SUPPLEMENTARY MATERIAL FOR

Precuneus magnetic stimulation for Alzheimer's disease: a randomized, sham-controlled trial (TMS-AD).

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SUPPLEMENTARY METHODS

Patients
Patients were eligible if they had an established diagnosis of probable mild-to-moderate Alzheimer’s disease (AD) according to National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association criteria; aged >50 ≤ 85 years; had a Clinical Dementia Rating Scale Sum of Boxes (CDR-SB) score of 0.5-1 and Mini Mental State Examination (MMSE) score of 18-26 at screening, indicating mild to moderate AD; had one caregiver; had been treated with acetylcholinesterase inhibitor for at least 6 months; had performed lumbar puncture for cerebrospinal fluid biomarkers analysis for diagnostic purposes. Patients underwent medical and neurological evaluations, including magnetic resonance imaging or computed tomography. Patients were excluded if had extrapyramidal signs, history of stroke, other neurodegenerative disorder, psychotic disorders and if they had been treated six months before enrollment with antipsychotics, antiparkinsonian, anticholinergics and antiepileptic drugs. The trial was approved by the review board and ethics committee at the Santa Lucia Foundation and was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines. All patients or their parents or legal representatives provided written informed consent. Patients could withdraw at any point without prejudice. This report followed the CONSORT reporting guideline for randomized studies.

Trial design
The study was a monocentric, randomized, sham-controlled, double-blind trial of rTMS over the PC in mild to moderate AD patients. Stimulation was given as an add-on to standard treatment with acetylcholinesterase inhibitors (for trial protocol details see supplementary file 1). The trial comprised a 24-week treatment period with a 2-week intensive course in which real rTMS of the PC (PC-rTMS) or sham-rTMS was applied daily 5 times per week, Monday to Friday, followed by a maintenance phase in which the same stimulation was applied weekly for 22 weeks. After recruitment and baseline assessments, patients were randomly assigned in a 1:1 ratio to receive PC-rTMS or sham-rTMS in addition to their stable drug regimen with acetylcholinesterase inhibitors therapy. All treatments were administered for 24 weeks with no interruptions. Each rTMS session consisted of forty trains of 2 seconds delivered at 20 Hz spaced-out by 28 seconds of no stimulation (total number of stimuli: 1600), lasting approximately 20 minutes. During the entire period of 24 weeks a total of 51200 were delivered for each patient. The efficacy assessments were rated at baseline (W0) for enrolled patients and caregivers and repeated at weeks 12 (W12) and 24 (W24) (or upon early termination) by raters who were blinded in respect to the assignment group.

Investigators, patients, and their caregivers were also blinded. At each clinical visit (or upon early termination), adverse events (AEs) were recorded, vital signs measured and physical and neurological examination performed. An independent Data Monitoring Committee monitored the patients’ safety according to the Data Monitoring Committee Charter

Intervention – rTMS
TMS was carried out using a Magstim Rapid^2 magnetic biphasic stimulator connected with a figure-of-eight coil with a 70-mm diameter (Magstim Company, Whitland, UK) that generates 2.2 T as maximum output. The entire protocol lasted 24 weeks and consisted of two phases, a daily “intensive” phase and a weekly “maintenance” phase. The intensive phase consisted of 10 daily rTMS sessions delivered in the first two weeks (W1 and W2) from Monday to Friday. The “maintenance” phase consisted of 22 weekly rTMS sessions delivered in the subsequent 22 weeks (W3-W24). Each rTMS session consisted of forty trains of 2 seconds delivered at 20 Hz spaced-out by 28 seconds of no stimulation (total number of stimuli: 1600), lasting approximately 20 minutes.

To select the intensity for rTMS treatment we used the following procedure. We first computed the resting motor threshold (RMT), defined as the lowest intensity producing MEPs of >50 μV in at least five out of 10 trials in the relaxed first dorsal interosseous (FDI) muscle of the right hand. RMT was assessed over the optimal stimulus site to elicit MEPs in the right FDI, termed “motor hotspot”, identified by positioning the coil approximately over the central sulcus and moving it on the scalp by 0.5 cm steps on left M1. Since the coil-to-cortex distance directly influences the magnitude of magnetic stimulation, for each patient we subsequently calculated a distance-adjusted RMT (AdjRMT). AdjRMT = RMT + m × (DsiteX– DM1) where AdjRMT is the adjusted MT in % of stimulator output, MT is the unadjusted MT in % of stimulator output, DM1 is the distance between the scalp and M1 hotspot, DSiteX is the distance between the scalp and a second cortical region (SiteX), and m is the distance-effect gradient. This procedure provides a more accurate index of cortical excitability and improves the efficacy of MT-calibrated TMS. Afterwards, each patient received 50 TMS single pulses at an initial intensity of 100% of adjMT, during a 64-channel EEG recording, over different scalp
positions corresponding to the PC region, identified based on previous fMRI works. Optimization of stimulation intensity was achieved by visualizing TMS-evoked potentials (TEPs) directly after each TMS delivery. Importantly, the choice of 50 single-pulse TEP was justified by previous studies showing a high correlational concordance coefficient (0.8) between a TEP evoked with 40 TMS single pulses and one evoked with 150 TMS single pulses. Intensity of TMS was eventually increased in steps of 2% of the maximal stimulator output (MSO) basing on the visualization of a first TEP peak of at least 6 µV. Target location optimization was further achieved by identifying the scalp location generating the highest response to TMS for each patient via a grid search over a 3x3 cm area centered around the original fMRI-defined stimulation target.

Coil orientation was parallel to the midline with the handle pointing downward, thus inducing the current in a posterior-anterior direction. The TMS coil position was constantly monitored using a neuronavigation system coupled with an infrared camera.

For sham treatment, stimulation was applied using the same parameters via a sham coil positioned in correspondence to the target area, in order to preserve the same auditory and somatosensory sensations. For each patient, source estimation on pre-processed TMS-EEG data was run at the beginning of each treatment session to confirm the correct anatomical targeting for rTMS. The induced E-field over the TMS target was computed via SimNIBS v3.2, an open-source simulation package that integrates segmentation of MRI scans, mesh generation, and FEM E-field computations. The software provides a realistic volume conductor head model, generated using the T1-and T2-weighted images and segmentation from the SimNIBS validation data set and based on anisotropic conductivity values for each tissue class, in S/m: gray matter, 0.276, cerebrospinal fluid, 1.790, bone, 0.010, scalp, 0.250. The final mesh, comprehensive of gray and white matter, scalp, bone, and cerebrospinal fluid, comprises approximately 200,000 nodes and 3.6 million tetrahedral elements. E-field distribution was computed for a Magstim 70 mm figure-of-8 coil (P/N 9925-00, Magstim Co., Spring Gardens, Whitland, Carmarthenshire, UK), both for a coil-to-scalp distance of 2 mm and a coil current measured in dl/dt corresponding to 67x10e6 A/s. The center of the coil was positioned with MNI coordinates: x=0, y=-65, z=55, based on a target selection approach accounting for functional MRI changes typical of AD patients and involving the default mode network (DMN) 7. The resulting norm E-field distribution is shown in Gmsh v4.7.1 with an output range from 0 to 70 V/m (see Figure S1).

TMS-EEG
Cortical evaluation was performed with TMS-EEG. Each session consisted of 80 TMS single-pulses applied at a random ISI of 2-4 s over the PC, targeted using a neuronavigation system. During TMS-EEG recordings, each participant wore in-ear plugs which continuously played a white noise that reproduced the specific time-at a random ISI of 2-4 s over the PC, targeted using a neuronavigation system. During TMS-EEG recordings, skin/electrode impedance was maintained below 5 kΩ. Horizontal and vertical eye movements were detected by recording the electrooculogram (EOG) to off-line reject the trials with ocular artifacts. TMS-EEG data were pre-processed offline with Brain Vision Analyzer (Brain Products GmbH, Munich, Germany). Physiological and TMS-related artefactual components were detected using INFOMAX-ICA and removed basing on their scalp distribution, frequency, timing and amplitude.

Effects of rTMS were evaluated on three domains: temporal, by means of TMS-evoked potentials (TEPs) from the site of stimulation, i.e. PC; oscillatory, by means of TMS-related spectral perturbation (TRSP) from the site of stimulation, i.e. PC; and spatial, by means of source analysis conducted over all the scalp. TEPs were computed considering a time window from -100 to 300 ms after TMS, with a baseline correction of -100 to 0. Frequency-domain analysis was performed using a time/frequency decomposition based on Morlet wavelet (parameters c=3; 41 linear 1 Hz steps from 4 to 45 Hz) and then by computing TRSP. TRSP is a measure of event-related changes in spectral power over time in a certain frequency range computed as:

$$TRSP(f, t) = \frac{1}{n} \sum_{k=1}^{n} |F_k(f, t)|^2$$

where, for n trials, the spectral estimate F was computed at trial k, at frequency f and time t. Spectral power was subsequently extracted for the theta (4-7 Hz), alpha (8-13 Hz), beta (14-30 Hz) and gamma band (31-45 Hz) and averaged in a time window lasting from 20 to 250 ms after TMS for the theta and alpha band and from 20 to 70 ms after TMS for the beta and gamma band.
SUPPLEMENTARY RESULTS

Statistical analysis

Distribution features of primary and secondary outcomes

Gaussianity assumptions were assessed by plot inspection (box-plot) and by the analysis of residuals after adjustments for socio-demographic characteristics. Association with socio-demographic (age and education) variables were assessed by linear model (for CDR-SB, ADAS-COG11, ADCS-ADL, MMSE, FAB and generalized linear model (Negative binomial) for the NPI total score.

Figure S1. Left: Box-plots of the clinical variables at baseline (W0) and week 24 (W24) of all subjects participating in the trial independently from group allocation. Right: observed means and standard deviations of the primary and secondary end-points by time and by treatment groups.

|                | Baseline | W24       |
|----------------|----------|-----------|
|                |          | Real rTMS | Sham rTMS | Real rTMS | Sham rTMS |
|                | Mean (SD)| Mean (SD) | Mean (SD) | Mean (SD) | Mean (SD) |
| MMSE           | 21.2 (2.7)| 21.5 (2.4)| 20.8 (2.4)| 19.7 (3.3)|          |
| ADAS-Cog       | 22.6 (7.4)| 24.8 (6.5)| 23.7 (8.0)| 28.8 (10.0)|          |
| FAB            | 10.7 (3.9)| 10.3 (3.4)| 10.8 (4.2)| 10.3 (3.5)|          |
| ADCS-ADL       | 58.6 (9.7)| 58.3 (9.7)| 59.7 (11.2)| 50.8 (14.7)|          |
| CRD-SB         | 4.1 (1.8)| 4.7 (1.5)| 4.1 (1.6)| 6.0 (2.4)|          |
| NPI            | 9.8 (10.2)| 12.6 (11.7)| 11.0 (7.9)| 17.8 (14.5)|          |

All clinical variables (except NPI) display low variability: coefficients of variation CV = (SD/mean) * 100 at baseline were equal to 38 12, 29, 34, 16 and 98 for CDR-SB, MMSE, ADAS-COG11, FAB, ADCS-ADL, and NPI respectively (and similar CVs were found at W24). Moreover, all the distributions appear symmetric and without outliers (that are present only in NPI distribution which is notably a skewness discrete count distribution and have to be modelled accordingly by a Negative binomial distribution).
Table S1 Analysis of the association between age, education and primary and secondary end-points at baseline and corresponding analysis of the residuals.

| Outcome     | Age p-value | Education p-value | Normality tests on residuals (K-S; S-W tests) |
|-------------|-------------|------------------|---------------------------------------------|
| CDR-SB      | 0.432       | 0.415            | 0.200; 0.054                               |
| MMSE        | 0.009       | 0.016            | 0.200; 0.310                               |
| ADAS-COG11  | 0.469       | 0.026            | 0.055; 0.129                               |
| FAB         | 0.059       | 0.022            | 0.200; 0.303                               |
| ADCS-ADL    | 0.221       | 0.239            | 0.200; 0.618                               |
| NPI #       | 0.492       | 0.766            | ----                                        |

Linear regression models were applied for CDR-SB MMSE, ADAS, FAB and ADCS-ADL; Negative binomial regression was applied for NPI.

K-S: Kolmogorov-Smirnov test; S-W: Shapiro-Wilk test.

# Negative binomial distribution resulted as the best fit (in terms of AIC) for NPI with respect to Zero-inflated distribution and Poisson distribution.

Age and education were significantly associated with MMSE, ADAS-COG11 and FAB, whereas no association was found for CDR-SB, ADCS-ADL and NPI. After adjustment for age and education, MMSE, ADAS-COG11 and FAB displayed Gaussian distributed residuals thus models with Gaussian distribution were adopted for further analyses on these outcomes. Same models, was applied also to CDR-SB, ADCS-ADL without adjustment for age and education. Finally, generalized (Negative binomial) linear models, without adjustment for age and education, was applied for NPI.

Primary and secondary outcomes analysis

The longitudinal assessment of the end-points across treatment groups (PC-rTMS vs sham-rTMS) was performed through generalized linear mixed model (GLMM) for repeated measures with random intercept and random slope to account for individual differences at baseline and to assess individual change through follow-up. GLMM were applied to CDR-SB and the other outcome measures of efficacy, ADAS-COG11, MMSE, ADCS-ADL, FAB and NPI, as dependent variables and “group”, “time” and “group×time” interaction as independent factors. In detail, considering the distribution of the end-points described in the section above, GLMM for Gaussian data with identity link function were applied for CDR-SB, ADAS-COG11, MMSE, ADCS-ADL and FAB, whereas GLMM for Negative binomial data, with log-link function, was used for NPI. The GLMM on MMSE, ADAS-COG11 and FAB were adjusted for age and education.

Neurophysiological data analysis

Normality assumption for the distributions of neurophysiological data was assessed by means of Shapiro-Wilks' test. The sphericity of the data will be tested with Mauchly's test; when sphericity is violated (i.e., Mauchly's test < 0.05) the Greenhouse–Geisser correction was used. Pairwise comparisons were corrected by the Bonferroni method.

TEPs analysis was conducted in two steps. First, to identify the exact the time windows at which there was a significant difference, we performed multiple t-tests (corrected with false discovery rate method) at each time point of the TEP waveform from -100 to 300 ms after TMS. This analysis was conducted for each group.
(PC-rTMS vs sham-rTMS) and for each evaluation (baseline W0 vs W24). Once detected the significant time windows, we compared the mean TMS-evoked activity (dependent variable) within these intervals with a generalized linear mixed model (GLMM - for Gaussian data-) for repeated measures with group (PC-rTMS vs. sham-rTMS), time (W0 vs. W24) and “window” as independent factors. The detailed results of GLMM are reported in the Table S3.

TRSP analysis was conducted with multiple dependent t-tests by comparing each frequency from 4 to 50 Hz in the two time points of evaluation (W0 and W24). To correct for multiple comparisons, difference in frequencies were considered significant when at least 10 successive t-test reached the significant threshold (p<0.05).

To assess the reliability and stability of TEPs in evaluating the impact of the rTMS over the PC, i.e. in distinguishing which group received real or sham rTMS, we used the intraclass correlation coefficient (ICC), a measure optimized to evaluate how strongly units in the same group resemble each other. For the ICC calculation, we considered all the between-subjects sources of variance and we computed it as:

\[
ICC = \frac{\sigma_{subjects}^2}{\sigma_{subjects}^2 + \sigma_{groups}^2 + \sigma_{residual}^2}
\]

ICC range from 0 to 1, we established a cut-off of 0.7 indicating a relatively stable and reliable measure to distinguish between the two groups. ICC was computed for each TEP peak of the two groups, both before and after rTMS.

To explore possible linear relationships between the clinical and neurophysiological data, we conducted a correlation analysis with Pearson’s coefficient between tested whether the change (W24-W0) in our clinical primary outcome, i.e. CDR, was correlated with (1) the baseline amplitude (W0) and (2) the change (W24-W0) in amplitude of the first TEP component. This analysis data, was conducted a correlation analysis by means of the Pearson’s coefficient between CDR and the first TEP component, i.e. between 10 and 30 ms. This component was chosen based on well-established evidence showing that it directly reflect the cortical excitability of the stimulated area, i.e. PC.

Neurophysiological results

In the temporal domain, Stimulation of the PC with single-pulse TMS evoked a TEP with three main components, a first biphasic component visible between 10 and 50 ms and two later components with maximum peaks at 70-90 ms and 130-150 ms, as previously observed. Analysis of TEP revealed two main windows, i.e. from 10 to 40 ms and from 90 to 130 ms, in which there was a significantly difference between W0 and W24 time points, in the sham condition (all ps<0.05 FDR corrected). The detailed information of the two TEP components in the different conditions are reported in Table S2. GLMM analysis showed a significant main effect of “Window” factor [F(1,126)=9.65; p=0.002] showing a large amplitude of the component in the second time window compared to the first (post-hoc p=0.002); and a significant “Group×Time” interaction showing a significant modulation of the two TEP components in the W24 time point for the only sham condition [F(1,126)=6.65; p=0.011]. Post-hoc analysis revealed a decrease of TEP amplitude in the W24, compared to the W0 evaluation, in the sham condition (post-hoc p=0.002). The detailed output of the GLMM analysis is reported in Table S3. In the oscillatory domain, stimulation of the PC with single-pulse TMS evoked an oscillatory activity in the beta-gamma range with a peak of frequency around 40 Hz lasting approximately 50 ms, observable in both groups. T-test analysis of spectral power showed an enhancement in the power of high frequency oscillations the gamma band ranging from 31 to 48 Hz (mean p-value = 0.033) at W24,
compared to W0 time point in the PC-rTMS group, whereas evoked oscillatory activity did not change in the sham-rTMS group (mean p-value>0.05). The detailed information of the two TEP components in the different conditions are reported in Table S2.

Reliability analysis showed a low ICC for each of the three pre-rTMS TEP peaks [peak 1: -0.364, p=0.931; peak 2: -0.139, p=0.709; peak 3: 0.008, p=0.437] showing that before the application of rTMS, TEPs were not able to discriminate the two groups, i.e. real and sham. When computed for the post-rTMS TEP, ICC was very high for each of the four TEP peaks [peak 1: 0.475, p=0.013; peak 2: 0.543, p=0.010; peak 3: 0.706, p=0.001] showing that after the application of rTMS, TEPs were highly reliable in distinguishing the two groups, i.e. real and sham.

Table S2. Mean (C.I. 95%) values for the main neurophysiological TMS measures

|                  | PC-rTMS W0       | PC-rTMS W24      | sham-rTMS W0     | sham-rTMS W24     |
|------------------|------------------|------------------|------------------|------------------|
| TEP peak 1 (μV)  | 0.62 (0.02, 1.22)| 0.97 (0.15, 1.79)| 1.49 (0.46, 2.52)| 0.02 (-1.16, 1.22)|
| TEP peak 2 (μV)  | 1.36 (0.52, 2.21)| 1.49 (0.84, 2.15)| 2.78 (2.04, 3.52)| 1.37 (0.28, 2.45)|
| TRSP theta (μV²) | 0.76 (0.63, 0.90)| 0.67 (0.64, 0.69)| 1.32 (1.08, 1.56)| 1.09 (0.93, 1.26)|
| TRSP alpha (μV²)| 0.31 (0.25, 0.37)| 0.47 (0.45, 0.49)| 0.86 (0.84,0.88)| 0.63 (0.59, 0.63)|
| TRSP beta (μV²)  | 0.87 (0.78, 0.96)| 1.10 (0.87, 1.34)| 1.36 (1.21, 1.51)| 1.26 (1.10, 1.43)|
| TRSP gamma (μV²)| 1.34 (1.25, 1.43)| 1.77 (1.72, 1.82)| 2.26 (2.16, 2.36)| 1.77 (1.72, 1.82)|
| rTMS treatment intensity (%MSO) | 53.4 (49.5, 57.2) | - | 52.5 (50.1, 54.9) |

Table S3. Effects on longitudinal evaluation of TEP variable

|                  | Parameter estimate beta [95%CI] | F (df) | P-value | Post-hoc adjusted | Bonferroni adjusted |
|------------------|---------------------------------|--------|---------|-------------------|---------------------|
| Time             |                                 |        |         |                   |                     |
| Time W24 (ref W0)| -1.43 [-2.3, 0.54]              | 3.62 (1, 126) | 0.060 | Time W0 – time W24=0.61, sem=0.32, (p=0.060) |                     |
| Group            |                                 |        |         |                   |                     |
| Real rTMS (ref sham) | 0.48 [-0.48, 1.44]              | 1.15 (1,126) | 0.286 |                     |                     |
| Window           |                                 |        |         |                   |                     |
| Window 10-24     |                                 |        |         |                   |                     |
| (ref 90-140ms)   | -0.9 [-1.60, -0.36]             | 9.65 (1,126) | 0.002 | Window 10-24ms -window 90-140ms =-0.98; sem=0.32; (p=0.002) |                     |
| Group x Time     |                                 |        |         |                   |                     |
| TimeW24 - real RTMS (ref W0-sham)| 1.64 [0.38, 2.90]              | 6.65 (1,126) | 0.011 | Sham W0 - sham W24=1.43, sem=0.45, (p=0.002); Real W0 – real W24 =-0.22, sem=0.45, (p=0.633) |                     |

sem: standard error mean; df: degree of freedom
SUPPLEMENTARY CODE

SPSS code/script of the applied generalized linear mixed models

Code for Gaussian distributed variables (CDR-SB, ADAS-Cog, ADCS-ADL, MMSE and FAB), with identity-link function:

**GENLINMIXED**

```
/DATA_STRUCTURE SUBJECTS=IDpts REPEATED_MEASURES=Time COVARIANCE_TYPE=DIAGONAL
/FIELDS TARGET=ADAScog TRIALS=NONE OFFSET=NONE
/TARGET_OPTIONS DISTRIBUTION=NORMAL LINK=IDENTITY
/FIXED EFFECTS=Time Treatment Treatment*Time Age Education USE_INTERCEPT=TRUE
/RANDOM EFFECTS=IDpts Time USE_INTERCEPT=False COVARIANCE_TYPE=VARIANCE_COMPONENTS
/BUILD_OPTIONS TARGET_CATEGORY_ORDER=ASCENDING INPUTS_CATEGORY_ORDER=ASCENDING MAX_ITERATIONS=100
     CONFIDENCE_LEVEL=95 DF_METHOD=RESIDUAL COVB=ROBUST
/EMMEANS TABLES=Time COMPARE=Time CONTRAST=PAIRWISE
/EMMEANS TABLES=Treatment COMPARE=Treatment CONTRAST=PAIRWISE
/EMMEANS TABLES=Time*Treatment COMPARE=Treatment CONTRAST=PAIRWISE
/EMMEANS_OPTIONS SCALE=ORIGINAL PADJUST=SEQSIDAK.
```

Code for Negative binomial distributed variable (NPI), with log-link function:

**GENLINMIXED**

```
/DATA_STRUCTURE SUBJECTS=IDpts REPEATED_MEASURES=Time COVARIANCE_TYPE=DIAGONAL
/FIELDS TARGET=NPI TRIALS=NONE OFFSET=NONE
/TARGET_OPTIONS DISTRIBUTION=NEGATIVE_BINOMIAL LINK=LOG
/FIXED EFFECTS=Treatment Time Treatment*Time Education Age USE_INTERCEPT=TRUE
/RANDOM EFFECTS=IDpts Time USE_INTERCEPT=False COVARIANCE_TYPE=VARIANCE_COMPONENTS
/BUILD_OPTIONS TARGET_CATEGORY_ORDER=ASCENDING INPUTS_CATEGORY_ORDER=ASCENDING MAX_ITERATIONS=100
     CONFIDENCE_LEVEL=95 DF_METHOD=RESIDUAL COVB=ROBUST
/EMMEANS TABLES=Treatment COMPARE=Treatment CONTRAST=PAIRWISE
/EMMEANS TABLES=Time COMPARE=Time CONTRAST=PAIRWISE
/EMMEANS TABLES=Time*Treatment COMPARE=Treatment CONTRAST=PAIRWISE
/EMMEANS_OPTIONS SCALE=ORIGINAL PADJUST=SEQSIDAK.
```
Code for Gaussian distributed variable TEP, with log-link function:

GENLINMIXED

/DATA_STRUCTURE SUBJECTS=IDpts REPEATED_MEASURES= Window * Time COVARIANCE_TYPE=DIAGONAL
/FIELDS TARGET=TEP TRIALS=NONE OFFSET=NONE
/TARGET_OPTIONS DISTRIBUTION=NORMAL LINK=IDENTITY
/FIXED EFFECTS=Treatment Time Window Treatment*Time USE_INTERCEPT=TRUE
/BUILD_OPTIONS TARGET_CATEGORY_ORDER=ASCENDING INPUTS_CATEGORY_ORDER=ASCENDING MAX_ITERATIONS=100

CONFIDENCE_LEVEL=95 DF_METHOD=RESIDUAL COVB=ROBUST
/EMMEANS TABLES=Treatment COMPARE=Treatment CONTRAST=PAIRWISE
/EMMEANS TABLES=Time COMPARE=Time CONTRAST=PAIRWISE
/EMMEANS TABLES=Window COMPARE=Window CONTRAST=PAIRWISE
/EMMEANS TABLES=Time*Treatment COMPARE=Time CONTRAST=PAIRWISE
/EMMEANS_OPTIONS SCALE=ORIGINAL PADJUST=SEQBONFERRONI.
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