Integrative analysis of the effects of cellular and organismal perturbations on the transcriptomes of hippocampal subfields

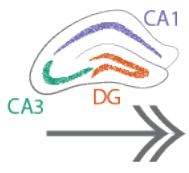
Rayna Harris | Hsin-Yi Kao | Juan Marcos Alarcon | Hans Hofmann | Andre Fenton

June 15, 2017

Advances in hippocampal neurogenomics

Gene expression studies at the level of single neurons may be especially important for understanding nervous system structure and function because of neuron-specific functionality and plasticity.

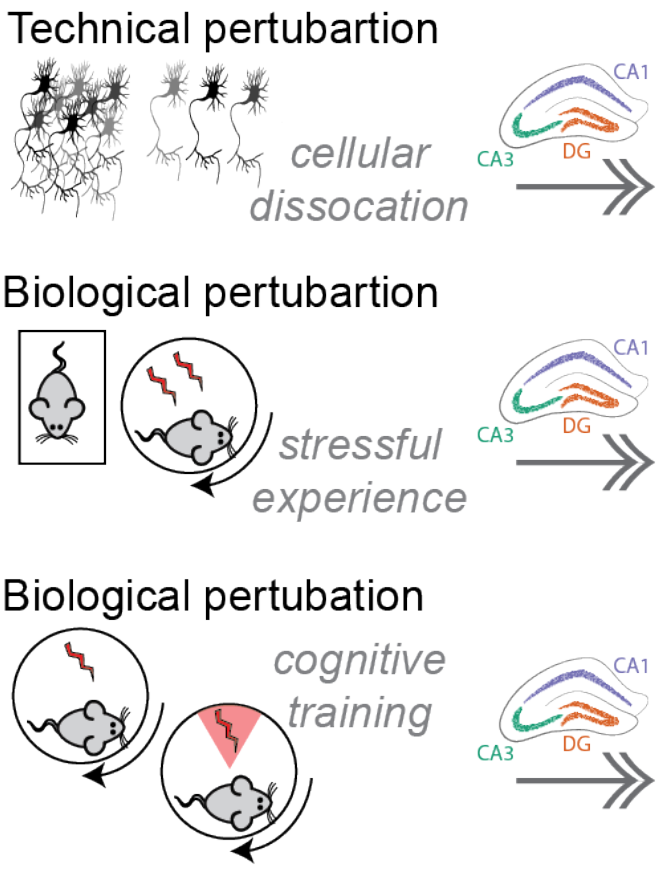
public RNA-seq data + primary RNA-seq data



robust patterns of hippocampal subfield-specific gene expression

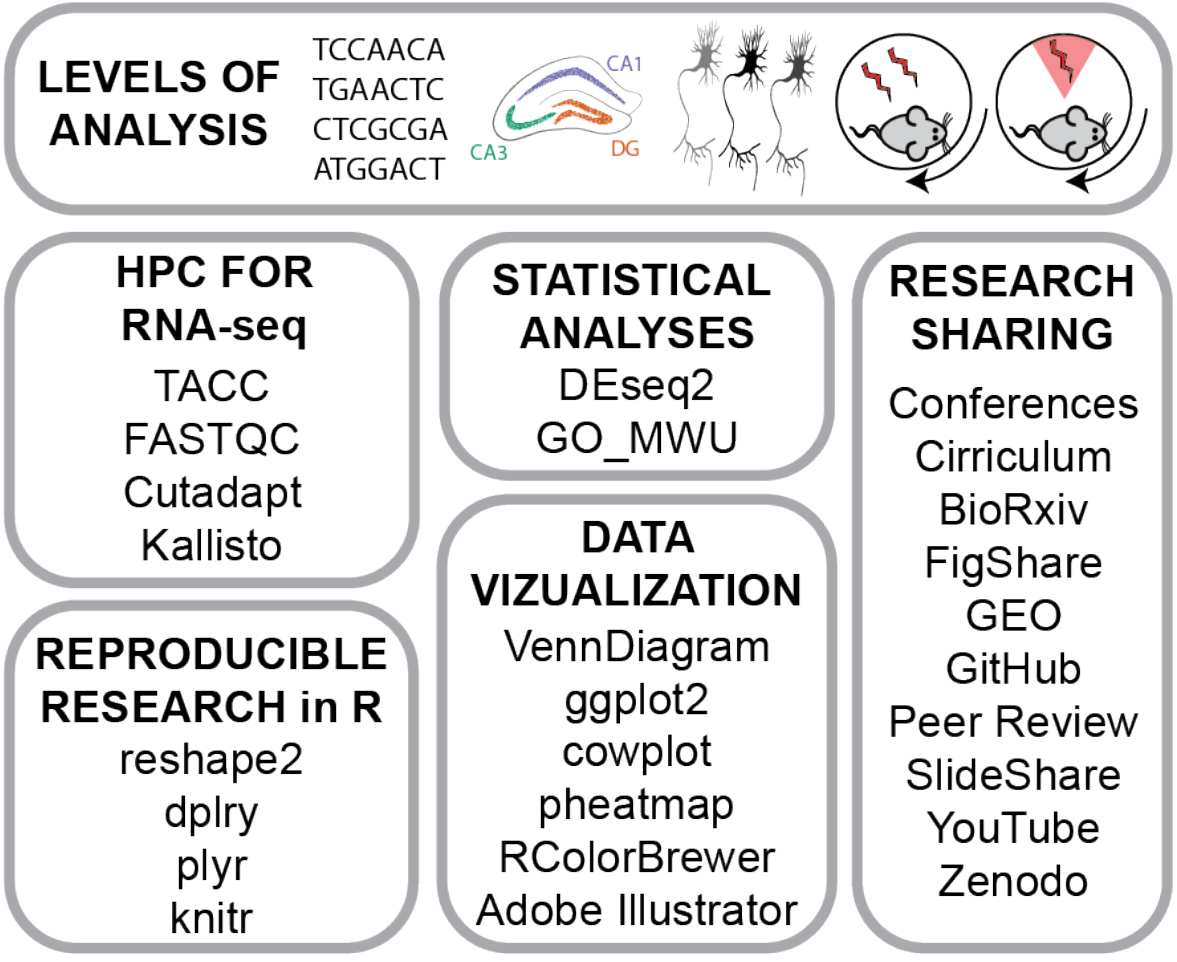
Objective

Here, we examine the effect of cellular dissociation on gene expression in the mouse hippocampus. We also determine to which extent such changes might confound studies on the behavioral and physiological functions of hippocampus.



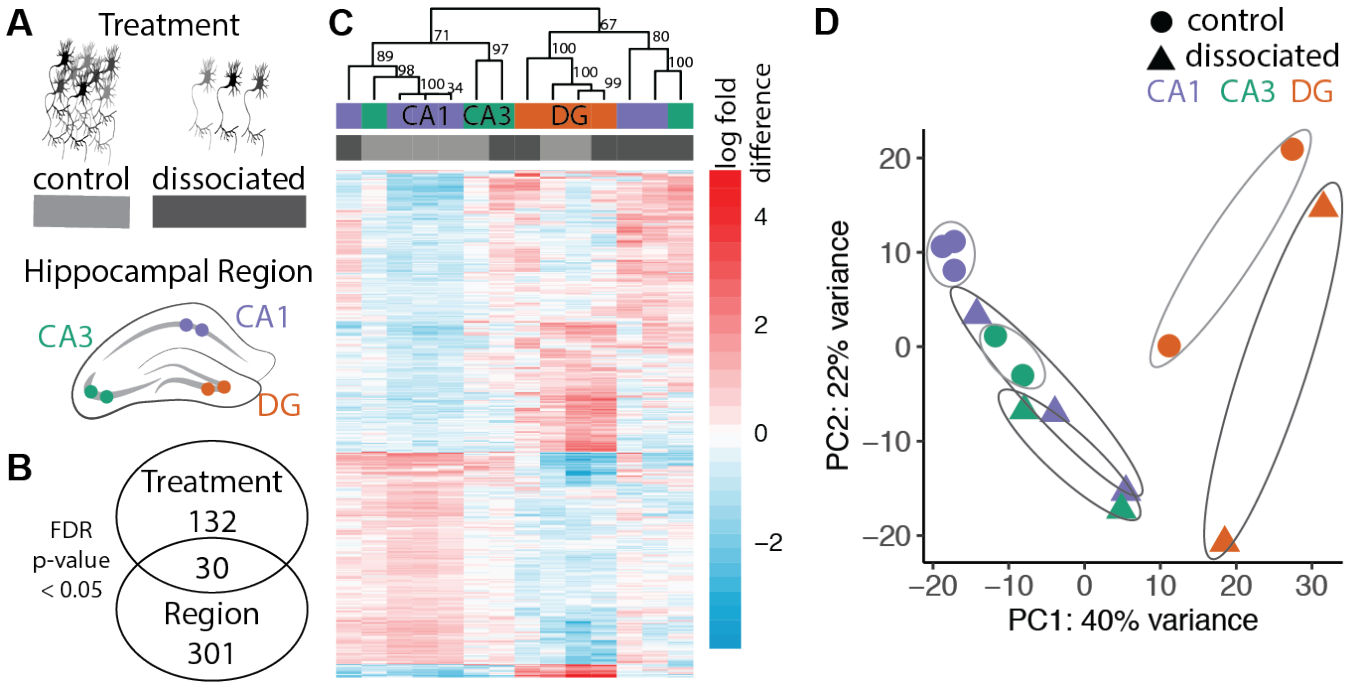
Materials & Methods

We processed dentate gyrus (DG), CA3, and CA1 hippocampus subfields tissue samples for RNA sequencing to quantify sub-field specific gene expression. This is a rough overview of the workflow.

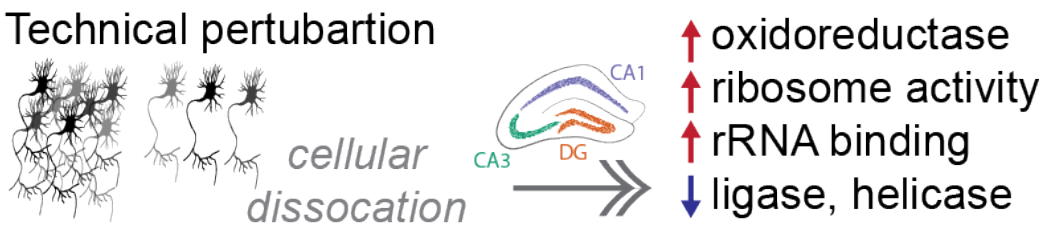


Technical: Cellular dissociation

We find that 1% of the hippocampal transcriptome responds to the process of cellular dissociation.

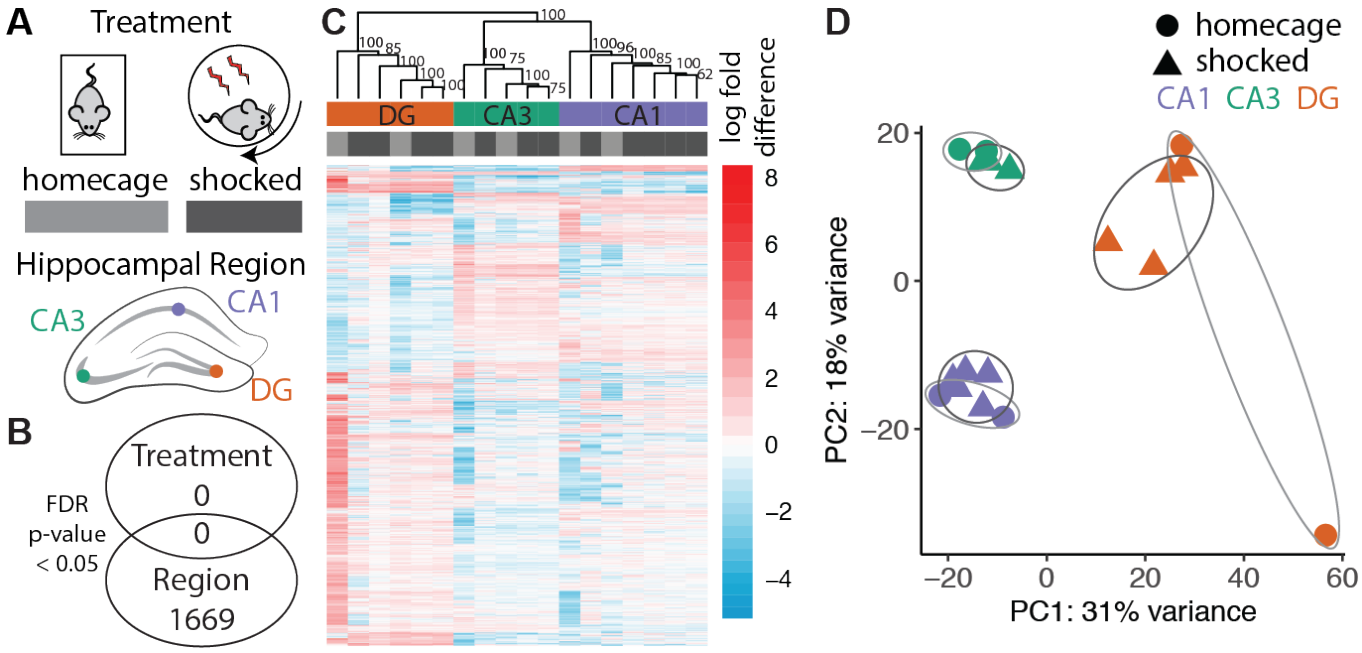


The genomic plasticity is specific to these molecular processes.

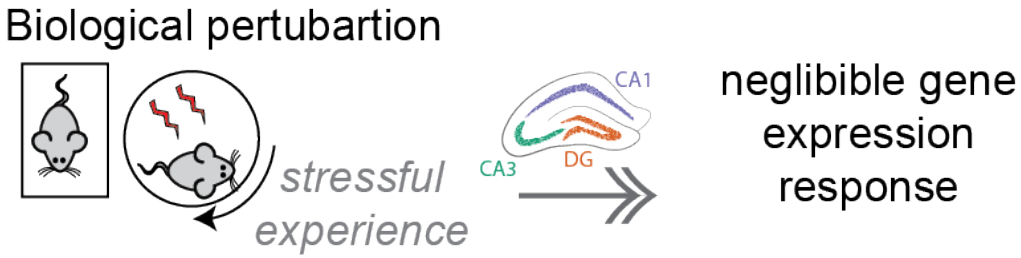


Biological: Stress

No genes or molecular pathways were differntially expressed between samples from non-stress and stressedmice.

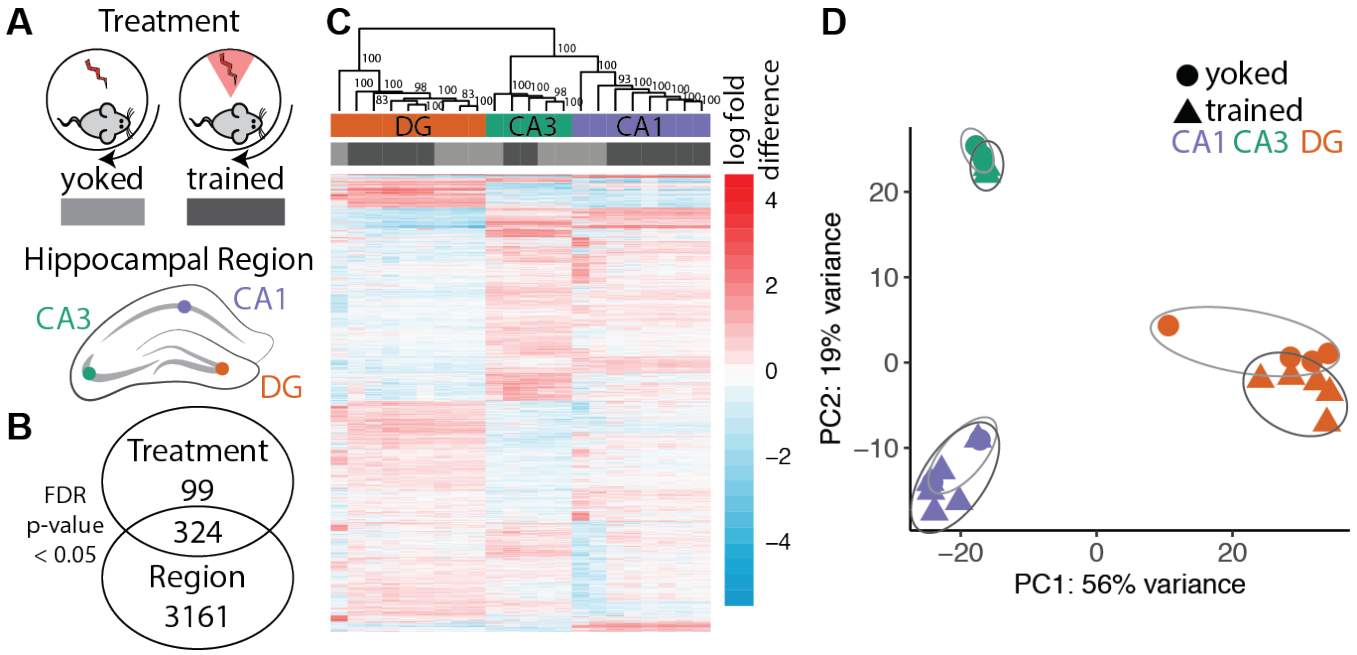


The hippocampus does not exhbit genomic plasticity in response to sress.

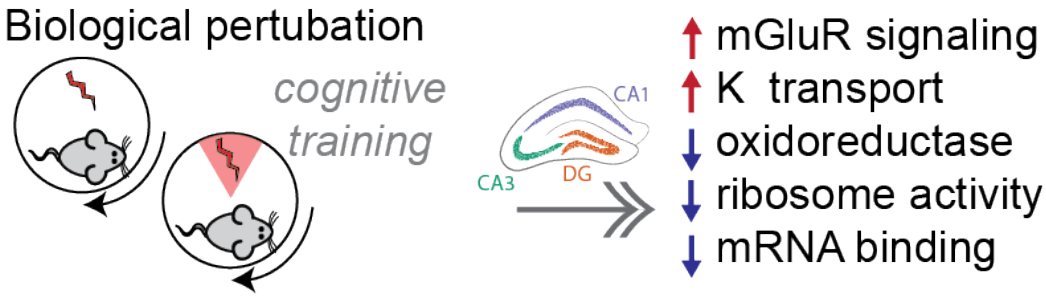


Biological: Cognitive training

Cognitive training does incuce genomic plastcity.



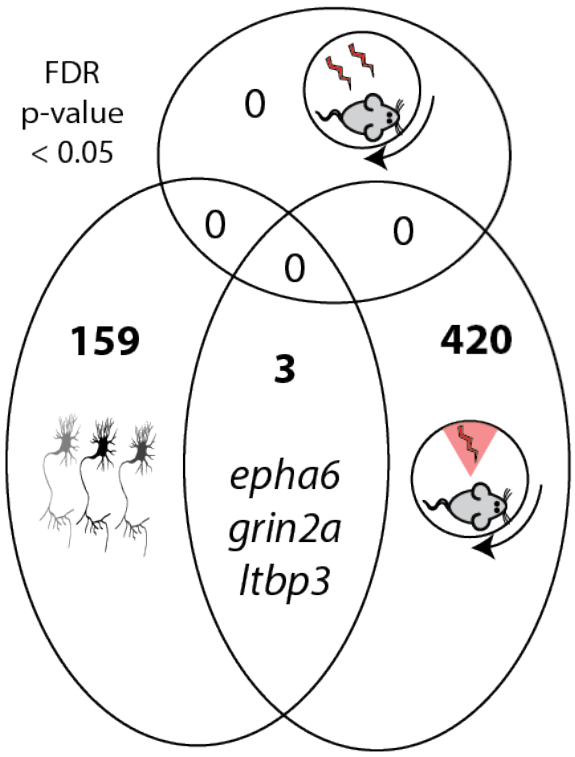
The genomic plasticity is specific to these molecular processes.



Integrative analysis

There was some overlap in the genomic response to different manipulation. These findings of the concordant and discordant effects should inform the design of future neural transcriptome studies.

A. Treatment-incuced gene expression changes



B. Dissociation-induced molecular functions

74/325 structural molecule
42/88 structural constituent of ribosome
15/55 rRNA binding
8/128 helicase
19/245 ligase, forming carbon–nitrogen bonds
32/433 ligase
12/62 oxidoreductase, acting on NAD(P)H
50/596 oxidoreductase
10/36 oxidoreductase, acting on NAD(P)H, quinone or similar
11/66 hydrogen ion transmembrane transporter

UP
Down
p < 0.00001
p < 0.0001
p < 0.001

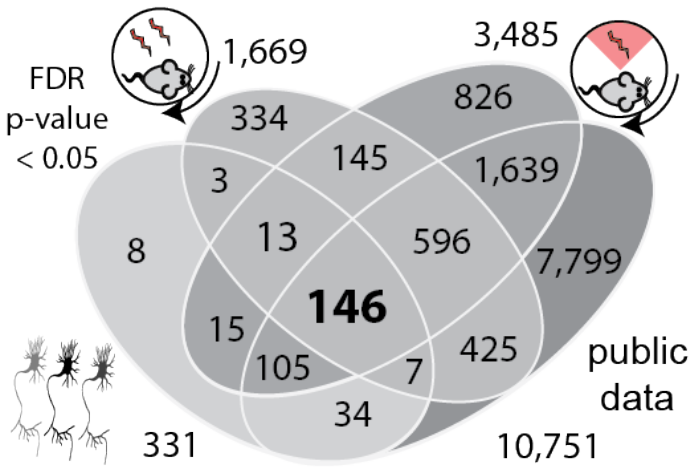
C. Cognitive training -induced molecular functions

180/801 poly(A) RNA binding
20/87 structural constituent of ribosome
10/36 oxidoreductase, acting on NAD(P)H, quinone or similar
11/25 glutamate receptor
128/801 signal transducer
105/678 receptor
13/66 hydrogen ion transmembrane transporter
143/735 transmembrane transporter
80/357 calcium ion binding

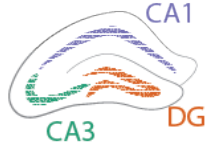
Meta analysis

We identified robust subfield-specific gene expression patterns that are consistent with those identified stored in public databases and repositories.

A. Shared region-specific expression



B. Enriched region-specific cellular compartments and molecular functions



17/522 synapse part
10/210 postsynaptic density
28/1239 neuron part
11/237 synaptic membrane
15/506 synapse

$p < 0.001$
$p < 0.01$
$p < 0.05$

21/818 integral component of plasma membrane

6/65 Rho guanyl–nucleotide exchange factor
7/110 Ras guanyl–nucleotide exchange factor
4/26 calcium channel regulator
4/24 proteoglycan binding

Conclusion

By determining the extent to which the process of cellular disassociation and stressful experience impacts our ability to correctly detect cognitive perturbations to gene expression, this study sets a baseline for future studies aimed at understanding molecular function in hippocampus and behavior.