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Charting the Transcriptional Life of the Mouse Hippocampus and Cortex

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01 · ABSTRACT

A contiguous map of brain development

The perinatal and early postnatal mouse hippocampus is one of the best-studied neurodevelopmental windows, with well-defined gene expression level changes associated with neurogenesis, synaptogenesis, and glial maturation milestones. Yet few contiguous datasets capture these changes in one framework built for cross-time-point comparison.

We developed a low-cost, high-throughput 3′ RNA-Seq method to characterize transcriptional changes from E18.5 to P28. We compare our results to well-described "textbook" developmental milestones and the associated gene expression dynamics as a benchmark.

02 · METHODS

Study design

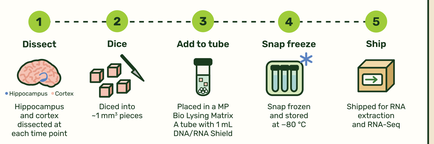
4 time points

2 brain regions

40 samples, n = 5/group

10M dedup. reads/sample

FIG 1 · SAMPLE WORKFLOW



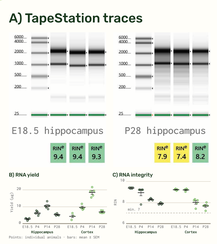
Hippocampus and cortex were dissected from C57BL/6J mice at E18.5, P4, P14, and P28 (n = 5 per group). Tissues were diced into ~1 mm³ pieces, preserved in Zymo DNA/RNA Shield, and shipped to Plasmidsaurus for RNA extraction and sequencing.

Libraries were prepared with Plasmidsaurus RNA-Seq (3′ end counting), sequenced to ~10 million deduplicated reads per sample, and processed with the Plasmidsaurus RNA-Seq pipeline v1.0.

FIG 2 · QUALITY CHECK

Automated extraction yields high-quality RNA.

RNA was isolated using automated purification and assessed by Qubit fluorometry and TapeStation electrophoresis. All 40 samples exceeded RNA integrity number and yield requirements (RIN ≥ 7; observed 7.2–9.4; RNA yield ≥ 0.3 µg; observed 0.8–10.75 µg).

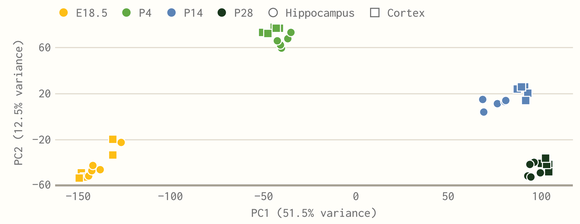


03 · RESULTS

Canonical developmental milestones, recovered at the transcript level

FIG 3 · REPRODUCIBILITY

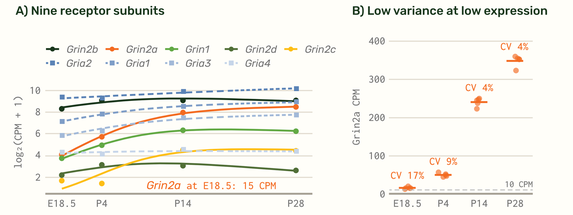
PCA reveals reproducible developmental profiles.



Principal component analysis (PCA) of all 40 samples shows tight replicate clustering and clear separation by developmental stage. PC1 and PC2 explain 51.5% and 12.5% of variance, respectively, demonstrating reproducible transcriptional profiles across samples.

FIG 6 · SENSITIVITY

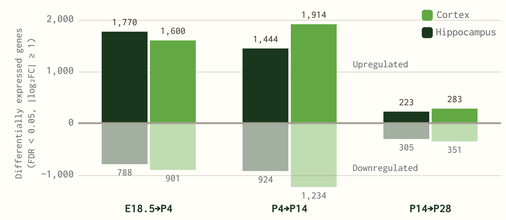
3′ RNA-Seq can distinguish closely related receptor transcripts.



Nine paralogous NMDA and AMPA receptor subunit genes show distinct expression trajectories across a ~300-fold dynamic range. Low-abundance Grin2a (~15 counts per million [CPM]) is reproducibly quantified.

FIG 4 · REMODELING

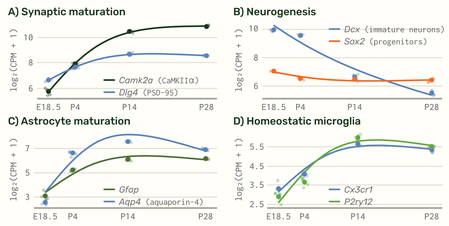
Transcriptional remodeling declines with maturation.



Differential expression analysis reveals extensive transcriptional changes during early development, followed by reduced remodeling at P14 → P28. Hippocampal differentially expressed genes (DEGs) decrease from 2,558 at E18.5 → P4 to 528 at P14 → P28, while cortical remodeling peaks at P4 → P14 (3,148 DEGs), consistent with progressive transcriptional stabilization.

FIG 7 · CELL-TYPE MARKERS

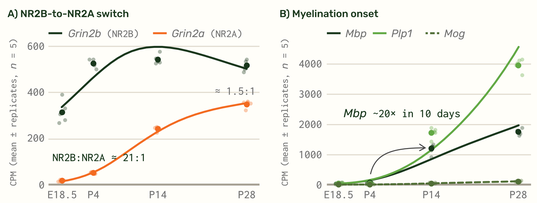
Neurogenesis markers decline as synaptic and glial markers rise.



(A) Synaptic markers Camk2a and Dlg4 increase (Lisman et al., 2002; Kim & Sheng, 2004), while (B) neurogenesis markers Dcx and Sox2 decline (Francis et al., 1999). (C) Astrocyte markers Aqp4 and Gfap rise postnatally (Nielsen et al., 1997), while (D) microglial markers Cx3cr1 and P2ry12 peak at P14 (Butovsky et al., 2014).

FIG 5 · CLASSIC MILESTONES

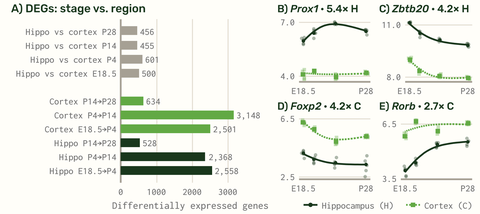
3′ RNA-Seq captures the NR2B-to-NR2A switch and myelination onset.



(A) Hippocampal Grin2a increases ~23-fold while Grin2b remains stable after P4 (Monyer et al., 1994; Sheng et al., 1994). (B) Myelination markers Mbp, Plp1, and Mog increase sharply between P4 and P14, marking myelination onset (Baumann & Pham-Dinh, 2001).

FIG 8 · STAGE VS REGION

Developmental stage drives greater transcriptional differences than brain region.



Early developmental transitions produce ~4–7 times more DEGs than regional comparisons. Region-specific markers (Prox1, Zbtb20, Foxp2, Rorb) remain distinct, indicating stable regional identity alongside shared developmental programs (Lein et al., 2007).

04 · CONCLUSIONS

What the map shows

- RNA-Seq at ~10 million deduplicated reads and 5 replicates per group generated a reproducible developmental atlas spanning E18.5 to P28 using 3′ end counting.
- The RNA-Seq time course captured textbook developmental milestones such as the NR2B-to-NR2A switch and P4 → P14 myelination, in addition to synaptic and glial maturation.
- Quantification shows low variance even at very low transcript abundance and retains fidelity across a 300-fold range.
- Hippocampus and cortex share parallel trajectories and differ in a stable set of patterning genes (Zeisel et al., 2015; Yao et al., 2023).



05 · REFERENCES

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