

Antidepressant effects of esketamine in adolescents with major depressive disorder and suicidal ideation: a case series

Reproducible analysis report

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Note

This R Markdown file will exactly reproduce our data tidying, transformation, analysis and graphing processes in the R software and produce an illustrative PDF file. Code-only scripts are also available in the Open Science Framework repository for this study, at <https://osf.io/2ujqn/>. The reproduction of this `markdown` file requires that the dataset available in the OSF repository is located in the same directory of this file, and that the user has the necessary dependencies to create a PDF using the `bookdown` package. Further information is available at the package website. Please refer to the repository for a detailed description of each variable contained herein. All files in the repository, including this one, are licensed under CC-BY-4.0.

```
# Required Packages
packages = c("tidyverse", "haven",
             "lsr", "rstatix", "exactRankTests", "boot", "skimr", "kableExtra",
             "patchwork", "RColorBrewer", "ggsci", "car", "printr")
package.check <- lapply(
  packages,
  FUN = function(x) {
    if (!require(x, character.only = TRUE)) {
      install.packages(x)
      library(x, character.only = TRUE)
    }
  }
)
```

Load and manage dataset

To correctly load the data, place the “dataset.sav” file in the same directory of this R Markdown script.

```
set.seed(252009)

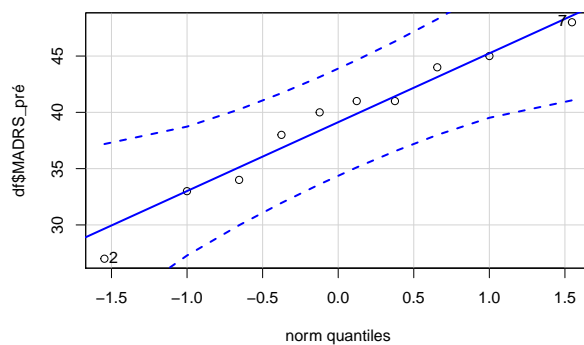
## Read the database
df <- haven::read_sav("Dataset.sav")
df <- haven::zap_formats(df) #remove unnecessary information from columns
```

Assessing distribution and descriptives

Visualize data distribution at each timepoint

MADRS total score at baseline

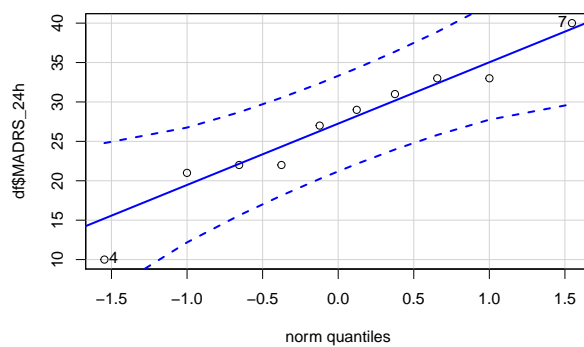
```
car::qqPlot(df$MADRS_pré)
```



```
## [1] 2 7
```

MADRS total score at 24h post-treatment

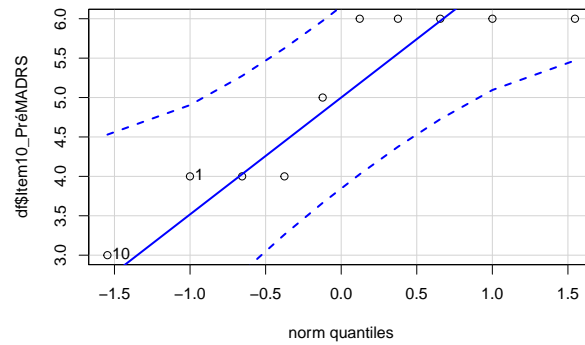
```
car::qqPlot(df$MADRS_24h)
```



```
## [1] 4 7
```

MADRS item 10 score at baseline

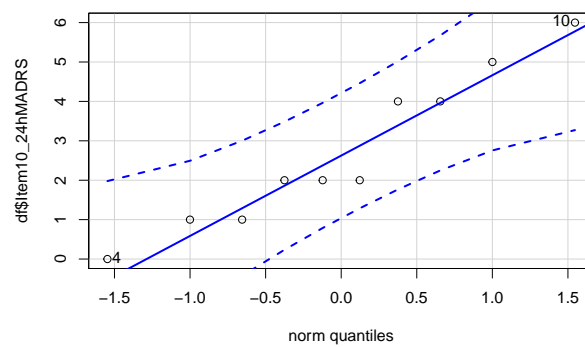
```
car::qqPlot(df$Item10_PréMADRS)
```



```
## [1] 10 1
```

MADRS item 10 score at 24h post-treatment

```
car::qqPlot(df$Item10_24hMADRS)
```



```
## [1] 10 4
```

MADRS total scores

```
madsr_total <- c(df$MADRS_pré, df$MADRS_24h)
time <- rep(c("baseline", "post"), each = 10)
data_madsr_total <- tibble(time, madsr_total)
data_madsr_total %>% group_by(time) %>%
  summarise(
    mean = mean(madsr_total),
    sd = sd(madsr_total)
  )
```

time	mean	sd
baseline	39.1	6.297266
post	26.8	8.403703

MADRS item 10 scores

```
item_10_total <- c(df$Item10_PréMADRS, df$Item10_24hMADRS)
time <- rep(c("baseline", "post"), each = 10)
data_madsr_total <- tibble(time, item_10_total)
data_madsr_total %>% group_by(time) %>%
  summarise(
    mean = mean(item_10_total),
    sd = sd(item_10_total)
  )
```

time	mean	sd
baseline	5.0	1.154700
post	2.7	1.946507

T-tests and effect sizes

```
### T-test - MADRS Total Scores
```

```
t.test(x = df$MADRS_pré,  
       y = df$MADRS_24h,  
       paired = T) ## do paired sample T-tests
```

```
##  
## Paired t-test  
##  
## data: df$MADRS_pré and df$MADRS_24h  
## t = 4.2213, df = 9, p-value = 0.002235  
## alternative hypothesis: true difference in means is not equal to 0  
## 95 percent confidence interval:  
## 5.708616 18.891384  
## sample estimates:  
## mean of the differences  
## 12.3
```

```
lsr::cohensD(df$MADRS_pré,  
             df$MADRS_24h,  
             method = "paired") ## calculate Cohen's effect size
```

```
## [1] 1.334908
```

```
### T-test - MADRS Item 10 scores
```

```
t.test(x = df$Item10_PréMADRS,  
       y = df$Item10_24hMADRS,  
       paired = T)
```

```
##  
## Paired t-test  
##  
## data: df$Item10_PréMADRS and df$Item10_24hMADRS  
## t = 3.1461, df = 9, p-value = 0.01181  
## alternative hypothesis: true difference in means is not equal to 0  
## 95 percent confidence interval:  
## 0.646234 3.953766  
## sample estimates:  
## mean of the differences  
## 2.3
```

```
lsr::cohensD(df$Item10_PréMADRS,  
             df$Item10_24hMADRS,  
             method = "paired")
```

```
## [1] 0.9948934
```

Bootstrapped 95% confidence intervals

Create a bootstrap function

This functions creates a main element, the `data_dens` data frame. It stores the bootstrapped samples of means as they are calculated using the bias-corrected and accelerated (Bca) method. These are later used to plot density graphs that compare bootstrapped distributions of pre-and post-treatment symptoms.

```
boot_funs <- function(df, f1, f2){  
  a <- df[[f1]]  
  b <- df[[f2]]  
  boot_a <- boot(a,  
    function(x, j) mean(x[j], na.rm = T), #Boot baseline variable  
    R = 10000)  
  boot_b <- boot(b,  
    function(x, j) mean(x[j], na.rm = T), #Boot 7 days variable  
    R = 10000)  
  boot_ci_a <- boot.ci(boot.out = boot_a, #Calculate baseline CI  
    conf = 0.95,  
    type = "bca")  
  boot_ci_b <- boot.ci(boot.out = boot_b, #Calculate post-treatment CI  
    conf = 0.95,  
    type = "bca")  
  print(boot_ci_a) # Return baseline bootstrapped CI  
  print(boot_ci_b) # Return post-treatment bootstrapped CI  
  
  ## Code to extract bootstrapped sample means  
  densitiy_a <- boot_a$t  
  densitiy_b <- boot_b$t  
  dens <- c(densitiy_a, densitiy_b)  
  time <- rep(c("Baseline", "Post-Treatment"), each = 10000)  
  data_dens <-< data.frame(dens, time)  
  data_dens$time <- factor(data_dens$time)  
}
```

Run bootstraps and create ggplot graph objects

Bootstrap - MADRS total score

```
### Bootstrap CI - MADRS total score
boot_funs(df, "MADRS_pré", "MADRS_24h")

## BOOTSTRAP CONFIDENCE INTERVAL CALCULATIONS
## Based on 10000 bootstrap replicates
##
## CALL :
## boot.ci(boot.out = boot_a, conf = 0.95, type = "bca")
##
## Intervals :
## Level      BCa
## 95%      (34.85, 42.30 )
## Calculations and Intervals on Original Scale
## BOOTSTRAP CONFIDENCE INTERVAL CALCULATIONS
## Based on 10000 bootstrap replicates
##
## CALL :
## boot.ci(boot.out = boot_b, conf = 0.95, type = "bca")
##
## Intervals :
## Level      BCa
## 95%      (21.1, 31.1 )
## Calculations and Intervals on Original Scale

plot_madrs <- ggplot(data_dens)+
  geom_density(aes(x = dens, fill = time),
               color = "white",
               alpha = 0.9)+
  labs(x = "Total MADRS scores")+
  scale_fill_brewer(name = "Time of assessment:",
                   palette = "Dark2")+
  theme_classic()+
  theme(text = element_text(family = "serif"),
        axis.text.x = element_text(size = 14),
        axis.title.x = element_text(size = 14),
        axis.text.y = element_text(size = 14),
        axis.title.y = element_text(size = 14),
        legend.text = element_text(size = 13),
        legend.title = element_text(size = 13)) ##ggplot2 graph
```

Bootstrap - MADRS item 10

```
### Bootstrap CI - MADRS item 10

boot_funs(df, "Item10_PréMADRS", "Item10_24hMADRS")

## BOOTSTRAP CONFIDENCE INTERVAL CALCULATIONS
## Based on 10000 bootstrap replicates
##
## CALL :
## boot.ci(boot.out = boot_a, conf = 0.95, type = "bca")
##
## Intervals :
## Level      BCa
## 95%      ( 4.1,  5.5 )
## Calculations and Intervals on Original Scale
## BOOTSTRAP CONFIDENCE INTERVAL CALCULATIONS
## Based on 10000 bootstrap replicates
##
## CALL :
## boot.ci(boot.out = boot_b, conf = 0.95, type = "bca")
##
## Intervals :
## Level      BCa
## 95%      ( 1.6,  3.9 )
## Calculations and Intervals on Original Scale

plot_madrs10 <- ggplot(data_dens)+
  geom_density(aes(x = dens, fill = factor(time)),
               color = "white",
               alpha = 0.9)+
  labs(x = "Item 10 MADRS scores",
       y = element_blank())+
  scale_fill_brewer(name = "Time of assessment:",
                   palette = "Dark2")+
  theme_classic()+
  theme(text = element_text(family = "serif"),
        axis.text.x = element_text(size = 14),
        axis.title.x = element_text(size = 14),
        axis.text.y = element_text(size = 14),
        axis.title.y = element_text(size = 14),
        legend.text = element_text(size = 13),
        legend.title = element_text(size = 13)) ##ggplot2 graph
```


Graphics

This first part creates an annotated plot using the `ggplot2` density plots for the bootstrapped sample means and the `patchwork` package.

```
## Density plots of bootstrapped sample means

## Creates patchwork object
graficos <- plot_madrs + plot_madrs10 &
  theme(legend.position = "bottom",
        text = element_text(family = "serif"),
        title = element_text(size = 12),
        legend.title = element_text(size = 12))

## Creates guided patchwork object
graficos_f <- graficos + plot_layout(guides = "collect")

## Edits and annotates patchwork object
plota <- graficos_f + plot_annotation(
  title = 'Supp. Fig. 1 - Bootstraped sample means for total and item 10 MADRS scores',
  subtitle = 'Density plots of results at baseline and 24 hours post-treatment')

## Saves plot in high resolution
ggsave("density_plot.png", plota, width=25, height=15, units="cm", dpi=450)
```

This next part uses a long formatted dataset to compare pre-and post-infusion results for each patient.

```
## Create dataset for total MADRS scores
madrs_total <- c(df$MADRS_pré, df$MADRS_24h)
time <- rep(c("baseline", "post"), each = 10)
id <- rep(1:10, 2)
id <- factor(id)
madrs_data_plot <- tibble(id, time, madrs_total)

## plot total MADRS scores
madrs_plot <- madrs_data_plot %>% ggplot()+
  geom_boxplot(aes(x = time, y = madrs_total),
               width = .3,
               alpha = .3,
               color = "grey")+
  scale_y_continuous(breaks = seq(from = 10,
                                   to = 50,
                                   by = 5))+
  scale_x_discrete(labels = c("Baseline", "24 hours post-infusion"))+
  geom_point(aes(x = time, y = madrs_total,
                 color = id,
                 group = id),
             size = 1.5)+
  geom_line(aes(x = time, y = madrs_total,
                color = id,
                group = id,
                alpha = .4),
            size = 1.5)+
  scale_color_npg()+
  theme_classic()+
```

```

labs(x = "Time of assessment",
     y = "Total MADRS scores")+
theme(axis.title.x = element_text(size = 14),
      axis.text.x = element_text(size = 13),
      axis.title.y = element_text(size = 15),
      axis.text.y = element_text(size = 13),
      legend.position = "none")

## Create dataset for MADRS Item 10

si_pre <- df$Item10_PréMADRS
si_post <- df$Item10_24hMADRS

madr_item10 <- c(si_pre, si_post)
time <- rep(c("baseline", "post"), each = 10)
id <- rep(1:10, 2)
id <- factor(id)
madr_item_plot <- tibble(id, time, madr_item10)

item10_plot <- madr_item_plot %>% ggplot()+
  geom_boxplot(aes(x = time, y = madr_item10),
               width = .3,
               alpha = .3,
               color = "grey")+
  scale_y_continuous(breaks = seq(from = 0,
                                  to = 6,
                                  by = 1))+
  scale_x_discrete(labels = c("Baseline", "24 hours post-infusion"))+
  geom_point(aes(x = time, y = madr_item10,
                 color = id,
                 group = id),
             size = 1.5,
             position = position_dodge(0.08))+
  geom_line(aes(x = time, y = madr_item10,
                color = id,
                group = id,
                alpha = .4),
            size = 1.5,
            position = position_dodge(0.08))+
  scale_color_npg()+
  theme_classic()+
  labs(x = "Time of assessment",
       y = "MADRS item 10 scores")+
  theme(axis.title.x = element_text(size = 14),
        axis.text.x = element_text(size = 13),
        axis.title.y = element_text(size = 15),
        axis.text.y = element_text(size = 13),
        legend.position = "none",
        text = element_text(family = "serif"))

```

Join and save plots

```
## Creates patchwork object
graficos_i10 <- madsr_plot + item10_plot &
  theme(text = element_text(family = "serif"),
        title = element_text(size = 16),
        legend.title = element_text(size = 14))

## Edits and annotates patchwork object
graficos_i10 <- graficos_i10 + plot_annotation(
  title = 'Total and item 10 MADRS scores at baseline and 24h post-treatment',
  subtitle = 'Scores are given for each patient')

## Saves plot in high resolution
ggsave("MADRS_plot.png", graficos_i10, width=25, height=15, units="cm", dpi=500)
```