SUPPLEMENTARY MATERIAL : Experience with opioids does not modify the brain network involved in expectations of placebo analgesia

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Contents

This is the supplementary material for the study:

Experience with opioids does not modify the brain network involved in expectations of placebo analgesia

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1 DESCRIPTIVE STATISTICS

1.1 Tables

Table I: Demographics distribution

DV	Group	Mean	SD	Median	IQR
Age	CondExp	24.824	6.525	22.50	6.00
Age	UncondExp	22.583	3.298	22.50	4.25
Sleep	CondExp	7.603	1.086	8.00	1.00
Sleep	UncondExp	7.507	0.651	7.50	1.00
AlcoholUnitsDaily	CondExp	0.340	0.557	0.00	0.50
AlcoholUnitsDaily	UncondExp	0.512	0.752	0.05	1.00
Height	CondExp	167.824	8.719	167.00	12.00
Height	UncondExp	173.472	7.894	172.50	10.25
Weight	CondExp	65.265	10.358	64.00	14.00
Weight	UncondExp	67.472	7.481	66.50	9.00

Note:
Parametric and non-parametric distribution parameters for the demographic variables. DV = Dependent Variable; IQR = Interquartile Range; SD = Standard Deviation.

1.2 Plots

Figure I: Demographics bee swarm plots

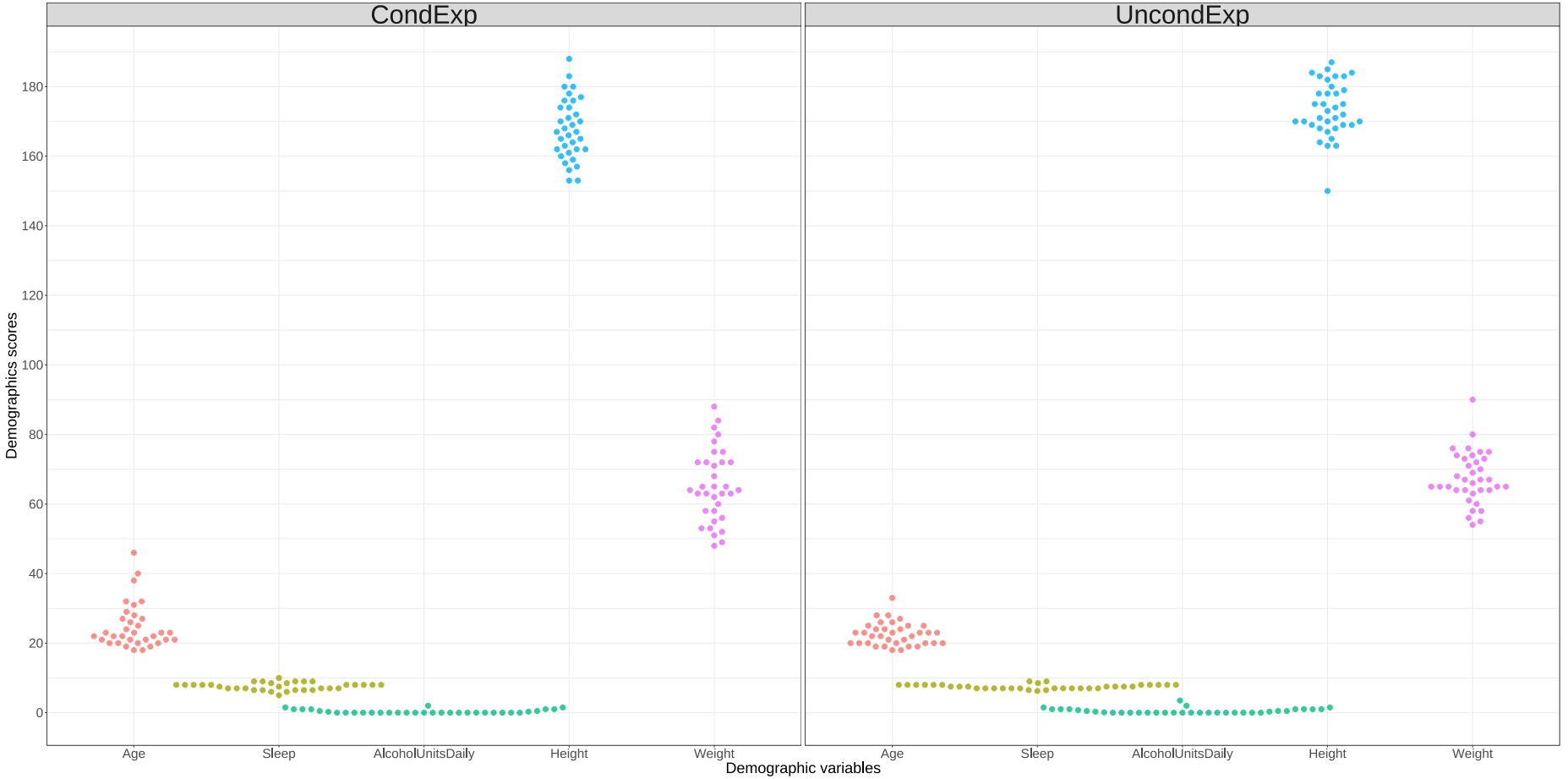
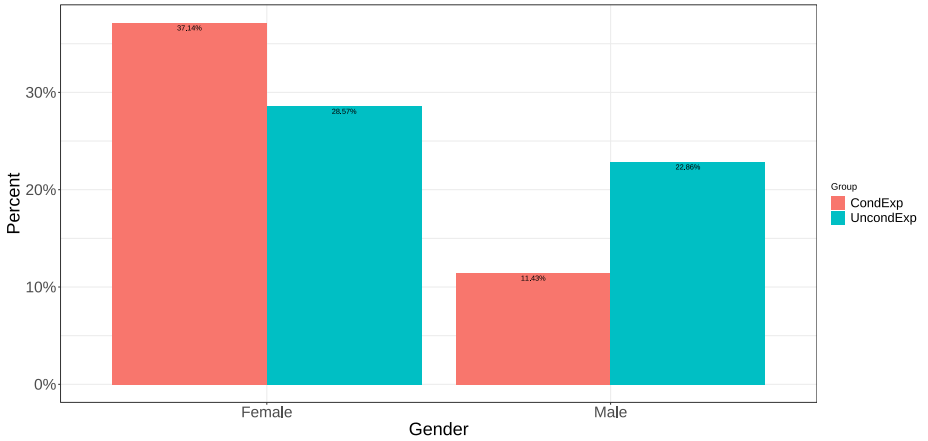
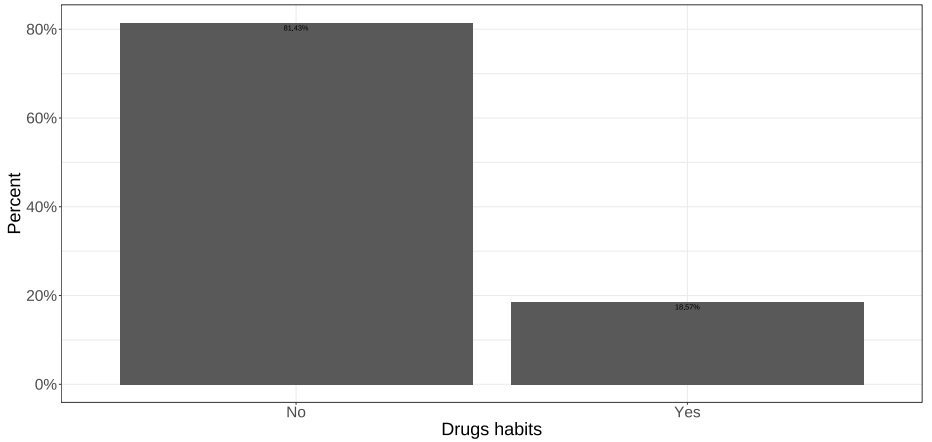


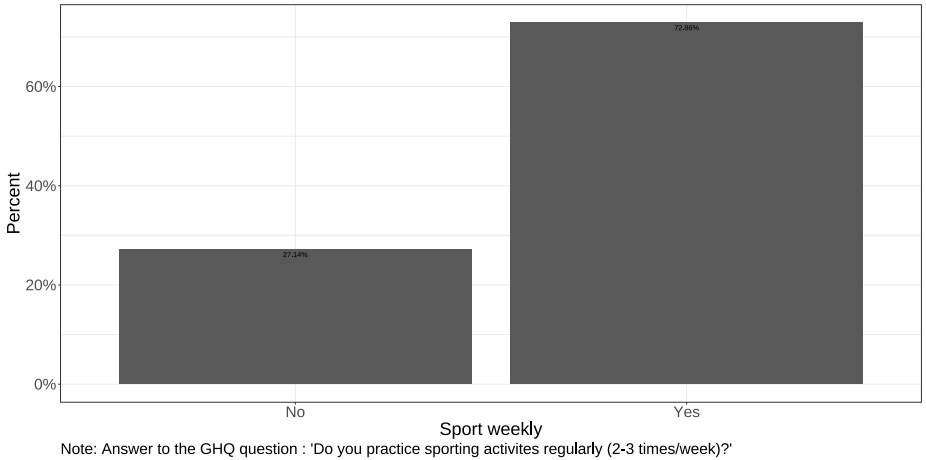
Figure II: Demographics bar plots



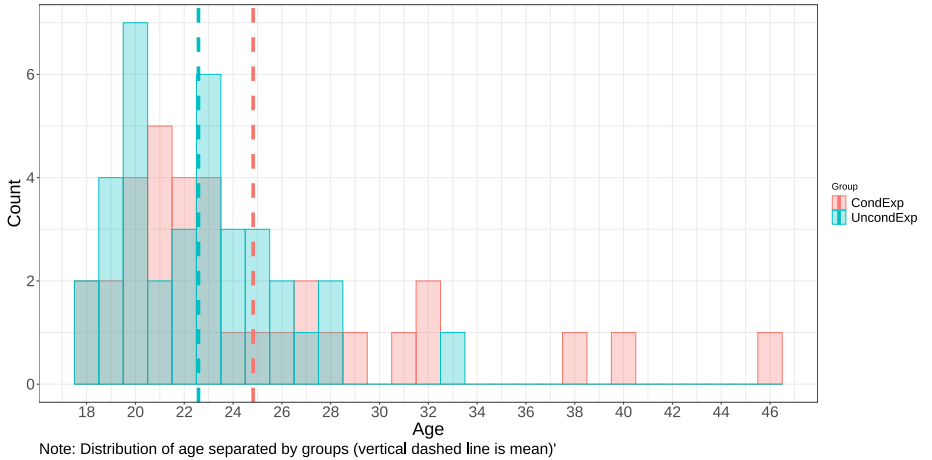
Note: Gender distribution



Note: Answer to the GHQ question : 'Do you happen to take illicit drugs ?'



Note: Answer to the GHQ question : 'Do you practice sporting activites regularly (2-3 times/week)?'



Note: Distribution of age separated by groups (vertical dashed line is mean)'

2 NORMALITY TESTS

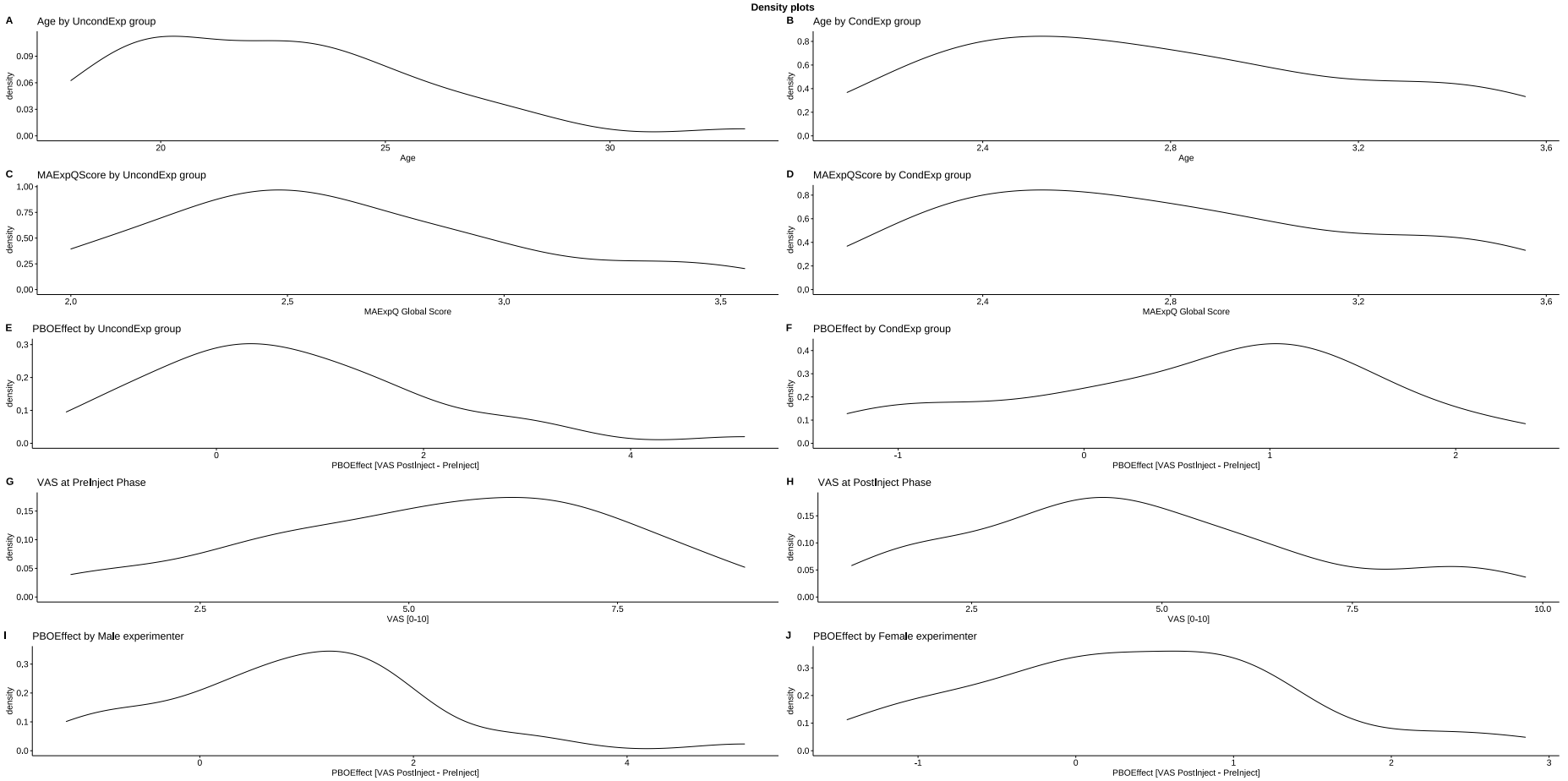
2.1 Table

Table II: Normality test (shapiro-Wilk) & Skewness/Kurtosis

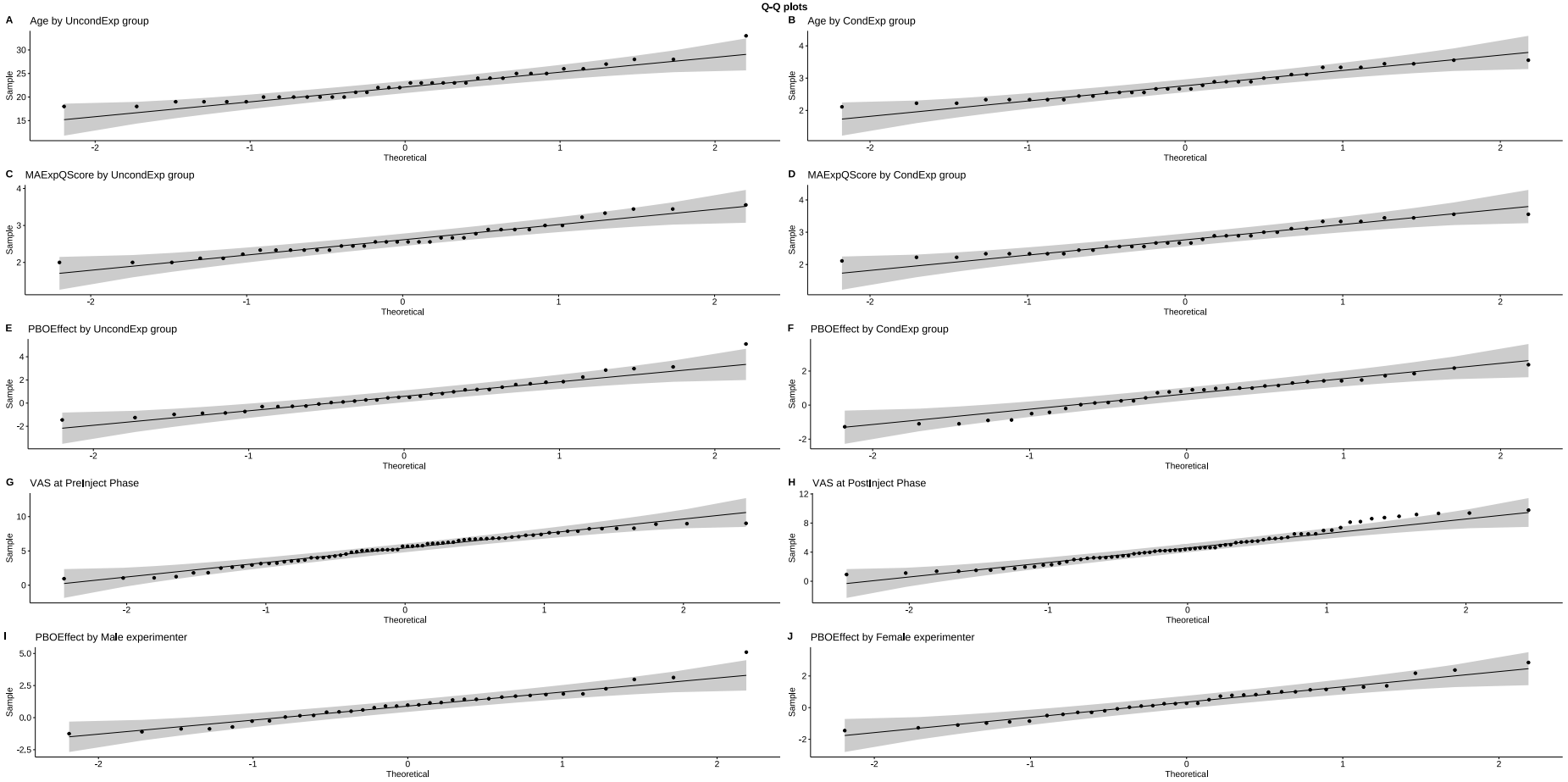
Variable	Group-Phase	statistic	p_value	sample	Skewness	Kurtosis
Age	CondExp	0.820	0.000	34	1.682	2.757
Age	UncondExp	0.928	0.021	36	0.978	1.348
MAExpQScore	CondExp	0.940	0.064	34	0.378	-0.973
MAExpQScore	UncondExp	0.944	0.068	36	0.594	-0.238
PBOEffect	CondExp	0.959	0.234	34	-0.360	-0.601
PBOEffect	UncondExp	0.946	0.077	36	0.985	1.546
VAS	PreInject	0.973	0.128	70	-0.330	-0.604
VAS	PostInject	0.962	0.031	70	0.477	-0.390
PBOEffect	Male	0.949	0.104	35	0.159	-1.314
PBOEffect	Female	0.976	0.637	35	-0.007	-1.182

Note:
Results of the Shapiro-Wilk normality tests on behavioral data distribution as well as the skewness and kurtosis distribution parameters.

2.2 Plots


Density plots
A
Age by UncondExp group
density
Age
B
Age by CondExp group
density
Age
C
MAExpQScore by UncondExp group
density
MAExpQ Global Score
D
MAExpQScore by CondExp group
density
MAExpQ Global Score
E
PBOEffect by UncondExp group
density
PBOEffect [VAS PostInject - PreInject]
F
PBOEffect by CondExp group
density
PBOEffect [VAS PostInject - PreInject]
G
VAS at PreInject Phase
density
VAS [0-10]
H
VAS at PostInject Phase
density
VAS [0-10]
I
PBOEffect by Male experimenter
density
PBOEffect [VAS PostInject - PreInject]
J
PBOEffect by Female experimenter
density
PBOEffect [VAS PostInject - PreInject]

Q-Q plots


A
Age by UncondExp group
B
Age by CondExp group
C
MAExpQScore by UncondExp group
D
MAExpQScore by CondExp group
E
PBOEffect by UncondExp group
F
PBOEffect by CondExp group
G
VAS at PreInject Phase
H
VAS at PostInject Phase
I
PBOEffect by Male experimenter
J
PBOEffect by Female experimenter
Sample
Theoretical

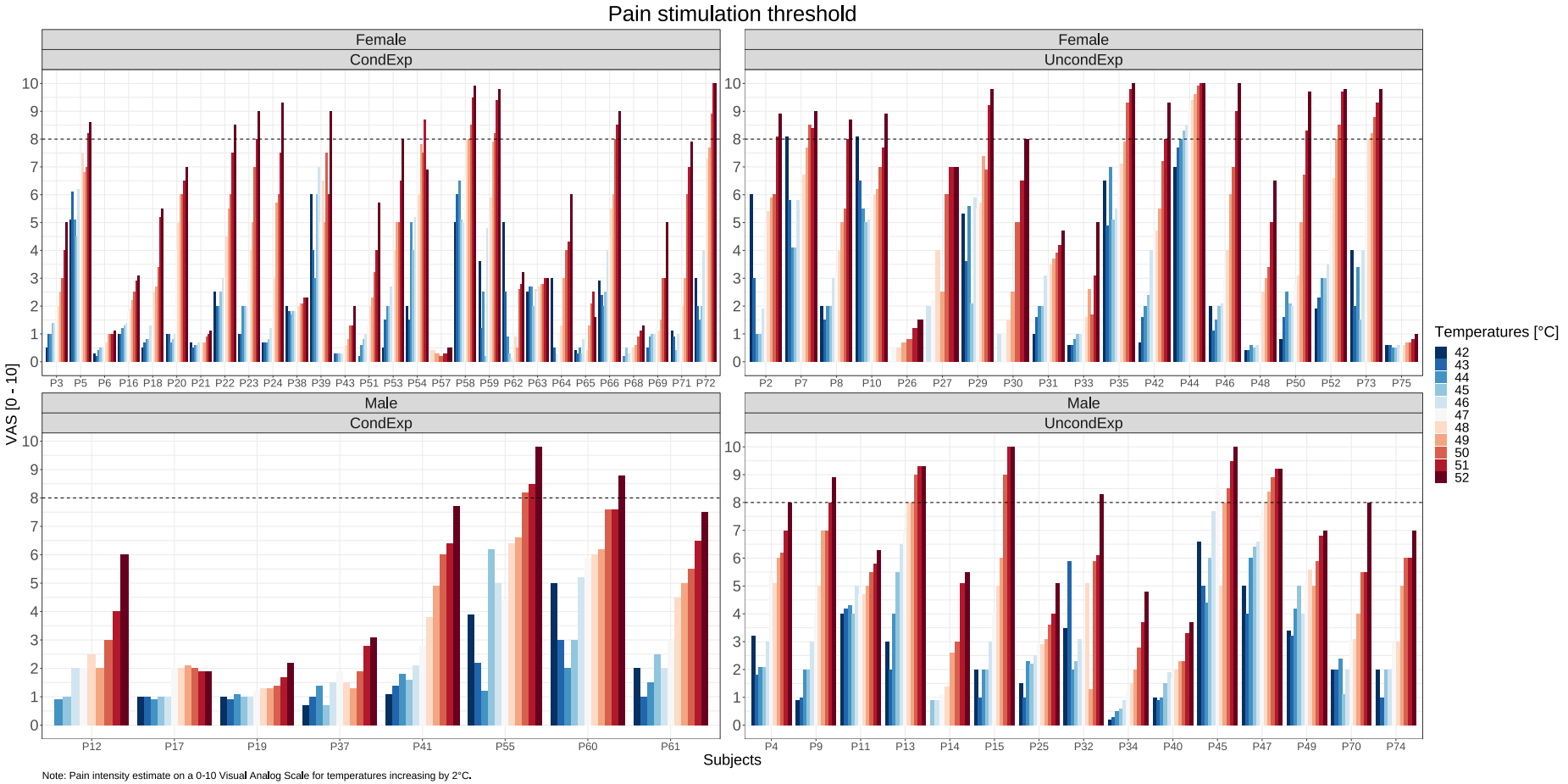
3 TASKS

3.1 Pain stimulation threshold

3.1.1 VAS corresponding to each temperature

Eleven pain stimulations were applied to reach an individualized temperature eliciting a pain level of 8 or higher on the Visual Analogue Scale (VAS; 0-10) or 52°C (if the corresponding VAS rating was lower than 8).

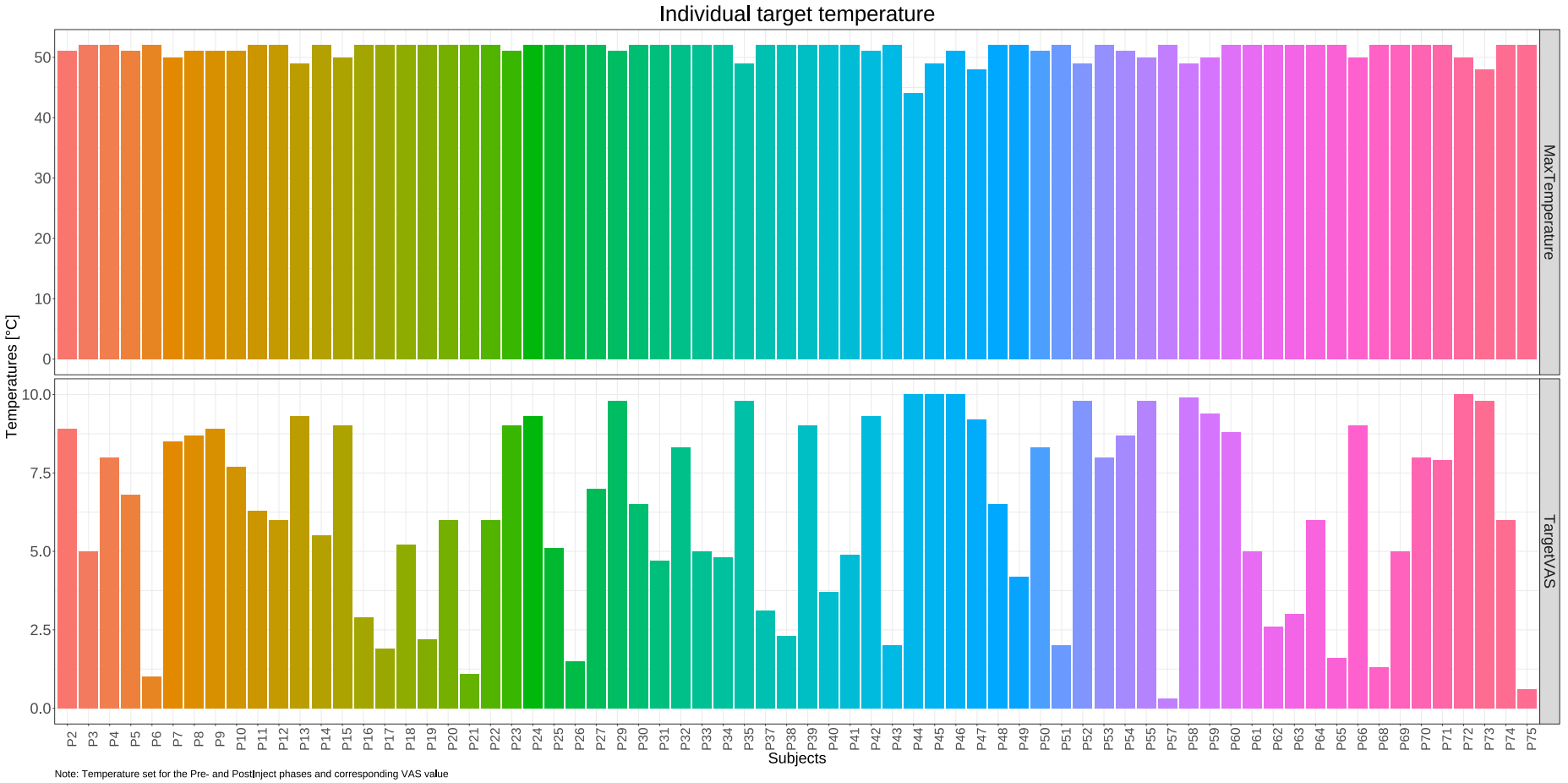
Figure III: Identification of pain stimulation threshold



3.1.2 Individual target temperature

This plot demonstrates which were the individual target temperatures used throughout the PreInject and PostInject phases and their corresponding VAS.

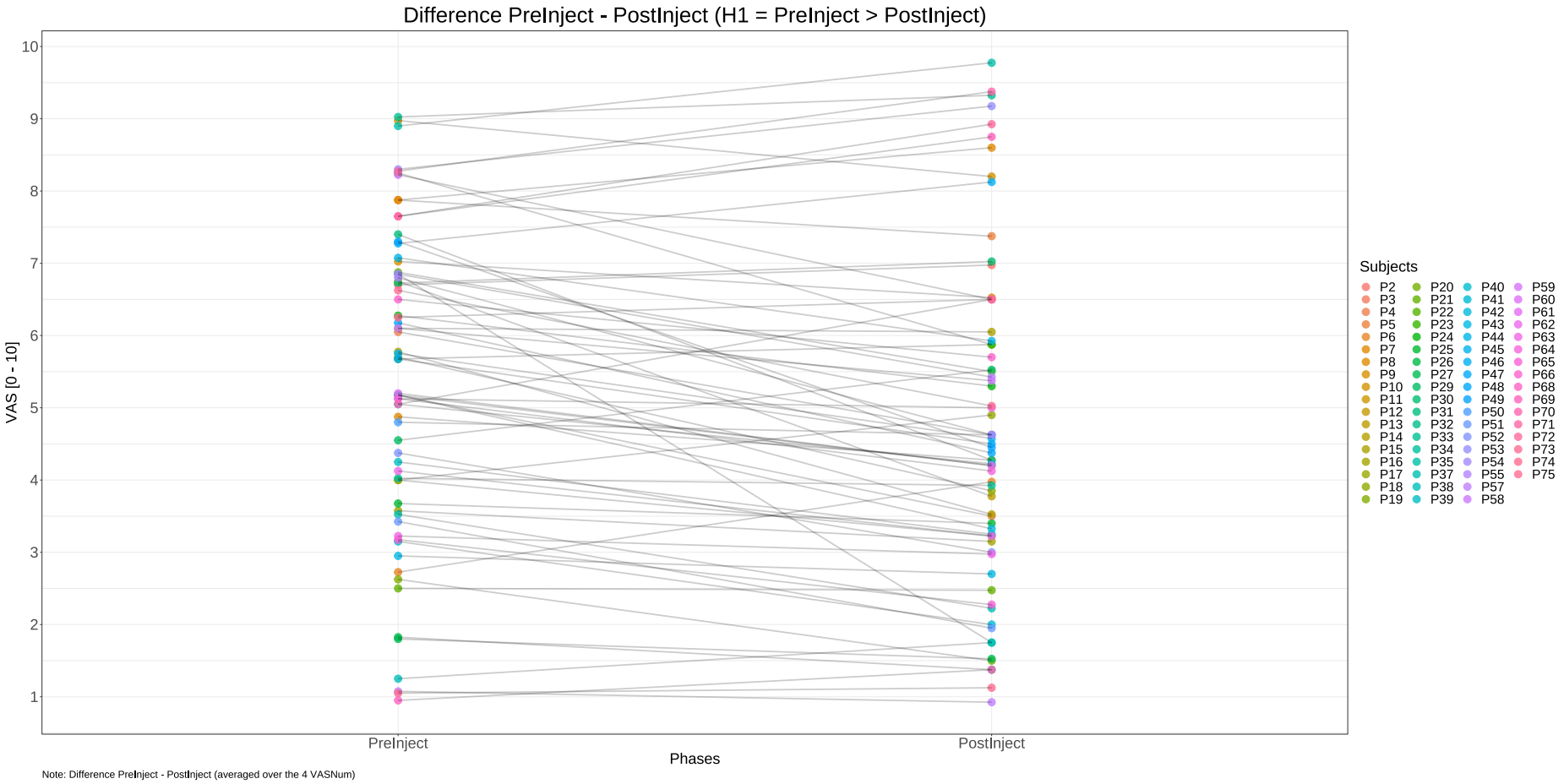
Figure IV: Individual target temperature



3.2 Experimental pain stimulation

The experimental painful stimulation paradigm was divided into two phases of two blocks of 12 trials (i.e., 24 trials in total).

Figure V: VAS estimates for PreInject and PostInject phases



Note: Difference PreInject - PostInject (averaged over the 4 VASNum)

4 ERP

4.1 Number of trials in each ERP

The minimum number of EEG trials for each task need to be higher or equal to 16 trials for each to-be-averaged ERPs.

Figure VI: Number of trials in each ERP

5 SANITY CHECKS

5.1 Common positive verbally-induced expectations

A. First, we ensured that participants from both groups shared common positive verbally-induced expectations of morphine analgesia to ensure that this factor did not confound our contrast of interest. To this aim, we controlled that the difference at the MAExpQ global score was smaller than Hedges' $g < 0.4$

If the first sanity check (i.e. A) was not fulfilled, participants with the value farther from the overall pooled median were successively excluded and replaced until the groups were balanced (i.e. since all participants should share the same expectations).

Refer to figure 4A in the manuscript for a graphical representation.

Table III: Positive verbally-induced expectations difference between groups (CondExp vs UncondExp)

t	Df	p.value	HedgesG	2.5CI	97.5CI	BayesFactor01	InterpBF
-1.564	67.693	0.123	0.37	-0.359	0.044	1.437	anecdotal evidence in favour of H0

Note:
Results of the Independent-samples t-test: UncondExp > CondExp

5.2 Placebo effect occurence (VAS)

B. We then ensured that a placebo effect indeed occurred after the injection and thus that we could interpret any electrophysiological effect in terms of PA. To this aim, we used one-sided differences of Hedges' gav >= 0.5 (0.9 power and alpha threshold of 0.05 for this contrast with our planned sample size) on the mean of VAS trials after the injection (PostInject phase) compared to trials before the injection (PreInject phase), on the whole population sample.

If the second sanity check (i.e. B) was not fulfilled, participants not showing placebo effects with the highest value compared to the difference score between the Δ VAS PreInject – VAS PostInject phases were successfully excluded and replaced until we reached the expected difference of Hedges' gav >= 0.5 between the phases.

Refer to figure 4B in the manuscript for a graphical representation.

Table IV: Placebo effect VAS PostInject - PreInject (H1: PreInject > PostInject)

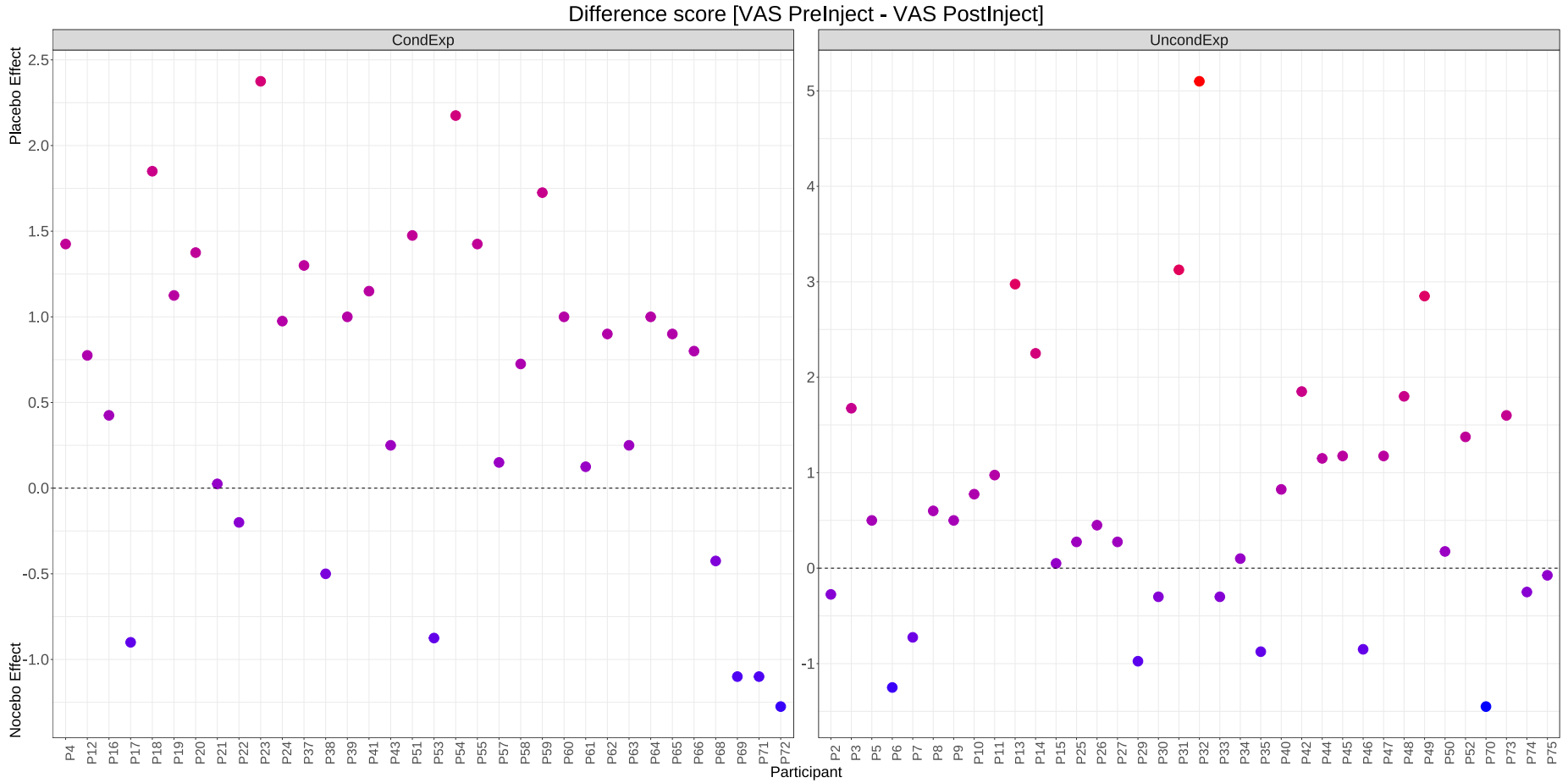
t	Df	p.value	HedgesG	2.5CI	97.5CI	BayesFactor01	InterpBF
4.669	69	0	0.552	0.428	Inf	0	extreme evidence against H0

Note:
Results of the Paired-samples t-test: PreInject > PostInject

5.2.1 Individual deviation from placebo effect

The figure below enables to better isolate the participants with large nocebo effects in each group.

Figure VII: Individual deviation from placebo effect

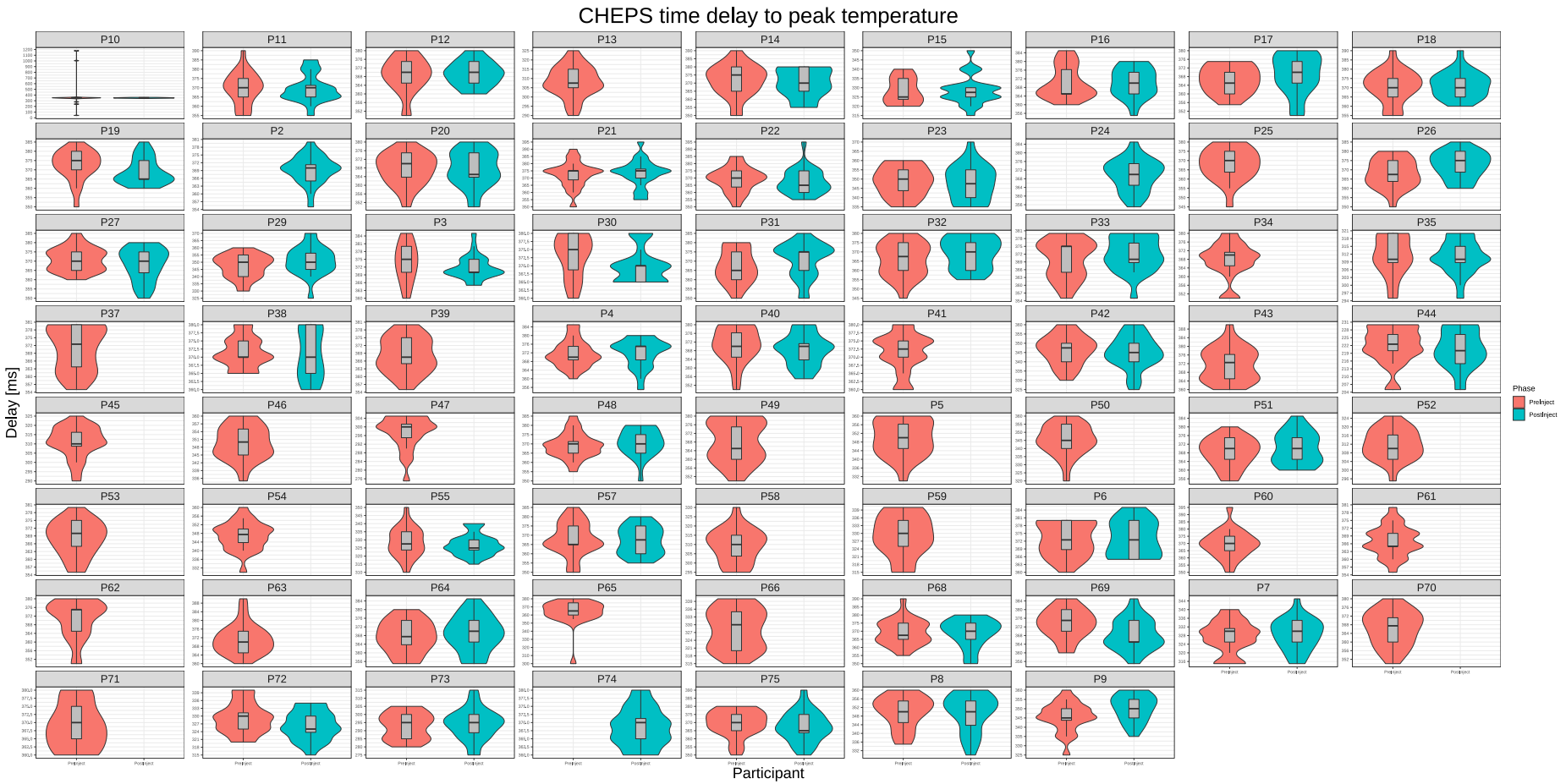


6 PATHWAY CHEPS DEVICE OUTPUTS

6.1 Time delay to peak temperature

The violin plots display the time it took for the device to reach the desired target temperature (in ms) for each trial, separated by participants and by phases (PreInject and PostInject).

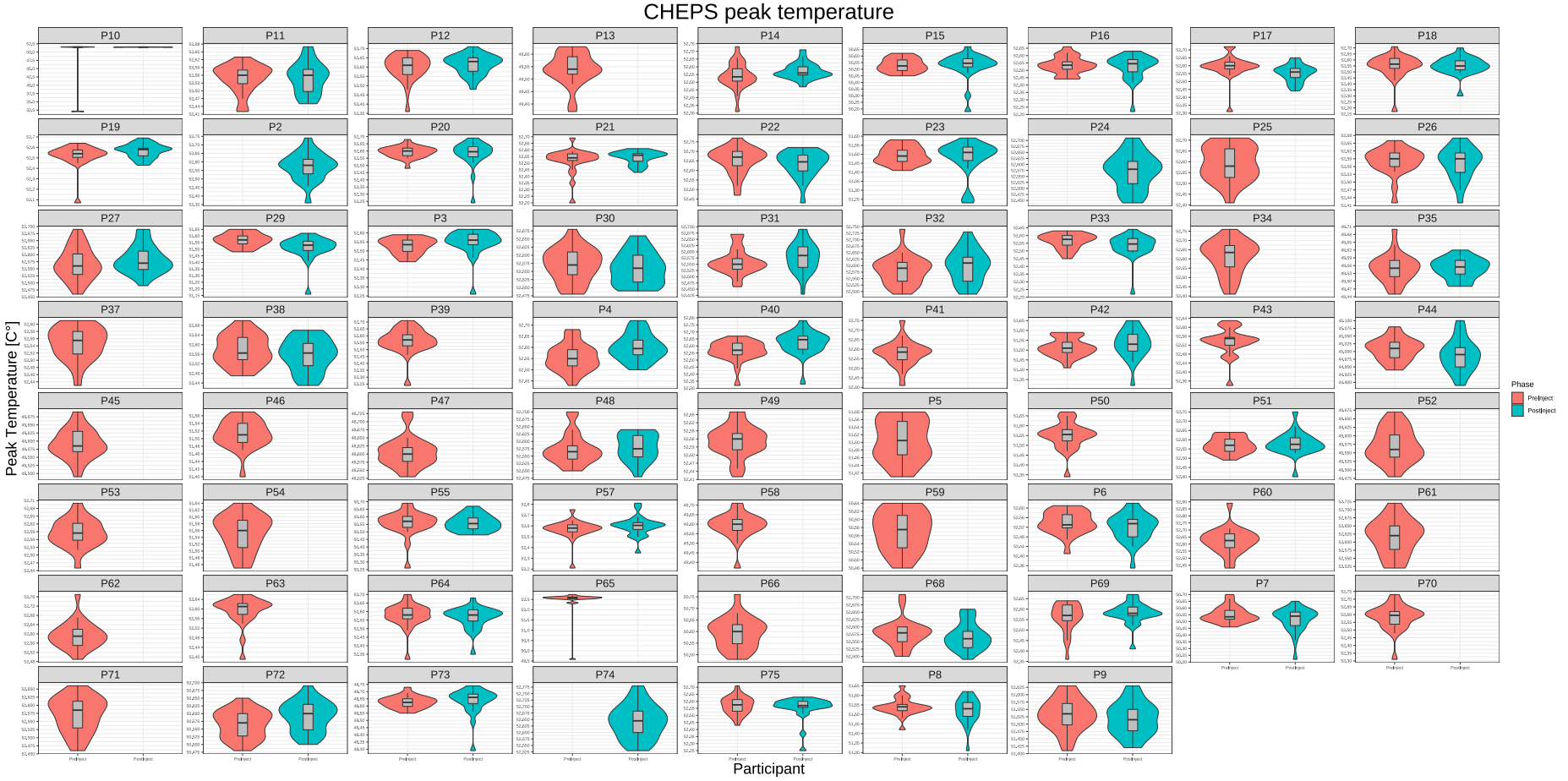
Figure VIII: CHEPS time delay to peak temperature



6.2 Peak temperature

The violin plots display the termpature that was reached by the device (in °C) for each trial, separated by participants and by phases (PreInject and PostInject).

Figure IX: CHEPS peak temperature

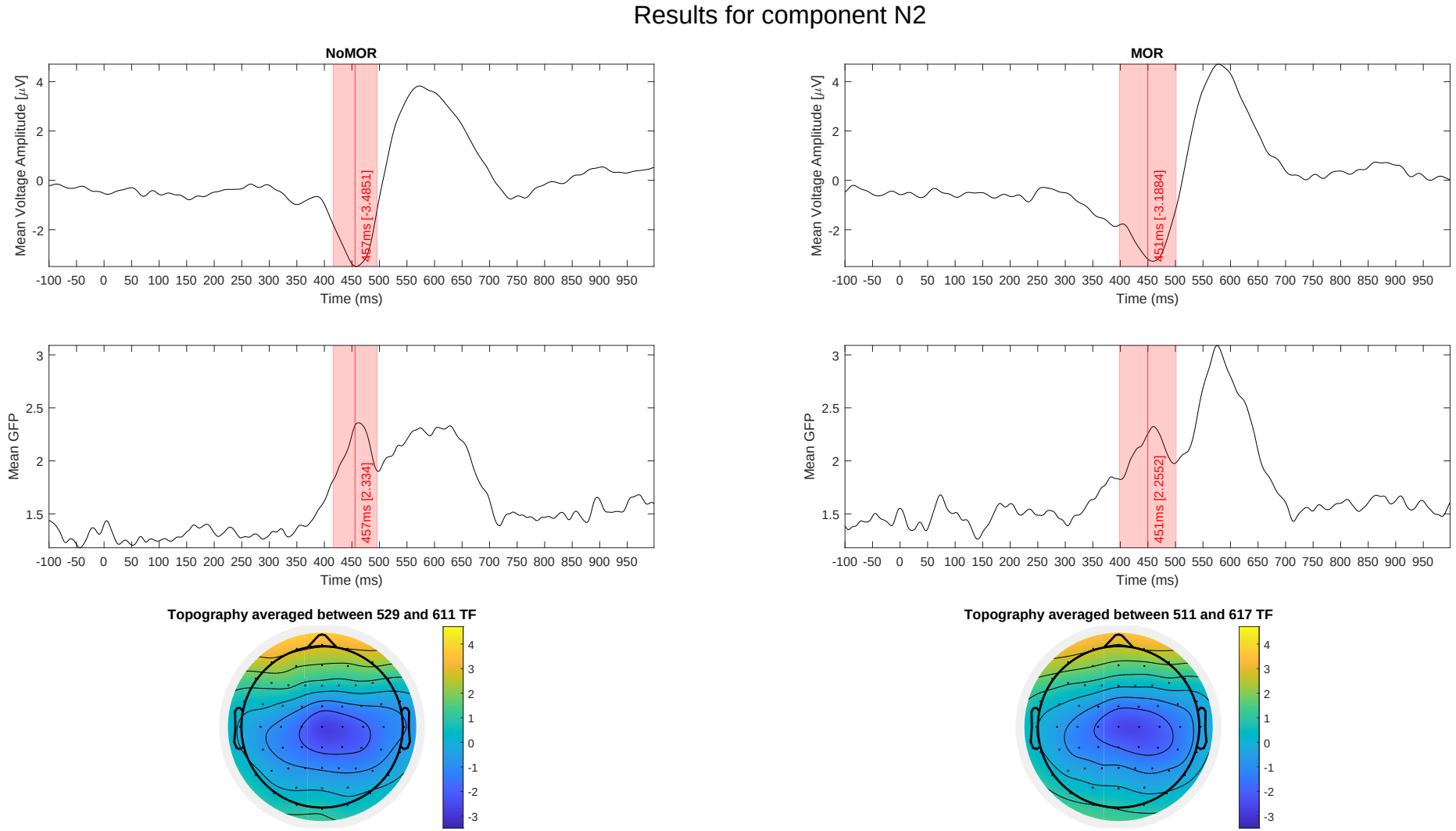


7 EVENT-RELATED POTENTIALS (ERP) PERIOD OF INTEREST (POI)

As specified in the manuscript (page 15), the POI was determined with a data-driven method based on individual GFP peak.
For additional details and related MATLAB codes, see https://github.com/CorentinWicht/GFPPeaks.

7.1 N2 component

Figure X: N2 Period of Interest (POI)



7.2 P2 component

Figure XI: P2 Period of Interest (POI)