Of mice and men– the utility of animals for modelling cognition

Cognition - kɒgˈnɪʃ(ə)n/

the mental action or process of acquiring knowledge and understanding through thought, experience, and the senses.

synonyms: perception, discernment, awareness, apprehension, learning, understanding, comprehension, enlightenment, insight, intelligence, reason, reasoning, thinking, (conscious) thought

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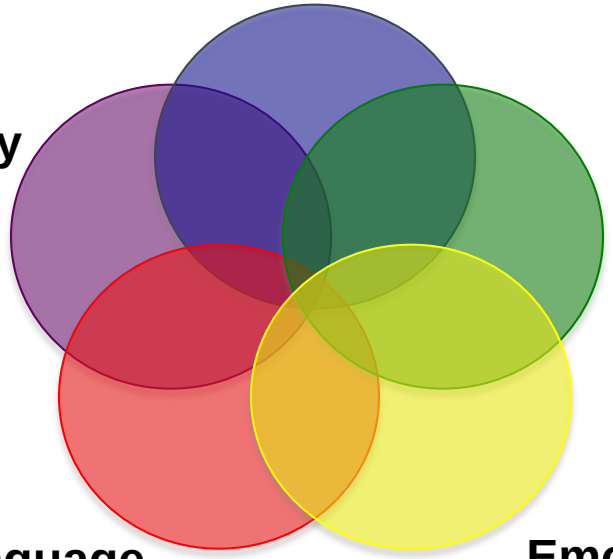
Caitlin E McOmish

Cognitive domains



Perceptual disturbance

Choice Impulsivity

Motor Impulsivity

Long/Short term

Spatial/Asssociative/…

Aggression

Anxiety

Vocalisation

Fear memory

Disruptions in cognition are a symptomatic of a breadth of neurodevelopmental, neurodegenerative, psychiatric, and neurological conditions

How can we further study the role of mechanisms underlying these disruptions?

Mouse models for dissecting domains

Probing circuits, regions, synapses, proteins and genes:

Manipulate a gene/protein
- knockouts and transgenics
- pharmacological

Manipulate a brain region/circuit
- lesion studies
- optogenetics

Manipulate environmental factors
- stress/deprivation
- immune activation
- enrichment

Decisions, decisions…

Male vs Female?

Murine gene?
Humanized?

Behavioural tests?

Knockout?
Conditional?

Reliability?

Reproducibility?

Strain?

Pharmacology? Dose?

Temporal control?
Spatial?

Aaargh!!! Why not just use humans? Or cells!

Male vs Female?

Murine gene?
Humanized?

Behavioural tests?

Knockout?
Conditional?

Reliability?

Reproducibility?

Strain?

Pharmacology? Dose?

Temporal control?
Spatial?

Advantages to rodent model

- Mammalian– substantial homology in genes and organisation of neural pathways. Humans and Mice have ~ 4/5ths of their genes in common.

- Relatively fast reproductive cycles, and, pragmatically, cost effective

- Notable findings in mice that have influenced medical 'best practice', and/or human research programs
  - Huntingtons
  - Adult Neurogenesis
  - Developmental Processes

Phenotyping Strategy

General Health Assessment

Are all variables controlled for? (housing, test order, parental care, blinded experimenter)

Sensory Ability Screen (sight, hearing, etc…)

Does strain affect the result?

Test for specific behavioural subdomains
(>2 per subdomain)

Is there any risk that the genetic manipulation impacts flanking genes? Can the phenotype be rescued by other means?

NPP: Do the above apply in the presence of the compounds used as well as baseline? Could the drugs be impacting a related behavioural subdomain?

Face validity, construct validity, predictive validity

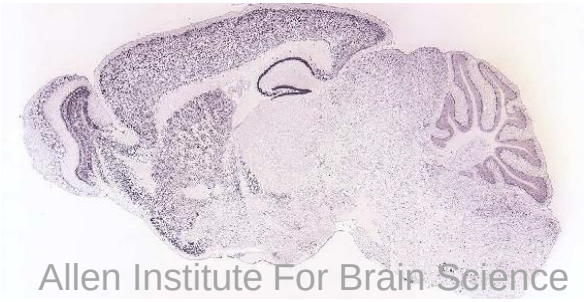
Cognitive Assessment in Mice

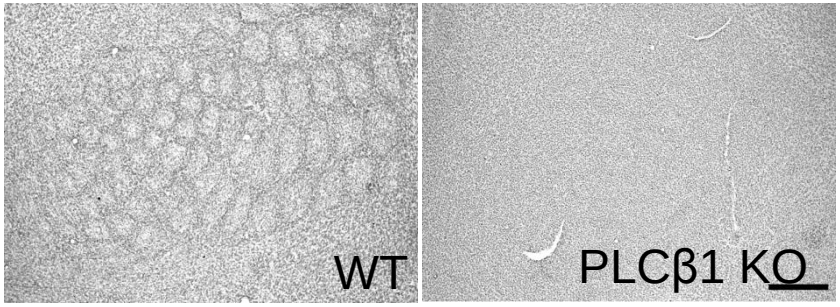
- ‘Traditional’
  - Morris Water Maze
  - Y maze
  - Fear Conditioning – Cued/Contextual
  - Novel Object/Novel Location Recognition
  - Operant/Goal directed behaviour/Motivation/Impulsivity
  - Prepulse Inhibition/Sensorimotor Gating
  - Porsolt’s Forced Swim Test/Tail Suspension Test
  - Novelty Suppressed Feeding
  - Light-Dark Box/Open Field/Elevated Plus Maze
- ‘Emerging’
  - Touchscreen Operant Tasks
  - Joystick Operant Tasks
  - New affective tests?

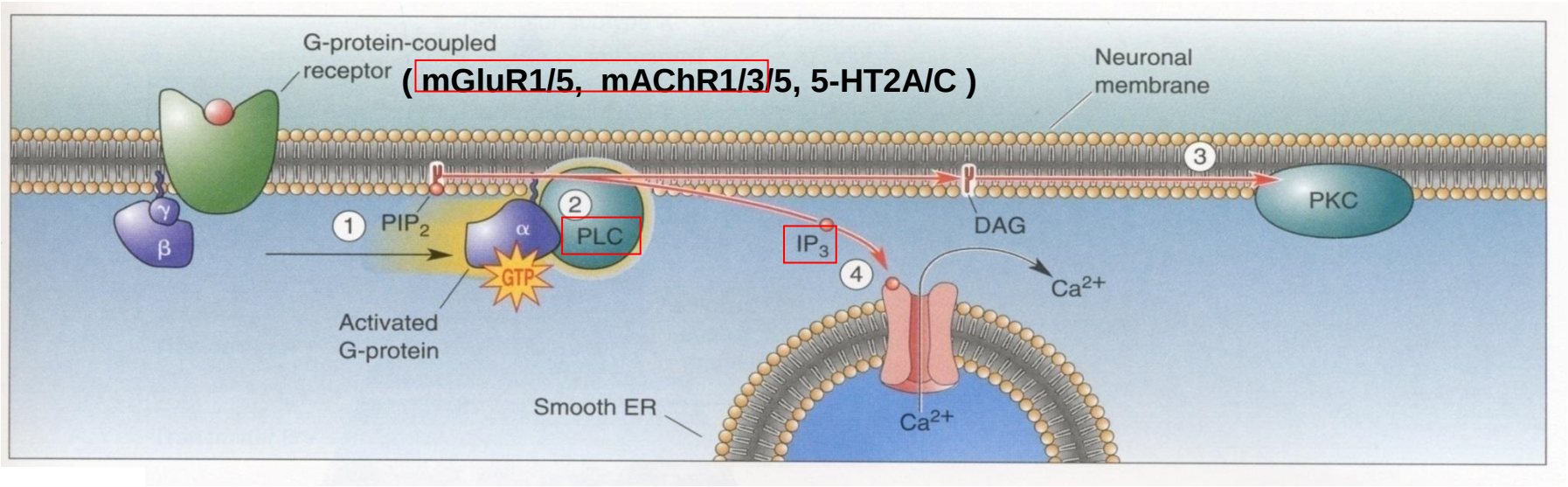
Using mouse models to identify novel mechanisms that translate to human

PLCβ1 and pathways regulating experience-dependent plasticity

- PLC-beta 1 plays a critical role in mediating development and plasticity

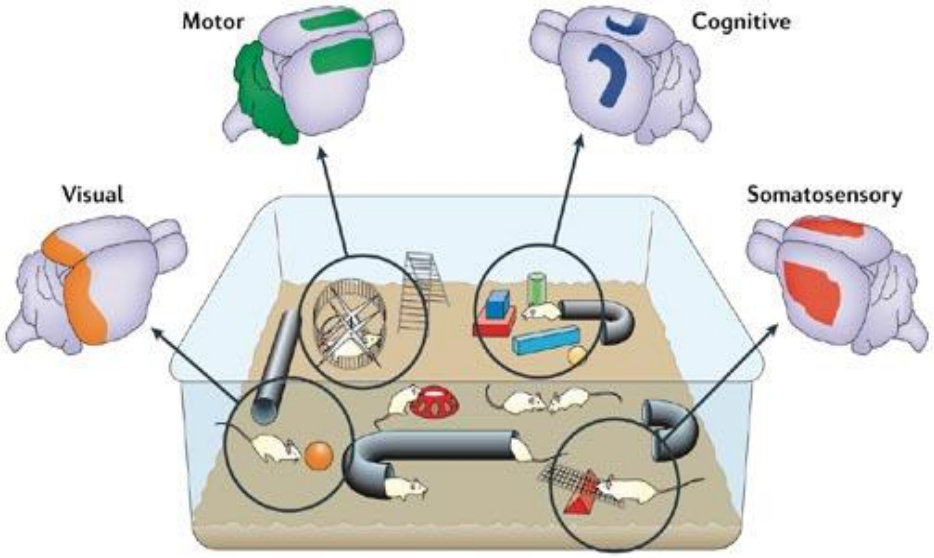






What impact do these processes have on behavioural function?

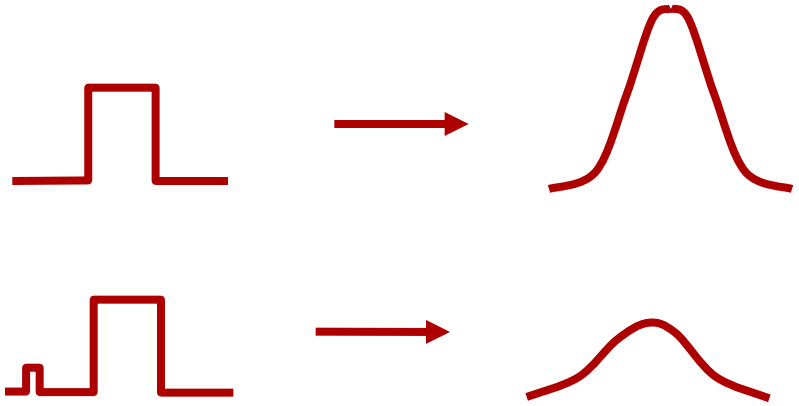
Do later behavioural manipulations influence the outcome?

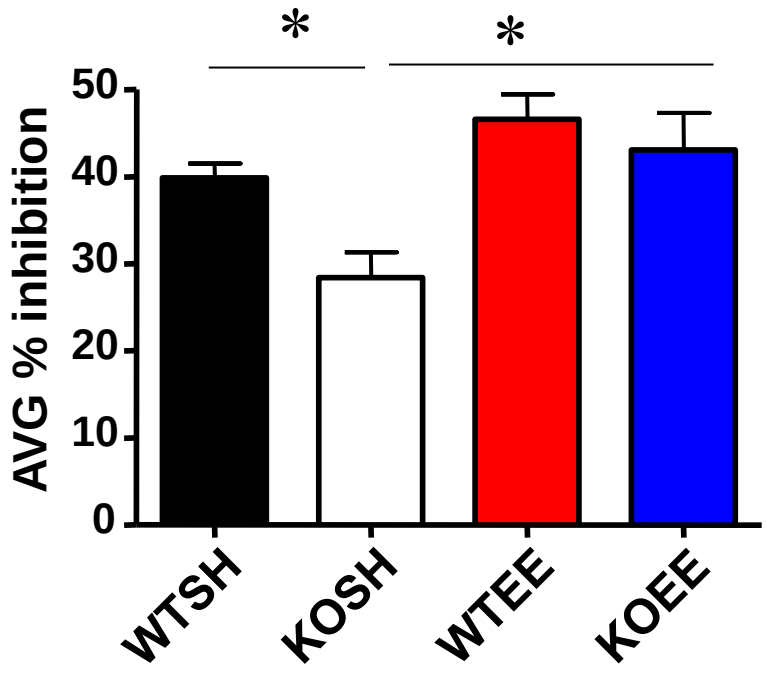


Nithianantharajah & Hannan, 2006, Nature Rev. Neurosci.

Startle and Sensorimotor Gating are impaired in PLCβ1 KO

Prepulse inhibition (PPI) of acoustic startle is a measure of sensorimotor gating used in animal models and humans (deficits have been found in schizophrenia)





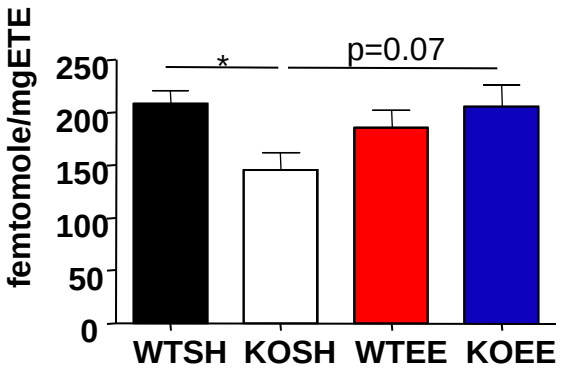
A PPI deficit is present in the PLCβ1 KO mice

EE rescues this deficit

McOmish et al., 2008, Mol. Psychiatry

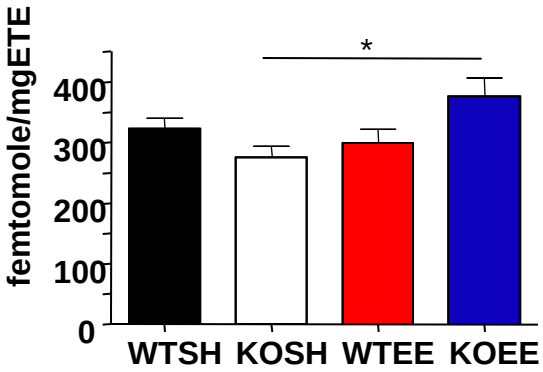
The PLC-β1 null mutation decreases M1/M4 receptor levels and this deficit is rescued by EE

Neocortex



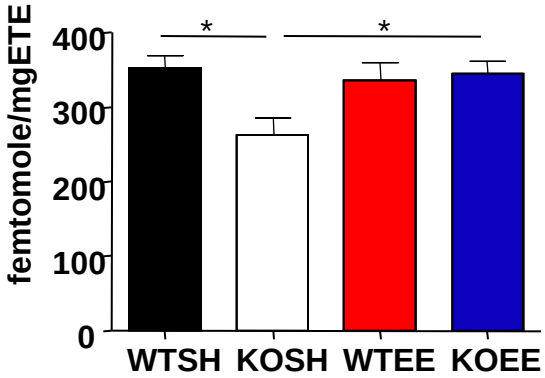
Genotype x Environment $p<0.05$

CA1



Genotype x Environment $p<0.05$

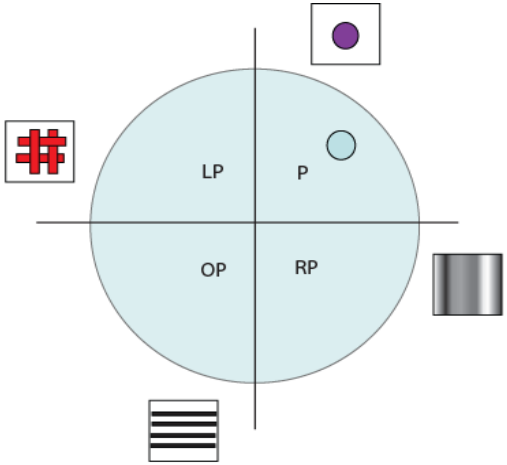
Dentate Gyrus

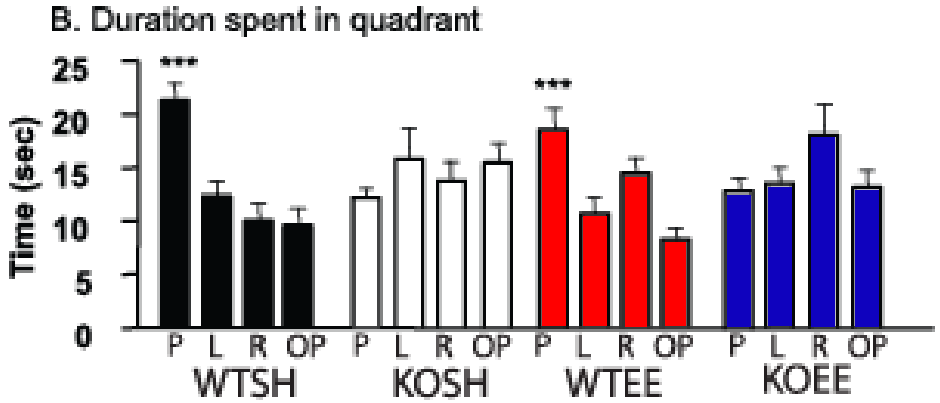


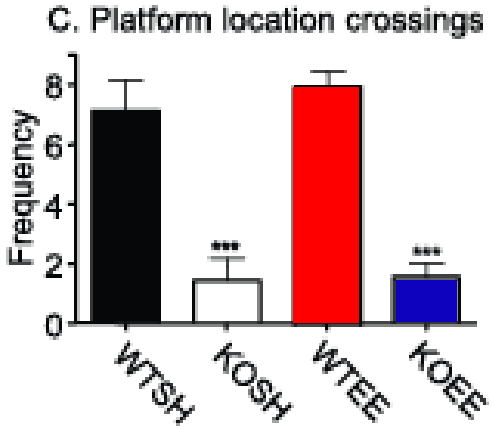
Genotype x Environment $p<0.05$

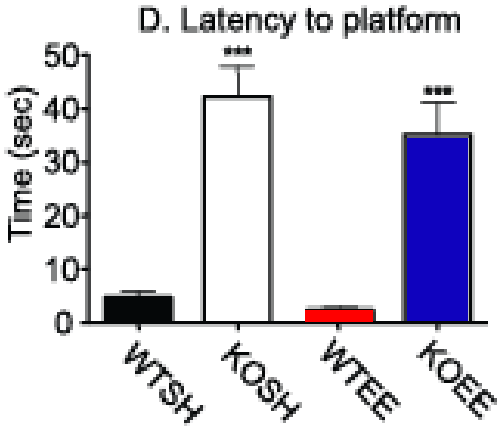
McOmish et al., 2008, Mol. Psychiatry

Hippocampal-dependent cognitive deficits in PLC-β1 KO



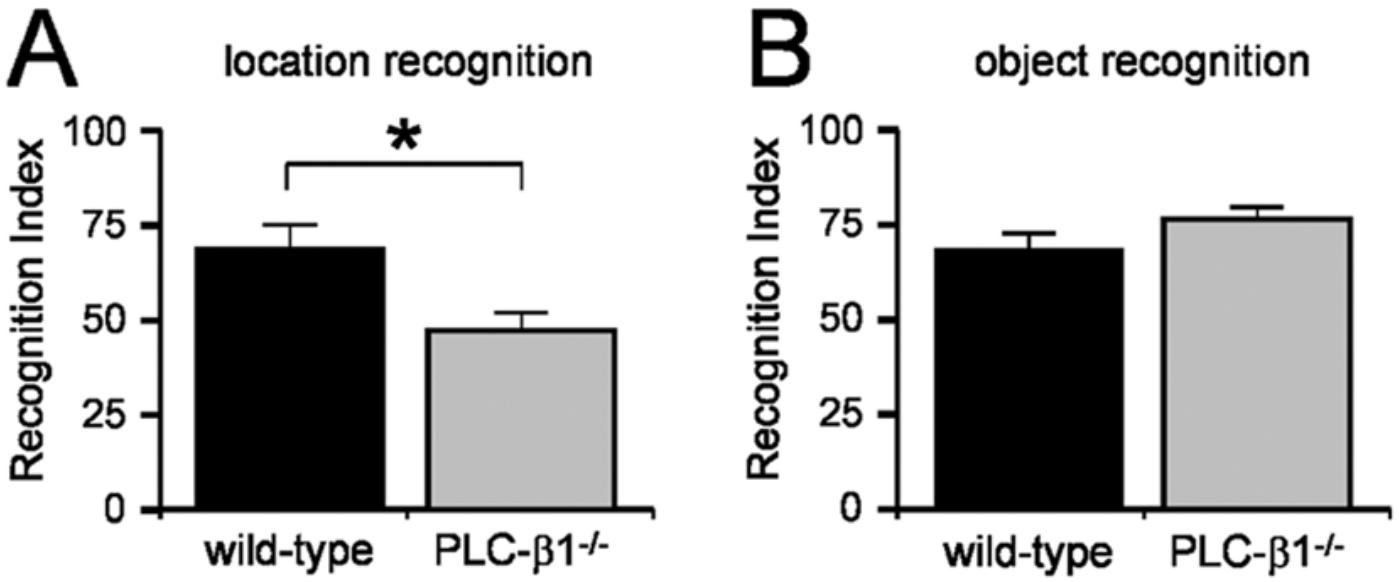






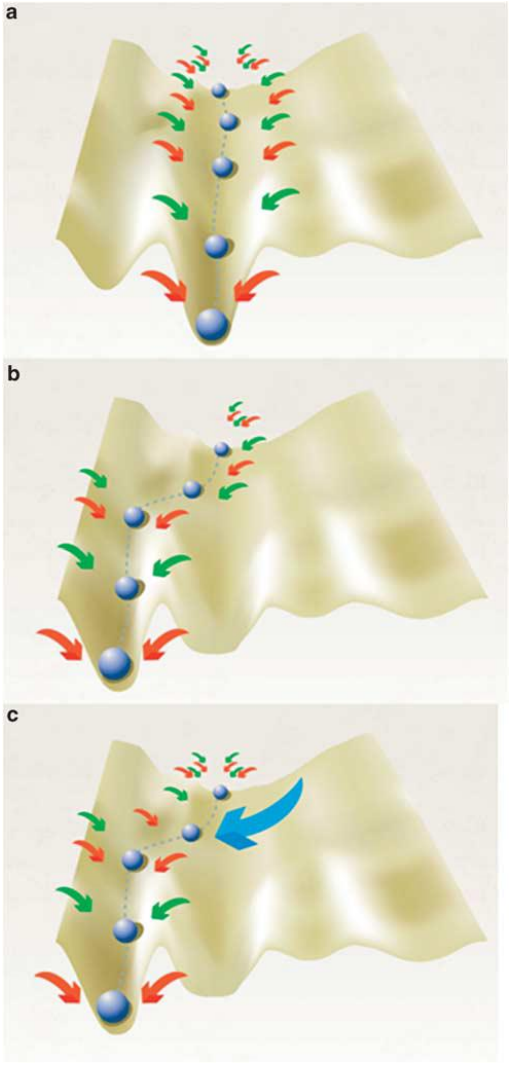
McOmish, Burrows et al., 2008, Mol. Psychiatry

Specific deficits in hippocampal-dependent spatial memory in PLC-β1 KO



Manning, Ransome, Burrows et al., 2012, Hippocampus

GxE interactions and 'experience expectant' brain development



Normally canalized brain development via genetic/environmental instructional vectors

Decanalization due to absence of 'expected' instructions (e.g. environmental stimuli)

Decanalization due to 'unexpected' instruction (e.g. major stressor)

McGrath, Hannan, Gibson, 2011, Transl. Psychiatry

Findings from the PLC-b1 KO mouse

- Behavioural abnormalities reflective of disrupted developmental processes
- Phenotypes have relevance to SCZ, a neurodevelopmental disorder
- PLC-b1 is a signaling molecular regulated by a multitude of genes/proteins implicated in SCZ
- → are PLC-b1 levels impacted in the disease?

Aust N Z J Psychiatry. 2011 Feb;45(2):140-7. **Phospholipase C beta 1 expression in the dorsolateral prefrontal cortex from patients with schizophrenia at different stages of illness.**
Udawela M1, Scarr E, Hannan AJ, Thomas EA, Dean B.

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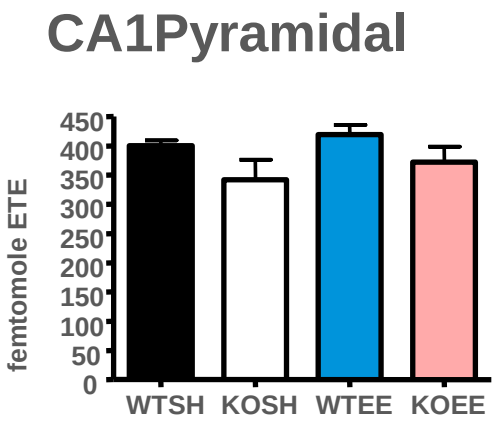
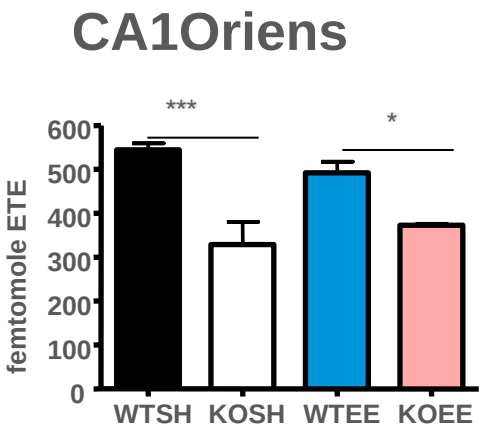
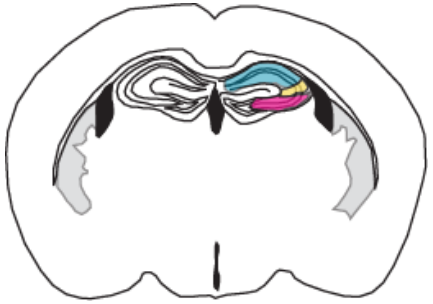
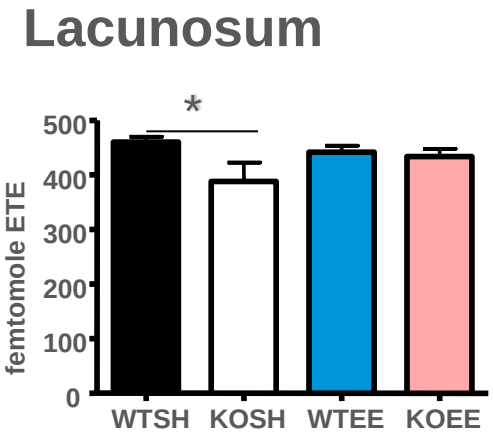
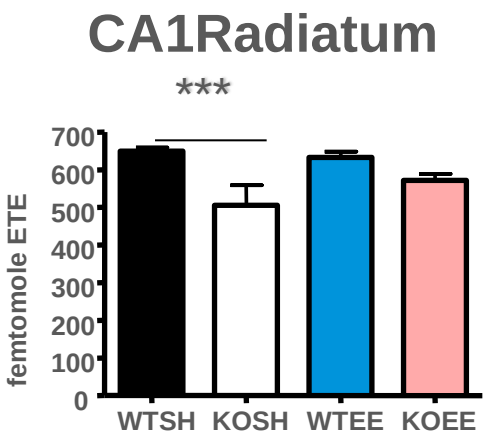
EE & NMDA receptors in PLCβ1 KO – CA1



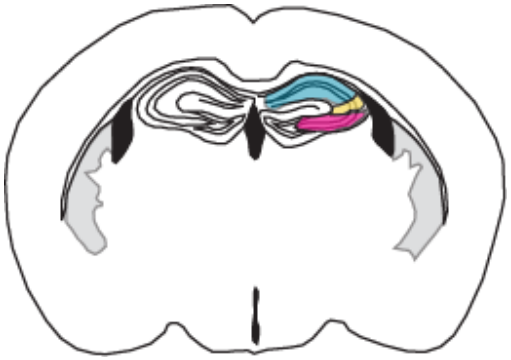


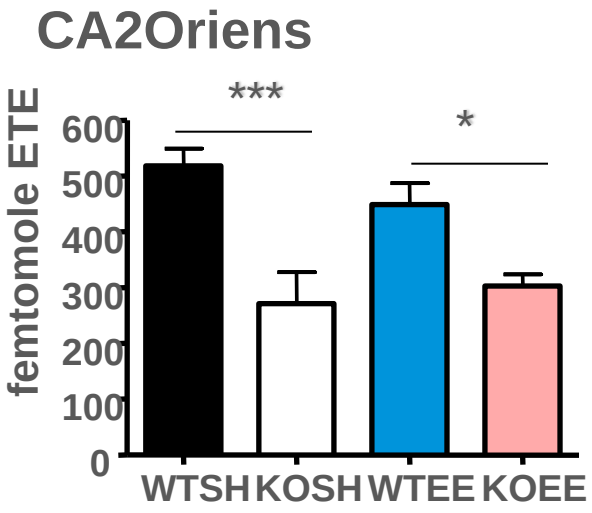


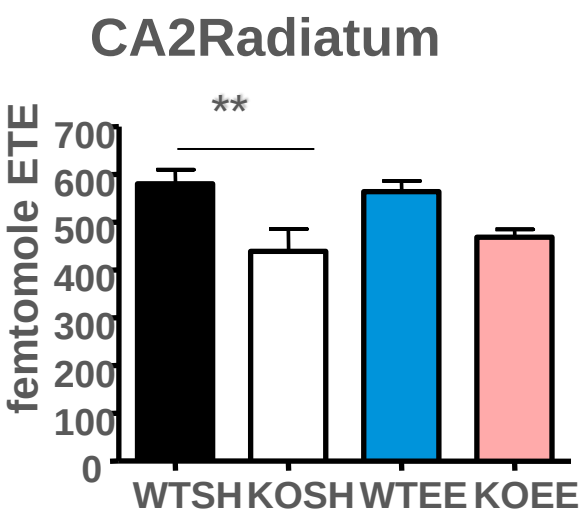


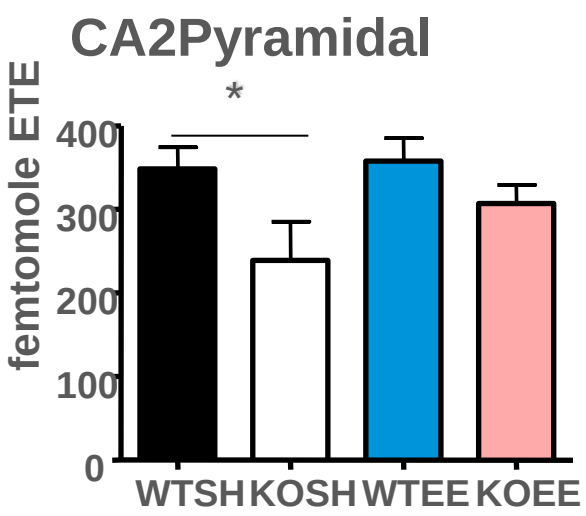


EE & NMDA receptors in PLCβ1 KO – CA2

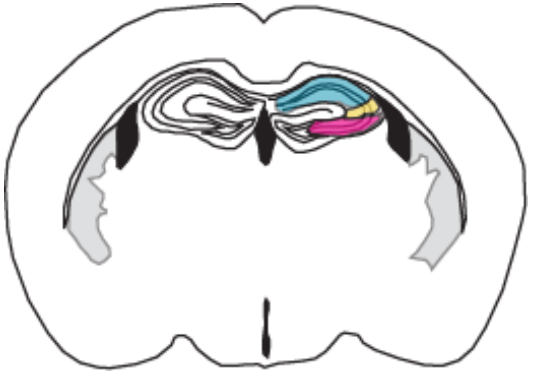




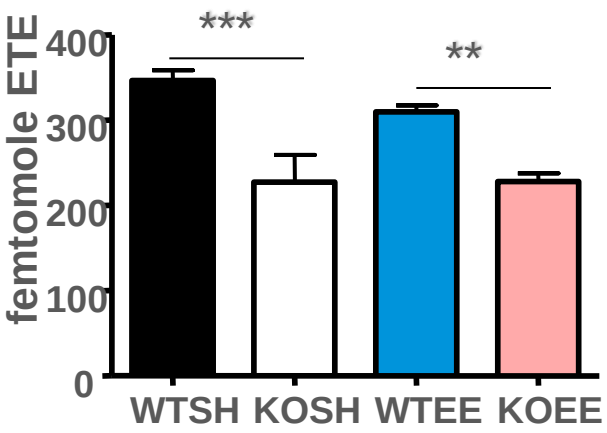




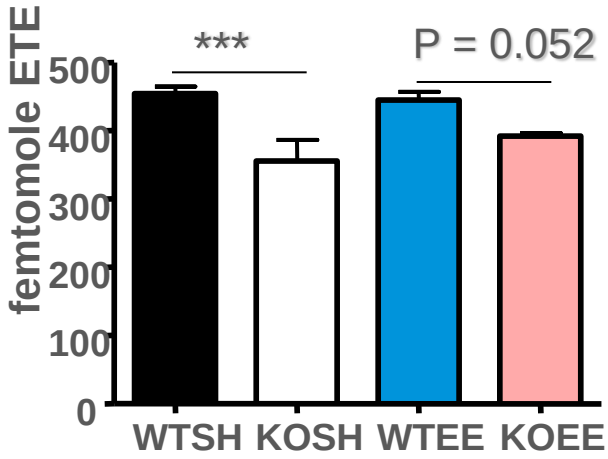
EE & NMDA receptors in PLCβ1 KO – CA3



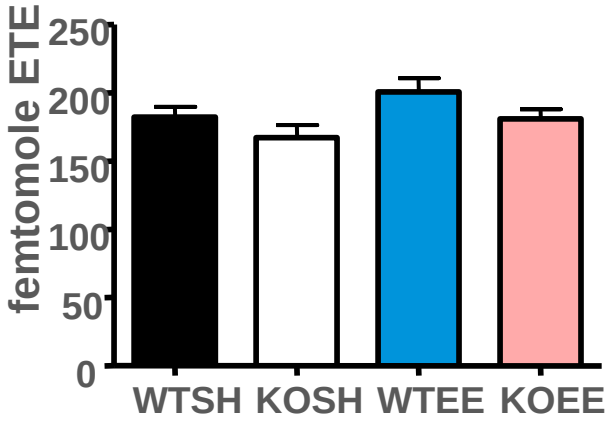
CA3Oriens



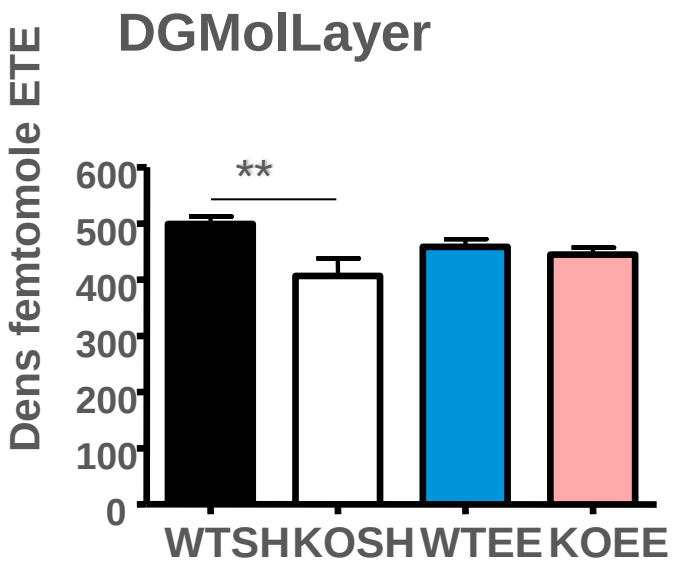
CA3Radiatum

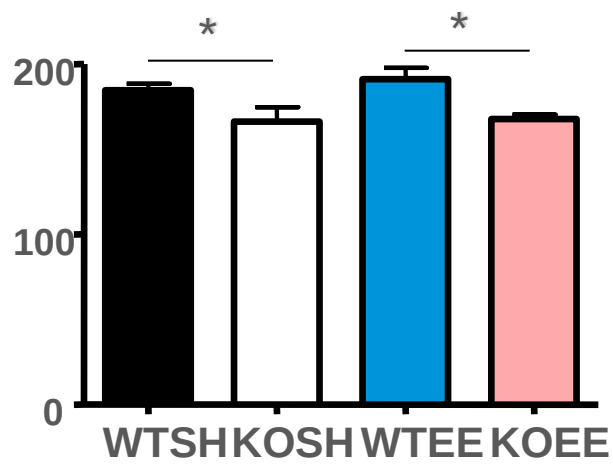


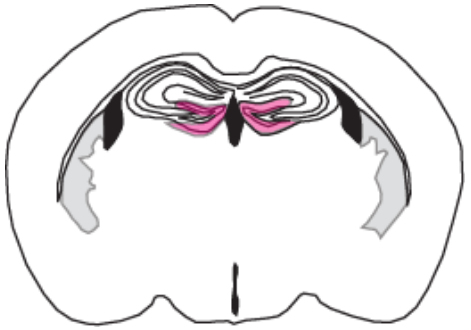
CA3Pyramidal



EE & NMDA receptors in PLCβ1 KO – DG







Is close enough good enough?

Knowing your system

PNAS

Genomic responses in mouse models poorly mimic human inflammatory diseases

Junhee Seok[a,1], H. Shaw Warren[b,1], Alex G. Cuenca[c,1], Michael N. Mindrinos[a], Henry V. Baker[c], Weihong Xu[a], Daniel R. Richards[d], Grace P. McDonald-Smith[e], Hong Gao[a], Laura Hennessy[f], Celeste C. Finnerty[g], Cecilia M. López[c], Shari Honari[f], Ernest E. Moore[h], Joseph P. Minei[i], Joseph Cuschieri[j], Paul E. Bankey[k], Jeffrey L. Johnson[h], Jason Sperry[l], Avery B. Nathens[m], Timothy R. Billiar[l], Michael A. West[n], Marc G. Jeschke[o], Matthew B. Klein[j], Richard L. Gamelli[p], Nicole S. Gibran[j], Bernard H. Brownstein[q], Carol Miller-Graziano[k], Steve E. Calvano[r], Philip H. Mason[e], J. Perren Cobb[s], Laurence G. Rahme[t], Stephen F. Lowry[r,2], Ronald V. Maier[j], Lyle L. Moldawer[c], David N. Herndon[g], Ronald W. Davis[a,3], Wenzhong Xiao[a,t,3], Ronald G. Tompkins[t,3], and the Inflammation and Host Response to Injury, Large Scale Collaborative Research Program[4]

Female vs male

COMMENT

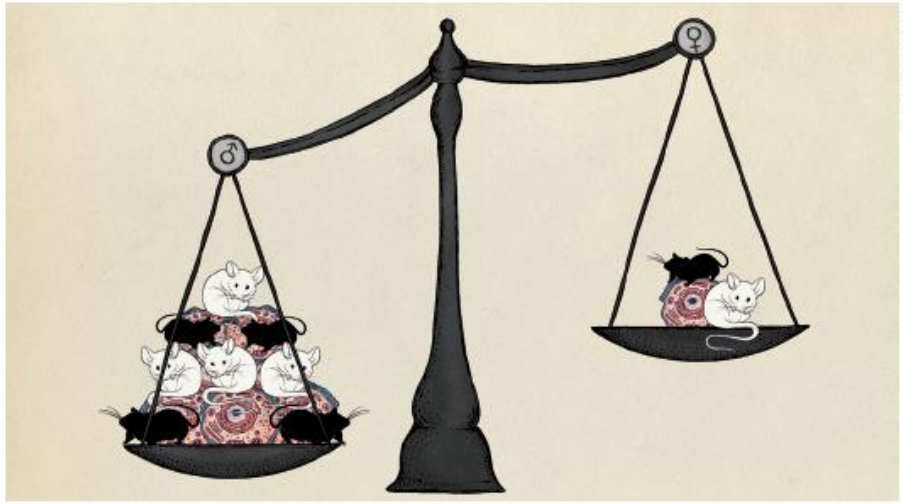


ILLUSTRATION BY KATE SCOTT

NIH to balance sex in cell and animal studies

Janine A. Clayton and **Francis S. Collins** unveil policies to ensure that preclinical research funded by the US National Institutes of Health considers females and males.

Olfactory exposure to males, including men, causes stress and related analgesia in rodents

Robert E Sorge[1,2,8], Loren J Martin[1,8], Kelsey A Isbester[1], Susana G Sotocinal[1], Sarah Rosen[1], Alexander H Tuttle[1], Jeffrey S Wieskopf[1], Erinn L Acland[1], Anastassia Dokova[1], Basil Kadoura[1], Philip Leger[1], Josiane C S Mapplebeck[1], Martina McPhail[3], Ada Delaney[4], Gustaf Wigerblad[4], Alan P Schumann[2], Tammie Quinn[2], Johannes Frasnelli[5,6], Camilla I Svensson[4], Wendy F Sternberg[3] & Jeffrey S Mogil[1,7]

- Experimenters AND subjects

- What is the right model?

- Are mice the best option or should we be using different animals for each subdomain that we aim to assess.

- Where does the line between pragmatism and good science get drawn?
  - Behavioural and pharmacological validity
  - Understanding the tests and appropriate interpretation

Mouse models

Manipulate a gene/protein
- knockouts and transgenics
- pharmacological

Manipulate a brain region/circuit
- lesion studies
- optogenetics

Manipulate environmental factors
- stress/deprivation
- immune activation
- enrichment

Mouse models

Manipulate a gene/protein
- Constitutive or Regulated
- Revalidate the line

Manipulate a brain region/circuit
- Non specific
- Comparable to in vivo?

Manipulate environmental factors
- stress/deprivation
- immune system similarity?
- What is the baseline?

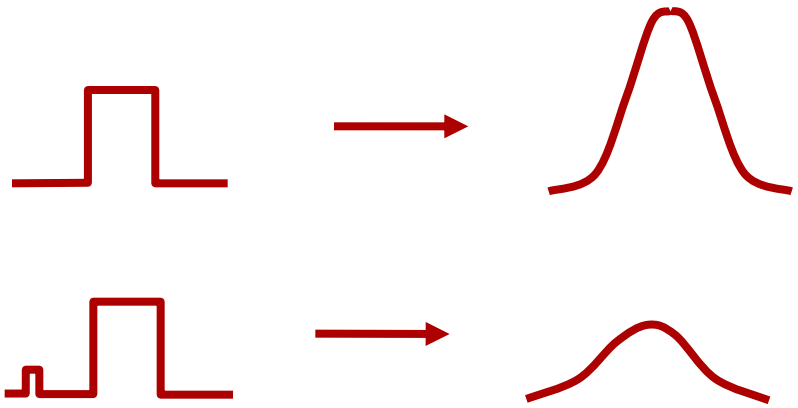
- Are mice the right model for the particular questions?
- Would rats be better? Songbirds? Owls? Kimodo Dragons?

- How many Tests do you need to draw a conclusions (counting both ruling something in AND out), what if the results diverge?

- Should we be reductionist (modelling single endophenotypes) or should we expect co-morbidity as is seen in human function and disease?

- What is the value and validity of humanised genes in a murine system? Pros and cons?

Startle and Sensorimotor Gating are impaired in PLCβ1 KO



Decreased startle response and a sensorimotor gating deficit is present in the PLCβ1 KO mice