

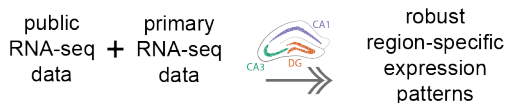
Integrative analysis of the effects of cellular and organismal perturbations on the transcriptomes of hippocampal subfields

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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.



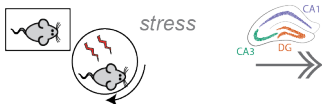
Objective

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.

Technical manipulation



Biological manipulation

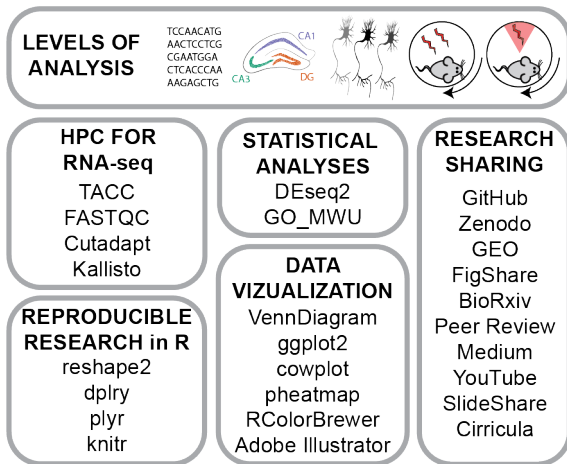


Biological manipulation



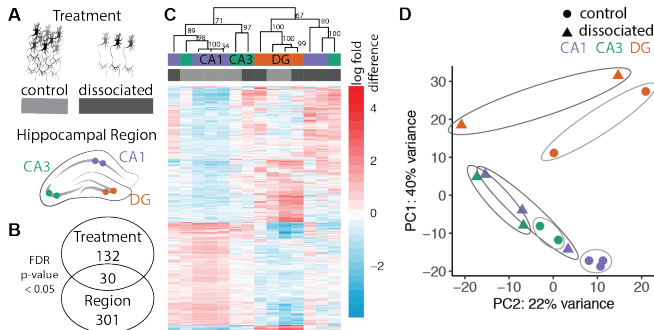
Materials & Methods

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.



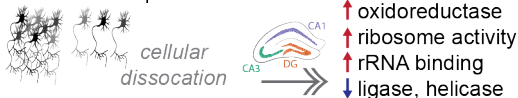
Technical: Cellular dissociation

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



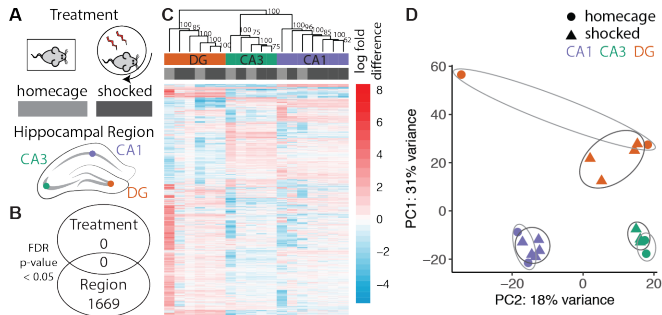
The genomic plasticity is specific to these molecular processes.

Technical manipulation



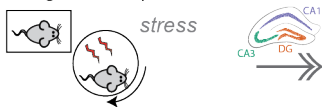
Biological: Stress

No genes or molecular pathways were differentially expressed between samples from non-stress and stressed mice.



The hippocampus does not exhibit genomic plasticity in response to stress.

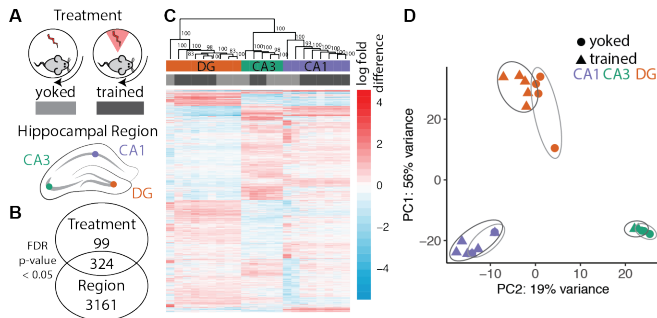
Biological manipulation



negligible gene
expression
response

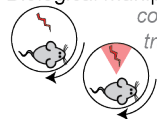
Biological: Cognitive training

Cognitive training does induce genomic plasticity.



The genomic plasticity is specific to these molecular processes.

Biological manipulation



cognitive training

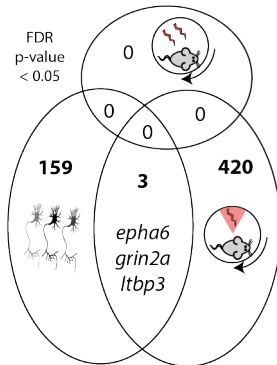


- ↑ mGluR signaling
- ↑ K transport
- ↓ oxidoreductase
- ↓ ribosome activity
- ↓ mRNA binding

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-incuded 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

$p < 0.00001$
 $p < 0.0001$
 $p < 0.001$

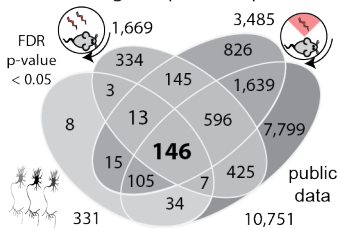
C. Cognitive training -induced molecular functions

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

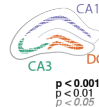
We identified robust subfield-specific gene expression patterns that are consistent with those identified stored in public databases and repositories.

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
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

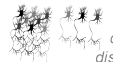


Conclusion

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.

public RNA-seq data + primary RNA-seq data → CA1 DG → robust region-specific expression patterns

Technical manipulation



cellular dissociation



↑ oxidoreductase
↑ ribosome activity
↑ rRNA binding
↓ ligase, helicase

Biological manipulation



stress



negligible gene expression response

Biological manipulation



cognitive training



↑ mGluR signaling
↑ K⁺ transport
↓ oxidoreductase
↓ ribosome activity
↓ mRNA binding