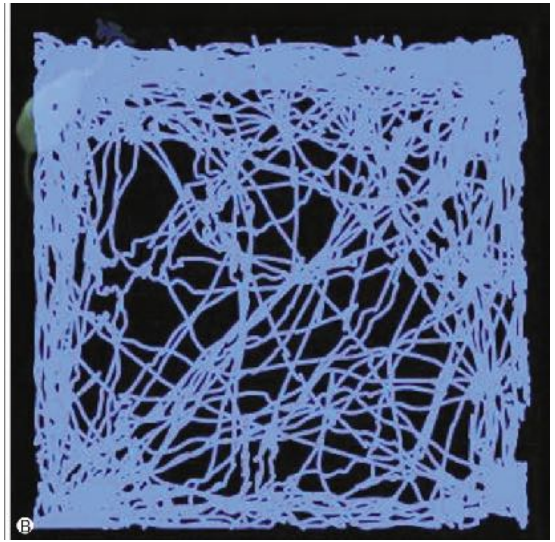


Delayed Nonmatching to Sample T-maze test

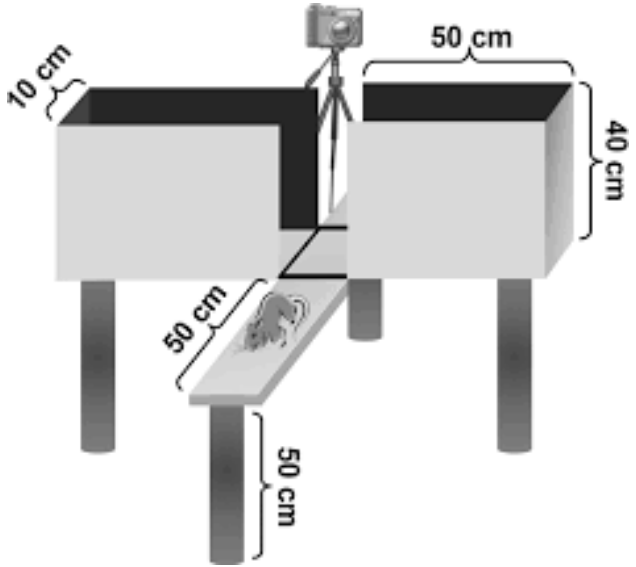


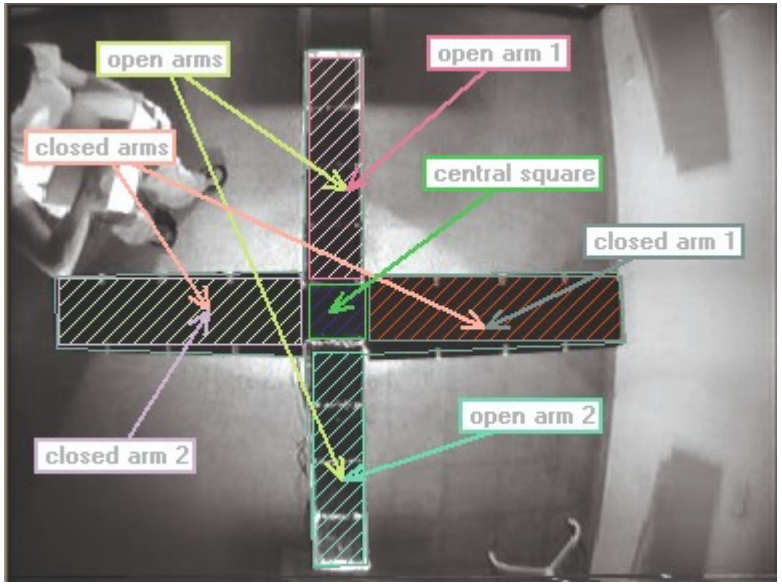
Locomotor activity test



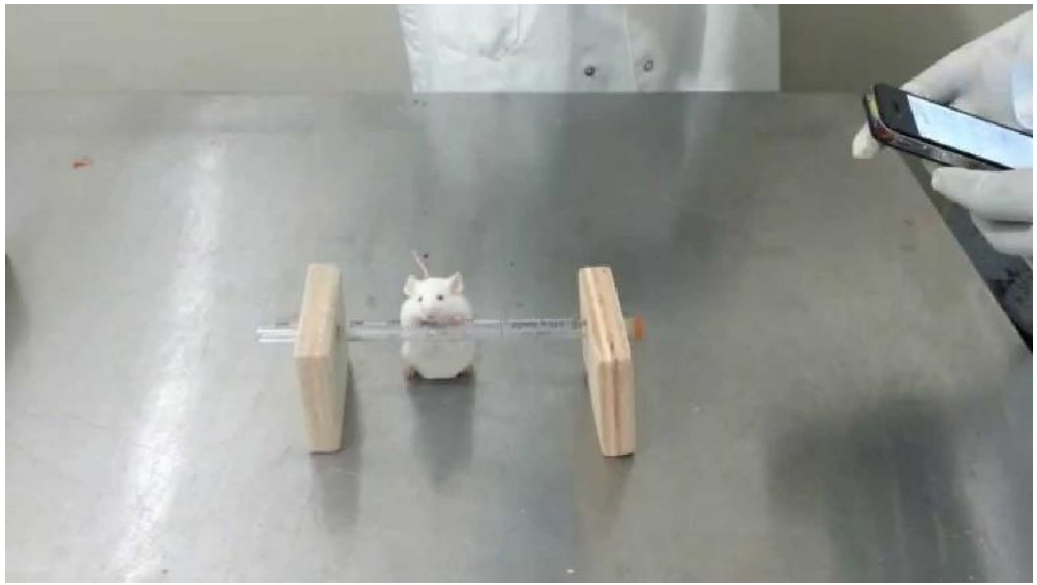


Elevated puzzle maze test





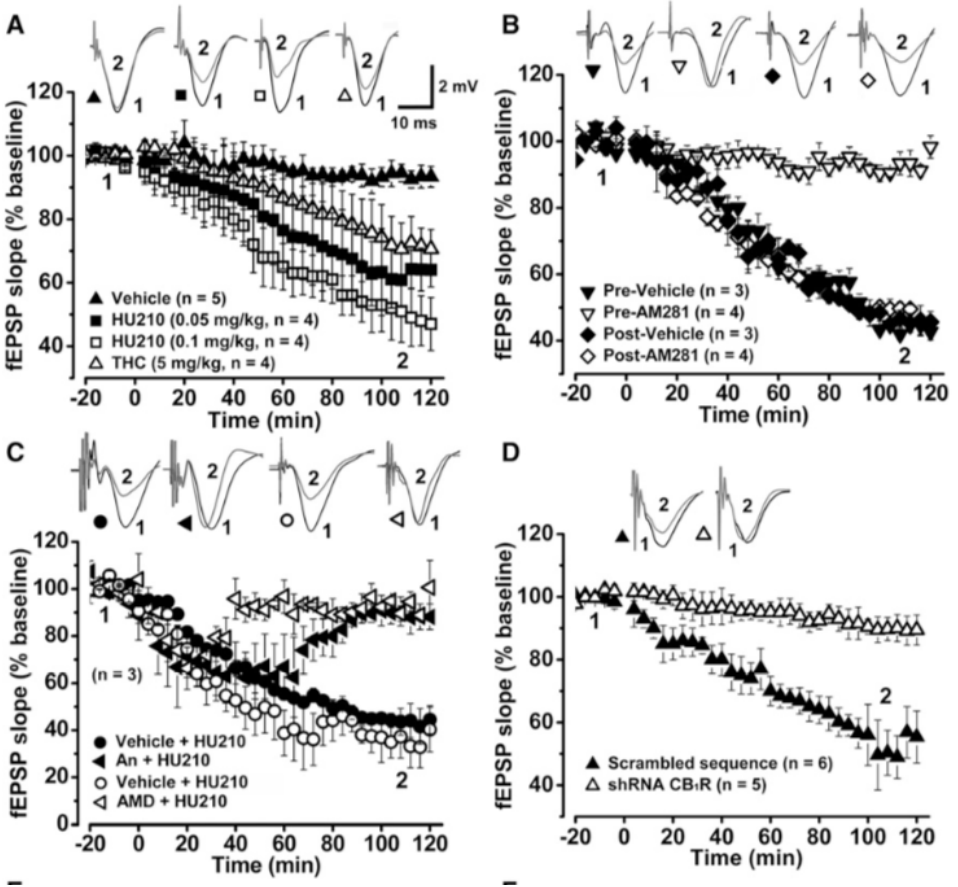
Motor balance test



Results Fig 1

Cannabinoids Induce In Vivo LTD at CA3-CA1 Synapses

fEPSP is reduced by applying endocannabinoids



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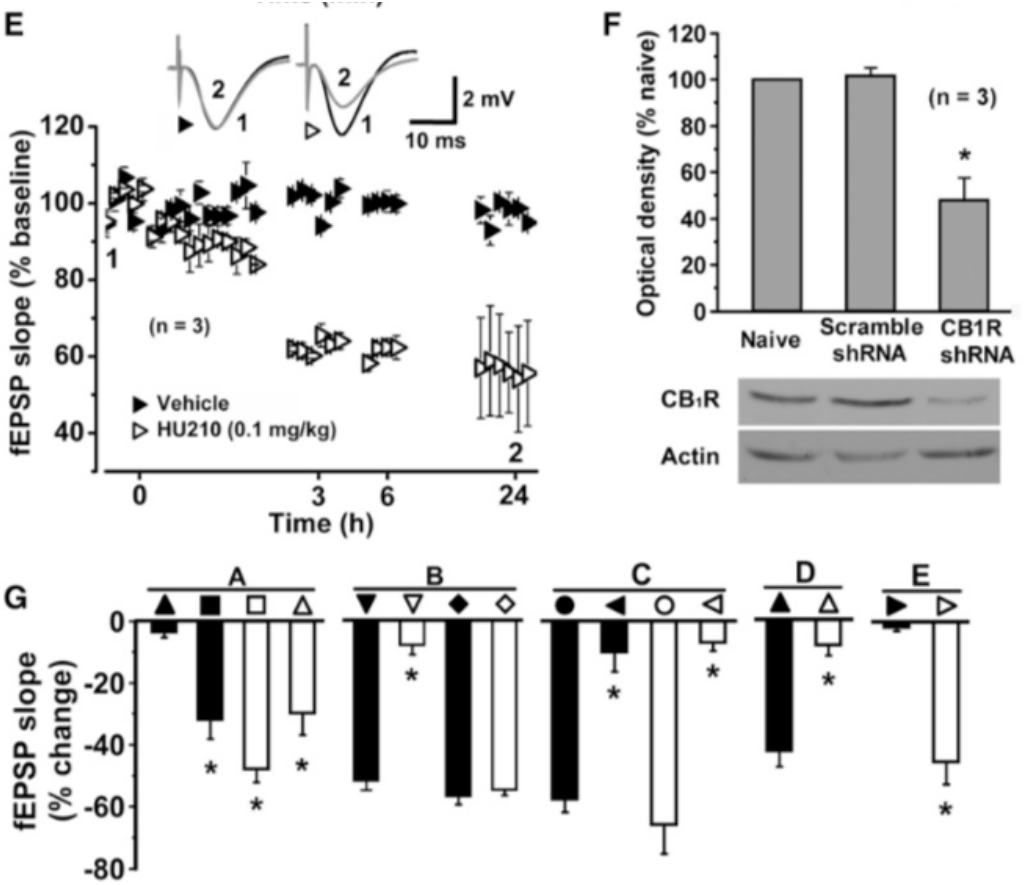
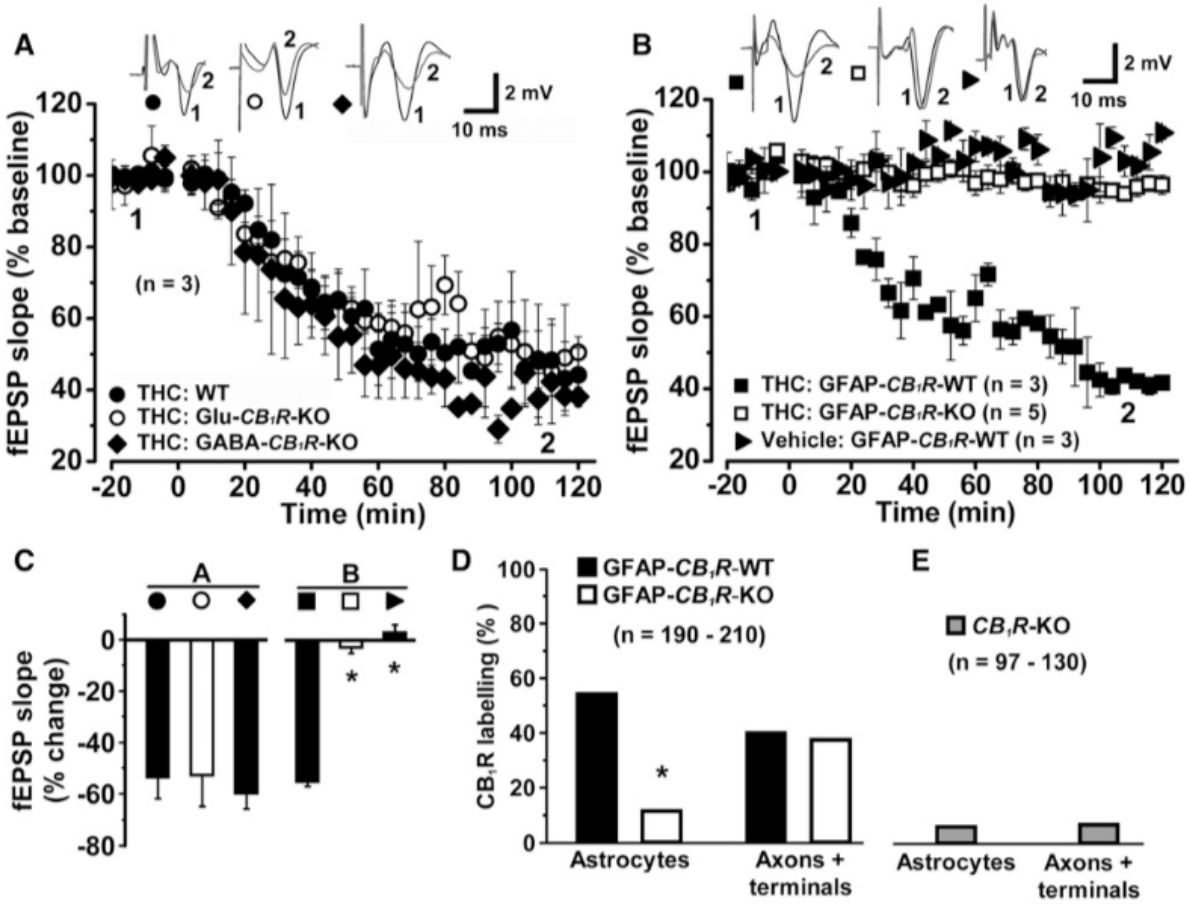


Cannabinoids Elicit CA1 LTD via Astroglial CB1R but Not Neuronal CB1R



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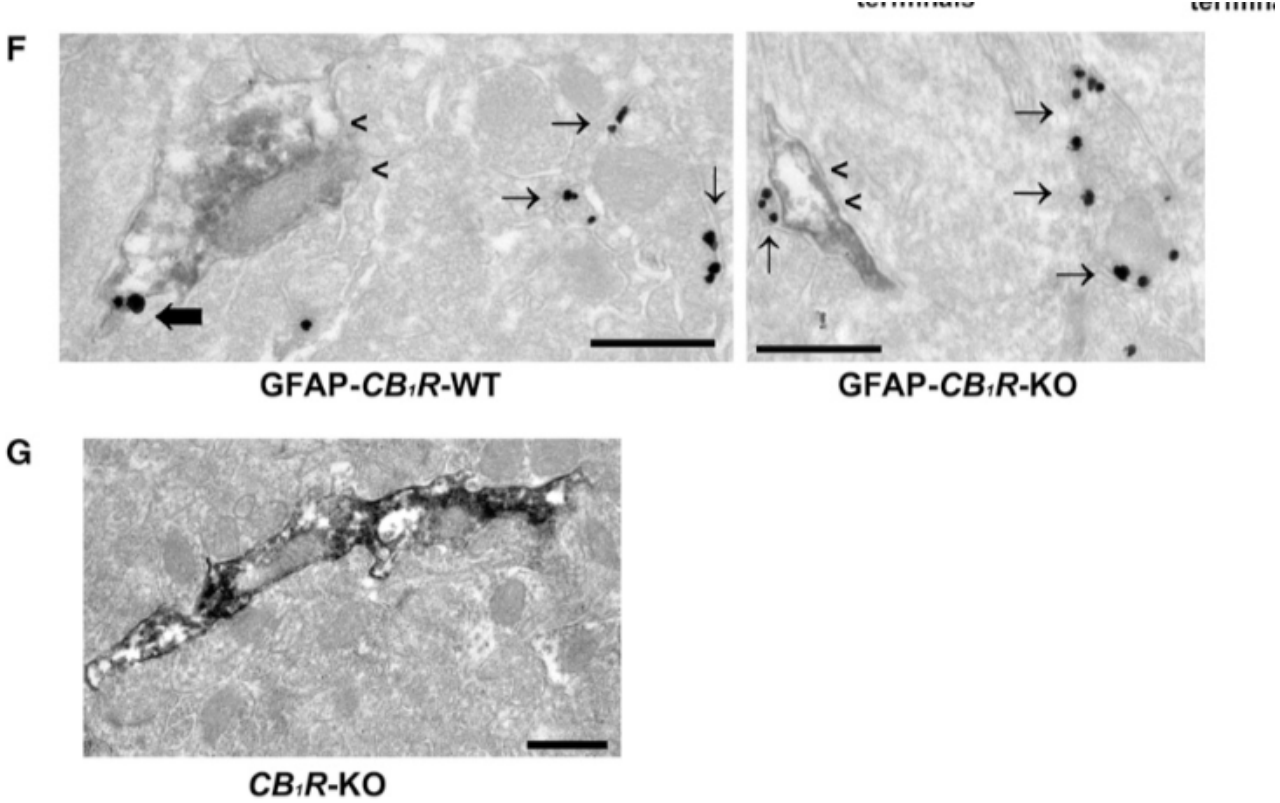
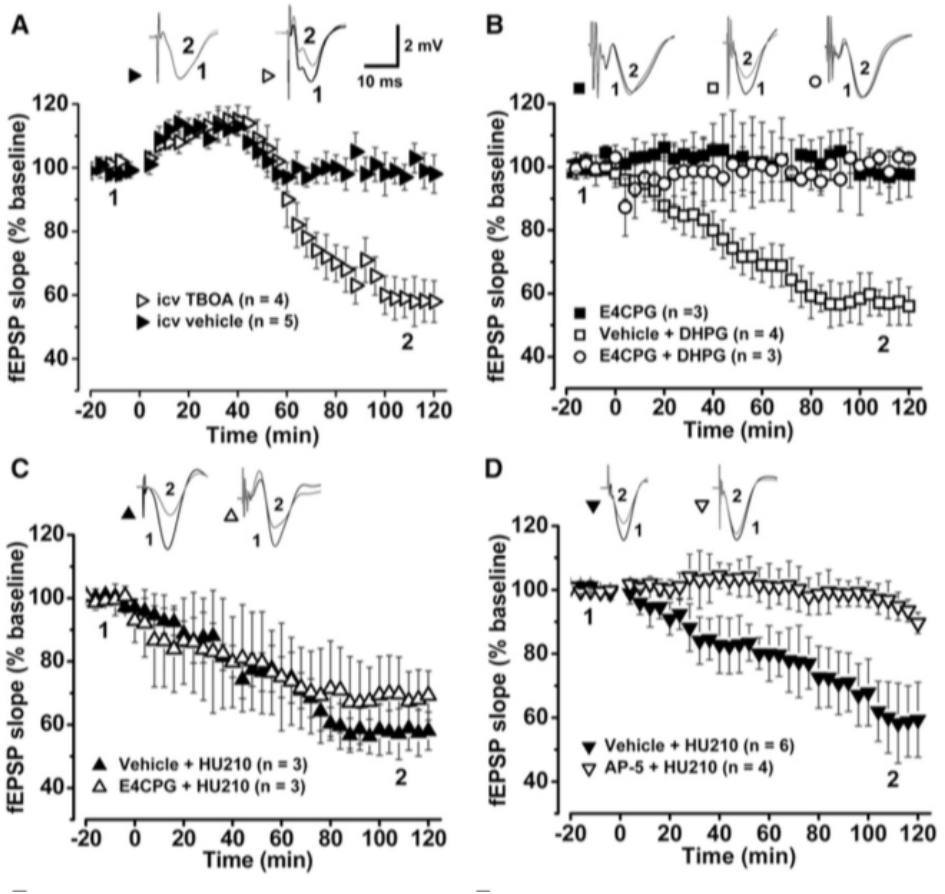
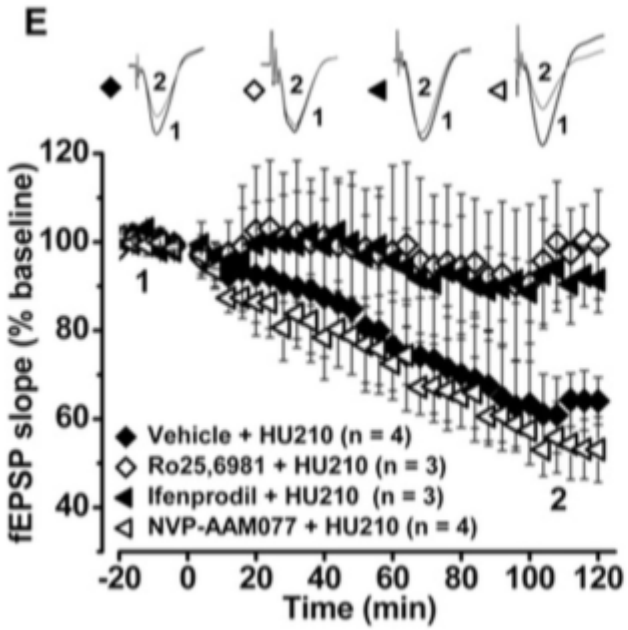
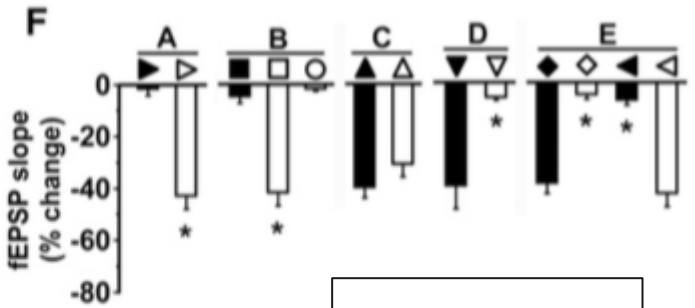


Cannabinoids Induce NMDAR Dependent LTD at CA3-CA1 Synapses Thus opposing LTP at these synapses







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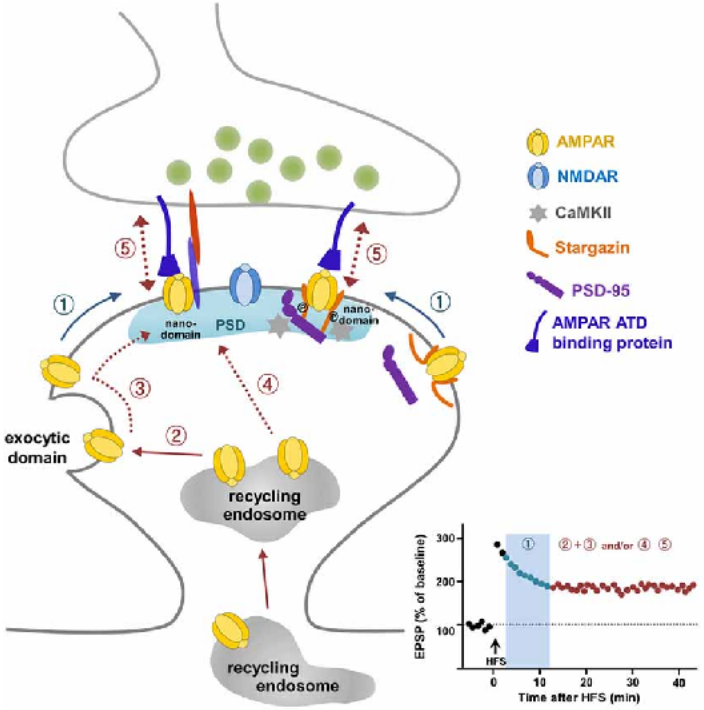
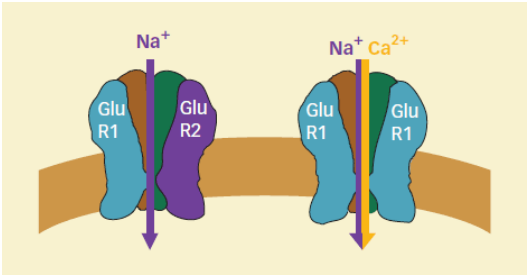
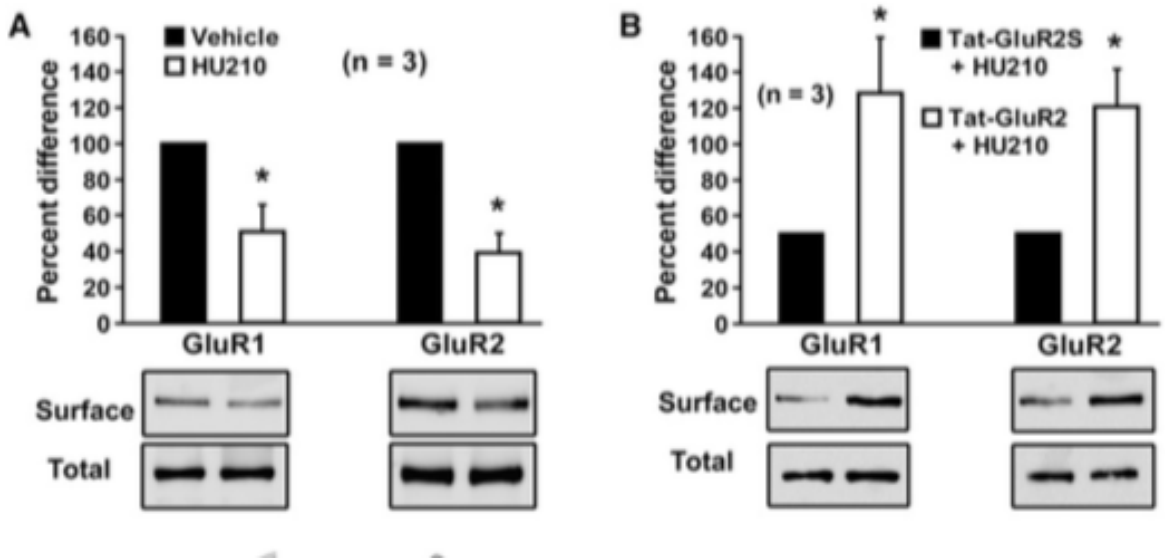
AMPA Receptor Recycling





Cannabinoids Induce AMPAR Endocytosis-Dependent Expression of CA1 LTD



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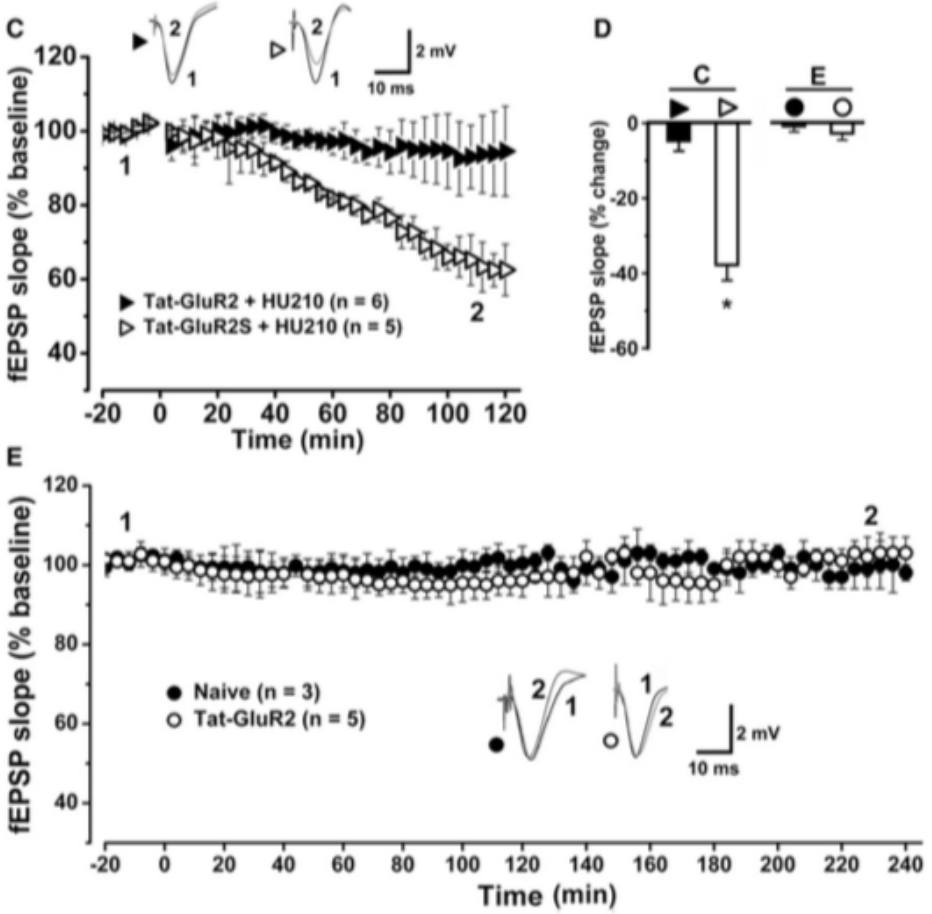
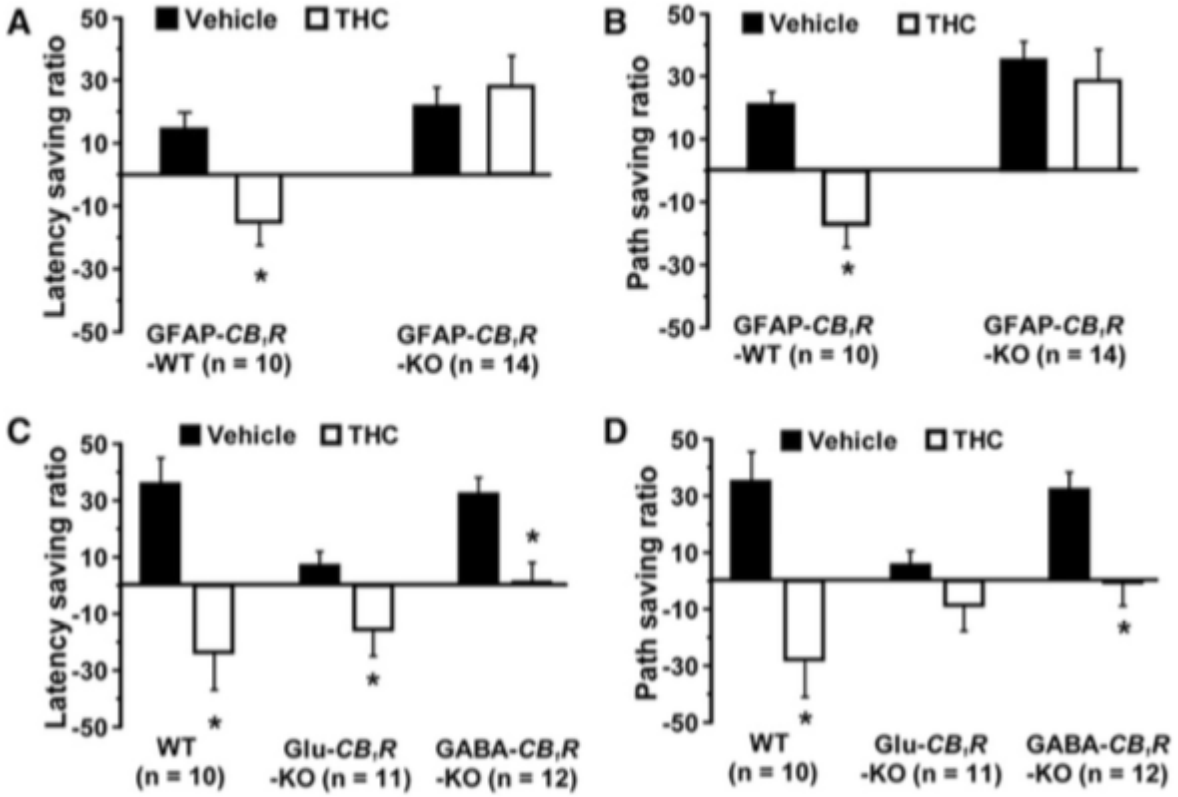


Astroglial CB1R, NMDAR, and AMPAR Mediate Cannabinoid Impairment of SWM



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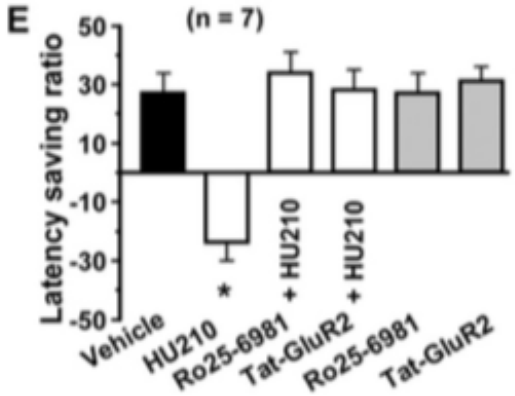
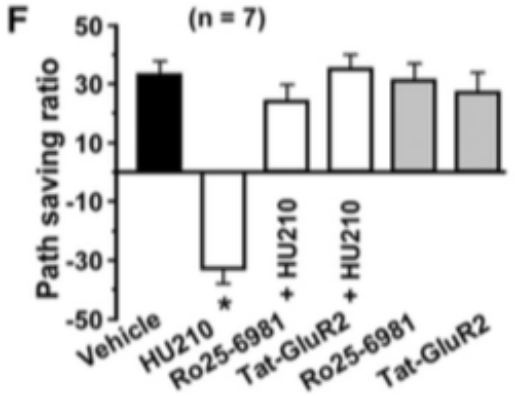
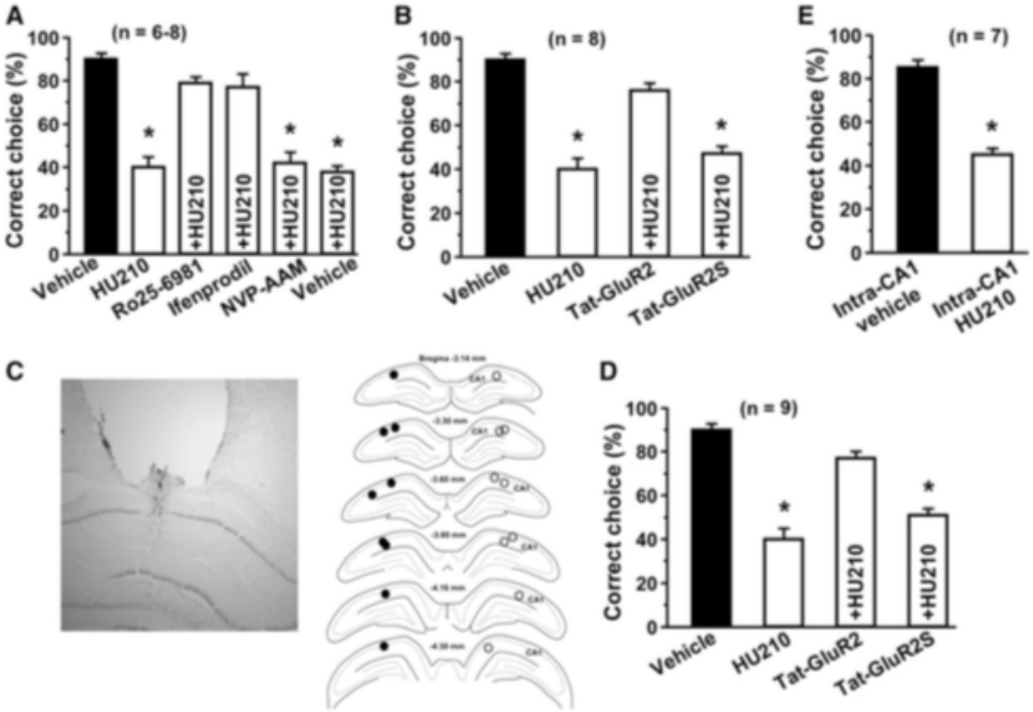
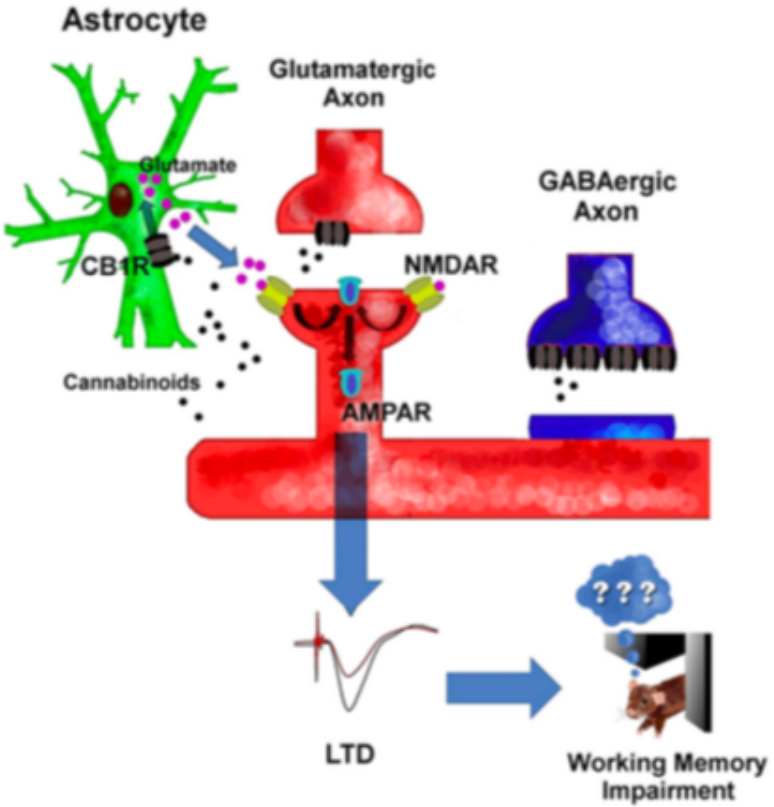




NMDAR and AMPAR Mediate Cannabinoid Impairment of SWM



Exogenous cannabinoids acting on the CB1R of the astrocytes
Impact the LTP of CA1 cells by changing glutamate levels that change the surface expression of AMPAR and NMDAR



Discussion

Common effects of cannabinoid intoxication in humans and animals, the **impairment of SWM**, is due to **activation of astroglial CB1R**

Cannabinoid exposure in vivo activates astroglial CB1R to increase ambient glutamate, which in turn activates **NR2B-containing NMDAR** to trigger **AMPAR internalization** at CA3-CA1 synapses.

In vivo exposure to exogenous cannabinoids **induced full CB-LTD** at excitatory CA3-CA1 synapses in both wild-type mice and mutant littermates **lacking CB1R in either CA1 glutamatergic or GABAergic neurons**

Questions