

Meta-Analysis

```
library(tidyverse)
library(kableExtra)
library(rmarkdown)
library(knitr)
library(janitor)
library(meta)
library(metafor)
library(readxl)
library(writexl)
```

Full data wrangling

```
full_data <- read.csv("full_data.csv") %>%
  filter(AnnotatorIdStr == "00374321-95a7-4a2a-a12c-af4c0f9e599b",
         NumberOfAnimals!= 0, #filters out studies with no n number
         StudyId != "6d537dfe-3d19-4dbf-b9af-bf9fad52bb4b")
```

#LTP data ## data wrangling to get the right data

```
LTPdata <- full_data %>%
  filter(Outcome.measure.category == "LTP") ##>%
# write_xlsx('newLTP_data.xlsx') # use this data to add n
# numbers
```

```
LTP_data <- read_xlsx("LTP_data_newn.xlsx") %>%
  ## removes studies not needed
group_by(ExperimentID) %>%
  filter(any(ModelType == "model control") & any(ModelType ==
    "model"))
```

selecting the right columns

```
LTP_model_data <- LTP_data %>%
  select(MatchId, StudyId, Author, OutcomeLabel, CohortId,
         ExperimentID, GreaterIsWorse, OutcomeResult, Outcome.measure.average.type,
         OutcomeError, Outcome.measure.error.type, ModelType,
         New_n, TimeInMinute, Sex.of.animals.in.cohort, What.age..weeks..were.animals.when.EPhys.outcome)
```

LTP 30 minutes

```
## LTP at 30 min
LTP_model_data_30 <- LTP_model_data %>%
  filter(TimeInMinute >29 & TimeInMinute< 31) %>% # first look at LTP at 30 min
  mutate(TimeInMinute = 30) %>%
  mutate(SD = ifelse(Outcome.measure.error.type == "SD",
                    OutcomeError, OutcomeError * sqrt(New_n)))%>%
  mutate(SEM = ifelse(Outcome.measure.error.type == "SEM",
                    OutcomeError, SD / sqrt(New_n))) %>%
  unique() %>% select(-OutcomeError) %>% # remove OutcomeError column
  mutate(Direction= ifelse(GreaterIsWorse ==TRUE, 1, -1)) %>%
  mutate(New_n = as.numeric(New_n)) %>%
  mutate(OutcomeResult = as.numeric(OutcomeResult)) %>%
  mutate(SEM = as.numeric(SEM)) %>%
  mutate(SD = as.numeric(SD))
```

Widen data set (30)

```
LTP_model_data_30_wide <- LTP_model_data_30 %>%
  pivot_wider(names_from = ModelType, values_from = c(New_n,
    SD, SEM, OutcomeResult, CohortId), values_fn = list) %>%
  unnest(cols = everything())
```

Calculating effect sizes (30)

```
LTP_model_data_30_final <- LTP_model_data_30_wide %>%
  mutate(combined_n = `New_n_model control` + New_n_model) %>%
  mutate(SPooled = sqrt(((`New_n_model control` - 1) * `SD_model control`^2 +
    (New_n_model - 1) * SD_model^2) / (combined_n-2))) %>%
  mutate(SMD_step1 = (`OutcomeResult_model control` - `OutcomeResult_model`)
    /SPooled) %>%
  mutate(SMD_step2 = (1 - (3/(4*combined_n-9)))) %>%
  mutate(SMD_ES = SMD_step1 * SMD_step2 * Direction) %>% #equation 15
  mutate(SMD_ES_SE = sqrt(
    combined_n/(New_n_model * `New_n_model control`) +
    SMD_ES^2/(2*(combined_n - 3.94)))) %>% #equation 16
  mutate(weight = 1/(SMD_ES_SE^2)) %>% #equation 20
  mutate(weighted_ES = SMD_ES * weight) %>% #equation 21
  group_by(StudyId) %>%
  mutate(id = cur_group_id()) %>%
  select(id, everything())
```

Random effects meta-analysis (30)

```
ma_results_ltp30 <- metagen(
  `SMD_ES`, # specify the effect size for each experiment
  `SMD_ES_SE`, # specify the variable that contains the standard error for each experiment
  sm = "SMD",
```

```

data = LTP_model_data_30_final, # specify the data set
studlab = id, # specify the study labels
comb.random = TRUE, # specify a random effects model
comb.fixed = FALSE,
method.tau = "REML") # specify which method is used to estimate the between-study variance

summary(ma_results_ltp30)

```

Forest Plot (30)

```

forest_plot_30 <- forest(
  ma_results_ltp30, # specify the meta-analysis to plot
  sortvar = TE, # sort the data according to effect size
  comb.fixed = FALSE, # do not plot the fixed effect estimate
  comb.random = TRUE, # plot the random effects estimate
  xlab = "SMD", # specify the x axis label
  smlab = "Standardised Mean Difference", # specify the effect size label
  label.right = "Increased LTP", # specify the graph label on right side of plot
  label.left = "Decreased LTP", # specify the graph label on left side of plot
  fontsize = 18, # specify the size of text (in points)
  plotwidth = "15cm", # specify the width of the plotting region
  digits = 1, # specify minimal number of significant digits for treatment effects
  digits.se = 1, # specify minimal number of significant digits for standard errors
  col.square="lightblue",
  leftcols = c("id"),
  leftlabs = c("id"),
  col.diamond = "darkblue",
  spacing=1.2
)

```

Publication Bias (30)

```

# Define fill colors for contour
col.contour = c("gray75", "gray85", "gray95")

# Generate funnel plot (we do not include study labels here)
funnel.meta(ma_results_ltp30, xlim = c(-8, 2), #took the SMD from the forest plot
  contour = c(0.9, 0.95, 0.99),
  col.contour = col.contour)

# Add a legend
legend(x = -7.5, y = 0.01,
  legend = c("p < 0.1", "p < 0.05", "p < 0.01"),
  fill = col.contour)

# Add a title
title("Funnel Plot of LTP after 30 min")

```

```
## Adds columns to the ma_results_ltp30 to use in the Pustejovsky analysis
ma_results_ltp30$n.e = LTP_model_data_30_final$New_n_model
ma_results_ltp30$n.c = LTP_model_data_30_final$`New_n_model control`

# Pustejovsky
metabias(ma_results_ltp30, method.bias = "Pustejovsky")
```

Trim and Fill (30)

Needed to load to find outliers <https://raw.githubusercontent.com/MathiasHarrer/dmetar/master/R/find.outliers.R>

```
## Trim Fill
tf_ltp30 <- trimfill(ma_results_ltp30)
summary(tf_ltp30)

# Define fill colors for contour
contour <- c(0.9, 0.95, 0.99)
col.contour <- c("gray75", "gray85", "gray95")
ld <- c("p < 0.1", "p < 0.05", "p < 0.01")

# Use 'par' to create two plots in one row (row, columns)
par(mfrow=c(1,2))

# Contour-enhanced funnel plot (full data)
funnel.meta(tf_ltp30,
            xlim = c(-8, 8), contour = contour,
            col.contour = col.contour)
legend(x = -7.5, y = 0,
       legend = ld, fill = col.contour)
title("Funnel Plot (Trim & Fill Method)")

# find outliers
find.outliers(ma_results_ltp30) ## have to load a package (chap 5.2 in handbook)

# filter out outliers and rerun meta and funnel plot
ltp30_nooutliers <- LTP_model_data_30_final %>%
  filter(id != 10,
         id != 5,
         id != 3)

ma_results_ltp30_nooutliers <- metagen(
  `SMD_ES`, # specify the effect size for each experiment
  `SMD_ES_SE`, # specify the variable that contains the standard error for each experimen
  sm = "SMD",
  data = ltp30_nooutliers, # specify the data set
  studlab = id, # specify the study labels
  comb.random = TRUE, # specify a random effects model
  comb.fixed = FALSE,
  method.tau = "REML") # specify which method is used to estimate the between-study variance
```

```
summary(ma_results_ltp30_nooutliers) ## reduces heterogeneity to 25%

tf_ltp30_nooutliers <- trimfill(ma_results_ltp30_nooutliers)
summary(tf_ltp30_nooutliers)

# Define fill colors for contour
contour <- c(0.9, 0.95, 0.99)
col.contour <- c("gray75", "gray85", "gray95")
ld <- c("p < 0.1", "p < 0.05", "p < 0.01")

# Contour-enhanced funnel plot (outliers removed)
funnel.meta(tf_ltp30_nooutliers,
            xlim = c(-8, 8), contour = contour,
            col.contour = col.contour)
legend(x = -7.5, y = 0.01,
       legend = ld, fill = col.contour)
title("Funnel Plot (Trim & Fill Method)
      -Outliers Removed")
```

LTP 60 minutes

```
## LTP at 30 min
LTP_model_data_60 <- LTP_model_data %>%
  filter(TimeInMinute >59 & TimeInMinute< 61) %>% # first look at LTP at 30 min
  mutate(TimeInMinute = 60) %>%
  mutate(SD = ifelse(Outcome.measure.error.type == "SD",
                    OutcomeError, OutcomeError * sqrt(New_n)))%>%
  mutate(SEM = ifelse(Outcome.measure.error.type == "SEM",
                    OutcomeError, SD / sqrt(New_n))) %>%
  unique() %>% select(-OutcomeError) %>% # remove OutcomeError column
  mutate(Direction= ifelse(GreaterIsWorse ==TRUE, 1, -1)) %>%
  mutate(New_n = as.numeric(New_n)) %>%
  mutate(OutcomeResult = as.numeric(OutcomeResult)) %>%
  mutate(SEM = as.numeric(SEM)) %>%
  mutate(SD = as.numeric(SD))
```

Widen data set(60)

```
LTP_model_data_60_wide <- LTP_model_data_60 %>%
  pivot_wider(names_from = ModelType, values_from = c(New_n,
    SD, SEM, OutcomeResult, CohortId), values_fn = list) %>%
  unnest(cols = everything())
```

Calculating effect sizes (60)

```
LTP_model_data_60_final <- LTP_model_data_60_wide %>%
  mutate(combined_n = `New_n_model control` + New_n_model) %>%
  mutate(SPooled = sqrt(((`New_n_model control` - 1) * `SD_model control`^2 +
    (New_n_model - 1) * SD_model^2) / (combined_n - 2))) %>%
  mutate(SMD_step1 = (`OutcomeResult_model control` - `OutcomeResult_model`)
    / SPooled) %>%
  mutate(SMD_step2 = (1 - (3 / (4 * combined_n - 9)))) %>%
  mutate(SMD_ES = SMD_step1 * SMD_step2 * Direction) %>% #equation 15
  mutate(SMD_ES_SE = sqrt(
    combined_n / (New_n_model * `New_n_model control` +
      SMD_ES^2 / (2 * (combined_n - 3.94)))) %>% #equation 16
  mutate(weight = 1 / (SMD_ES_SE^2)) %>% #equation 20
  mutate(weighted_ES = SMD_ES * weight) %>% #equation 21
  group_by(StudyId) %>%
  mutate(id = cur_group_id()) %>%
  select(id, everything())
```

Random effects meta-analysis (60)

```
ma_results_ltp60 <- metagen(
  `SMD_ES`, # specify the effect size for each experiment
  `SMD_ES_SE`, # specify the variable that contains the standard error for each experiment
  sm = "SMD",
  data = LTP_model_data_60_final, # specify the data set
  studlab = id, # specify the study labels
  comb.random = TRUE, # specify a random effects model
  comb.fixed = FALSE,
  method.tau = "REML") # specify which method is used to estimate the between-study variance

summary(ma_results_ltp60)
```

Forest Plot (60)

```
forest_plot_60 <- forest(
  ma_results_ltp60, # specify the meta-analysis to plot
  sortvar = TE, # sort the data according to effect size
  comb.fixed = FALSE, # do not plot the fixed effect estimate
  comb.random = TRUE, # plot the random effects estimate
  xlab = "SMD", # specify the x axis label
  smlab = "Standardised Mean Difference", # specify the effect size label
  label.right = "Increased LTP", # specify the graph label on right side of plot
  label.left = "Decreased LTP", # specify the graph label on left side of plot
  fontsize = 18, # specify the size of text (in points)
  plotwidth = "15cm", # specify the width of the plotting region
  digits = 1, # specify minimal number of significant digits for treatment effects
  digits.se = 1, # specify minimal number of significant digits for standard errors
```

```
col.square="lightblue",
leftcols = c("id"),
leftlabs = c("id"),
col.diamond = "darkblue",
spacing=1.2
)
```

#I/O data

```
IO_data <- full_data %>%
  filter(OutcomeLabel == "I/O") #>%
# write_xlsx('IO_data.xlsx')

IO_data <- read_xlsx("IO_data_newn.xlsx") %>%
  group_by(ExperimentID) %>%
  filter(any(ModelType == "model control") & any(ModelType ==
    "model"))
```

selecting the right columns

```
IO_model_data <- IO_data %>%
  select(MatchId, StudyId, Author, OutcomeLabel, CohortId,
    ExperimentID, GreaterIsWorse, OutcomeResult, Outcome.measure.average.type,
    OutcomeError, Outcome.measure.error.type, ModelType,
    New_n, TimeInMinute, Sex.of.animals.in.cohort, What.age..weeks..were.animals.when.EPhys.outcome
  mutate(TimeInMinute = "1")
```

calculating SD and SEM

```
IO_model_data <- IO_model_data %>%
  mutate(SD = ifelse(Outcome.measure.error.type == "SD", OutcomeError,
    OutcomeError * sqrt(New_n))) %>%
  mutate(SEM = ifelse(Outcome.measure.error.type == "SEM",
    OutcomeError, SD / sqrt(New_n))) %>%
  unique() %>% select(-OutcomeError) %>% # remove OutcomeError column
  mutate(Direction= ifelse(GreaterIsWorse ==TRUE, 1, -1)) %>%
  mutate(New_n = as.numeric(New_n)) %>%
  mutate(OutcomeResult = as.numeric(OutcomeResult)) %>%
  mutate(SEM = as.numeric(SEM)) %>%
  mutate(SD = as.numeric(SD))
```

Widen data set I/O

```
IO_model_data_wide <- IO_model_data %>%
  pivot_wider(names_from = ModelType, values_from = c(New_n,
    SD, SEM, OutcomeResult, CohortId), values_fn = list) %>%
  unnest(cols = everything())
```

Calculating effect sizes I/O

```
IO_model_data_final <- IO_model_data_wide %>%
  mutate(combined_n = `New_n_model control` + New_n_model) %>%
  mutate(SPooled = sqrt(((`New_n_model control` - 1) * `SD_model control`^2 +
    (New_n_model - 1) * SD_model^2) / (combined_n - 2))) %>%
  mutate(SMD_step1 = (`OutcomeResult_model control` - `OutcomeResult_model`)
    / SPooled) %>%
  mutate(SMD_step2 = (1 - (3 / (4 * combined_n - 9)))) %>%
  mutate(SMD_ES = SMD_step1 * SMD_step2 * Direction) %>% #equation 15
  mutate(SMD_ES_SE = sqrt(
    combined_n / (New_n_model * `New_n_model control` +
      SMD_ES^2 / (2 * (combined_n - 3.94)))) %>% #equation 16
  mutate(weight = 1 / (SMD_ES_SE^2)) %>% #equation 20
  mutate(weighted_ES = SMD_ES * weight) %>% #equation 21
  group_by(StudyId) %>%
  mutate(id = cur_group_id()) %>%
  select(id, everything())
```

Random effects meta-analysis I/O

```
ma_results_IO <- metagen(
  `SMD_ES`, # specify the effect size for each experiment
  `SMD_ES_SE`, # specify the variable that contains the standard error for each experiment
  sm = "SMD",
  data = IO_model_data_final, # specify the data set
  studlab = id, # specify the study labels
  comb.random = TRUE, # specify a random effects model
  comb.fixed = FALSE,
  method.tau = "REML") # specify which method is used to estimate the between-study variance

summary(ma_results_IO)

smd_IO <- ma_results_IO %>%
  as.data.frame() %>%
  select("SMD" = "TE", "id" = "studlab") ## gets the SMD into a data frame
```

Forest Plot I/O

```
forest_plot_IO <- forest(
  ma_results_IO, # specify the meta-analysis to plot
  sortvar = TE, # sort the data according to effect size
  comb.fixed = FALSE, # do not plot the fixed effect estimate
  comb.random = TRUE, # plot the random effects estimate
  xlab = "SMD", # specify the x axis label
  smlab = "Standardised Mean Difference", # specify the effect size label
  label.right = "Increased I/O", # specify the graph label on right side of plot
```



```

label.left = "Decreased I/O", # specify the graph label on left side of plot
fontsize = 18, # specify the size of text (in points)
plotwidth = "15cm", # specify the width of the plotting region
digits = 1, # specify minimal number of significant digits for treatment effects
digits.se = 1, # specify minimal number of significant digits for standard errors
col.square="lightblue",
leftcols = c("id"),
leftlabs = c("id"),
col.diamond = "darkblue",
spacing=1.2
)

```

Other Data needed

```

PPF_data <- full_data %>%
  filter(OutcomeLabel == c("PPF", "PPR")) %>%
  group_by(ExperimentID) %>%
  filter(any(ModelType == "model control") &
    any(ModelType == "model")) %>%
  select(StudyId, Author, OutcomeLabel,
    CohortId, ExperimentID, GreaterIsWorse, OutcomeResult,
    Outcome.measure.average.type, OutcomeError,
    Outcome.measure.error.type, ModelType, Number.of.animals.in.cohort,
    TimeInMinute, Sex.of.animals.in.cohort,
    What.age..weeks..were.animals.when.EPhys.outcomes.were.assessed.) %>%
  filter(TimeInMinute == "50")

LTP_90_data <- full_data %>%
  filter(OutcomeLabel == "LTP") %>%
  group_by(ExperimentID) %>%
  filter(any(ModelType == "model control") &
    any(ModelType == "model")) %>%
  select(StudyId, Author, OutcomeLabel,
    CohortId, ExperimentID, GreaterIsWorse, OutcomeResult,
    Outcome.measure.average.type, OutcomeError,
    Outcome.measure.error.type, ModelType, Number.of.animals.in.cohort,
    TimeInMinute, Sex.of.animals.in.cohort,
    What.age..weeks..were.animals.when.EPhys.outcomes.were.assessed.) %>%
  filter(TimeInMinute >89 & TimeInMinute< 91) %>% # first look at LTP at 30 min
  mutate(TimeInMinute = 90)

LTD_30_data <- full_data %>%
  filter(OutcomeLabel == "LTD") %>%
  group_by(ExperimentID) %>%
  filter(any(ModelType == "model control") &
    any(ModelType == "model")) %>%
  select(StudyId, Author, OutcomeLabel,
    CohortId, ExperimentID, GreaterIsWorse, OutcomeResult,
    Outcome.measure.average.type, OutcomeError,

```

```

      Outcome.measure.error.type, ModelType, Number.of.animals.in.cohort,
      TimeInMinute, Sex.of.animals.in.cohort,
      What.age..weeks..were.animals.when.EPhys.outcomes.were.assessed.) %>%
filter(TimeInMinute >29 & TimeInMinute< 31) %>% # first look at LTP at 30 min
mutate(TimeInMinute = 30)

LTD_60_data <- full_data %>%
  filter(OutcomeLabel == "LTD") %>%
  group_by(ExperimentID) %>%
  filter(any(ModelType == "model control") &
         any(ModelType == "model")) %>%
  select(StudyId, Author, OutcomeLabel,
         CohortId, ExperimentID, GreaterIsWorse, OutcomeResult,
         Outcome.measure.average.type, OutcomeError,
         Outcome.measure.error.type, ModelType, Number.of.animals.in.cohort,
         TimeInMinute, Sex.of.animals.in.cohort,
         What.age..weeks..were.animals.when.EPhys.outcomes.were.assessed.) %>%
  filter(TimeInMinute >59 & TimeInMinute< 61) %>% # first look at LTP at 30 min
  mutate(TimeInMinute = 60)

```