Analysis of Drug Effects on Learning in Knock-In and Wild-Type Mice

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1 Introduction

We investigated whether S1928A Knock-In (KI) and Wild-Type (WT) mice learn a platform-finding task, and how SKF treatment modulates their performance. Learning was quantified by path efficiency over four trials under Saline or SKF (3.0 mg/kg). We used a linear mixed-effects model (LMM) fitted by maximum likelihood (ML) in `lme4` [Bates et al., 2015], with p-values from `lmerTest`, to account for repeated measurements.

2 Data Description

The data are in long format: each row is one trial for one mouse, with the columns:

- **Id**: Unique identifier for each mouse. Mice with Id ≤ 100 were prepared by Reuben, and mice with Id > 100 were prepared by Mimi.
- **Expiriment**: The experiment session number. Reuben's mice each participated in 2 experiments, and Mimi's mice each participated in 3 experiments.
- **Sex**: Biological sex of the mouse (M for male, F for female).
- **Drug**: Drug condition administered during the trial (Saline or SKF (at dosage of 3.0 mg/kg)).
- **Genotype**: Genetic type of the mouse (KI for Knock-In or WT for Wild-Type).
- **Trial**: Trial number within the experiment session (1 through 4).
- **Outcome**: Path efficiency score for that trial (numeric).

The experiments were performed by two different people: Reuben who contributed 24 mice (7 F KI, 7 F WT, 5 M KI, 5 M WT) and Mimi who contributed 37 mice (11 F KI, 12 F WT, 7 M KI, 7 M WT), for a total of 61 mice.

3 Learning Curve Analysis

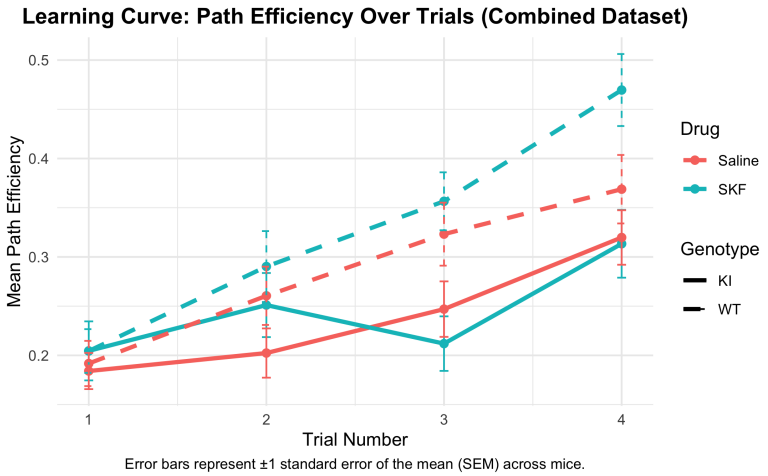

Figure 1: Learning Curve: Mean Path Efficiency Over Trials (Combined Dataset).

Based upon the graph, all the mice seem to be learning as their path efficiency is greater in trial 4 than in trial 1. WT also seems to have the greatest rate of improvement, especially when treated with SKF. In contrast, KI mice improve more gradually, and their learning appears less sensitive to drug treatment.

4 Model Specification and Fitting

Because each mouse can have a different baseline path efficiency, we include random intercepts for mice. This accounts for individual differences unrelated to treatment or genotype. Additionally, since each mouse completes multiple experiments and trials, we model experiments nested within mouse ID. Nesting correctly handles the repeated-measures structure of the data, allowing us to separate within-mouse variability from between-mouse variability.

Therefore, we fit:

$$\begin{aligned}\text{Outcome}_{ijkl} = {} & \beta_0 + \beta_1\,\text{Drug}_i + \beta_2\,\text{Genotype}_j + \beta_3\,\text{Trial}_k + \beta_4\,\text{Sex}_l + \beta_5\,(\text{Drug}\times\text{Genotype})_{ij} \\ & + \beta_6\,(\text{Drug}\times\text{Trial})_{ik} + \beta_7\,(\text{Genotype}\times\text{Trial})_{jk} + \beta_8\,(\text{Sex}\times\text{Trial})_{lk} \\ & + \beta_9\,(\text{Drug}\times\text{Genotype}\times\text{Trial})_{ijk} + u_i + u_{ij} + \varepsilon_{ijkl},\end{aligned}$$

where:

- $u_i \sim N(0, \tau_1^2)$ is a random intercept for mouse ID, accounting for baseline differences between mice,

- $u_{ij} \sim N(0, \tau_2^2)$ is a random intercept for experiments nested within mice, capturing variability across repeated experiments,
- $\varepsilon_{ijkl} \sim N(0, \sigma^2)$ is the residual error, representing unexplained trial-to-trial variability.

Code:

```
lmm <- lmer(
  Outcome ~ Drug*Genotype*Trial + Sex*Trial + (1|Id/Expiriment),
  data = df,
  REML = FALSE
)
```

5 Model Diagnostics

We followed the diagnostics recommended in [Bates et al., 2015]:

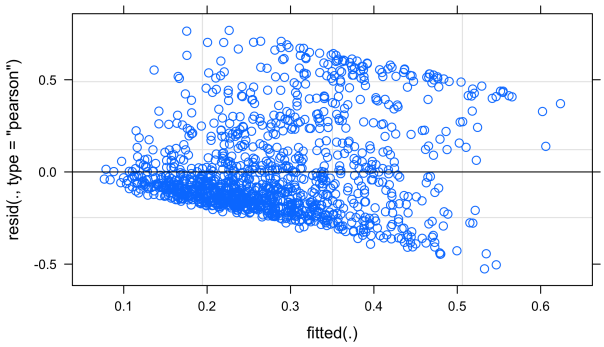

Figure 2: Residuals vs. Fitted Plot

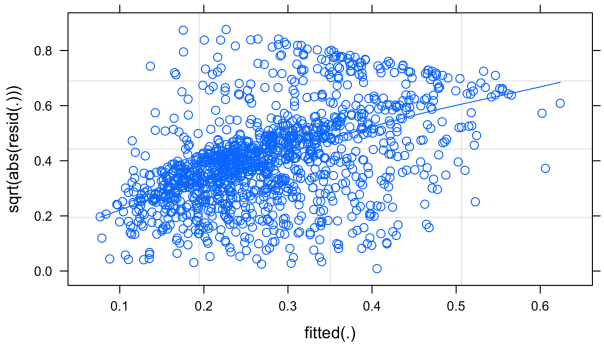

Figure 3: Scale-Location Plot

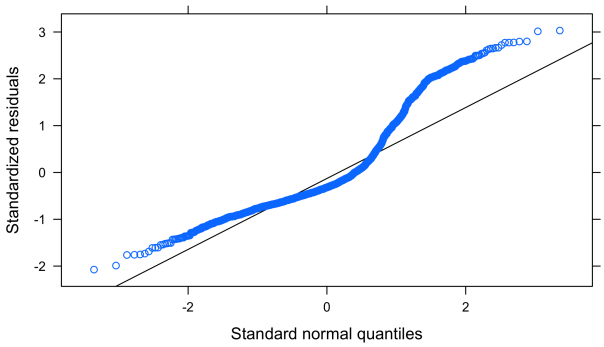

Figure 4: Q-Q Plot of Residuals

Some minor deviation from normality was observed; no strong heteroscedasticity or nonlinearity was evident.

6 Results

Fixed effects:

Term	Estimate	Std. Error	p-value
(Intercept)	0.1304	0.0401	< 0.001 ***
Drug (SKF)	0.0624	0.0497	0.2093
Genotype (WT)	0.0159	0.0521	0.7606
Trial	0.0503	0.0138	< 0.001 ***
Sex (M)	-0.0094	0.0393	0.8118
Drug×Genotype	-0.0870	0.0698	0.2127
Drug×Trial	-0.0234	0.0181	0.1970
Genotype×Trial	0.0122	0.0181	0.4998
Sex×Trial	-0.0095	0.0131	0.4680
Drug×Genotype×Trial	0.0500	0.0255	0.0499 *

Table 1: LMM fixed-effects estimates (ML, p-values via `lmerTest`).

Key findings:

- **Learning over trials** was significant ($\beta = 0.050, p < 0.001$).
- **Three-way interaction** (Drug : Genotype : Trial) was significant ($p = 0.0499$), indicating WT + SKF learned faster than KI + SKF.
- No significant main effects of Drug or Genotype alone, and no sex differences.

7 Conclusion

WT mice treated with SKF displayed a significantly steeper learning curve compared to KI mice, while KI mice still showed overall learning across trials. No evidence of a sex effect was found. All code and data are available at `https://github.com/snaderi2000/mouse_data_analysis`.

References

[Bates et al., 2015] Bates, D., Mächler, M., Bolker, B., and Walker, S. (2015). Fitting linear mixed-effects models using lme4. *Journal of Statistical Software*, 67(1):1–48.