BRAIN
CLINICAL TRIAL

# Precuneus magnetic stimulation for Alzheimer's disease: a randomized, sham-controlled trial

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Repetitive transcranial magnetic stimulation (rTMS) is emerging as a non-invasive therapeutic strategy in the battle against Alzheimer's disease. Alzheimer's disease patients primarily show alterations of the default mode network for which the precuneus is a key node. Here, we hypothesized that targeting the precuneus with TMS represents a promising strategy to slow down cognitive and functional decline in Alzheimer's disease patients.

We performed a randomized, double-blind, sham-controlled, phase 2, 24-week trial to determine the safety and efficacy of precuneus stimulation in patients with mild-to-moderate Alzheimer's disease. Fifty Alzheimer's disease patients were randomly assigned in a 1:1 ratio to either receive precuneus or sham rTMS (mean age 73.7 years; 52% female). The trial included a 24-week treatment, with a 2-week intensive course in which rTMS (or sham) was applied daily five times per week, followed by a 22-week maintenance phase in which stimulation was applied once weekly. The Clinical Dementia Rating Scale–Sum of Boxes was selected as the primary outcome measure, in which post-treatment scores were compared to baseline. Secondary outcomes included score changes in the Alzheimer's Disease Assessment Scale–Cognitive Subscale, Mini-Mental State Examination and Alzheimer's Disease Cooperative Study–Activities of Daily Living scale. Moreover, single-pulse TMS in combination with EEG was used to assess neurophysiological changes in precuneus cortical excitability and oscillatory activity.

Our findings show that patients that received precuneus repetitive magnetic stimulation presented a stable performance of the Clinical Dementia Rating Scale–Sum of Boxes score, whereas patients treated with sham showed a worsening of their score. Compared with the sham stimulation, patients in the precuneus stimulation group also showed also significantly better performances for the secondary outcome measures, including the Alzheimer's Disease Assessment Scale–Cognitive Subscale, Mini-Mental State Examination and Alzheimer's Disease Cooperative Study–Activities of Daily Living scale. Neurophysiological results showed that precuneus cortical excitability remained unchanged after 24 weeks in the precuneus stimulation group, whereas it was significantly reduced in the sham group. Finally, we found an enhancement of local gamma oscillations in the group treated with precuneus stimulation but not in patients treated with sham.

We conclude that 24 weeks of precuneus rTMS may slow down cognitive and functional decline in Alzheimer's disease. Repetitive TMS targeting the default mode network could represent a novel therapeutic approach in Alzheimer's disease patients.

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## Introduction

There is an urgent need for the development of new, effective therapeutic interventions in the battle against Alzheimer's disease.[1,2] Recent work has suggested that non-invasive repetitive transcranial magnetic stimulation (rTMS) may improve cognition in patients with Alzheimer's disease.[3,4] The potential of this technique lies in the possibility to promote changes in synaptic plasticity,[5] which is altered in Alzheimer's disease due to both amyloid and tau pathology.[6] So far, short-term beneficial effects have been obtained mostly by stimulating the dorsolateral prefrontal cortex (DLPFC), with rTMS sessions lasting 2–6 weeks.[7,8] Despite some promising results, rTMS therapy is currently limited by the relatively short duration of treatment sessions and the uncertainty of which brain area is most beneficial to target.

In the early phases of Alzheimer's disease neuropathological abnormalities are mostly distributed in posterior cortical regions of the brain.[9] For instance, amyloid plaques and neurofibrillary tangles are initially found in the precuneus (PC), the posterior cingulate, the retrosplenial, and the lateral posterior parietal cortex.[9] FDG-PET imaging studies consistently show in Alzheimer's disease patients an early regional hypometabolism of these posterior areas,[10] which is associated with alterations in the connectivity of the so-called default mode network (DMN) that can be detected using resting-state functional MRI (fMRI).[11] Notably, the precuneus is considered a main hub of DMN and is the most prominent area of tau pathology deposition and neuroinflammation.[12] Decreases in functional connectivity or deactivation disturbances[13] have also been reported within the precuneus of patients with mild cognitive impairment, being interpreted as the effect of local atrophy.[14] At the early clinical stages of Alzheimer's disease, disconnection of the precuneus precedes and contributes to the occurrence of regional brain atrophy, which becomes prominent at later disease stages.[15] The occurrence of precuneus atrophy would reflect a long-term effect of brain disconnection and lead to the conversion from mild cognitive impairment to Alzheimer's disease.[15] Moreover, Alzheimer's disease patients often show a reduction of precuneus cortical thickness accompanied by an abnormal activation during memory tasks and decreased functional connectivity.[11] This is especially relevant since the activity of the precuneus is considered necessary for episodic memory retrieval,[16] whose impairment represents the clinical onset of typical Alzheimer's disease. Together, this suggests that targeting the precuneus with rTMS is a promising strategy to slow down cognitive decline in Alzheimer's disease patients.

Previous studies performed on healthy subjects revealed that precuneus rTMS is able to modulate long-term memory functions[17] and to strengthen the connectivity between the precuneus and the temporal cortex.[18] Based on this evidence, we recently performed a randomized, sham-controlled trial in which we evaluated the effects of a 2-week course of high-frequency precuneus rTMS in mild Alzheimer's disease patients. In that study, precuneus rTMS resulted in an enhancement of long-term memory and a parallel increase of neural activity within the DMN[19] in Alzheimer's disease patients.

The present study aimed to confirm our hypothesis that the precuneus is an ideal target for non-invasive brain stimulation interventions to slow down cognitive and functional decline in Alzheimer's disease patients. Hence, we performed a randomized, phase 2, sham-controlled, double-blinded trial to evaluate the safety and efficacy of precuneus rTMS in mild-to-moderate Alzheimer's disease patients when rTMS is applied over a clinically relevant period of 24 weeks.

## Materials and methods

### Patients and study design

This was a monocentric, sham-controlled, randomized, and double-blind phase 2 trial of precuneus rTMS in patients with mild-to-moderate dementia due to Alzheimer's disease (TMS-AD). rTMS was given as an add-on to standard treatment with acetylcholinesterase inhibitors. The study was conducted in a research hospital in Italy (Santa Lucia Foundation IRCCS). The trial was approved by the review board and the local ethics committee in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines. All patients or their relatives 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. The TMS-AD study was registered on the clinicaltrial.gov website (NCT03778151). An independent committee monitored the patients' safety according to the Data Monitoring Committee Charter.

Patients were eligible if they had an established diagnosis of probable mild-to-moderate Alzheimer's disease according to the International Working Group recommendations.[20] Alzheimer's disease patients aged $50 \leq 85$ years; had a Clinical Dementia Rating (CDR)[21] score of 0.5–1; a Mini-Mental State Examination (MMSE)[22] score of 18–26 at screening; CSF biomarker evidence of Alzheimer's disease amyloid and tau pathology;[20] had one

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caregiver; and had been treated with acetylcholinesterase inhibitor for at least 6 months. Patients were excluded if they had extrapyramidal signs, history of stroke, other neurodegenerative disorders, psychotic disorders and if they had been treated 6 months before enrolment with antipsychotics, antiparkinsonian, anticholinergics and antiepileptic drugs, history of seizure, metal in the head, or implanted cranial or thoracic devices or any other contraindication to TMS.

## Randomization and masking

Patients were randomly assigned in a 1:1 ratio to receive PC-rTMS or sham-rTMS. Randomization was performed and assigned independently by an external statistician (C.F.), held centrally, and not divulged to any other person involved in the trial. Study groups were balanced in terms of age, sex and APOE carriers with a covariate-adaptive randomization procedure (minimization method).[23] Alzheimer's disease patients were enrolled by expert neurologists (G.K., C.M., A.M.) who were blinded to treatment allocation. Cognitive evaluations were performed by expert neurologists and neuropsychologists (S.B., I.B., M.A., M.M., S.P.) who were blinded to treatment allocation. rTMS sessions were performed by dedicated technicians (F.P., A.D.). Changes in cortical activity were monitored by combining single-pulse transcranial magnetic stimulation with electroencephalography. The recording and analysis of neurophysiological data were performed by expert neurophysiologists blinded to treatment allocation (E.P.C., M.M., M.C.P.).

## Trial procedures

The trial included a 24-week treatment, with a 2-week intensive course where rTMS (or sham) was applied over the precuneus daily (five times per week, Monday to Friday), followed by a 22-week maintenance phase in which the same stimulation was applied weekly (Fig. 1). Each rTMS session consisted of 40, 2-s trains delivered at 20 Hz that were spaced-out by 28 s (total number of stimuli: 1600). This protocol lasted approximately for 20 min.[19] TMS was carried out using a Magstim Rapid2 magnetic biphasic stimulator connected with a with a 70-mm diameter figure-of-eight coil (Magstim Company). Coil was orientated parallel to the midline to induce a posterior-anterior directed current. Throughout the entire 24-week period, a total of 51 200 stimuli were delivered for each patient across 32 sessions. Patients were not engaged in any cognitive rehabilitation programmes during the trial. The TMS coil position was constantly monitored using a neuronavigation system (Softaxic, EMS) coupled with an infrared camera. We used the individual structural MRI previously performed for diagnostic purposes to accurately position the coil over the target area through the neuronavigation system. This ensured that the same spot was reached across different sessions performed days or weeks apart. The precuneus spot was kept the same during the entire study for each patient. rTMS sham treatment was applied with a sham coil positioned in correspondence to the target area (Fig. 1). The intensity and positioning of rTMS treatment were established using single-pulse TMS in combination with a 64-channel EEG (TMS-EEG) based on the evaluation of TMS-evoked potentials (TEPs).[19] EEG was recorded using a TMS-compatible DC amplifier (BrainAmp MR plus, BrainProducts). The amplifier was optically connected to a PC with BrainVision Recorder, through which the EEG was monitored online, and to a 64-channels EEG cap (EasyCap Inc). Each patient preliminarily underwent a series of TMS-EEG recordings recording over a site corresponding to the precuneus, identified based on previous fMRI works [Montreal Neurological Institute (MNI) coordinates: $x = 0$, $y = -65$, $z = 45$].[9,18] To select the intensity for rTMS treatment, we used the following procedure. We first computed the resting motor threshold (RMT). Since the coil-to-cortex distance directly influences the magnitude of magnetic stimulation, for each patient, we subsequently calculated a distance-adjusted RMT (AdjRMT).

$$\mathrm{AdjRMT} = \mathrm{RMT} + \mathrm{m} \times (\mathrm{DsiteX} - \mathrm{DM1}) \quad (1)$$

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.[19] This procedure provides a more accurate index of cortical excitability and improves the efficacy of MT-calibrated TMS. Afterwards, each patient received a series of single TMS pulses at an initial intensity of 100% of AdjRMT, during a 64-channel EEG recording, over the scalp positions corresponding to the precuneus region. If TEPs were not elicited with this initial intensity, it was eventually increased in steps of 2% of the maximal stimulator output (MSO) until a visualization of a first TEP peak of at least 6 μV was reached (Supplementary material).[9,18]

## Outcomes measures

The primary outcome measure was the change at 24 weeks from baseline of the CDR Scale Sum of Boxes (CDR-SB) score (CDR-SB scores range from 0 to 18, with higher scores indicating worse cognition and daily function).[24] A clinical 1–2 point increase in CDR-SB is considered clinically meaningful (minimal clinically important difference, MCID).[25] The intention-to-treat analysis set included all patients who had post-baseline efficacy data. The secondary outcome measures included the change at 24 weeks from baseline of the (i) Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog)[26]; (ii) MMSE score; (iii) Activities of Daily Living (ADCS-ADL)[27]; (iv) Frontal Assessment Battery (FAB)[28]; and (v) Neuropsychiatric Inventory (NPI).[29] Finally, we used single-pulse TMS-EEG to monitor the effects of treatment on cortical activity.[19,30,31] We assessed local cortical excitability and oscillatory activity through two reliable measures based on the combination of single-pulse TMS applied over the precuneus during EEG recordings, namely TEPs, for cortical excitability, and TMS-related spectral perturbation (TRSP), for cortical oscillations.[32]

The efficacy assessments were rated at baseline (W0) for the enrolled patients and repeated at Weeks 12 (W12) and 24 (W24) (or upon early termination) by raters who were blinded. Investigators, patients, and caregivers were all blinded. At each clinical visit (or upon early termination), adverse events were recorded, vital signs measured, and physical and neurological examination were performed.

## Statistical analysis

A total of 50 randomly assigned patients (25 per group) were based-on the power calculation from our previous study.[19] In this study, an effect size of 0.39 (obtained as post-pre means over pooled standard deviation, SD) was observed for Ray Auditory Verbal Learning Test (RAVLT) with a treatment of 2 weeks. Thus, for the current study, it was plausible to estimate a doubled effect size (i.e. ~0.75) considering that the treatment duration was designed 10 times longer. With this effect size, adopting a two-tailed paired Wilcoxon signed-rank, with type I error alpha = 0.05 and a plausible correlation between pre-post measured variables of 0.7, the minimum sample for reaching a power of 0.8 was estimated equal to $n = 17$; and up to $n = 23$ to ensure a power

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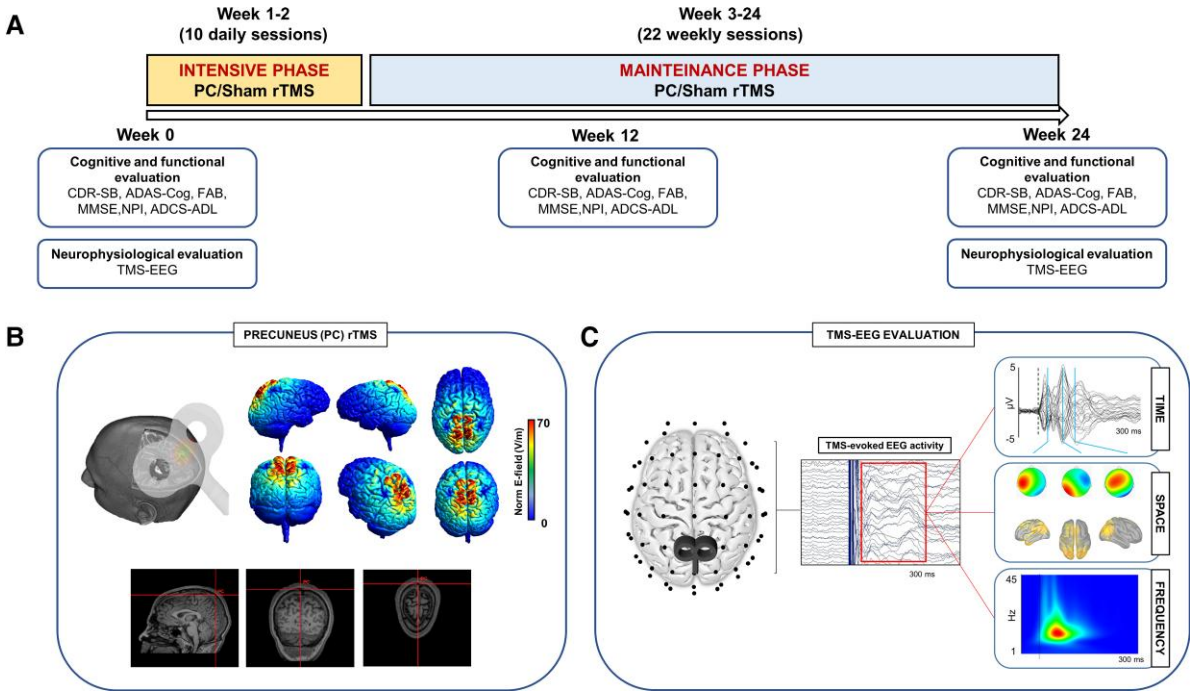


**Figure 1 Schematic representation of the trial**. (**A**) The trial consisted of a 24-week treatment that included a 2-week intensive course, in which PC-rTMS or sham-rTMS was applied daily (five times per week, Monday to Friday), followed by a maintenance phase in which the same stimulation was applied weekly for 22 weeks. (**B**) Location of the TMS coil on the scalp using neuronavigation, as visualized on a template head (*top left*), as well as the specific location in MRI space (*bottom*). Biophysical modelling based on simulated induced electric field are also shown for a representative subject (*top right*). (**C**) Cortical activity was evaluated with concurrent TMS and EEG applied over the PC and analysed in the temporal and oscillatory domain.

of 0.9 (see study protocol in the Supplementary material for details). The choice of $n = 50$ (25 per group) ensured adequate size for within group analyses as well. Normality assumption of end-point variables was assessed by inspection of the distribution plots and by Kolmogorov-Smirnov and Shapiro-Wilk tests. The longitudinal assessment of the end-points across groups was performed through generalized linear mixed model (GLMM) with a random intercept and a random slope to account for individual differences at baseline and to assess individual change through follow-up. GLMM was applied to CDR-SB and the other outcome measures (i.e. ADAS-$Cog_{11}$, MMSE, ADCS-ADL, FAB and NPI), as the dependent variables and the 'Group', 'Time' and 'Group × Time' interaction were set as independent factors. The interaction term allows us to evaluate potential change difference across group. Proper adjustment for sociodemographic variables (age and education) was decided *ad hoc* for each outcome measure, as reported in the Supplementary material. Effects on TEPs were evaluated with a GLMM with 'Group' (between factor), 'Time' and 'Window' (within factors) as independent variables. To explore possible linear relationships between the clinical and neurophysiological data, we tested whether the change (W0–W24) in our clinical primary outcome, i.e. CDR-SB, was correlated with (i) the baseline amplitude (W0); and (ii) the change (W0–W24) in amplitude of the main TEP component. This analysis was conducted by Pearson's correlation coefficient. All statistical tests were two-tailed. Alpha level was set to 0.05.

### Data availability

The datasets, including the redacted study protocol, redacted statistical analysis plan, and individual participants' data supporting the results reported in this article, will be made available within 3 months from initial request to researchers who provide a methodologically sound proposal. The data will be provided after their de-identification, in compliance with applicable privacy laws, data protection and requirements for consent and anonymization. After a signed data access agreement has been received, the study's protocol, statistical analysis plan, blank case report forms, clinical study report, de-identified individual patient data, and a data dictionary defining each field in the dataset will be made available.

## Results

Eighty-six patients were screened, of which 50 underwent randomization between 1 February 2018 and 30 April 2020. The mean age of the total sample of patients was 73.7 years (SD = 6.6, range 62 to 84), of which 52% were female. Patients had a mean MMSE raw score at baseline of 21.3 (SD = 2.5). The baseline patients' demographics and clinical characteristics did not differ between the PC-rTMS and sham-rTMS groups (Table 1). A total of 5 patients withdrew from the trial before completion (three in the PC-rTMS group and two in the sham-rTMS group). A total of 45 patients (90%) completed the treatment period (Fig. 2). On average, the mean number of rTMS sessions completed for 24 weeks did not vary between patients allocated to either experimental group (PC-rTMS: 30.2; sham-rTMS 30.5). Mean rTMS treatment intensity (%MSO) was 53.4 (SD = 9.8) in the PC-rTMS group and 52.5 (SD = 8.4) in the sham-rTMS group. The two groups of Alzheimer's disease patients did not differ for any of the demographical variable considered (all *P*-values > 0.05). The coil-to-cortex distance for the precuneus was 22.3 ± 4.6 for the PC-rTMS group, 21.5 ± 4.1 for the sham-rTMS group, with not significant difference between the two coil-to-cortex distances. All the

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**Table 1 Baseline patients' demographics and clinical characteristics**

| | PC-rTMS ($n = 25$) | Sham-rTMS ($n = 25$) | Group differences |
|---|---|---|---|
| Age, mean (SD) | 75.0 (5.6) | 72.3 (7.2) | $P = 0.12$ |
| Sex, female, *n* (%) | 14 (56%) | 12 (48%) | $P = 0.31$ |
| Education, years, mean (SD) | 10.2 (4.4) | 8.6 (4.1) | $P = 0.26$ |
| Time—years since diagnosis of Alzheimer's disease, median (IQR) | 1.4 (0.6–1.9) | 1.2 (0.4–1.7) | $P = 0.21$ |
| Proportion of patients taking cholinesterase inhibitors, *n* (%) | 25 (100%) | 25 (100%) | $P = 0.9$ |
| Proportion of patients taking memantine, *n* (%) | 2 (8%) | 3 (12%) | $P = 0.71$ |
| Time—years since current AChEI treatment initiated, median (IQR) | 0.8 (0.5–1.1) | 0.9 (0.4–1.1) | $P = 0.51$ |
| APOE e4 carriers, *n* (%) | 16 (60%) | 18 (64%) | $P = 0.3$ |
| Aβ42 CSF values, mean pg/ml (SD) | 412.1 (89.6) | 388.5 (72.1) | $P = 0.15$ |
| Total-tau CSF values, mean pg/ml (SD) | 720.1 (198.6) | 800.7 (261.9) | $P = 0.13$ |
| p-tau181 CSF values, mean pg/ml (SD) | 103.6 (36.1) | 111.3 (41.7) | $P = 0.11$ |
| MMSE raw score, mean (SD) | 21.2 (2.7) | 21.5 (2.4) | $P = 0.66$ |
| CDR-SB raw score, mean (SD) | 4.1 (1.8) | 4.6 (1.5) | $P = 0.12$ |
| ADAS-Cog raw score, mean (SD) | 22.6 (7.4) | 24.8 (6.5) | $P = 0.18$ |
| ADCS-ADL score, mean (SD) | 58.6 (9.7) | 58.3 (9.7) | $P = 0.88$ |
| NPI score, mean (SD) | 9.87 (10.2) | 12.6 (11.7) | $P = 0.56$ |
| FAB raw score, mean (SD) | 10.7 (3.9) | 10.2 (3.4) | $P = 0.20$ |

patients received a stimulation of at least 45 V/m with no difference between the two estimated e-fields: $58 \pm 7.3$ V/m for the PC-rTMS group, $60 \pm 8.2$ V/m for the sham-rTMS group.

The procedure was safe and well tolerated. Eight participants reported adverse events, seven in the PC-rTMS, one in the sham-rTMS group. All events were mild, and most of them resolved on the day of occurrence with either minor or no action [mild headache ($n = 3$), scalp/skin discomfort ($n = 4$), neck pain/stiffness ($n = 3$), and fatigue ($n = 2$)].

## Primary outcome measure

The mean baseline CDR-SB total score did not differ between the PC-rTMS (mean = 4.1, SD = 1.8) and the sham-rTMS (mean = 4.6, SD = 1.5) group. GLMM on CDR-SB scores showed a significant result in terms of the difference between Group ($P = 0.038$) and Time × Group ($P = 0.009$) interaction. Patients in the PC-rTMS group showed a stable performance while patients treated with sham-rTMS showed a general worsening of cognitive performance. The GLMM estimated mean change (W0–W24) in CDR-SB score was −0.25 for PC-rTMS [95% confidence interval (CI) (−4.8, 4.3)] and −1.42 for sham-rTMS group [95% CI (−6.0, 3.3)] (Fig. 3A). The rate of responders, defined as the percentage of patients with a ΔCDR-SB score of ≤1 (i.e. minimal decline)[25] was 68.2% in the PC-rTMS group and 34.7% in the sham group (Fig. 4).

## Secondary outcome measures

The analysis of secondary clinical outcomes showed significant longitudinal differences between the PC-rTMS group and the sham-rTMS group for the ADAS-$COG_{11}$, the MMSE and the ADCS-ADL scores (Table 2). At baseline there were similar baseline ADAS-$COG_{11}$ scores for the PC-rTMS group and the sham-rTMS group (PC-rTMS mean = 22.6, SD = 7.4; sham-rTMS mean = 24.8, SD = 6.5; $P > 0.05$). GLMM on ADAS-$Cog_{11}$ scores showed a significant Time × Group ($P = 0.035$) interaction. GLMM estimated mean change in ADAS-$Cog_{11}$ score was −0.67 for PC-rTMS [95% CI (−21.5, 20.2)], whereas a −4.2 change was found for sham-rTMS group [95% CI (−25.1, 16.6)], showing an improvement of the PC-rTMS with respect to sham-rTMS (Fig. 3B). Similar baseline MMSE scores were found for the PC-rTMS group and sham-rTMS group (PC-rTMS mean = 21.2, SD = 2.7; sham-rTMS mean = 21.5, SD = 2.4; $P > 0.05$). GLMM for the MMSE scores showed a significant Time × Group ($P = 0.041$) interaction. The GLMM estimated mean change in MMSE score was 0.30 for PC-rTMS [95% CI (−5.2, 5.8)] and 1.8 for sham-rTMS group [95% CI (−3.8, 7.3)] (Fig. 3C), indicating the MMSE scores were maintained better for the PC-rTMS group when compared to sham-rTMS. Comparable baseline ADCS-ADL scores were found for the PC-rTMS and sham-rTMS group (PC-rTMS mean = 58.6, SD = 9.7; sham-rTMS mean = 58.3, SD = 9.7; $P > 0.05$). The estimated mean change in ADCS-ADL scores was −0.7 for PC-rTMS [95% CI (−27.2, 25.8)] and 7.5 for sham-rTMS group [95% CI (−20.5, 35.5)], showing an improvement of the PC-rTMS with respect to sham-rTMS (interaction effect: $P < 0.001$) (Fig. 3D). The baseline mean NPI score was similar for the PC-rTMS and sham-rTMS group (PC-rTMS mean = 9.8, SD = 10.2; sham-rTMS mean = 12.6, SD = 11.7; $P > 0.05$). The estimated mean change in NPI score was −1.4 for PC-rTMS [95% CI (−15.7, 13.6)] and −3.7 for sham-rTMS group [95% CI (−25.8, 21.9)], which revealed no significant effects (Fig. 3E). Finally, baseline mean FAB score were similar for both the PC-rTMS and sham-rTMS group (PC-rTMS mean = 10.7, SD = 3.9; sham-rTMS mean = 10.2, SD = 3.4; $P > 0.05$). The estimated mean change in FAB score was −0.01 for PC-rTMS [95% CI (−7.7, 7.7)] and 0.29 for sham-rTMS group [95% CI (−7.4, 8.0)], with no significant effects (Fig. 3F).

## Neurophysiological evaluation

TMS-evoked cortical activity over the precuneus did not vary after 24 weeks in the PC-rTMS group, while it decreased in the sham-rTMS group (Fig. 5A). 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 reported. 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 significant difference between W0 and W24 time points, in the sham condition (all *P*-values < 0.05 FDR corrected, Supplementary Table 2). 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 Time × Group interaction showing a significant modulation of the two TEP components in the W24 time point for the only sham condition [$F(1,126) = 6.65$; $P = 0.011$].

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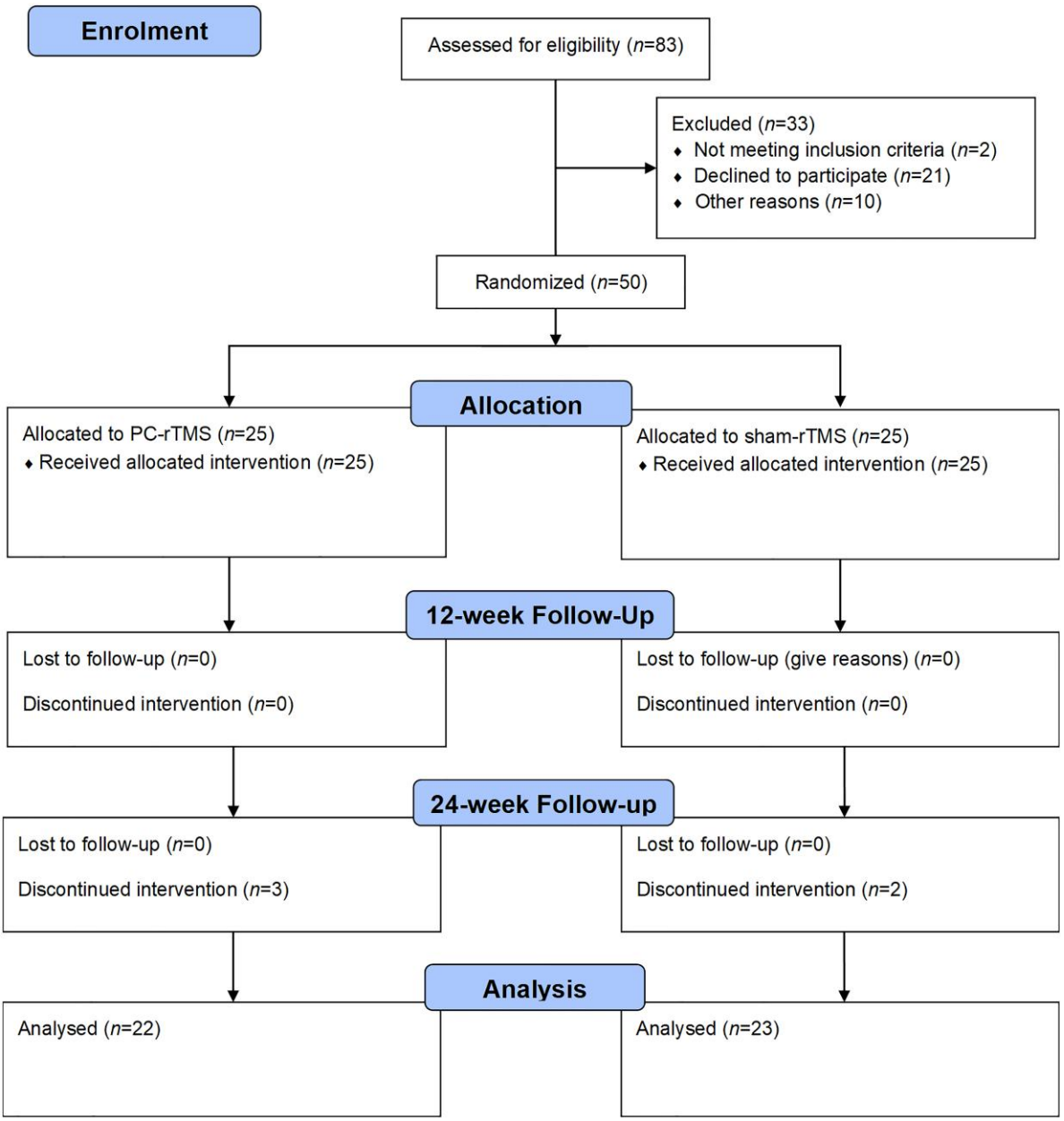


**Figure 2 Flow diagram of the trial.** Randomization, trial-group assignment, and follow-up in the trial.

*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 Supplementary Table 3. We found that TEP amplitude at baseline correlated with the CDR-SB score after 24 weeks in the PC-rTMS ($r = -0.449$; $P = 0.021$) but not in the sham-rTMS group, showing that patients presenting with higher cortical activity at baseline had better clinical response to the rTMS treatment. We also found that CDR-SB score change from baseline to W24 correlated with TEP amplitude variation in the PC-rTMS ($r = -0.484$; $P < 0.04$) but not in the sham-rTMS group, showing that CDR-SB score improvement was paralleled by an increase of cortical activity (all $P > 0.05$) (Fig. 5B). We also observed that among the patients who had an improvement at the CDR-SB score, the mean TEP change from baseline to W24 was 1.23 μV [95% CI (−0.17, 2.29)]. Stimulation of the precuneus with single-pulse TMS evoked an oscillatory activity in the beta-gamma range with a peak of frequency at around 40 Hz lasting ∼50 ms. *T*-test analysis conducted on spectral power showed an enhancement of high frequency oscillations in the gamma band ranging from 31 to 48 Hz (mean *P*-value = 0.033) at W24 in the PC-rTMS group. Evoked oscillatory activity did not change in the sham-rTMS group (mean *P*-value > 0.05) (Fig. 5C). There were no significant correlations among the clinical scores and the changes in oscillatory activity. The detailed information of the TRSP in the different frequency bands are reported in Supplementary Table 2.

## Discussion

Here we present the results of a 24-week non-invasive brain stimulation treatment with rTMS targeting the precuneus in patients

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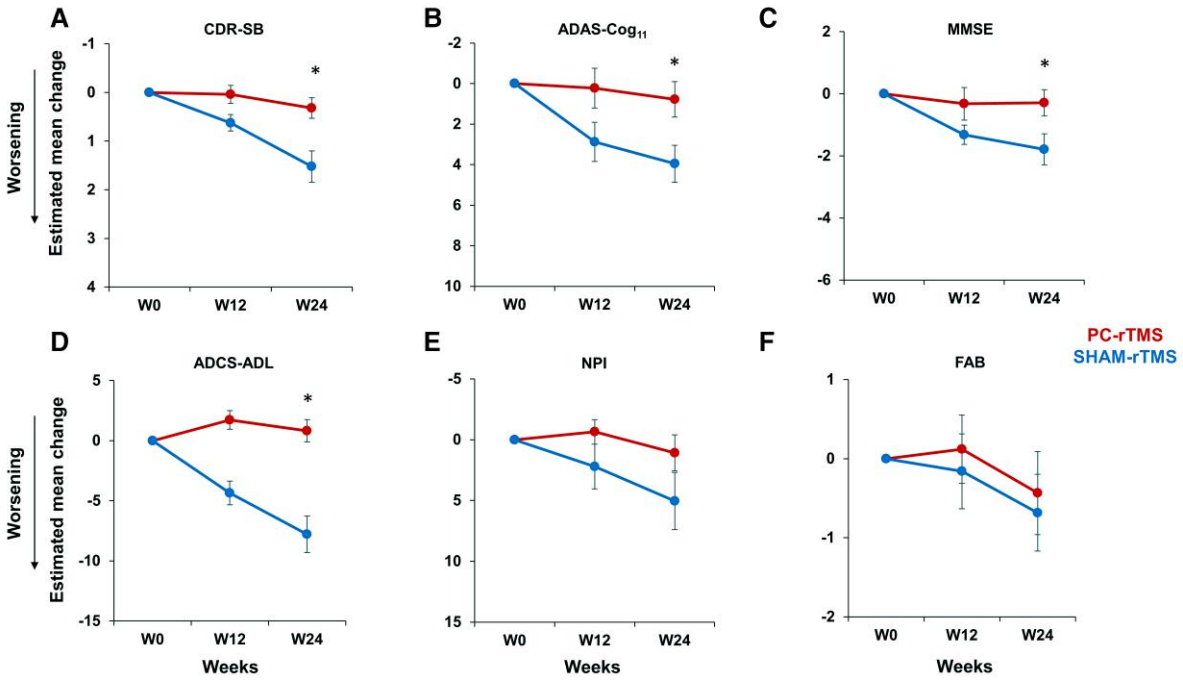


**Figure 3 Estimated mean group changes for clinical scores**. Estimated mean group changes from baseline (W0) in the CDR-SB, ADAS-$Cog_{11}$, MMSE, ADCS-ADL, NPI, and FAB following 12 weeks (W12) and 24 weeks (W24) of PC-rTMS and sham-rTMS. Y-axis of each outcome was adapted in order to considering all depicted descending trend as a worsening. (**A**) GLMM estimated mean score change from baseline on the CDR-SB scale; scores are obtained by summing each of the domain box scores, with scores ranging from 0 to 18, with higher scores indicating worse cognition. (**B**) GLMM estimated mean score change from baseline for the ADAS-$Cog_{11}$; scores range from 0 to 70, with higher scores indicating worse cognition. (**C**) GLMM estimated mean score change from baseline on the MMSE; scores range from 0 to 30, with lower scores indicating worse cognition. (**D**) GLMM estimated mean score change from baseline for the ADCS-ADL; scores range from 0 to 78, with lower scores indicating worse function. (**E**) GLMM mean score change from baseline on the NPI; scores range from 0 to 144, with higher scores indicating worse behavioural symptoms. (**F**) GLMM mean score change from baseline for the FAB; score ranges from 0 to 18, with higher scores indicating better frontal cognitive functions. Baseline is plotted at Week 0, which is the baseline measurement before the first rTMS session. Error bars indicate standard errors.

with mild-to-moderate dementia due to Alzheimer's disease. To the best of our knowledge, this is one of the largest trials of brain stimulation ever done in Alzheimer's disease suggesting a therapeutic benefit, and the first one to evaluate the safety and effectiveness of rTMS compared to sham treatment over a long-term interval of 24 weeks. Overall, our results show that PC-rTMS is safe and well tolerated by Alzheimer's disease patients. Adverse events were uncommon and mild, as similarly reported in randomized-controlled trials using rTMS in patients with Alzheimer's disease of comparable disease severity.[4,7,8]

In this trial, stimulation of the precuneus proved beneficial for the primary clinical outcome (change in the CDR-SB score at Week 24). Patients treated with PC-rTMS showed almost no decline in the CDR-SB score, presenting a clear advantage in terms of cognitive functions in contrast to the worsening of the CDR-SB score observed in the sham-rTMS group.[33] Positive PC-rTMS effects on cognitive functions were also confirmed by the analysis of secondary outcome measures (ADAS-$COG_{11}$, MMSE).[33,34] Moreover, rTMS to the precuneus was effective in reducing patients' functional decline. In fact, we observed an ameliorative effect on the autonomies of daily living as revealed by the ADCS-ADL, suggesting the potential use of PC-rTMS in treating both cognitive and functional impairments in the early disease stages of Alzheimer's disease.

The magnitude of differences observed in these scales confirmed that rTMS induced clinically meaningful changes, although patients treated with sham-rTMS declined slightly faster than the expected rate observed in other studies.[33,34] In this regard, Alzheimer's disease patients recruited in our study had a MMSE score of 21 at baseline, which is compatible with a relatively more advanced stage of disease when compared to the recently published multicentre randomized control trials, and is associated with a higher probability of faster decline.[35,36] Moreover, a recent meta-analysis showed that approximately 30–40% of Alzheimer's disease patients experience rapid decline, defined as a 4-point decrease in MMSE score within 6 months.[37] Therefore, it is possible that the clinical progression in the sham-rTMS group could also be influenced by this naturally occurring phenomenon of rapid decline.

Yet, it should be emphasized that all recruited patients received pharmacologic standard of care for mild-to-moderate Alzheimer's disease,[34] regardless of their randomly assigned treatment group. Thus, the beneficial effects of stimulation shown here might be considered as an additive to the concomitant use of acetylcholinesterase inhibitor (AChEI) and memantine. The rate of responders to the treatment was 68% in the PC-rTMS group and 34% in the sham group, with a high differential between treated and controls. This high percentage is similar to that reported in rTMS clinical trials for depression,[38] which is currently approved by the Food and Drug Administration (FDA) and covered by insurers in the USA and other countries.

Supporting the positive effects observed on cognitive functions, we found that rTMS induced remarkable changes in cortical activity, as demonstrated by TMS-EEG recordings. Specifically, in patients receiving PC-rTMS we observed a stabilization of the initial

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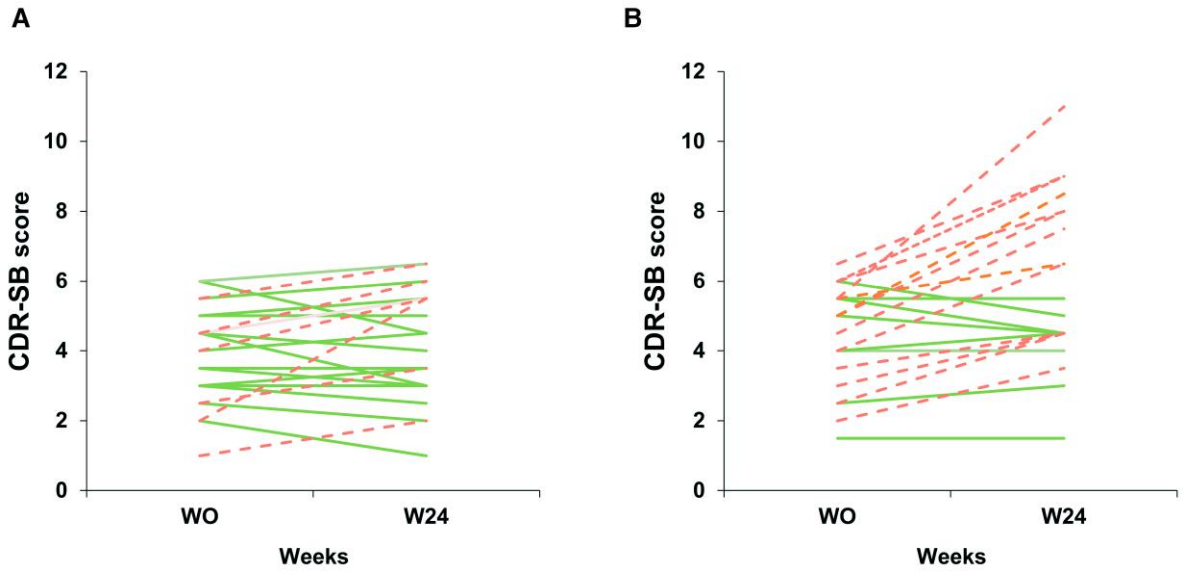


**Figure 4 Individual changes in the CDR-SB scale**. Line plot representing the individual CDR-SB scores before (W0) and at the end of the trial (W24) for the PC-rTMS group (**A**) and for the sham-rTMS group (**B**). Within each group, the solid lines indicate the responders, while the dashed lines represent the non-responders.

**Table 2 Changes in primary and secondary outcomes from baseline to Week 24: GLMM estimated effects**

| Outcome | Estimated change (W0–W24) | | Group effect | | Time effect | | Group × Time effect | |
|---|---|---|---|---|---|---|---|---|
| | PC-rTMS Mean [95%CI] | Sham-rTMS Mean [95%CI] | F -test | P-value | F-test | P-value | F-test | P-value |
| CDR-SB | −0.25 [−4.8, 4.3] | −1.42 [−6.0, 3.3] | $F(1,89) = 4.70$ | **0.033*** | $F(1,89) = 0.21$ | 0.646 | $F(1,89) = 7.05$ | **0.009*** |
| ADAS-Cog[a] | −0.67 [−21.5, 20.2] | −4.19 [−25.1, 16.6] | $F(1,84) = 2.81$ | 0.098 | $F(1,84) = 0.02$ | 0.889 | $F(1,84) = 4.63$ | **0.035*** |
| MMSE[a] | 0.30 [−5.2, 5.8] | 1.75 [−3.8, 7.3] | $F(1,88) = 0.04$ | 0.950 | $F(1,88) = 0.14$ | 0.710 | $F(1,88) = 4.29$ | **0.041*** |
| ADCS-ADL | −0.70 [−27.2, 25.8] | 7.54 [−20.5, 35.5] | $F(1,89) = 1.37$ | 0.245 | $F(1,89) = 0.06$ | 0.800 | $F(1,89) = 15.07$ | **<0.001*** |
| FAB[a] | −0.01 [−7.7, 7.7] | 0.29 [−7.4, 8.0] | $F(1,87) = 0.01$ | 0.997 | $F(1,87) = 0.001$ | 0.972 | $F(1,87) = 0.17$ | 0.681 |
| NPI | −1.43 [−15.7, 13.6] | −3.68 [−25.8, 21.9] | $F(1,91) = 1.91$ | 0.170 | $F(1,91) = 0.08$ | 0.782 | $F(1,91) = 0.33$ | 0.570 |

[a]GLMM adjusted for age and education.
*Statistically significant values ($P < 0.05$).

level of cortical excitability which remained unchanged after 24 weeks, whereas this was dramatically reduced in the sham-rTMS group. Such decline of cortical excitability in the sham group was expected based on a recent study in which TMS-EEG was used as a readout of frontal lobe activity to examine the effects of the dopaminergic agonist rotigotine as compared to placebo in mild-to-moderate Alzheimer's disease patients.[30] In the current study, we also observed an enhancement in the local fast gamma oscillations for the PC-rTMS group, that was not evident in the sham-rTMS group. In addition, our data showed that the individual baseline level of cortical excitability, as measured by the TEP amplitude, was strictly correlated to the subsequent clinical response to rTMS-treatment as assessed by the changes in the CDR-SB score. Moreover, we also found that changes in the CDR-SB score were associated with a parallel change in precuneus cortical excitability. Hence TMS-EEG could be potentially useful to predict response to therapy and could represent a useful biomarker of rTMS efficacy.

We argue that the positive effects induced by rTMS may be ascribed to the impact on cortical plasticity mechanisms, which are known to be impaired in Alzheimer's disease at the early disease stages.[12] In animal models of Alzheimer's disease, 20Hz rTMS has been reported to increase the expression of dopamine DR4 gene and of neurogenic proteins such as brain-derived neurotrophic factor (BDNF) in the cerebral cortex and the hippocampus.[39] Moreover, it was suggested that rTMS could counteract mechanisms of apoptosis leading to a decrease in p-Tau, APP, Aβ, and PP2A expression.[39] We also found that rTMS fostered neuronal oscillations in the gamma band (40 Hz). Gamma oscillations are disrupted in Alzheimer's disease patients and animal models, with the severity of cognitive decline being associated with the degree of rhythm disruption.[40] Notably, an increase of gamma activity in Alzheimer's disease has been shown to accelerate amyloid-plaque clearance and increase microglia activation in animal models of Alzheimer's disease.[40] Further studies are needed to better clarify the potential of rTMS in modulating these crucial pathophysiological aspects.

We chose a 24-week trial duration to evaluate potential clinical effects in terms of cognitive and functional decline that could be comparable to those obtained by pharmacological trials.[41] On the other hand, changes in cognitive functions in other rTMS trials have been tested only with a few weeks of rTMS treatment.[4] These previous studies were aimed to evaluate a possible 'acute

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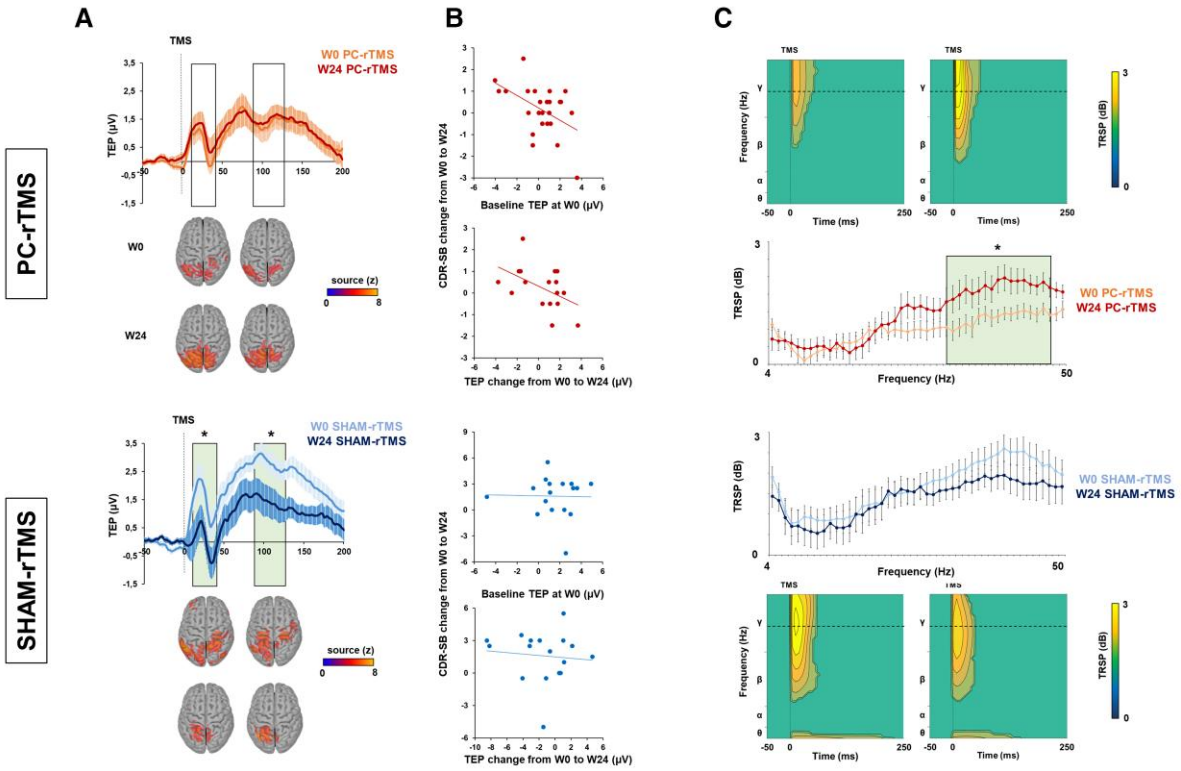


**Figure 5 Changes in precuneus cortical activity.** (**A**) TEPs before (W0) and after 24 weeks (W24) of PC-rTMS (light and dark lines, *top*) and sham-rTMS (light and dark lines, *bottom*). TEPs did not change in patients treated with PC-rTMS, while decreased TEP amplitudes were found in the sham-rTMS group. (**B**) Correlation analysis performed between the CDR-SB individual score change from baseline (W0) to 24 weeks (W24) in both PC-rTMS (*top*) or sham-rTMS (*bottom*) groups with individual TEP amplitude at baseline (W0) and with the TEP amplitude change from W0 to W24. Correlations were significant in the PC-rTMS but not in the sham-rTMS group. (**C**) TRSP before (W0) and after 24 weeks (W24) of PC-rTMS (*top*) and sham-rTMS (*bottom*), representing the power of oscillatory activity after single-pulse TMS over the precuneus. An increase of gamma activity was evident in the PC-rTMS, but not in the sham-rTMS group.

effect' on cognitive functions but not to observe changes in the trajectory of cognitive and functional decline.

The current trial design was based on a first intensive session lasting 2 weeks with daily treatments followed by a maintenance phase with weekly sessions for the following 22 weeks of the trial duration. The intensive phase was chosen based on our recent pilot study in which we found an improvement in long-term memory in mild Alzheimer's disease patients treated with PC-rTMS for 2 weeks.[19] The choice of keeping one session per week in the following months was taken to allow the caregivers and the patients to adhere to the treatment without causing excessive discomfort. Thus, it is possible that larger effects could be achieved if the intensive period is expanded to more weeks or if the number of rTMS sessions would be increased during the maintenance phase. Future investigations would be helpful to refine the current protocol in order to replicate and expand the present results.

It is important to notice that we chose to stimulate the precuneus, the main hub of the DMN (refer to the 'Introduction' for the rationale), in contrast with most of the previous rTMS studies that attempted to stimulate the DLPFC, resembling other rTMS protocols used to treat depression. These studies showed initially short-term improvement in language and memory functions including object naming, auditory sentence comprehension and associative memory.[8,41–47] A recent meta-analysis showed a lateralization of rTMS effects, suggesting that high-frequency left DLPFC stimulation is associated with a larger improvement of memory functions.[48] However, other outcome measures such as activities of daily living and global cognition did not show a clear improvement and recent evidence-based guidelines did not endorse rTMS of left DLPFC as an effective therapeutic option for the treatment of Alzheimer's disease .[49,50] Another strategy used high frequency rTMS in conjunction with concurrent cognitive training, with rTMS being delivered during a few weeks at six different cortical sites with patients receiving cognitive training overlapping with TMS delivery. This approach showed some promising results, although it is not clear how cognitive training itself may have produced some beneficial effects.[7,51] Notably, in the current trial, Alzheimer's disease patients were not treated with concomitant cognitive training. Hence, the potential synergistic effects of PC-rTMS with cognitive training could be explored in future studies.

## Limitations

The current study has some limitations. First, targeting of the precuneus did not take in account individual functional brain MRI and induced electric fields modelling. Hence further studies are needed to refine the personalized targeting approach of the precuneus site of stimulation. Second, in our study the rate of progression in the sham group was in the upper bound of the normal progression for similar patients observed in previous studies. Third, our data were collected in the context of a single-site trial although with a

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relatively adequate sample size. Fourth, evidence for the biological effects of rTMS should be provided in future confirmatory trials by measuring changes in Tau and Aβ pathology. Finally, the described clinical effects were evident over a period of 24 weeks. Hence, future trials must establish whether such effects can be maintained or extended by expanding the treatment period.

## Conclusions

PC-rTMS may reduce the progression of cognitive decline and delay the impairment of autonomies of daily living. Further personalization and longer treatment interventions might pave the way to a novel class of non-pharmacological intervention for Alzheimer's disease.

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## Competing interests

G.K. reports grants from the Alzheimer's Drug Discovery Foundation, the Italian Ministry of Health, the European Commission and non-financial support from UCB Pharma outside the submitted work. A.M. reports grants from Alzheimer's Drug Discovery Foundation, Italian Ministry of Health and non-financial support from UCB Pharma outside the submitted work. E.S. reports grants from Alzheimer's Drug Discovery Foundation and the National Institute of Health. G.K. has a patent on precision neuromodulation in patients with Alzheimer's disease partially including the methodology described in this report. E.S. has patents on non-invasive brain stimulation applications in neurodegenerative diseases.

## Supplementary material

Supplementary material is available at *Brain* online.

## References

1. Scheltens P, De Strooper B, Kivipelto M, *et al*. Alzheimer's disease. *Lancet*. 2021; 397:1577–1590.
2. Kuller LH, Lopez OL. ENGAGE And EMERGE: truth and consequences? *Alzheimers Dement*. 2021;17:692–695.
3. Canter RG, Penney J, Tsai LH. The road to restoring neural circuits for the treatment of Alzheimer's disease. *Nature*. 2016; 539:187–196.
4. Weiler M, Stieger KC, Long JM, Rapp PR. Transcranial magnetic stimulation in Alzheimer's disease: are we ready? *eNeuro*. 2020;7:ENEURO.0235–19.2019.
5. Francesco DL, Koch G. Synaptic impairment: the new battlefield of Alzheimer's disease. *Alzheimers Dement*. 2021;17:314–315.
6. Walsh DM, Selkoe DJ. Deciphering the molecular basis of memory failure in Alzheimer's disease. *Neuron*. 2004;44:181–193.
7. Sabbagh M, Sadowsky C, Tousi B, *et al*. Effects of a combined transcranial magnetic stimulation (TMS) and cognitive training intervention in patients with Alzheimer's disease. *Alzheimers Dement*. 2020;16:641–650.
8. Rutherford G, Lithgow B, Moussavi Z. Short and long-term effects of rTMS treatment on Alzheimer's disease at different stages: a pilot study. *J Exp Neurosci*. 2015;9:43–51.
9. Yokoi T, Watanabe H, Yamaguchi H, *et al*. Involvement of the precuneus/posterior cingulate Cortex is significant for the development of Alzheimer's disease: a PET (THK5351, PiB) and resting fMRI study. *Front Aging Neurosci*. 2018;10:304.
10. Strom A, Iaccarino L, Edwards L, *et al*. Cortical hypometabolism reflects local atrophy and tau pathology in symptomatic Alzheimer's disease. *Brain*. 2022;145:713–728.
11. Gili T, Cercignani M, Serra L, *et al*. Regional brain atrophy and functional disconnection across Alzheimer's disease evolution. *J Neurol Neurosurg Psychiatry*. 2011;82:58–66.
12. Veitch DP, Weiner MW, Aisen PS, *et al*. Understanding disease progression and improving Alzheimer's disease clinical trials: recent highlights from the Alzheimer's disease neuroimaging initiative. *Alzheimers Dement*. 2019;15:106–152.
13. Rombouts SARB, Barkhof F, Goekoop R, Stam CJ, Scheltens P. Altered resting state networks in mild cognitive impairment and mild Alzheimer's disease: an fMRI study. *Hum Brain Mapp*. 2005;26:231–239.
14. Bai F, Zhang Z, Yu H, *et al*. Default-mode network activity distinguishes amnestic type mild cognitive impairment from healthy aging: a combined structural and resting-state functional MRI study. *Neurosci Lett*. 2008;438:111–115.
15. Serra L, Cercignani M, Mastropasqua C, *et al*. Longitudinal changes in functional brain connectivity predicts conversion to Alzheimer's disease. *J Alzheimers Dis*. 2016;51:377–389.
16. Specific and disease stage-dependent episodic memory-related brain activation patterns in Alzheimer's disease: a coordinate-based meta-analysis | SpringerLink. Accessed 20 May 2022. https://link.springer.com/article/10.1007/s00429-014-0744-6
17. Bonnì S, Veniero D, Mastropasqua C, *et al*. TMS Evidence for a selective role of the precuneus in source memory retrieval. *Behav Brain Res*. 2015;282:70–75.
18. Mancini M, Mastropasqua C, Bonnì S, *et al*. Theta burst stimulation of the precuneus modulates resting state connectivity in the left temporal pole. *Brain Topogr*. 2017;30:312–319.
19. Koch G, Bonnì S, Pellicciari MC, *et al*. Transcranial magnetic stimulation of the precuneus enhances memory and neural activity in prodromal Alzheimer's disease. *Neuroimage*. 2018;169:302–311.
20. Dubois B, Feldman HH, Jacova C, *et al*. Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. *Lancet Neurol*. 2014;13:614–629.
21. Morris JC. The clinical dementia rating (CDR): current version and scoring rules. *Neurology*. 1993;43:2412.2–4.
22. Goldstein MZ, Fogel BS. Cognitive change after elective surgery in nondemented older adults. *Am J Geriatr Psychiatry*. 1993;1:118–125.
23. Lin Y, Zhu M, Su Z. The pursuit of balance: an overview of covariate-adaptive randomization techniques in clinical trials. *Contemp Clin Trials*. 2015;45:21–25.
24. Coley N, Andrieu S, Jaros M, Weiner M, Cedarbaum J, Vellas B. Suitability of the clinical dementia rating-sum of boxes as a single primary endpoint for Alzheimer's disease trials. *Alzheimers Dement*. 2011;7:602–610.e2.
25. Andrews JS, Desai U, Kirson NY, Zichlin ML, Ball DE, Matthews BR. Disease severity and minimal clinically important differences in clinical outcome assessments for Alzheimer's disease clinical trials. *Alzheimers Dement (N Y)*. 2019;5:354–363.

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26. Mohs RC, Knopman D, Petersen RC, *et al*. Development of cognitive instruments for use in clinical trials of antidementia drugs: additions to the Alzheimer's disease assessment scale that broaden its scope. The Alzheimer's disease cooperative study. *Alzheimer Dis Assoc Disord*. 1997;11:S13–S21.
27. Galasko D, Bennett D, Sano M, *et al*. An inventory to assess activities of daily living for clinical trials in Alzheimer's disease. The Alzheimer's disease cooperative study. *Alzheimer Dis Assoc Disord*. 1997;11:S33–S39.
28. Dubois B, Slachevsky A, Litvan I, Pillon B. The FAB: a frontal assessment battery at bedside. *Neurology*. 2000;55:1621–1626.
29. Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. The neuropsychiatric inventory: comprehensive assessment of psychopathology in dementia. *Neurology*. 1994;44:2308–2314.
30. Koch G, Motta C, Bonnì S, *et al*. Effect of rotigotine vs placebo on cognitive functions among patients with mild to moderate Alzheimer disease. *JAMA Netw Open*. 2020;3:e2010372.
31. Kumar S, Zomorrodi R, Ghazala Z, *et al*. Extent of dorsolateral prefrontal Cortex plasticity and its association with working memory in patients with Alzheimer disease. *JAMA Psychiatry*. 2017;74:1266–1274.
32. Casula EP, Pellicciari MC, Bonnì S, *et al*. Evidence for interhemispheric imbalance in stroke patients as revealed by combining transcranial magnetic stimulation and electroencephalography. *Hum Brain Mapp*. 2021;42:1343–1358.
33. Teylan M, Mock C, Gauthreaux K, *et al*. Cognitive trajectory in mild cognitive impairment due to primary age-related tauopathy. *Brain*. 2020;143:611–621.
34. Birks JS, Harvey RJ. Donepezil for dementia due to Alzheimer's disease. *Cochrane Database Syst Rev*. 2018;2018:CD001190.
35. Tchalla AE, Clément JP, Saulnier I, *et al*. Predictors of rapid cognitive decline in patients with mild-to-moderate Alzheimer disease: a prospective cohort study with 12-month follow-up performed in memory clinics. *Dement Geriatr Cogn Disord*. 2018;45:56–65.
36. Schmidt C, Wolff M, Weitz M, Bartlau T, Korth C, Zerr I. Rapidly progressive Alzheimer disease. *Arch Neurol*. 2011;68:1124–1130.
37. Ito K, Ahadieh S, Corrigan B, French J, Fullerton T, Tensfeldt T. Disease progression meta-analysis model in Alzheimer's disease. *Alzheimers Dement*. 2010;6:39–53.
38. Brunoni AR, Chaimani A, Moffa AH, *et al*. Repetitive transcranial magnetic stimulation for the acute treatment of major depressive episodes: a systematic review with network meta-analysis. *JAMA Psychiatry*. 2017;74:143–152.
39. Choung JS, Kim JM, Ko MH, Cho DS, Kim M. Therapeutic efficacy of repetitive transcranial magnetic stimulation in an animal model of Alzheimer's disease. *Sci Rep*. 2021;11:437.
40. Iaccarino HF, Singer AC, Martorell AJ, *et al*. Gamma frequency entrainment attenuates amyloid load and modifies microglia. *Nature*. 2016;540:230–235.
41. Cummings J, Lee G, Nahed P, *et al*. Alzheimer's disease drug development pipeline: 2022. *Alzheimers Dement (N Y)*. 2022;8:e12295.
42. Cotelli M, Borroni B, Manenti R, *et al*. Action and object naming in frontotemporal dementia, progressive supranuclear palsy, and corticobasal degeneration. *Neuropsychology*. 2006;20:558–565.
43. Cotelli M, Manenti R, Cappa SF, Zanetti O, Miniussi C. Transcranial magnetic stimulation improves naming in Alzheimer disease patients at different stages of cognitive decline. *Eur J Neurol*. 2008;15:1286–1292.
44. Cotelli M, Calabria M, Manenti R, *et al*. Improved language performance in Alzheimer disease following brain stimulation. *J Neurol Neurosurg Psychiatry*. 2011;82:794–797.
45. Nguyen JP, Suarez A, Le Saout E, Meignier M, Nizard J, Lefaucheur JP. Combining cognitive training and multi-site rTMS to improve cognitive functions in Alzheimer's disease. *Brain Stimul*. 2018;11:651–652.
46. Ahmed MA, Darwish ES, Khedr EM, El serogy YM, Ali AM. Effects of low versus high frequencies of repetitive transcranial magnetic stimulation on cognitive function and cortical excitability in Alzheimer's dementia. *J Neurol*. 2012;259:83–92.
47. Drumond Marra HL, Myczkowski ML, Maia Memória C, *et al*. Transcranial magnetic stimulation to address mild cognitive impairment in the elderly: a randomized controlled study. *Behav Neurol*. 2015;2015:287843.
48. Chou YH, Ton That V, Sundman M. A systematic review and meta-analysis of rTMS effects on cognitive enhancement in mild cognitive impairment and Alzheimer's disease. *Neurobiol Aging*. 2020;86:1–10.
49. Lefaucheur JP, André-Obadia N, Antal A, *et al*. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). *Clin Neurophysiol*. 2014;125:2150–2206.
50. Lefaucheur JP, Aleman A, Baeken C, *et al*. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): an update (2014–2018). *Clin Neurophysiol*. 2020;131:474–528.
51. Nguyen JP, Suarez A, Kemoun G, *et al*. Repetitive transcranial magnetic stimulation combined with cognitive training for the treatment of Alzheimer's disease. *Neurophysiol Clin*. 2017;47:47–53.


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