How neglect differentially affects sexes: a resilient phenotype or a hidden vulnerability?

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9/05/2024

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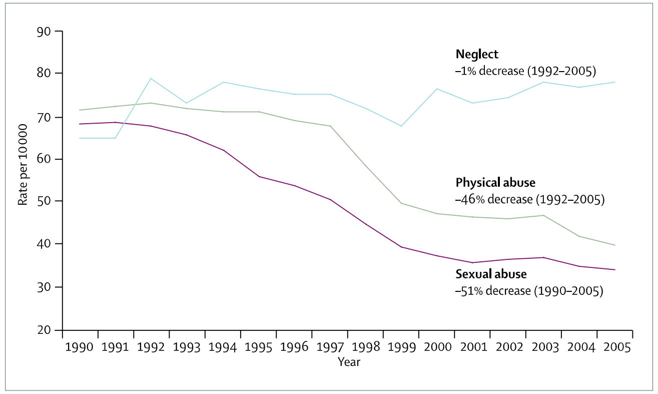
A historical perspective

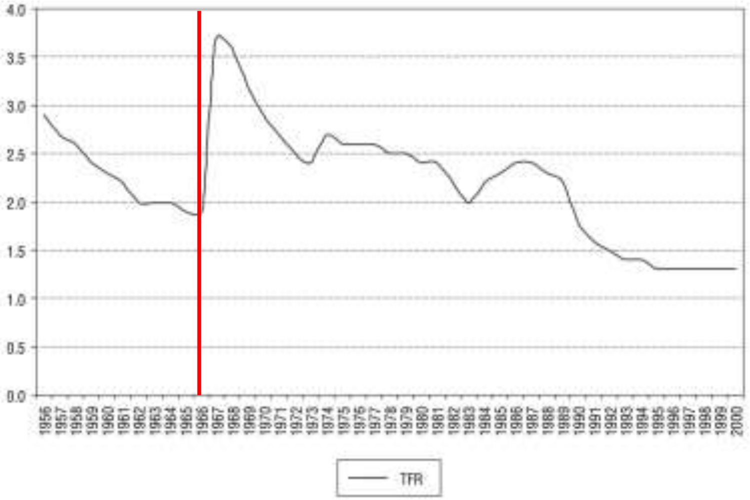
«From a neurobiological perspective, neglect is the **absence of experiences** required to express an **underlying genetic potential** in a key **developing neural system**.»[1]

Burden and consequences of child maltreatment in high-income countries



US Department of Health and Human Services, Administration on Children Youth and Families. Child Maltreatment 2006.

Decree 770 was a decree of the communist Romanian government of Nicolae Ceausescu, signed in 1967.



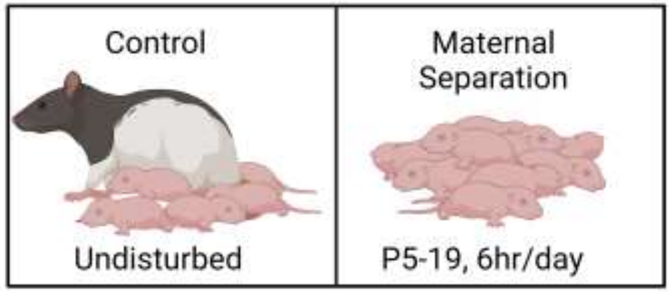
Total Fertility Rate (TFR) in Romania, 1956-2000 [2]

Codruta, a Romanian child, at 13 years of age in 1990, as her hundreds of thousends other children were systematically neglected in Romaninan «orphanages». Angela Catlin public domain

The original project

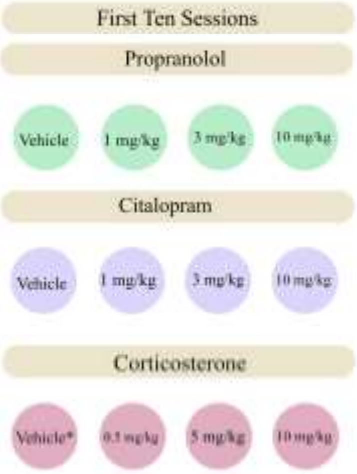
Ultimate Goal:

Multilevel biomarkers and treatment outcomes differences

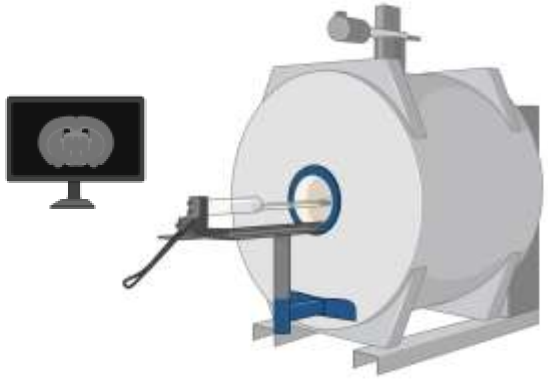


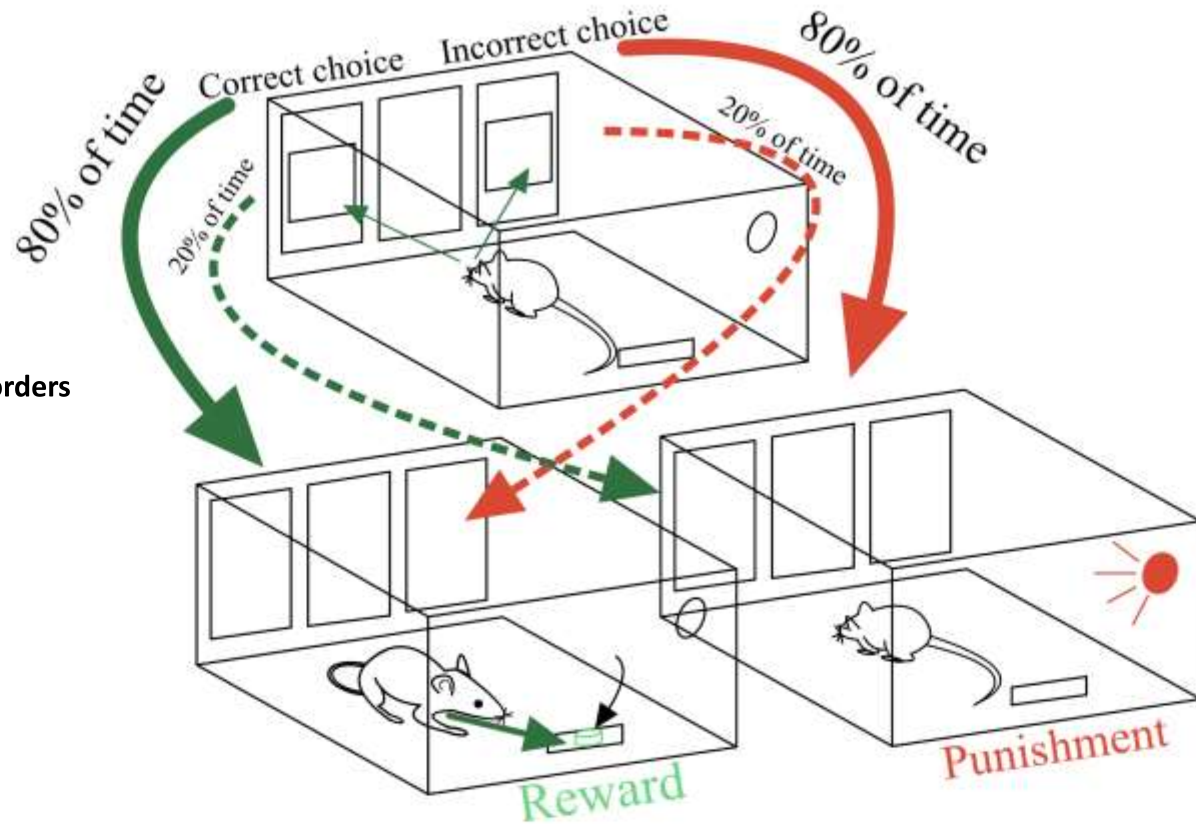
1 The model: Repeated Maternal Separation (RMS)

4 Pharmacological treatments for stress-related disorders



5 High resolution neuroimaging data collection





3 Touchscreen-based spatial Probabilistic Reversal Learning (PRL) task.

Dataset and first steps description

- **64 rats**, male and females; 32 exposed to early **repeated maternal separation**

- 17 initial **columns** and two target variables (sex and group) for the supervised learning part

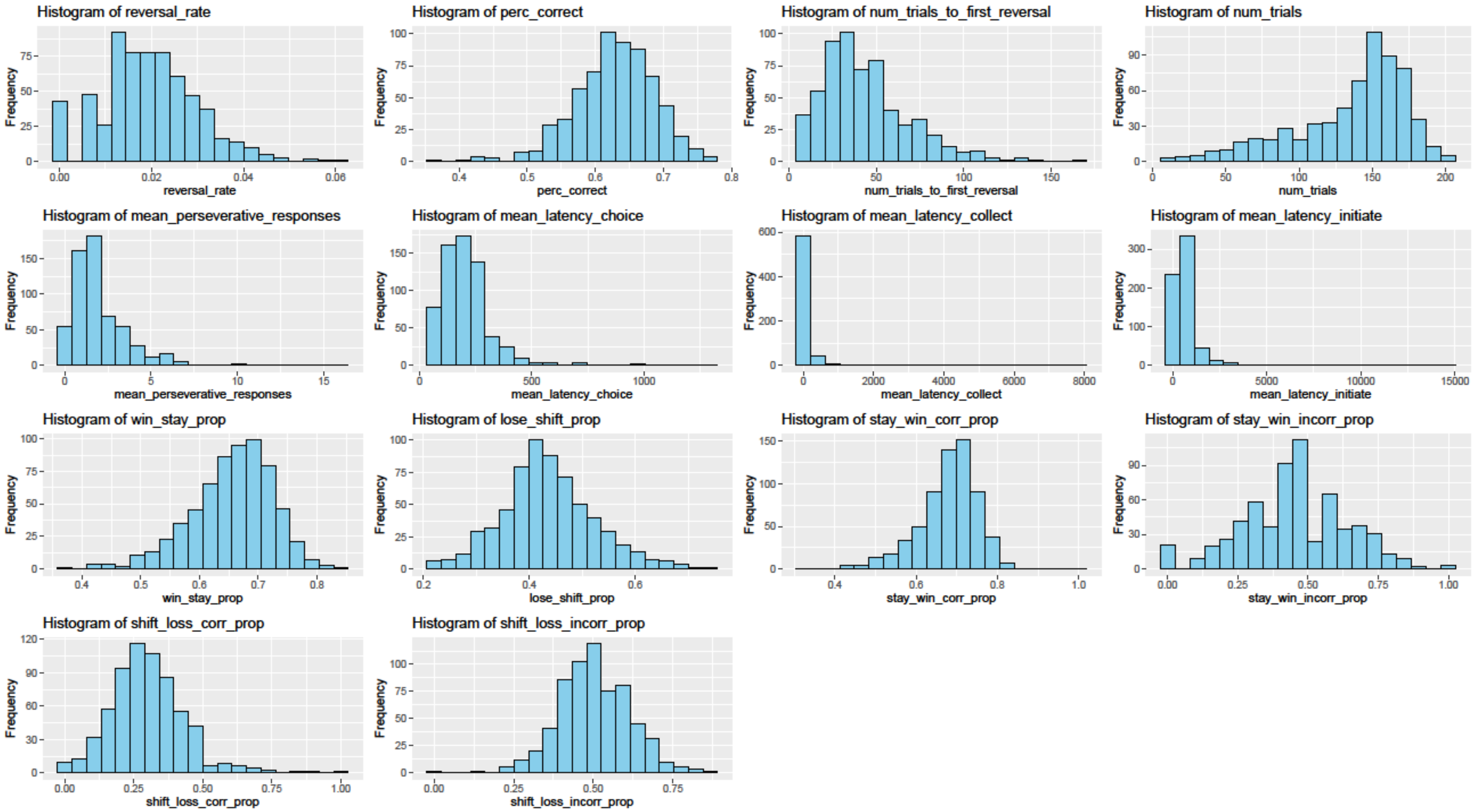
- **640** initial **rows**, 10 for each of the **10 sessions** all the rats completed, then brought to 64, each summarizing one rat's performance

How?

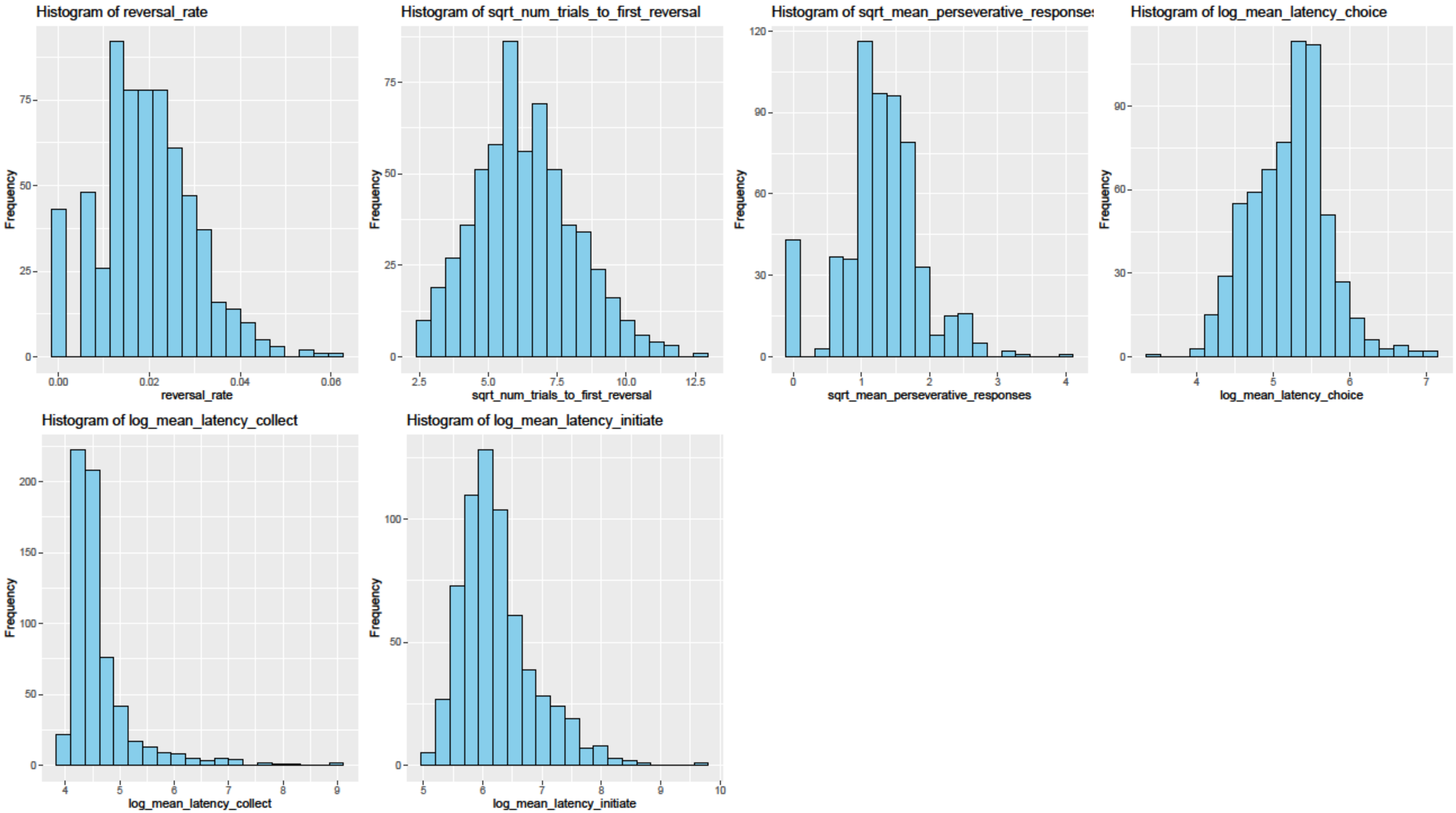
Two ways choosen to summarize the data panel: **mean** of the 10 (best performance) or **difference** between the first value and the last

In supervised learning we had **two datasets** (**dif, mn**) and **two variables** to **predict** (**sex, group**). We found sex differences and group differences only for females

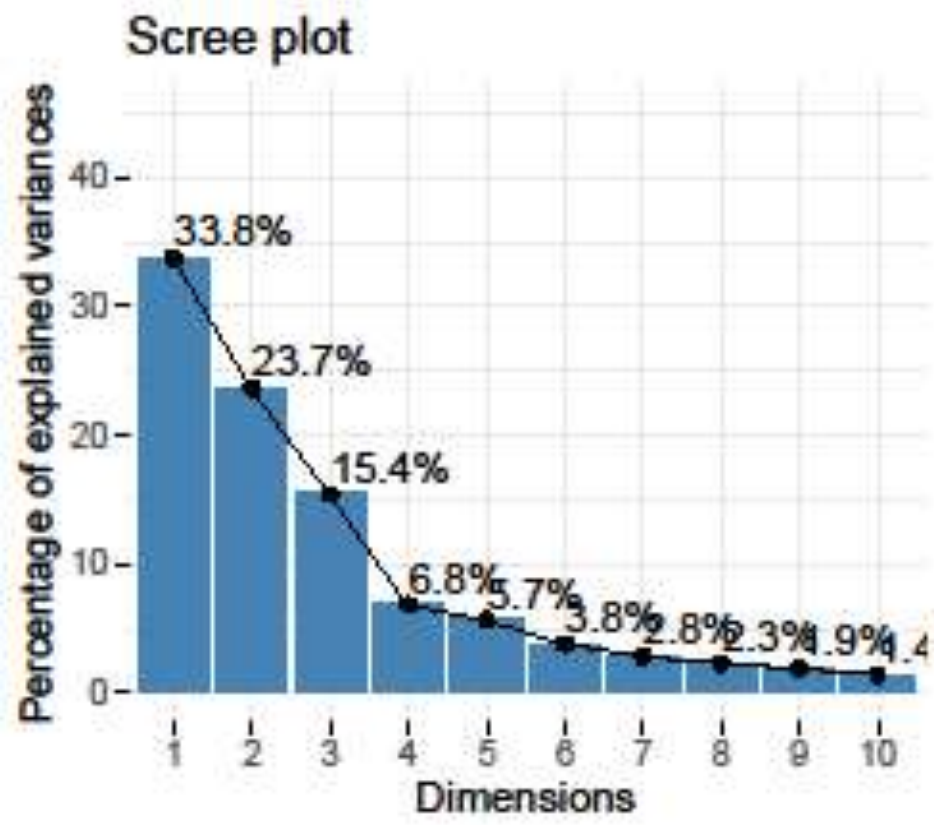
Some histograms to explore which column to transform

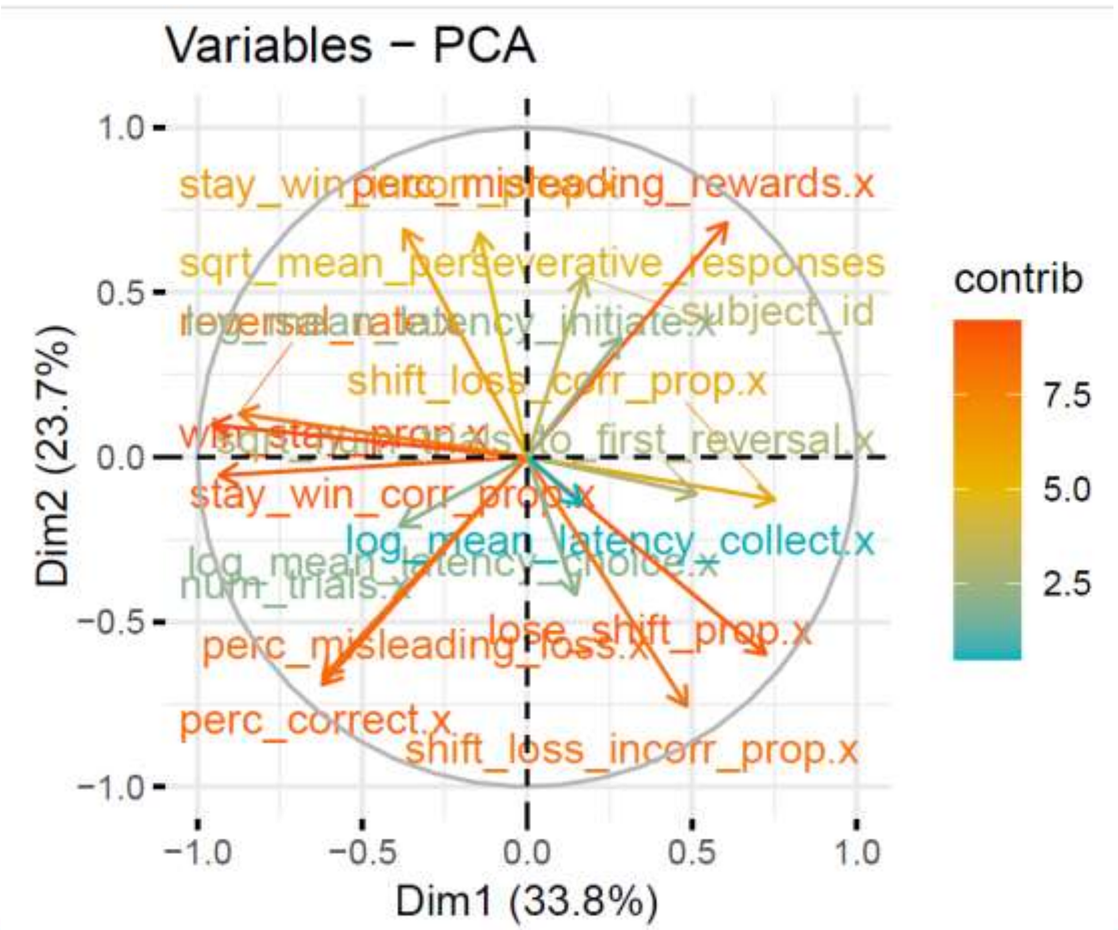


Outcome of preprocessing and data wrangling



Some unsupervised analysis: PCA results





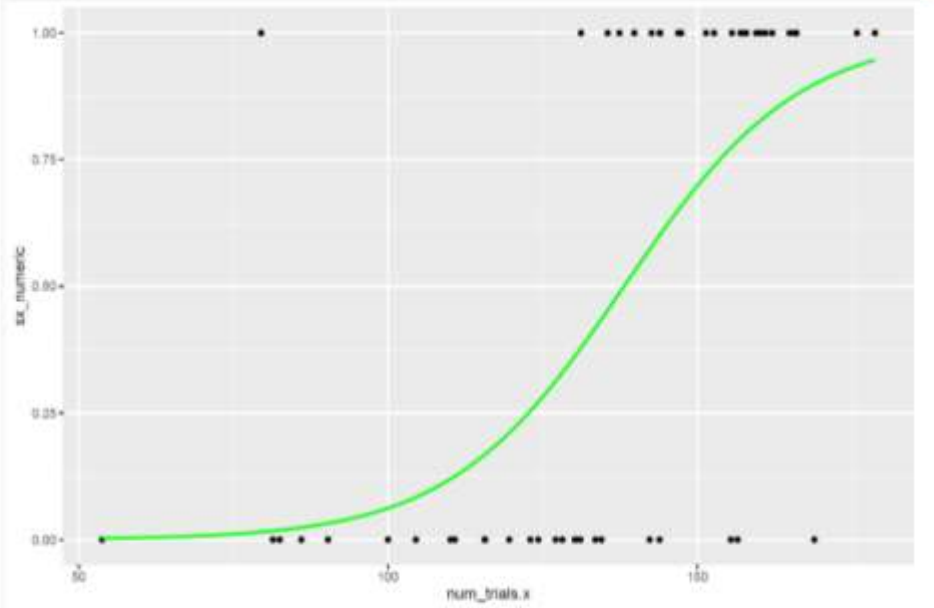
Logistic regression 1: mn dataset, predicting sex

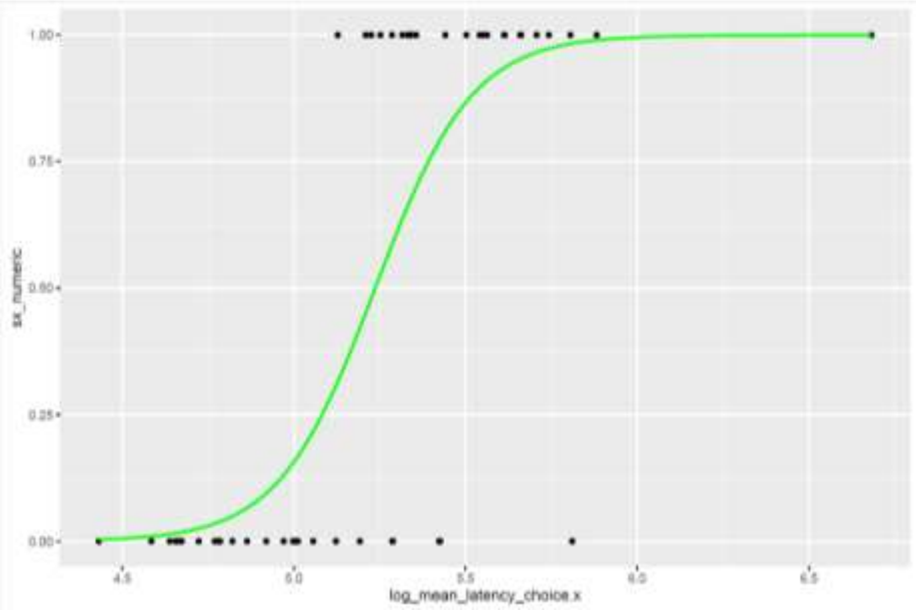
Legenda:
Females = 1

Accuracy = 0.667

```
$num_trials.x
Effect sizes were labelled following Chen's (2010) recommendations.

very small (Std. beta = 0.12, 95% CI [-0.54, 0.81])
medium (Std. beta = -1.59, 95% CI [-2.69, -0.75])
```



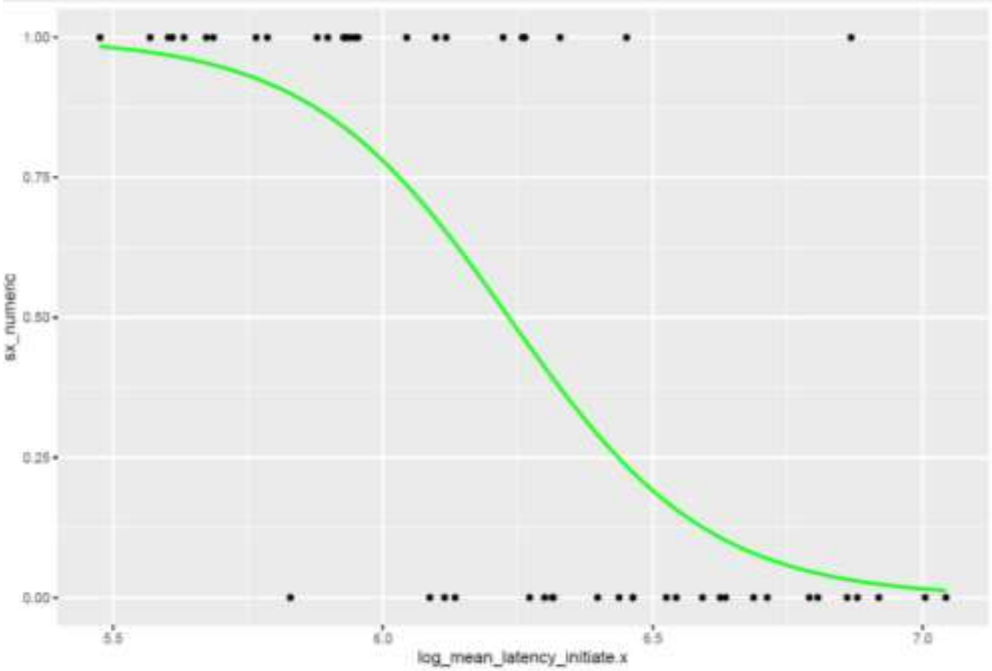


Accuracy = 1

```
$log_mean_latency_choice.x
Effect sizes were labelled following Chen's (2010) recommendations.

very small (Std. beta = 0.11, 95% CI [-0.72, 0.99])
large (Std. beta = -3.14, 95% CI [-5.17, -1.76])
```

Logistic regression 1: mn dataset, predicting sex

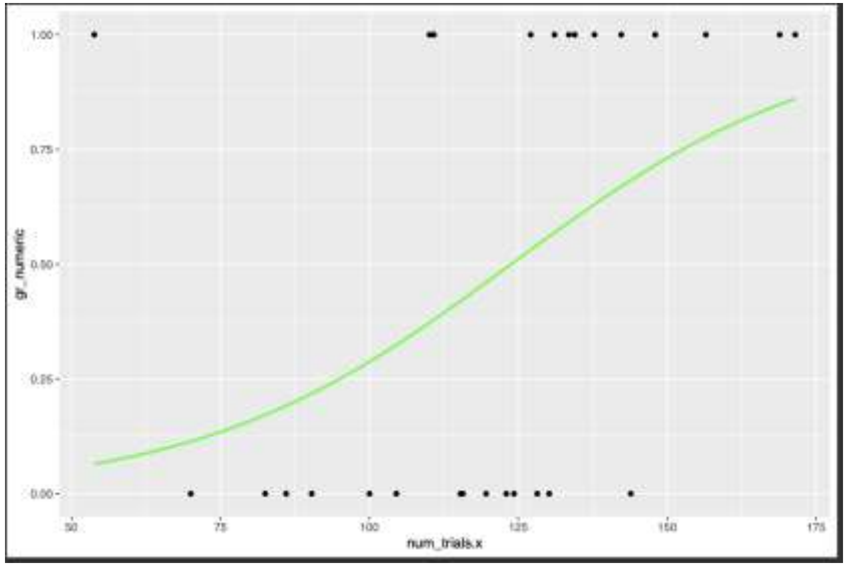



```
$log_mean_latency_initiate.x
Effect sizes were labelled following Chen's (2010) recommendations.

very small (Std. beta = 0.03, 95% CI [-0.70, 0.78])
large (Std. beta = 2.04, 95% CI [1.11, 3.30])
```

Accuracy: 0.75

Logistic regression 2: mn dataset, sex differences in predicting group

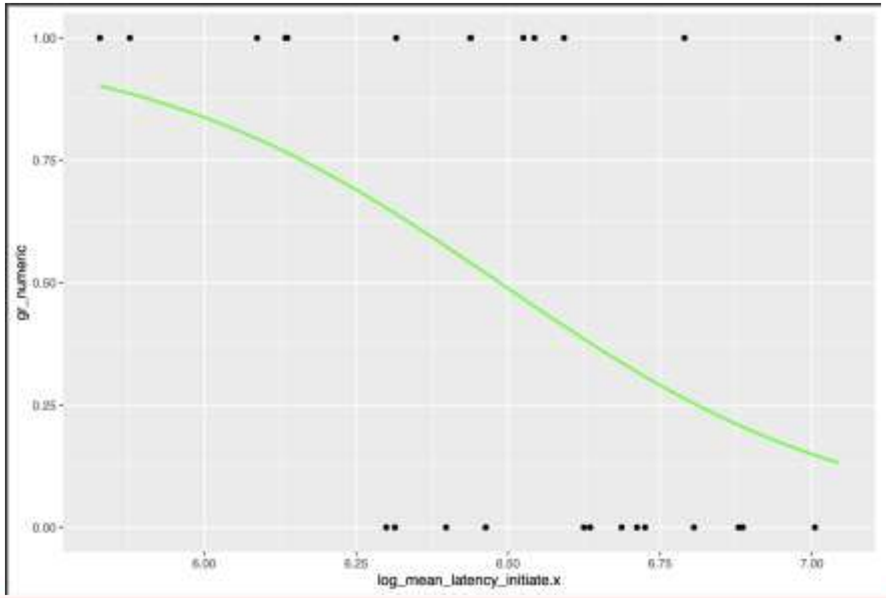



```
$num_trials.x
Effect sizes were labelled following Chen's (2010) recommendations.

very small (Std. beta = -0.12, 95% CI [-0.99, 0.72])
small (Std. beta = 1.07, 95% CI [0.15, 2.34])
```

```
$log_mean_latency_initiate.x
Effect sizes were labelled following Chen's (2010) recommendations.

very small (Std. beta = -0.07, 95% CI [-0.93, 0.79])
small (Std. beta = -1.07, 95% CI [-2.27, -0.17])
```



Comparing complete linear regressions

```
simple_glm1<- glm(sx_numeric ~ log_mean_latency_choice.x, data=train1, family = 'binomial')
summary(simple_glm1)

glm_complete1 <- glm(sx_numeric ~ log_mean_latency_choice.x + log_mean_latency_initiate.x  ,
           data=train1[,-18], family = 'binomial')
summary(glm_complete1)

glm_stepwise1 <- glm_complete1 %>%
  MASS::stepAIC(direction='both', trace = T)
```

```
> AIC(simple_glm1, glm_complete1, glm_stepwise1)
              df      AIC
simple_glm1    2 40.16955
glm_complete1  3 14.48311
glm_stepwise1  3 14.48311
```

```
> accuracy
[1] 0.6666667
```

```
simple_glm2<- glm(gr_numeric ~ log_mean_latency_collect.x, data=train2, family = 'binomial')
summary(simple_glm2)

glm_complete2 <- glm(gr_numeric ~ ., data=train2, family = 'binomial')
summary(glm_complete2)

glm_stepwise2 <- glm_complete2 %>%
  MASS::stepAIC(direction='both', trace = T)
```

```
> AIC(simple_glm2, glm_complete2, glm_stepwise2)
              df      AIC
simple_glm2    2 75.09014
glm_complete2 18 86.68958
glm_stepwise2  8 70.10396
```

```
> accuracy
[1] 1
```

LDA: application and results

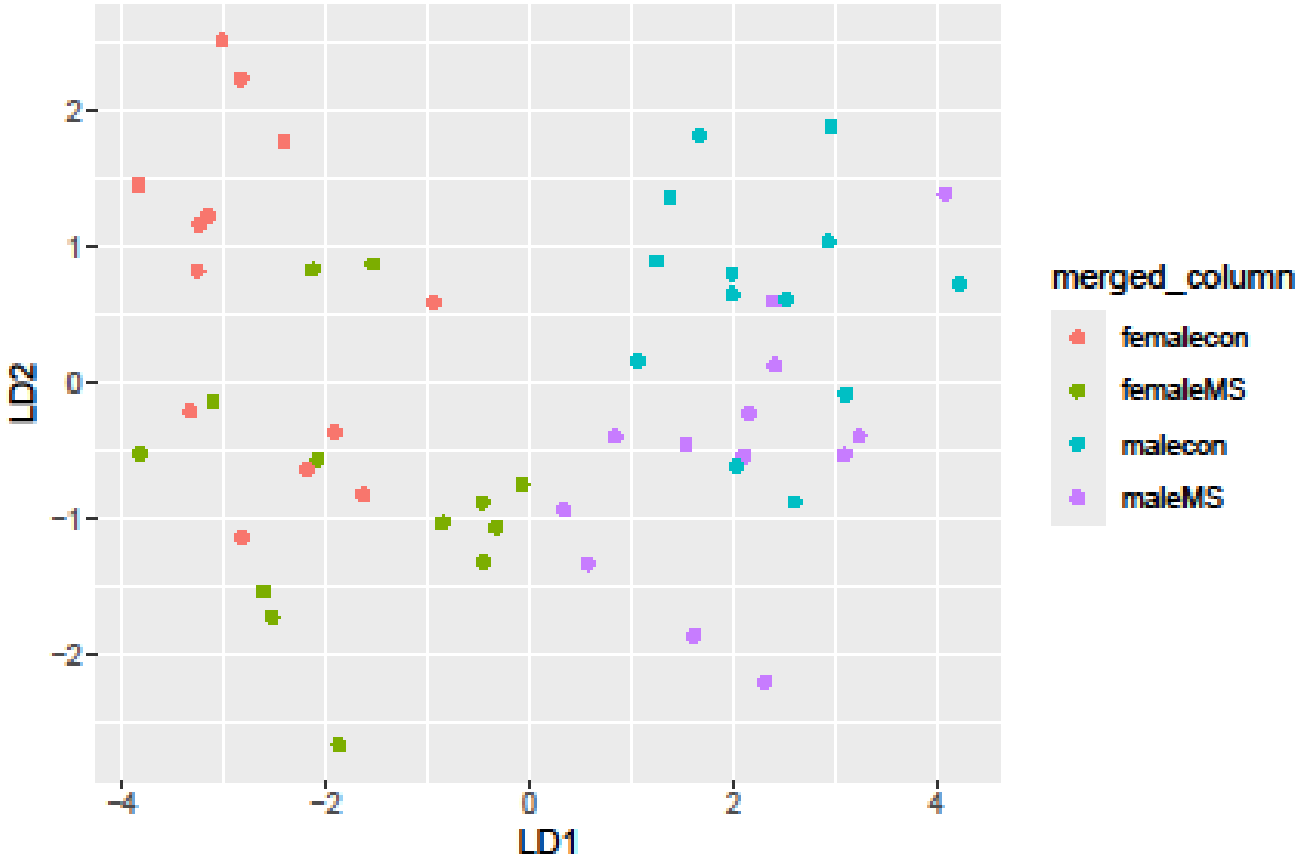
```
lda <- lda(factor(merged_column)~ ., data=train_transformed1[,-c(17,18)])
```

```
Overall Statistics

               Accuracy : 0.5962
                 95% CI : (0.451, 0.7299)
    No Information Rate : 0.25
    P-Value [Acc > NIR] : 1.26e-07

Confusion Matrix and Statistics
```

	Reference			
Prediction	femalecon	femaleMS	malecon	maleMS
femalecon	1	0	0	0
femaleMS	2	3	0	1
malecon	0	0	2	2
maleMS	0	0	1	0

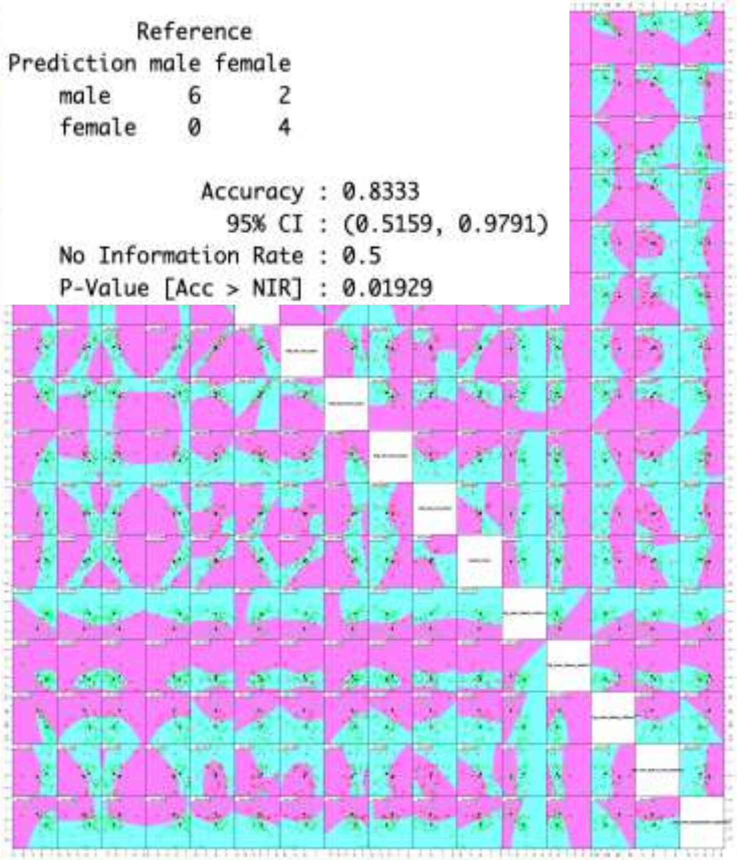


QDA with two classes

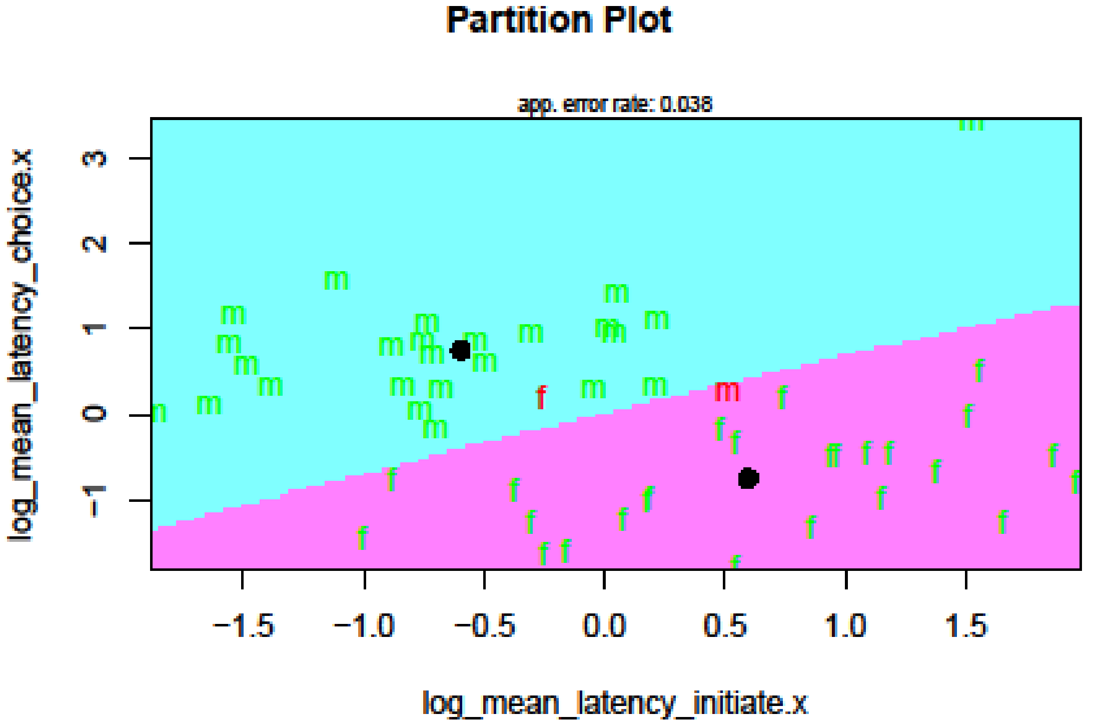
```
qda3 <- qda(factor(sex)~  ., data=train_transformed3)
```

```
          Reference
Prediction male female
    male      6      2
    female    0      4

               Accuracy : 0.8333
                 95% CI : (0.5159, 0.9791)
    No Information Rate : 0.5
    P-Value [Acc > NIR] : 0.01929
```



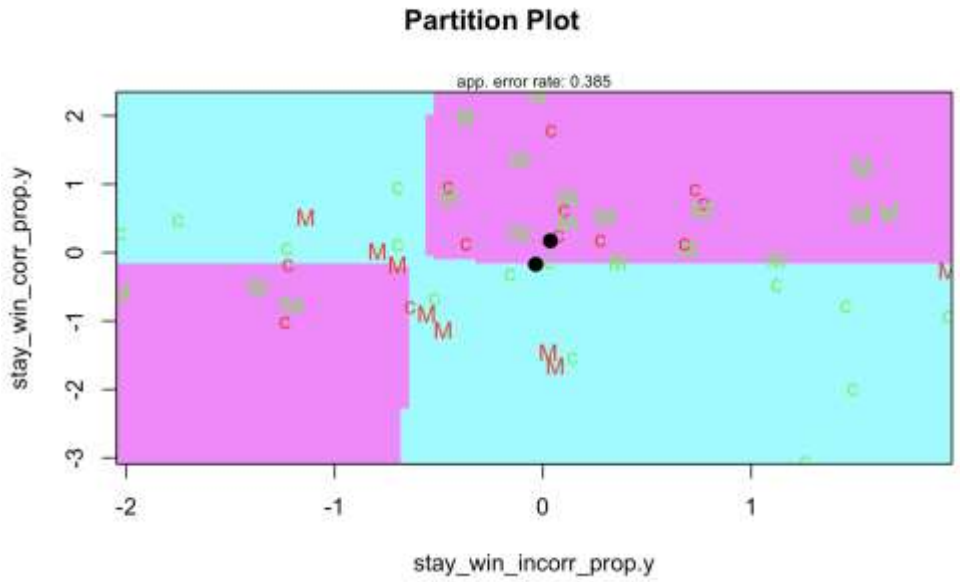
```
partimat(factor(sex) ~ log_mean_latency_choice.x + log_mean_latency_initiate.x,
         data=train_transformed3, method = "qda",
         col.correct='green', col.wrong='red')
```



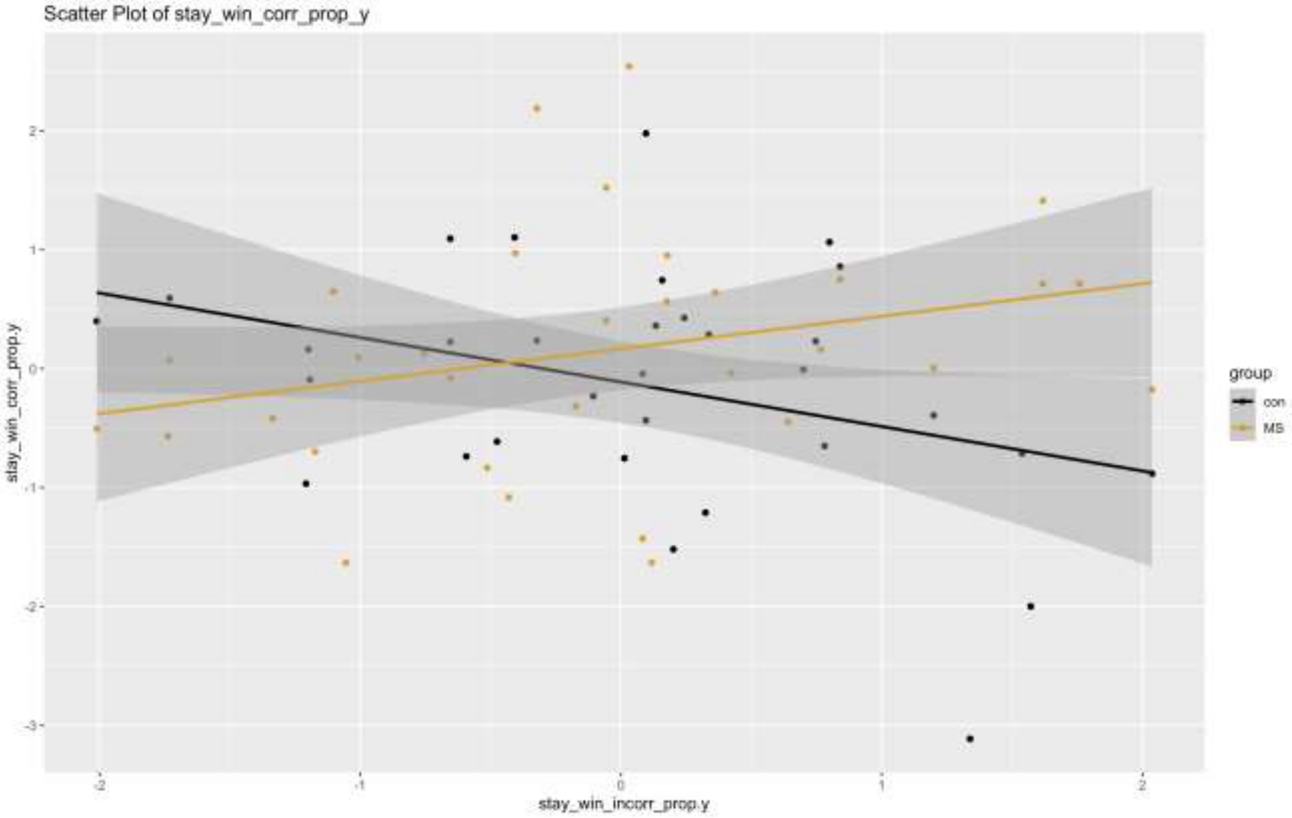
Some other interesting results

```
          Reference
Prediction con MS
       con   5  1
       MS    1  5

               Accuracy : 0.8333
                 95% CI : (0.5159, 0.9791)
    No Information Rate : 0.5
    P-Value [Acc > NIR] : 0.01929
```



- The effect of stay win incorr prop y × group [MS] is statistically significant and positive (beta = 0.65, 95% CI [0.16, 1.13], t(60) = 2.66, p = 0.010; Std. beta = 0.65, 95% CI [0.16, 1.13])



Conclusions

- There are **basal behavioural differences between sexes** on the PRL task, females have higher number of trials and higher choice latency while lower latency to initiate.

- **Differences for groups** in behavioural measures seem to be present **only** in **female rats**, highlighting a differential developmental effect of neglect dependent on sex.

- There is a **"resilient" phenotype** in maltreated females that confers them better task scores but this effect could **hide** a more subtle **vulnerability**

Possible further developments

- **Cross validate** the models to better estimate performances
- Are maltreated female rats really that "resilient"? Could there be **differences in treatment outcomes**? -> Data on pharmacological tests
- Are there **brain-wide alterations** associated with maltreatment status and behavioural differences? -> Analyze **MRI data**
- **Functional data analysis** using all the 640 rows of the longitudinal dataset instead of only the 64 rows used in the current analysis

Thank you for the attention!

References

- [2] Bradatan C, Firebaugh G. History, Population Policies, and Fertility Decline in Eastern Europe. J Fam Hist 2007;32:179–92. https://doi.org/10.1177/0363199006297732.
- Grolemund, Garrett, and Hadley Wickham. R for Data Science. O'Reilly Media, 2017.
- [1] McLaughlin KA, Sheridan MA, Lambert HK. Childhood adversity and neural development: Deprivation and threat as distinct dimensions of early experience. Neurosci Biobehav Rev 2014;47:578–91. https://doi.org/10.1016/j.neubiorev.2014.10.012
- Young-Southward G, Svelnys C, Gajwani R, Bosquet Enlow M, Minnis H. Child Maltreatment, Autonomic Nervous System Responsivity, and Psychopathology: Current State of the Literature and Future Directions. Child Maltreat 2020;25:3–19. https://doi.org/10.1177/1077559519848497
- Z. Q. John Lu, The Elements of Statistical Learning: Data Mining, Inference, and Prediction, *Journal of the Royal Statistical Society Series A: Statistics in Society*, Volume 173, Issue 3, July 2010, Pages 693–694, https://doi.org/10.1111/j.1467-985X.2010.00646_6.x