Effects of Different Pain Relievers and Dosages on Cognitive Retention

Navya Hooda Mohammed Yusuf Shaikh Shivank Goel
Vanshika Vanshika Jena Shah

April 2, 2025

Painkillers are commonly used to manage pain, and their effects are often associated with physical relief. While they provide immediate physical comfort, their impact on cognitive performance is often overlooked. This study explores how different painkillers and dosages influence cognitive function. Using simulated testing from a virtual population, participants were randomly assigned a treatment (drug type and dosage) while controlling for variables such as age. Our findings indicate no significant relationship between drug type, dosage, and overall cognitive performance post-treatment. However, we observed some correlation between certain drug-dosage combinations and memory improvement, suggesting a potential area for further research. While the results were not statistically significant, this study contributes to a deeper understanding of the cognitive effects of painkillers and highlights the need for further investigation into their potential impact on memory and cognition.

Table of contents

1 Acknowledgements

No auto-complete tools such as co-pilot were used in the course of this project, however, the Language Learning Model 'ChatGPT' was used while writing this paper. It was used for the purpose of code debugging, understanding models, and knowledge of certain topics, which we were not aware of. The chat with the AI bot is also attached as a reference under Section 9.

2 Introduction

Pain can make everyday tasks harder, particularly when mental focus and clarity are required. Study has shown that individuals with pain tend to have cognitive dysfunction symptoms (Hu 2009). Common pain relievers like Aspirin, Paracetamol, and Tramadol are often used to reduce physical discomfort, but their impact on cognitive functions are not well understood. Memory retention is a process that requires mental effort – which becomes more difficult when we're in pain. This study investigates how different pain relievers (Aspirin, Paracetamol, and Tramadol) at standard dosages affect memory performance. We will also look at how the interaction between drug type and dosage level influence memory function. Since the ability to recall information is a basis for optimized human function, understanding how pain relief might impact cognitive performance is important for managing pain without affecting productivity.

2.1 Research Questions

This study aims to explore and answer the following questions.

Research Question 1. *How does the type of pain reliever (Aspirin 500 mg, Paracetamol 500 mg, Tramadol 50 mg, and Placebo) affect memory game performance?*

- Null Hypothesis: All pain relievers at normal dosages act the same for cognitive retention game performances.
- Alternative Hypothesis: There exists at least one pair of distinct pain relievers at normal dosages which act differently for cognitive retention game performances.

Research Question 2. *Is there an interaction effect between the type of pain reliever and dosage level on the improvement in memory game performance?*

- Null Hypothesis: There is no interaction effect between the type of pain reliever and dosage level on the improvement in memory task performance.
- Alternative Hypothesis: There is an interaction effect between at least one of the types of pain reliever and dosage level on the improvement in memory task performance.

3 Methodology

In February, our group members collected observations from participants belonging to a virtual population to assess whether the treatment had any effect on memory performance, this resulted in a total of 240 observations. Each participant was **randomly** assigned a treatment.

The experiment utilized a two-way ANOVA design, where the experimental unit was the participant, the explanatory variables were the type of painkiller and dosage level (low/high), and the response variable was the memory performance, measured by the memory game score.

3.1 Study Design and Treatments

We selected three brands of painkillers: Aspirin, Paracetamol, and Tramadol. Additionally, we considered a placebo treatment. As a result, this study involves 2 factors: pain reliever type (4 levels - Aspirin, Paracetamol, Tramadol, Placebo) and dosage (2 levels - Low, High). Crossing the two factors provides us with a total of *8 treatment groups*, with **30 participants** assigned to each. The total crossed treatment groups are shown in Table 1.

This results in **240 total observations** ($8 \times 30 = 240$).

For each treatment, we selected 30 different people (n = 30). Through randomly picking the virtual citizens, we replicated 30 experimental units per treatment. The even observations per treatment group ensures we have a balanced design.

Table 1: Treatment Groups

	Drug Type			
Dosage	Aspirin	Paracetamol	Tramadol	Placebo
Low	Aspirin 500 mg	Paracetamol 500 mg	Tramadol 50 mg	Placebo 1 Tablet
High	Aspirin 1000 mg	Paracetamol 1000 mg	Tramadol 100 mg	Placebo 2 Tablets

3.1.1 Nuisance Variable: Age

To reduce bias, we consider **controlling** the experiment by limiting participant ages to be strictly 18+. Hence in this study, **age** acts as a **nuisance variable**. We also used **blocking** for age by ensuring participants were categorized into three even groups to prevent bias created through age. Table 2 shows the breakdown of the groups.

3.2 Quantitative and Qualitative Variables

In our study the quantitative and qualitative variables are as follows:

1. Quantitative variables: Memory Game Scores, Memory Test Cards Scores
2. Qualitative variables: Type of pain reliever, dosage level (low/high)

Table 2: Summary of Age Groups

Age Group	Count	Percentage
18-34	80	33.33
35-50	80	33.33
50+	80	33.33

The structure of the paper is as follows: Section 2 outlines our data and methodology. Section 3 presents our quantitative analysis. In Section 4, we discuss the results and address our findings from the analysis. Section 5 covers the limitations of our study, and Section 6 presents a conclusion to our analysis. After that, we have the bibliography in Section 7. Lastly, we attached the code for our study into the Appendix in Section 8.

Table 3: Summary Statistics for Quantitative Variables

Statistic	Memory Game Score	Memory Cards Score
Mean	62.57583	7.945833
Median	61.50000	9.000000
SD	15.63703	1.960164
IQR	23.35000	2.000000

Table 4: Summary of Drug Types

Drug	Count	Percentage
Aspirin	60	25
Paracetamol	60	25
Placebo	60	25
Tramadol	60	25

3.3 Summary of quantitative variables

Table 3 shows the summary statistics of memory game scores before and after the treatment. The mean is similar across all groups, however, the standard deviation (SD) is relatively high. The median game scores remain close to the mean, and the IQR (Interquartile Range) is smaller than the SD. The cards memory task shows little change before and after treatment, suggesting that pain relievers may not have a major effect on this specific task.

Evident through the results, Paracetamol is the drug that has the greatest mean & median improvement in the game scores after administering the drug (without dosage taken into account). Aspirin appears to negatively impact the results of the game after being given to people, this was seen through the mean and median improvements.

Table 5: Summary of Dosage Levels

Dosage	Count	Percentage
High	120	50
Low	120	50

3.4 Summary of counts and percentage for qualitative variables

Table 4 shows the distribution of participants across drug types. Aspirin, Paracetamol, and Tramadol, and Placebo each have 60 participants (25%), ensuring balance.

Table 5 shows the dosage levels assigned to participants. There is an equal split between high-dose (120 participants, 50%) and low-dose (120 participants, 50%) conditions.

4 Plots

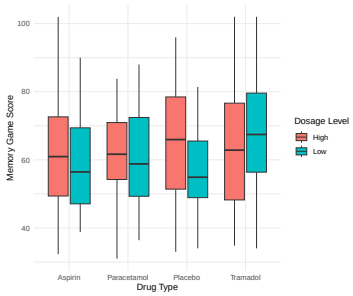


Figure 1: Boxplots: Memory Game Scores by Drug Type and Dosage Level

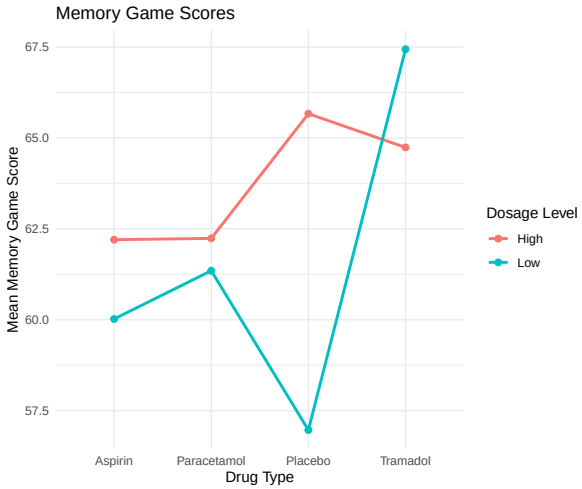


Figure 2: Interaction Plot: Drug Type vs. Dosage Level

4.1 Game Score Distribution by Drug and Dosage Level

Figure 3 shows the distribution of memory game scores across different drug types using box plots.

1. The median scores for all drugs appear similar.
2. All drugs have a higher median on the higher dosage, level expect for Tramadol which is lower.

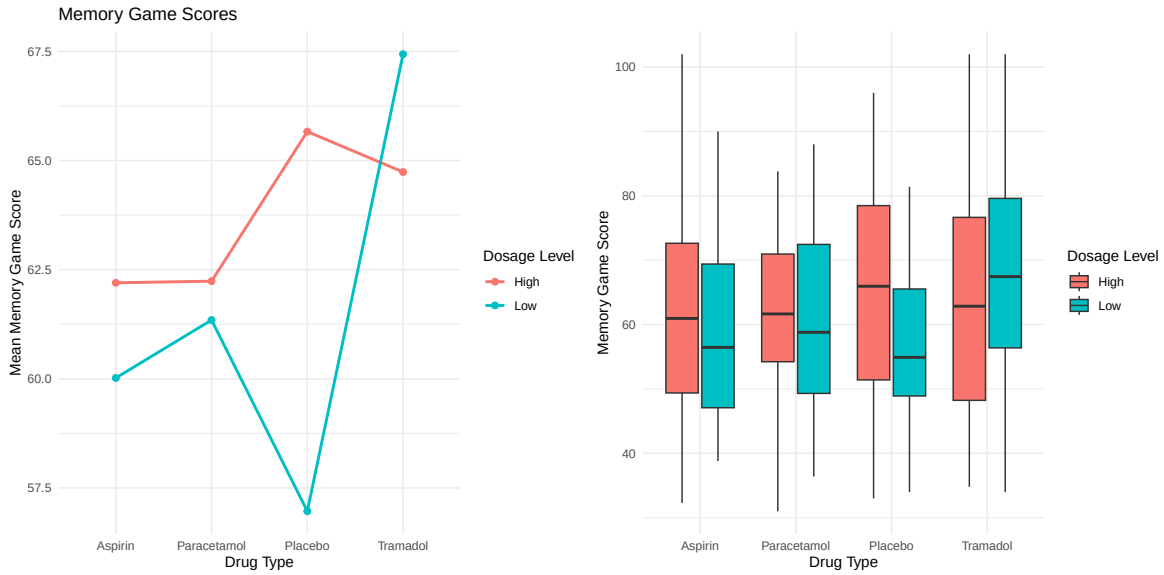


Figure 3: Interaction Plot and Boxplot: Memory Game Scores by Drug Type and Dosage Level

3. The Placebo group has a slightly lower median score compared to other drugs.
4. The (IQR) is **similar across all drug types**, though Tramadol and Placebo see a higher IQR in the memory game scores in the high dosage.

This boxplot provides an initial comparison of memory game performance and drug administration.

5 Analysis

5.1 Model

The method of Wwo-way ANOVA is used to estimate the mean of a memory game score changes according to the levels of two categorical variables that is drug and dosage level. The general statistical form of the model is:

$$Y_{ijk} = \mu + \alpha_i + \beta_j + (\alpha\beta)_{ij} + \varepsilon_{ijk}$$

Where

- Y_{ijk}: Memory score for the k-th participant receiving the i-th drug and j-th dosage level

- μ: Overall mean
- α_i: Effect of the i-th drug ((Aspirin, Tramadol, Paracetamol, Placebo))
- β_j: Effect of the j-th dosage level (High Dosage, Low dosage)
- $(\alpha\beta)_{ij}$: Interaction effect between drug and dosage
- $\epsilon_{ijk} \sim N(0, \sigma^2)$: Random error

In this analysis where our focus in on Two-Way ANOVA Model and so we fit using linear regression model using dummy variable coding using Treatment Aspirin-High dosage as the baseline group. The aim is to interpret estimated coefficients relative to reference group. The model we used in our analysis can be expressed as:

$$\begin{aligned} Y_i = \beta_0 &+ \beta_1 \cdot \text{Paracetamol}_i + \beta_2 \cdot \text{Placebo}_i + \beta_3 \cdot \text{Tramadol}_i \\ &+ \beta_4 \cdot \text{LowDosage}_i + \beta_5 \cdot (\text{Paracetamol}_i \times \text{LowDosage}_i) \\ &+ \beta_6 \cdot (\text{Placebo}_i \times \text{LowDosage}_i) + \beta_7 \cdot (\text{Tramadol}_i \times \text{LowDosage}_i) + \varepsilon_i \end{aligned}$$

Where

- β_0: Intercept (Aspirin at High dosage — the reference group)
- $\beta_1, \beta_2, \beta_3$: Main effects of Paracetamol, Placebo, and Tramadol relative to Aspirin
- β_4: Effect of Low dosage relative to High
- $\beta_5, \beta_6, \beta_7$: Interaction effects for each drug under Low dosage
- ϵ_i: Residual error for the i-th participant

The Intercept term β_0 accounts for the reference group. All other coefficients β_j represent the mean difference between the specified group and the reference group, holding other factors constant for j = *1, 2, 3, 4, 5, 6, 7*

5.2 Assumption Checks

We verified the assumption of the two-way ANOVA model as seen from using Q-Q plot as seen in Figure 4. The Shapiro-Wilk Test confirms a p-value = 0.05553 as per Table 9, so we fail to reject the null hypothesis and the result confirms that the dataset is *normally distributed*. Our second assumption of *homogeneity of variance* is verified by the p-value = 0.3346 from the Bartlett test in Table 10, which is greater than 0.05. Due to this, we fail to reject the

Table 6: Coefficient Estimates from Linear Model for Memory Game Score

Predictor Term	Estimate	Std. Error	t-statistic	p-value
(Intercept)	62.2000000	2.839371	21.9062572	0.0000000
drugParacetamol	0.0366667	4.015478	0.0091313	0.9927222
drugPlacebo	3.4633333	4.015478	0.8624960	0.3893053
drugTramadol	2.5366667	4.015478	0.6317223	0.5281903
dosage_levelLow	-2.1800000	4.015478	-0.5428993	0.5877203
drugParacetamol:dosage_levelLow	1.2900000	5.678743	0.2271630	0.8204971
drugPlacebo:dosage_levelLow	-6.5166667	5.678743	-1.1475545	0.2523345
drugTramadol:dosage_levelLow	4.8800000	5.678743	0.8593451	0.3910372

Table 7: Model Summary Statistics for Memory Game Score

F-Statistic	Model df	Residual df	p-value	Residual Std. Error	Sample Size (n)
1.374906	7	232	0.216744	15.55188	240

Table 8: Two-Way ANOVA Results for Memory Game Score

	Df	Sum Sq	Mean Sq	F value	Pr(>F)
drug	3	1000.7542	333.5847	1.379242	0.2498211
dosage_level	1	308.2667	308.2667	1.274562	0.2600786
drug:dosage_level	3	1018.7310	339.5770	1.404018	0.2423452
Residuals	232	56111.7280	241.8609	NA	NA

Table 9: Shapiro-Wilk Test for Normality

	Statistic	P-Value	Method
W	0.9886	0.0555	Shapiro-Wilk normality test

Table 10: Bartlett's Test for Homogeneity of Variance

	Statistic	DF	P-Value	Method
Bartlett's K-squared	7.9776	7	0.3346	Bartlett test of homogeneity of variances

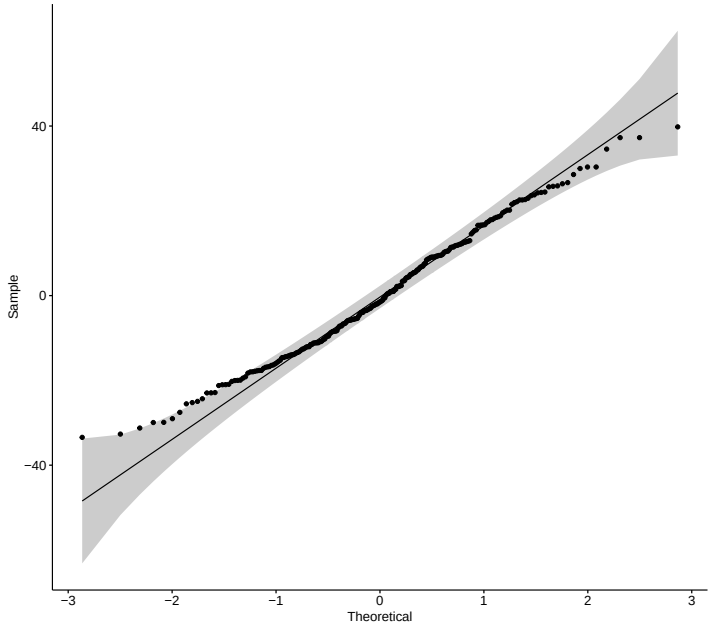


Figure 4: Q-Q Plot of Residuals

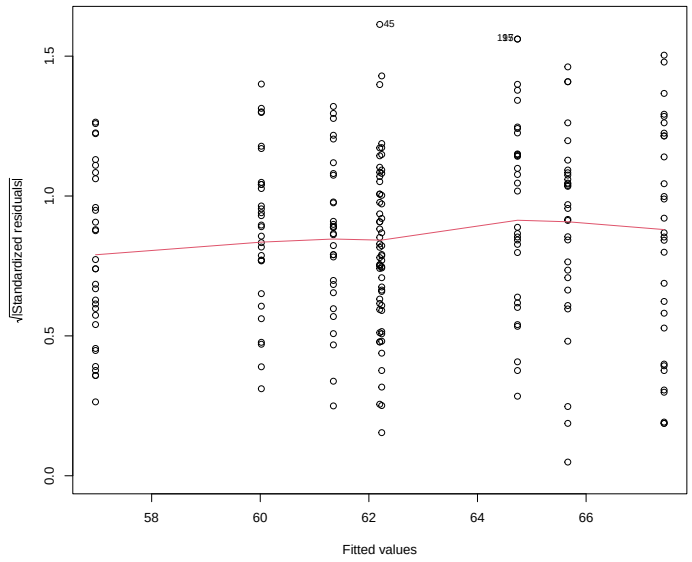


Figure 5: Q-Q Plot of Residuals

null hypothesis. Thirdly, for our two-way ANOVA model, the different combinations of pain reliever type and dosage levels, the treatments were randomly assigned to all participants which ensures *independence*.

5.3 need to work on it

"The two-way ANOVA factorial design involves the linear regression model followed by the ANOVA model. The model uses the reference (baseline) group which is Aspirin (Drug) & High (Dosage level). The regression model from the Table 6 shows the intercept(beta_0) which represents the predicted mean of memory game score for participants receiving high dosage of aspirin is 62.20 and the p-value = 0.00000 indicates the intercept is statistically significant. The variance explained by the model is R^2 = 0.03983, approximately 4% of the response variable. And the p-value = 0.2167 of the model can be interpreted as not statistically significant"

6 Discussion

6.1 Interpretation of Results

The two-way ANOVA analysis revealed no statistically significant main effects of drug type ($p = 0.25$) or dosage level ($p = 0.26$) on memory game scores. Similarly, the interaction effect between drug type and dosage level was not significant ($p = 0.24$). These results suggest that neither the type of pain reliever (Aspirin, Paracetamol, Tramadol, or Placebo) nor its dosage (low vs. high) had a meaningful impact on memory game scores, which is representative of cognitive improvement in this study. The lack of significance persisted even after accounting for age as a confounding variable, which was controlled through participant stratification into three balanced groups (18–34, 35–50, and 50+ years).

7 Limitations

Our study is overall focused on memory, which may have links to one's education and IQ level, as they are all related to mental function and cognition. In the future, we could test everyone for IQ scores and their highest level of education – these two nuisance variables can be taken care of by using the four principles of experimental design. Additionally, we used 30 observations for each treatment group which may not be large enough. We can increase this number for future studies. To add on, not all participants were in pain, so the efficacy of the improvement of pain killers may be biased and using a virtual population may not ensure whether this aspect could be captured. Lastly, cognitive retention was measured immediately post-treatment – the long term impacts are not yet explored. To improve our study, we can

try to consider individuals with real pain symptoms before the study to ensure a reduction of bias, and provide a realistic test setting. Additionally, carrying the experiment out in the long-term would help with understanding the effects of painkillers and dosages on memory.

There's also a chance that the participants' expectations influenced their results if they knew which treatment they were getting (we cannot expand on this as it was a virtual experiment). In the future, bias could be minimized through having a double-blind design in which neither the participants nor the researchers know who's getting what. We only tested low and high dosages, so we might be missing more subtle effects that show up with intermediate doses. So if we were to include a wider range of dosages in future studies, it could give a fuller picture. Another issue is that our sample might not fully represent the general population since we selected participants from specific clusters of locations – not all locations were covered equally. This means our findings might not apply to everyone. Next time, we could choose more diverse and evenly spread-out clusters to make the results more general. Lastly, despite our efforts to control for confounding factors, there are still some variables (like sleep quality, stress levels, or baseline cognitive function) that could affect memory performance. Being more thorough in accounting for these factors could improve the accuracy of the results.

8 Conclusion

This study did not find clear evidence that pain relievers or their dosages have a significant impact on cognitive retention. However, the exploratory trends observed, particularly with Paracetamol and Tramadol, highlight the need for larger-scale studies to investigate subtle or context-dependent effects. Future research could incorporate longitudinal designs, broader age-specific analyses, and alternative cognitive metrics to deepen understanding of painkillers' cognitive implications.

9 Appendix

```
library(tidyverse)
library(janitor)
library(here)
library(lubridate)
library(patchwork)
library(arrow)
library(dplyr)
library(knitr)
library(performance)
library(modelsummary)
library(kableExtra)
library(performance)
library(ggpubr)


clean_data <- read.csv(here("data", "analysis_data", "clean_data.csv"))
```

```
# Compute statistics for Memory Game Score
mean_game <- mean(clean_data$memory_game_score, na.rm = TRUE)
median_game <- median(clean_data$memory_game_score, na.rm = TRUE)
sd_game <- sd(clean_data$memory_game_score, na.rm = TRUE)
iqr_game <- IQR(clean_data$memory_game_score, na.rm = TRUE)

# Compute statistics for Memory Cards Score
mean_cards <- mean(clean_data$memory_cards_score, na.rm = TRUE)
median_cards <- median(clean_data$memory_cards_score, na.rm = TRUE)
sd_cards <- sd(clean_data$memory_cards_score, na.rm = TRUE)
iqr_cards <- IQR(clean_data$memory_cards_score, na.rm = TRUE)

# Combine into a summary table
summary_table <- data.frame(
  Statistic = c("Mean", "Median", "SD", "IQR"),
  `Memory Game Score` = c(mean_game, median_game, sd_game, iqr_game),
  `Memory Cards Score` = c(mean_cards, median_cards, sd_cards, iqr_cards)
)

colnames(summary_table) <- c("Statistic", "Memory Game Score", "Memory Cards Score")

# Display table
```

```r
kable(summary_table, format = "latex", booktabs = TRUE)
```

Statistic	Memory Game Score	Memory Cards Score
Mean	62.57583	7.945833
Median	61.50000	9.000000
SD	15.63703	1.960164
IQR	23.35000	2.000000

```r
drug_counts <- table(clean_data$drug)

# percentages
drug_percentages <- prop.table(drug_counts) * 100

#  summary dataframe
drug_summary <- data.frame(
  Drug = names(drug_counts),
  Count = as.numeric(drug_counts),
  Percentage = round(as.numeric(drug_percentages), 2)
)

# Display table
kable(drug_summary, format = "latex", booktabs = TRUE)
```

Drug	Count	Percentage
Aspirin	60	25
Paracetamol	60	25
Placebo	60	25
Tramadol	60	25

```r
dosage_counts <- table(clean_data$dosage_level)

# percentage for each dosage level
dosage_percentages <- prop.table(dosage_counts) * 100

# summary dataframe
dosage_summary <- data.frame(
  Dosage = names(dosage_counts),
  Count = as.numeric(dosage_counts),
  Percentage = round(as.numeric(dosage_percentages), 2)
)
```

```r
# Display table
kable(dosage_summary, booktabs = TRUE, row.names = FALSE)
```

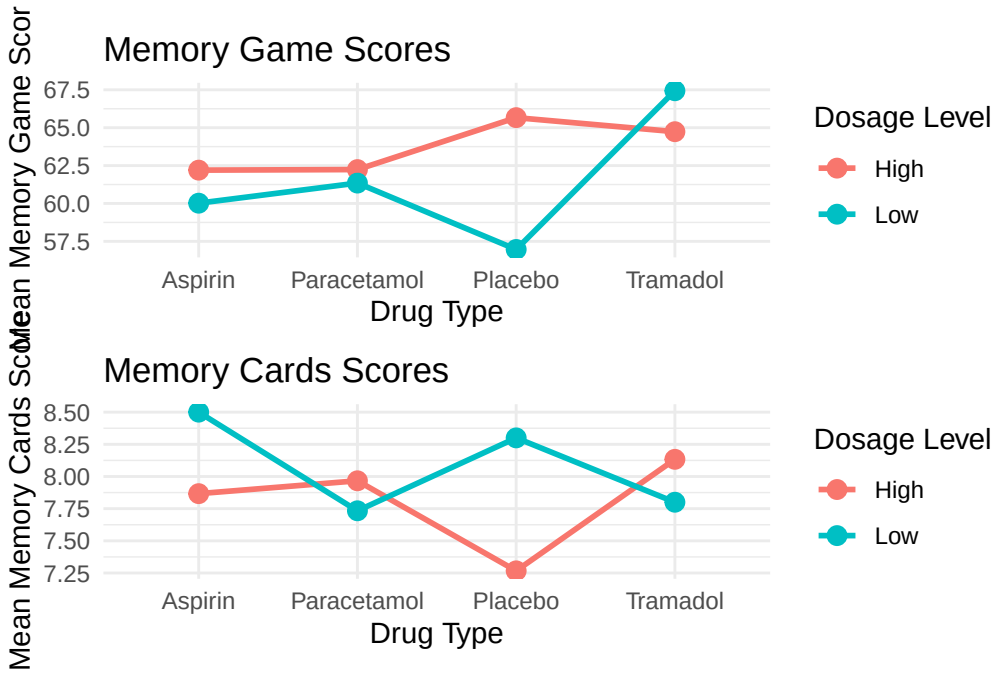
Dosage	Count	Percentage
High	120	50
Low	120	50

```r
age_counts <- table(clean_data$age_group)

# percentages for each age group
age_percentages <- prop.table(age_counts) * 100

# summary dataframe
age_summary <- data.frame(
  `Age Group` = names(age_counts),
  Count = as.numeric(age_counts),
  Percentage = round(as.numeric(age_percentages), 2)
)
colnames(age_summary)[colnames(age_summary) == "Age.Group"] <- "Age Group"


# Display table
kable(age_summary, booktabs = TRUE, row.names = FALSE)
```

Age Group	Count	Percentage
18-34	80	33.33
35-50	80	33.33
50+	80	33.33

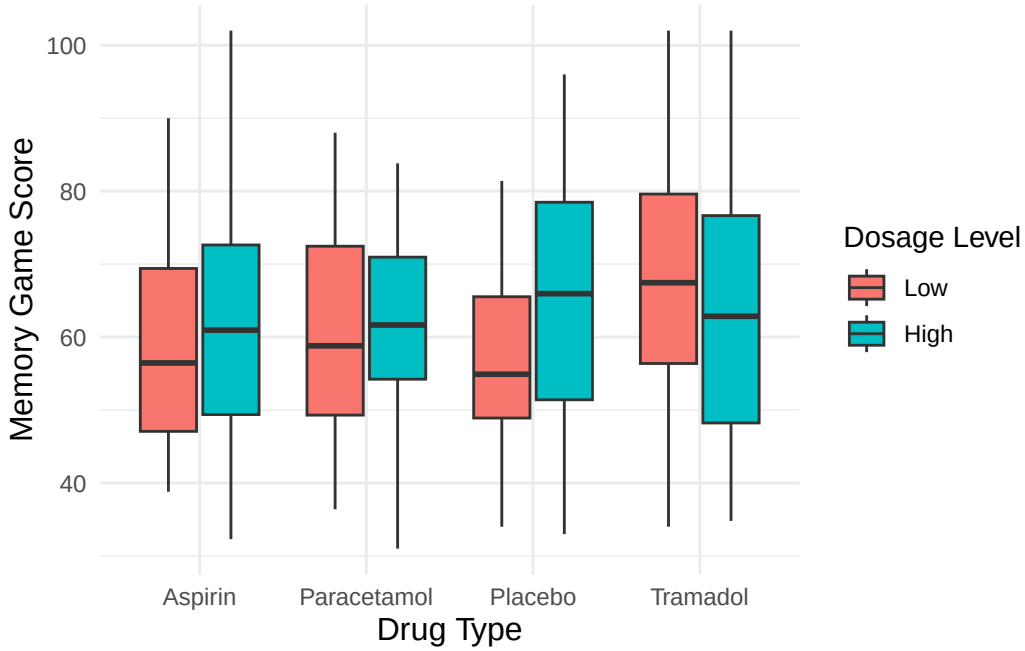
```r
p1 <- ggplot(clean_data, aes(x = drug, y = memory_game_score, color = dosage_level, group = d
  stat_summary(fun = mean, geom = "point", size = 3) +
  stat_summary(fun = mean, geom = "line", size = 1) +
  labs(title = "Memory Game Scores",
       x = "Drug Type",
       y = "Mean Memory Game Score",
       color = "Dosage Level") +
  theme_minimal()
```

```r
# Interaction plot for Memory Cards Scores
p2 <- ggplot(clean_data, aes(x = drug, y = memory_cards_score, color = dosage_level, group =
  stat_summary(fun = mean, geom = "point", size = 3) +
  stat_summary(fun = mean, geom = "line", size = 1) +
  labs(title = "Memory Cards Scores",
       x = "Drug Type",
       y = "Mean Memory Cards Score",
       color = "Dosage Level") +
  theme_minimal()

# Combine the two plots vertically
combined_plot <- p1 / p2
combined_plot
```

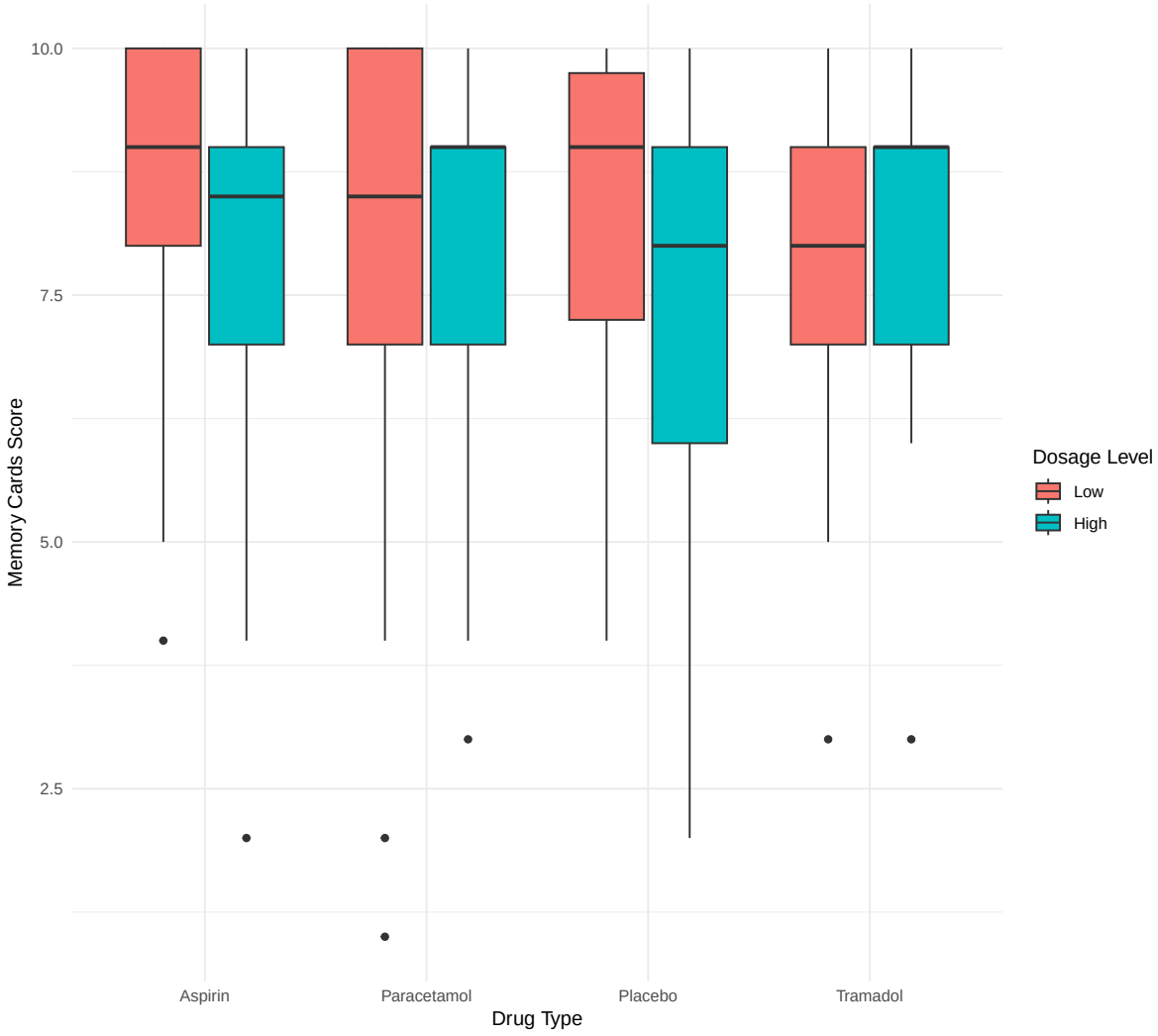



```r
clean_data$dosage_level <- factor(clean_data$dosage_level, levels = c("Low", "High"))

# Boxplot of Memory Game Scores by Drug, colored by Dosage Level
ggplot(clean_data, aes(x = drug, y = memory_game_score, fill = dosage_level)) +
  geom_boxplot() +
  labs(
    x = "Drug Type",
    y = "Memory Game Score",
```

```
    fill = "Dosage Level"
  ) +
  theme_minimal() +
  theme(
    plot.title = element_text(size = 14, face = "bold"),
    axis.title = element_text(size = 12)
  )
```




```
ggplot(clean_data, aes(x = drug, y = memory_cards_score, fill = dosage_level)) +
  geom_boxplot() +
  labs(
    x = "Drug Type",
    y = "Memory Cards Score",
    fill = "Dosage Level"
  ) +
  theme_minimal()
```



term	estimate	std.error	statistic	p.value
(Intercept)	60.020000	2.839371	21.1384816	0.0000000
drugParacetamol	1.326667	4.015478	0.3303883	0.7414048
drugPlacebo	-3.053333	4.015478	-0.7603911	0.4477929
drugTramadol	7.416667	4.015478	1.8470198	0.0660176
dosage_levelHigh	2.180000	4.015478	0.5428993	0.5877203
drugParacetamol:dosage_levelHigh	-1.290000	5.678743	-0.2271630	0.8204971
drugPlacebo:dosage_levelHigh	6.516667	5.678743	1.1475545	0.2523345
drugTramadol:dosage_levelHigh	-4.880000	5.678743	-0.8593451	0.3910372

r.squared	adj.r.squared	sigma	statistic	p.value	df	logLik	AIC	BIC	deviance	df.residual	nobs
0.0398318	0.0108612	15.55188	1.374906	0.216744	7	-995.0806	2008.161	2039.487	56111.73	232	240

```
model_glance <- glance(anova_model)
kable(model_glance, format = "latex", booktabs = TRUE) %>%
   kable_styling(latex_options = "scale_down")
```

```
# Two way ANOVA result
anova_result <- anova(anova_model)

anova_table_df <- as.data.frame(anova_result)

kable(anova_table_df, format = "latex", booktabs = TRUE)
```

	Df	Sum Sq	Mean Sq	F value	Pr(>F)
drug	3	1000.7542	333.5847	1.379242	0.2498211
dosage_level	1	308.2667	308.2667	1.274562	0.2600786
drug:dosage_level	3	1018.7310	339.5770	1.404018	0.2423452
Residuals	232	56111.7280	241.8609	NA	NA

```
# Normality Check
ggqqplot(residuals(anova_model))
```

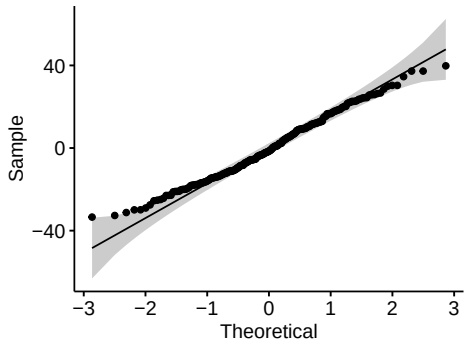


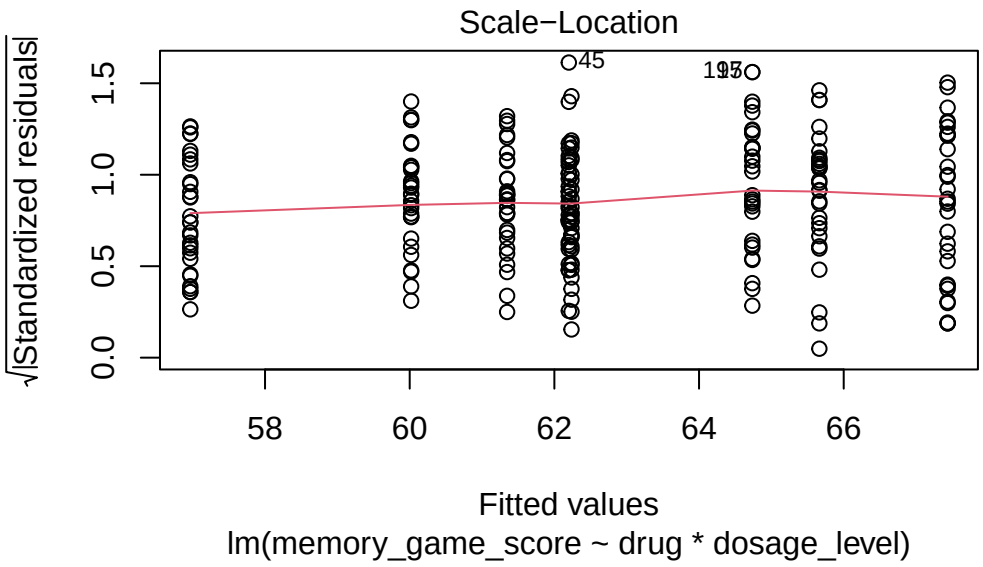
Figure 6: Q-Q Plot of Residuals

```
#| fig.width: 9
#| fig.height: 8
#| dpi: 300
```

```r
#| fig-cap: "Q-Q Plot of Residuals"

# Shapiro-Wilk Normality Test
shapiro_test <- shapiro.test(residuals(anova_model))
shapiro_table <- data.frame(
  Statistic = round(shapiro_test$statistic, 4),
  P_Value = round(shapiro_test$p.value, 4),
  Method = shapiro_test$method
)

kable(shapiro_table, format = "latex", booktabs = TRUE)
```

	Statistic	P_Value	Method
W	0.9886	0.0555	Shapiro-Wilk normality test

```r
plot(anova_model, which = 3)
```



References

Hu, Yifeng. 2009. "Amitriptyline Rather Than Lornoxicam Ameliorates Neuropathic Pain-Induced Deficits in Abilities of Spatial Learning and Memory." *European Journal of Anaesthesiology*. https://journals.lww.com/ejanaesthesiology/FullText/2010/02000/Amitriptyline_rather_than_lornoxicam_ameliorates.6.aspx.