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Analyzing structural and functional brain changes related to an integrative cognitive remediation program for schizophrenia: A randomized controlled trial

Agurne Sampedro [a], Naroa Ibarretxe-Bilbao [a], Javier Peña [a,*], Alberto Cabrera-Zubizarreta [b], Pedro Sánchez [c,d], Ainara Gómez-Gastiasoro [e], Nagore Iriarte-Yoller [c], Cristóbal Pavón [c], Mikel Tous-Espelosin [f], Natalia Ojeda [a]

[a] University of Deusto, Faculty of Health Sciences, Department of Psychology, Bilbao, Spain
[b] Hospital of Galdakao, OSATEK, MR Unit, Galdakao, Spain
[c] Bioaraba, New Therapies in Mental Health, Osakidetza Basque Health Service, Araba Mental Health Service, Alava Psychiatric Hospital, Vitoria-Gasteiz, Spain
[d] University of Deusto, Faculty of Health Sciences, Department of Medicine, Bilbao, Spain
[e] University of the Basque Country (UPV/EHU), Faculty of Psychology, Department of Basic Psychological Processes and Development, Donostia, Spain
[f] University of the Basque Country (UPV/EHU), Faculty of Education and Sport, Department of Physical Education and Sport, Vitoria-Gasteiz, Spain

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ABSTRACT

Cognitive remediation has been shown to improve cognition in schizophrenia, but little is known about the specific functional and structural brain changes related to the implementation of an integrative cognitive remediation program. This study analyzed the functional and structural brain changes identified after implementing an integrative cognitive remediation program, REHACOP, in schizophrenia. The program combined cognitive remediation, social cognitive training, and functional and social skills training. The sample included 59 patients that were assigned to either the REHACOP group or an active control group for 20 weeks. In addition to a clinical and neuropsychological assessment, T1-weighted, diffusion-weighted and functional magnetic resonance images were acquired during a resting-state and during a memory paradigm, both at baseline and follow-up. Voxel-based morphometry, tract-based spatial statistics, resting-state functional connectivity, and brain activation analyses during the memory paradigm were performed. Brain changes were assessed with a 2 × 2 repeated-measure analysis of covariance for group x time interaction. Intragroup paired *t*-tests were also carried out. Repeated-measure analyses revealed improvements in cognition and functional outcome, but no significant brain changes associated with the integrative cognitive remediation program. Intragroup analyses showed greater gray matter volume and cortical thickness in right temporal regions at post-treatment in the REHACOP group. The absence of significant brain-level results associated with cognitive remediation may be partly due to the small sample size, which limited the statistical power of the study. Therefore, further research is needed to clarify whether the temporal lobe may be a key area involved in cognitive improvements following cognitive remediation.

Cognitive impairment in both neurocognition and social cognition is a core characteristic of schizophrenia (Green et al., 2019). It has been suggested that multiple structural and functional brain alterations could underlie these cognitive deficits (Kronbichler et al., 2017; Minzenberg et al., 2009; Penadés et al., 2019). Due to the impact that cognitive impairment has on daily functioning (Fu et al., 2017; Galderisi et al., 2014; Green et al., 2000; Peña et al., 2018; Strassnig et al., 2015), this has become an important treatment target for schizophrenia. For this reason, in the last few decades non-pharmacological treatments such as cognitive remediation have gained importance in this field (Wykes et al., 2007). Cognitive remediation is an intervention based on behavioral training aimed at improving cognitive processes (e.g., attention, memory, and executive functions) with the goal of long-term maintenance and generalization (Wykes et al., 2011). Specifically, cognitive remediation has been shown to be an effective intervention for improving cognition (Cella et al., 2020; McGurk et al., 2007; Revell et al., 2015;

* Corresponding author at: University of Deusto, Faculty of Health Sciences, Department of Psychology, Avda. Universidades 24, 48007 Bilbao, Spain.
E-mail address: javier.pena@deusto.es (J. Peña).

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Wykes et al., 2011). Moreover, cognitive remediation has also been shown to produce some brain structural and functional changes in schizophrenia (Hegde et al., 2020; Matsuda et al., 2019; Penadés et al., 2017). In addition, brain changes induced by cognitive remediation have been associated with multiple cognitive improvements (Eack et al., 2010; Morimoto et al., 2018; Penadés et al., 2013). However, the specific brain changes produced by cognitive remediation are still heterogeneous and inconclusive across studies (Matsuda et al., 2019; Penadés et al., 2017). Studies suggest that combining cognitive remediation with additional interventions, such as social cognitive training or social and functional skill training, can enhance the effect of cognitive remediation (Cella et al., 2015). Nevertheless, evidence of brain changes after the combination of cognitive remediation with other types of training has come from a small number of magnetic resonance imaging (MRI) studies (Eack et al., 2010; Eack et al., 2016; Keshavan et al., 2017; Subramaniam et al., 2014).

Both functional and structural changes have been found following cognitive remediation in schizophrenia (Matsuda et al., 2019; Penadés et al., 2017). With respect to functional changes, task-based and resting-state functional MRI (fMRI) studies have reported increased activation after cognitive remediation mainly in prefrontal regions (Eack et al., 2016; Fan et al., 2017; Keshavan et al., 2017; Subramaniam et al., 2012; Vianin et al., 2014; Wykes et al., 2002), although increased activation in other brain regions, including the inferior and superior parietal lobe, middle occipital cortex, cingulate cortex, and thalamic regions has also been found (Bor et al., 2011; Donohoe et al., 2018; Edwards et al., 2010; Fan et al., 2017; Habel et al., 2010; Ramsay et al., 2017b; Ramsay and Macdonald, 2015; Vianin et al., 2014; Wei et al., 2016). Studies have begun to focus in recent years on the functional connectivity within different brain networks at task-based and resting-state fMRI (Penadés et al., 2017). In fact, some studies (Karbasforoushan and Woodward, 2013; Orliac et al., 2013; Shao et al., 2018; Woodward et al., 2011) have reported abnormal connectivity (both hyper- and hypo-connectivity) in patients with schizophrenia, mainly in the default mode network (DMN), but also in other cognitive networks such as the frontal-parietal or executive control network (ECN), the dorsal attention network (DAN), and the salience network (SN). It has been suggested that an improvement after cognitive remediation does not necessarily involve increased brain activation, but more efficient connectivity within brain networks, that is, activating or deactivating different brain regions when necessary (Penadés et al., 2017). This is the case of the DMN, which should be active during resting-state, but deactivated during the performance of cognitive tasks (Penadés et al., 2017). In the study by Penadés et al. (2013), patients with schizophrenia showed decreased activation of several areas within the DMN during the performance of a cognitive task after cognitive remediation, achieving activation patterns similar to those of healthy controls.

Few studies have analyzed the structural changes induced by cognitive remediation in schizophrenia (Eack et al., 2010; Matsuoka et al., 2019; Morimoto et al., 2018; Penadés et al., 2013; Ramsay et al., 2017a). Only two studies have found significant changes in gray matter (GM) volume after cognitive remediation, mainly in temporal regions (Eack et al., 2010; Morimoto et al., 2018). While Eack et al. (2010) showed greater preservation of GM volume in the left hippocampus, parahippocampal gyrus, and fusiform gyrus, and increased left amygdala GM volume, Morimoto et al. (2018) found increased GM volume in the right hippocampal region. Only a small number of studies have analyzed white matter (WM) integrity (Matsuoka et al., 2019; Penadés et al., 2013). Specifically, an increase in fractional anisotropy (FA) has been reported in various regions, including the anterior part of the genu of the corpus callosum, the right posterior thalamic radiations, and the posterior lobe of the left cerebellum after cognitive remediation (Matsuoka et al., 2019; Penadés et al., 2013). Matsuoka et al. (2019) also found a decrease in radial diffusivity (RD) and mean diffusivity (MD) in patients who performed cognitive remediation. Results from both studies (Matsuoka et al., 2019; Penadés et al., 2013) suggest that cognitive remediation may induce white matter microstructural plasticity (e.g., increased myelination in fiber tracts) and therefore, impact on the structural connectivity between different regions. Altogether, these results on structural changes in GM and WM suggest that cognitive remediation could have a neuroprotective effect on the brains of patients with schizophrenia (Hegde et al., 2020; Penadés et al., 2017).

Overall, the literature suggests that cognitive remediation may be effective in inducing brain changes in patients with schizophrenia and that these brain changes may be associated with cognitive improvements (Matsuda et al., 2019; Penadés et al., 2017). However, results are still inconclusive, and little is known about the brain changes when using a combined cognitive remediation approach. In a previous study of this project (Sampedro et al., 2021) cognitive, functional and clinical improvements were found after an integrative group-based cognitive remediation program (REHACOP) that combined training in neurocognition, social cognition, social skills, and functional skills in comparison with an active control group of patients with schizophrenia. Therefore, the main objective of this study was to analyze the structural (GM volume, cortical thickness, and WM integrity) and functional (resting-state functional connectivity and brain activation during a memory paradigm) brain changes associated with integrative cognitive remediation among patients with schizophrenia. An additional objective was to analyze the associations between brain changes, if any, and cognitive changes after the intervention.

For the first objective, with respect to structural changes and based on literature (Eack et al., 2010; Morimoto et al., 2018), it was hypothesized that patients from the REHACOP group would show greater GM volume and cortical thickness in the temporal lobe compared with the active control group after the cognitive remediation. Given the paucity of evidence on white matter changes following cognitive remediation and the heterogeneity of the results found (Matsuoka et al., 2019; Penadés et al., 2013), it was hypothesized that remediation would produce subtle increases in white matter integrity in some brain regions of both intra- and interhemispheric tracts. Regarding functional brain changes, considering previous evidence (Donohoe et al., 2018; Penadés et al., 2020), it was hypothesized that patients from the REHACOP group would show an increased resting-state connectivity within diverse networks, mainly in the DMN. Based on previous studies using a memory fMRI paradigm (Guimond et al., 2018; Hofer et al., 2003), it was also hypothesized that patients from the REHACOP group would show higher activation during the performance of the recognition memory fMRI paradigms in frontal and temporal regions. For the second objective, in line with previous studies (Eack et al., 2010; Penadés et al., 2013; Ramsay et al., 2017b), it was hypothesized brain changes would be associated with cognitive changes produced after the cognitive remediation.

1. Methods

1.1. Participants

The sample included 59 patients diagnosed with schizophrenia who were recruited from the Psychiatric Hospital of Álava and the Mental Health Network in Álava (Spain). The flow diagram of the sample can be seen in Fig. 1. All patients had been diagnosed with schizophrenia according to the criteria contained in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5; American Psychiatric Association, 2013). Exclusion criteria were: (a) clinical instability, according to the relapse criteria provided by Csernansky et al. (2002); (b) significant changes to their antipsychotic treatment in the previous three months; (c) cognitive impairment secondary to another medical condition; (d) diagnosis of an active Major Affective Disorder; (e) being in another specific cognitive remediation program; (f) incompatibilities with MRI; and (g) diagnosis of Substance Use Disorder (DSM-5), including alcohol during the three months prior to study inclusion (with the exception of nicotine).

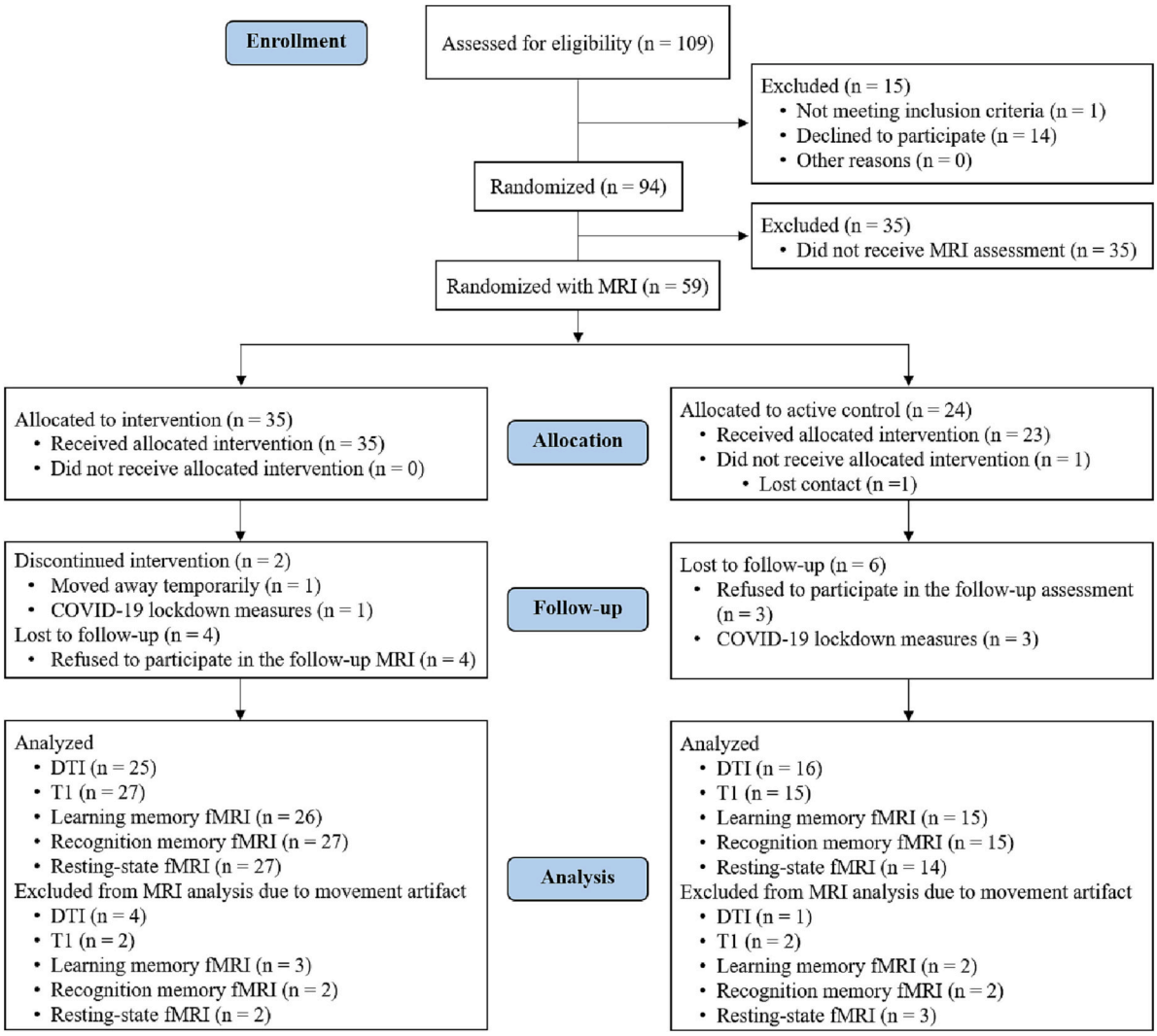

Fig. 1. CONSORT flow diagram.
CONSORT = Consolidated Standards of Reporting Trials; MRI = Magnetic Resonance Imaging; DTI = Diffusion Tensor Imaging; fMRI = Functional Magnetic Resonance Imaging.

1.2. Procedure

A parallel-group randomized trial design was used. The patients' psychiatrists gave them the opportunity to participate in the study. The participants were randomly assigned to a cognitive remediation group and an active control group (as shown in the flow diagram in Fig. 1), using an online computer-generated randomization system. All participants underwent an MRI, a neuropsychological and a psychiatric assessment at baseline and at the 6-month follow-up. Post-treatment assessment was performed within three weeks after completing the intervention. All raters were blind to the experimental treatment condition and had no other role in the study that could undermine the trial blinding. Data about the effectiveness of REHACOP on cognitive, functional, and clinical data is provided in a previous study (Sampedro et al., 2021). The study protocol had the approval of the Clinical Research Ethics Committees of the Autonomous Region of the Basque Country in Spain (PI2017044). The project is registered with clinicaltrials.gov (NCT03509597). All patients participated voluntarily and gave their informed consent to take part. They did not receive a monetary reward for participating in the project.

1.3. Intervention

REHACOP is a group-based integrative cognitive remediation program that combines training in neurocognition, social cognition, social skills, and functional skills (Ojeda and Peña, 2012). It is based on the principles of restoration, compensation and optimization and it includes top-down and bottom-up strategies. The REHACOP includes paper-and-pencil tasks, active group discussions, and role-playing. Specifically, this intervention program includes up to 300 different and novel tasks that are divided into different skill units and subtypes. Tasks within each unit are hierarchically ordered according to subtype of abilities and levels of complexity to ensure gradual increase in cognitive demand.

The program was implemented with seven groups of between 4 and 8 patients each at several centers from the Mental Health Network in Álava (the Psychiatric Hospital of Álava, the Association of Relatives and Patients with Mental Illness from Ayala, and the Community Rehabilitation Service Center). The clinical team who conducted the intervention was trained on administering the REHACOP and used the same materials and instructions in all the groups. The sessions lasted 60 min and were held 3 days a week, for a total of 20 weeks (in total 60 one-hour sessions). The REHACOP program included training in the following units: Attention unit (4 weeks), with training in selective, sustained, alternating, and divided attention; Learning and Memory unit (4 weeks),

including visual and verbal learning, recall, recognition memory, working memory, and compensatory strategies; Language unit (3 weeks) focused on syntax, vocabulary, grammar, verbal comprehension, verbal fluency, and abstract language; Executive Functions unit (3 weeks), including cognitive and objective planning, novel problem solving, cognitive flexibility, reasoning, categorization, and conceptualization; Social Cognition unit (3 weeks), with training in emotion processing, social reasoning, moral dilemmas, and theory of mind; Social Skills unit (2 weeks); and Functional Skills unit (1 week), including activities involved in daily living. Processing speed was also trained throughout the first four units.

When a patient missed one or more sessions for different reasons, they either received individual training on the contents that had been delivered in the group session or, alternatively, completed the tasks of that session through homework and received feedback on those tasks. This allowed the patient to meet the objectives of all the missed training sessions. The patient then rejoined the experimental group, so that patients made up all the missed sessions. Due to the COVID-19 pandemic, several experimental ($n = 5$) and active control ($n = 1$) groups were temporarily discontinued at the beginning of the interventions. Therefore, individual booster sessions were conducted for two weeks before intervention groups were resumed.

The active control group carried out occupational group activities with the same duration and frequency as the cognitive remediation group (60 one-hour sessions during 20 weeks). The occupational activities carried out included: reading the daily news, gardening, sewing, handicrafts and building things from different materials (e.g., paper or wood), painting, and music. In addition, as part of the usual treatment, patients from both the experimental and active control groups received psychoeducation sessions.

1.4. Measures

1.4.1. Neurocognition

The complete neuropsychological battery used is described in Sampedro et al. (2021). Neurocognition was measured through the following tests assessing cognitive flexibility, processing speed, working memory, verbal memory, and inhibition: the number of categories completed and the number of perseverative errors from the Modified Wisconsin Card Sorting Test (Schretlen, 2010); Word, Color, and Word-Color values from the Stroop Color and Word Test (Golden, 2010); the Backward Digit Span subtest from the Wechsler Adult Intelligence Scale-III (WAIS-III; Wechsler, 1997); the three learning trials and the delayed recall trial from the Hopkins Verbal Learning Test (Brandt and Benedict, 2001); and the Symbol-Coding subtest from the WAIS-III (Wechsler, 1997). Some scores were adjusted so that higher scores indicated better cognitive performance. All these scores were converted into *Z*-scores based on the sample of the study and a neurocognition composite was calculated using these Z-scores (Cronbach's alpha = 0.81).

1.4.2. Social cognition

Social cognition was measured by means of the following tests assessing theory of mind, social perception, and emotion processing: the Happé Test "Strange Stories Task"(Happé, 1994); the Social Attribution Task-Multiple Choice (Johannesen et al., 2013); and Spanish adaptation of the Bell Lysaker Emotion Recognition Test (Bell et al., 1997). A composite score of social cognition was calculated from the Z scores of these measures (Cronbach's alpha = 0.74).

1.5. Functional outcome

Functional competence was measured through the Spanish Version of the University of California, San Diego, Performance-Based Skills Assessment (UPSA; Garcia-Portilla et al., 2013).

1.6. Clinical symptoms

Positive symptoms, disorganization, excitement, and depression were assessed by means of the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987) and following the consensus 5-factor solution proposed by Wallwork et al. (2012). Negative symptoms were measured through the Brief Negative Symptom Scale (BNSS; Kirkpatrick et al., 2011), as recommended by the NIMH-MATRICS Consensus Statement on Negative Symptoms (Carpenter et al., 2016; Kirkpatrick et al., 2006).

1.6.1. Handedness

Handedness was assessed by means of the Edinburgh Handedness Inventory (Oldfield, 1971). Participants were considered as right-handed, left-handed or mixed- handed according to the score obtained.

1.6.2. Neuroimaging acquisition

Functional and structural imaging data were acquired on a 3 T MRI (Philips Achieva Dstream) at OSATEK, Hospital of Galdakao (Spain). All sequences were acquired during a single session and the same protocol was used for pre- and post-treatment acquisitions.

T1-weighted images were acquired in a sagittal orientation (TR = 7.4 ms, TE = 3.4 ms, matrix size = 228 × 218 mm; flip angle = 9°, FOV = 250 × 250 × 180 mm, slice thickness = 1.1 mm, 300 slices, voxel size = 0.98 × 0.98 × 0.60 mm, acquisition time = 4′55″).

Diffusion-weighted images were obtained in an axial orientation in an anterior-posterior phase direction, using a single-shot EPI sequence (TR = 7540 ms, and TE = 76 ms, matrix size = 120 mm × 117 mm; flip angle = 90°, FOV = 240 × 240 × 130, slice thickness = 2 mm, no gap, 65 slices, acquisition time = 9′31″, voxel size = 1.67 × 1.67 × 2.0) with diffusion weighting in 32 uniformly distributed directions (b = 1000 s/mm2) and 1 b = 0 s/mm2.

The resting-state fMRI was obtained in an axial orientation in an anterior-posterior phase direction. A multiband multi-slice gradient echo EPI sequence (TR = 1121 ms, TE = 30 ms, matrix size = 80 × 78 mm, flip angle = 80°, FOV = 240 × 240 × 142.75 mm, slice thickness = 3 mm, 214 slices, voxel size = 3.00 × 3.00 × 3.00 mm, acquisition time = 4′05″) sensitive to blood oxygen level dependent (BOLD) contrast was used.

Finally, an fMRI was obtained using a memory paradigm (learning and recognition tasks). The fMRI images were acquired using a multi-slice gradient echo EPI sequence (TR = 2000 ms, TE = 29 ms, matrix size = 100 × 100 mm, flip angle = 90°, FOV = 240 × 240 × 136 mm, slice thickness = 3 mm; 140 slices, voxel size = 1.67 × 1.67 × 3.00 mm, acquisition time = 4′48″. The same parameters were used for the learning and recognition task.

Each of the two entire experiments of the memory fMRI paradigm, learning task and recognition task, included a 10-block paradigm that alternated activation and control conditions (5 blocks each). During the activation condition of the learning memory fMRI task, participants viewed 30 words, and were asked to indicate through a response box whether they liked or disliked the word. During the activation condition of the recognition task (20 min later), participants were asked to indicate from a list of 30 words if they remembered having read the word in the list during the learning task or not. In the control condition, six concatenations of letters were projected. Participants were asked to indicate whether the item was "AAAAAA" or if other letter combinations appeared (e.g., "BBBBBB"). Responses from the recognition task were coded as behavioral data and converted to percentage scores using the following categories: hits, correct rejections, false positives, and false negatives. These behavioral data were extracted to be analyzed using IBM SPSS. A more detailed description of the memory fMRI paradigm is included in Supplementary Material 1.

1.7. Neuroimaging pre-processing

A comprehensive description of the neuroimaging pre-processing in

GM volume, cortical thickness, WM, resting-state fMRI and memory fMRI paradigm is included in Supplementary Material 1.

1.7.1. GM volume

A voxel-based morphometry (VBM) analysis (Douaud et al., 2007) was carried out using the FMRIB Software Library (FSL; Smith et al., 2004). The default preprocessing pipeline was followed, which included the following steps: brain-extraction, GM segmentation, registration into a standard space, creation of a study-specific GM template, registration of all images to the template, modulation, and smoothing with an isotropic Gaussian kernel of 8 mm FWMH. Finally, voxel-wise whole brain general lineal model (GLM) was applied using permutation-based non-parametric testing, correcting for multiple comparisons across space.

1.7.2. Cortical thickness

Statistical analyses for cortical thickness changes were performed using FreeSurfer. For the reconstruction of the cortical surface, the default analysis pipeline of FreeSurfer (Dale et al., 1999; Fischl et al., 1999; Reuter et al., 2012; Ségonne et al., 2004) was performed, which included numerous steps such as: motion correction, intensity non-uniformity correction, removal of non-brain tissue, automated Talairach transformation, segmentation of the subcortical WM and deep GM volumetric structures, intensity normalization, tessellation of the GM/WM boundary, automated topology correction, and surface deformation following intensity gradients to optimally place the gray/white and gray/cerebrospinal fluid borders at the location. Subsequently, for longitudinal processing, the longitudinal stream of FreeSurfer was used (Reuter et al., 2012), creating an unbiased within-subject template space and image using robust, inverse consistent registration (Reuter et al., 2010). Whole brain longitudinal differences between and within groups in cortical measures were assessed for each hemisphere using a vertex-by-vertex GLM. Data were smoothed with a Gaussian kernel of 15-mm FWHM and cluster-wise correction for multiple comparisons was applied.

1.7.3. WM indexes

The FSL was used for the preprocessing and statistical analysis of the diffusion data. The preprocessing pipeline included the following steps: motion correction, brain-extraction, extraction of FA, MD, RD, axial diffusivity (AD), and mode of anisotropy (MO) data, and a voxel-wise statistical analysis of the data using a tract-based spatial statistic (TBSS; Smith et al., 2006). Finally, voxel-wise whole brain GLM was applied using permutation-based non-parametric testing, correcting for multiple comparisons across space.

1.7.4. Resting-state fMRI

Resting-state fMRI data was preprocessed using Conn Functional Connectivity (CONN) Toolbox (Whitfield-Gabrieli and Nieto-Castanon, 2012). The default preprocessing pipeline was followed, which included the following steps: realignment and unwarp of functional images; functional centering; detection of functional outliers; functional segmentation (GM, WM, and cerebrospinal fluid) and normalization into the standard MNI space; structural centering; structural segmentation and normalization into the standard MNI space; and functional smoothing using a Gaussian kernel of 8 mm FWHM. In addition, the default denoising pipeline (Nieto-Castanon, 2020) was used. Based on previous studies (Orliac et al., 2013; Seeley, 2019; Seeley et al., 2007; Shao et al., 2018; Spreng et al., 2016; Woodward et al., 2011), a region of interest (ROI-to-ROI) analysis corrected for multiple comparisons was performed to assess functional connectivity within the following networks: the DMN, the ECN, the DAN, and the SN (more information in Supplementary Material 1).

1.7.5. Memory fMRI paradigm

Statistical analyses were performed for memory fMRI paradigm data using Statistical Parametric Mapping (SPM; Ashburner et al., 2020). The functional data of each participant were reoriented, motion-corrected, coregistered, spatially normalized into the standard MNI space, and smoothed using a Gaussian kernel of 8 mm FWMH. Previous studies with patients with schizophrenia have found that mainly frontal and temporal regions are involved in the performance of memory tasks (Guimond et al., 2018; Hofer et al., 2003). However, given the scarce literature, whole brain statistical analyses were performed, corrected for multiple comparisons.

1.8. Statistical analyses

Statistical analyses were carried out using IBM SPSS version 26.0 (SPSS Inc., Chicago, USA). Data were tested for normality using the Shapiro-Wilk test. A missing value for the "previous hospitalizations" variable was imputed using the expectation maximization algorithm. Behavioral data from the recognition memory fMRI task were extracted to be analyzed using IBM SPSS. Differences between groups on socio-demographic, clinical, and behavioral data at baseline were assessed by a two-tailed independent *t*-test or Mann-Whitney *U* test. Chi-squared (X^2) test was used to analyze differences between groups in categorical data. Longitudinal changes between groups in behavioral data of the recognition memory paradigm and cognitive and functional competence data were tested with repeated measures analysis of variance 2 × 2 for group x time interaction analysis. Paired *t*-test (Wilcoxon test) analyses were also performed for intragroup changes in behavioral data.

Regarding neuroimaging analysis, first, two-sample *t*-test analysis was used for baseline differences between groups. Then, a 2 × 2 repeated-measures analysis of covariance for group x time interaction analysis was used to test differences between pre-treatment and post-treatment for the REHACOP group and the active control group. The between-subjects factor was "group" (REHACOP group or active control group), and the within-subjects factor was "time" (pre-treatment and post-treatment). The group x time interaction included baseline negative symptoms as covariate, since baseline differences were found between both groups in this variable. In the case of cortical thickness analyses with FreeSurfer, the "Different Offset, Same Slope" (DOSS) design matrix was used. Finally, intragroup changes were explored through paired *t*-test analysis. Again, baseline negative symptoms were included as a covariate to regress out their possible effect. All neuroimaging analyses were performed at $p < .05$ corrected for multiple comparisons. Cortical thickness analyses were also performed with a threshold of $p < .001$, as recently suggested by Greve and Fischl (2018). Specific information about the neuroimaging analyses performed is included in Supplementary Material 1.

Finally, Spearman's Rho and Pearson's *r* correlations were performed to determine the relationships between change in behavioral data of the recognition memory paradigm, neurocognitive and social cognitive performance, and GM volume and cortical thickness among patients from the REHACOP group. Specifically, correlations were performed with two brain composite scores (one for GM volume and another one for cortical thickness) calculated from those brain regions in which significant results had been found in previous paired *t*-test analyses. Additionally, a signal detection metric ($d' = Z$ [false positives] – Z [hits]) was calculated for the recognition memory paradigm data. Correlation analyses were carried out with the change scores of the brain composite scores and the cognitive composite scores (signal detection *d'*, neurocognition, and social cognition). Multiple testing correction was performed using the Benjamini-Hochberg false discovery rate method (Benjamini and Hochberg, 1995). The resulting adjusted significance level was $p < .008$.

2. Results

2.1. Baseline sociodemographic, clinical characteristics and behavioral data

Fifty-six patients completed the intervention, but 46 patients completed the post-treatment MRI assessment, resulting in an attrition rate of 22.03 %. After excluding patients due to movement artifact, 43 patients were included in MRI analysis (see Fig. 1 for further information). There were no significant differences between the sociodemographic characteristics of both groups at baseline, but significant differences were found in baseline negative symptoms (see Table 1). The defined daily dose method was used to change medication to chlorpromazine (Leucht et al., 2016; Rothe et al., 2018). There were no baseline differences between groups in medication dose. In addition, no baseline differences were found between groups in the behavioral data of the recognition memory fMRI paradigm, neurocognition, social cognition, and functional outcome.

2.2. Longitudinal changes in behavioral data, cognition and functional outcome

Regarding behavioral data from the recognition memory fMRI paradigm, repeated measures analysis (interaction effect group x time) showed no significant differences at post-treatment, but intragroup analysis indicated that the REHACOP group obtained significantly higher scores in correct rejections ($Z = 2.436$, $p = .015$) and lower scores in false positives errors ($Z = -2.705$, $p = .007$).

Additionally, repeated measures analysis of variance revealed significant improvements at post-treatment in neurocognition, social cognition, and functional outcome in the REHACOP group compared to the active control group (see Table 2).

Table 2
Repeated measures analysis of variance for cognitive and functional performance in the REHACOP and active control groups at baseline and follow-up.

		REHACOP group (n = 27)	Active control group (n = 16)	Group x time interaction		Effect size
		Mean (SD)	Mean (SD)	*F*	*p*	η_p^2
Neurocognition	Pre	0.11 (0.66)	−0.19 (0.53)	10.10	0.003	0.198
	Post	0.25 (0.68)	−0.43 (0.52)			
Social cognition	Pre	0.02 (0.74)	−0.03 (0.95)	25.79	0.001	0.386
	Post	0.28 (0.54)	−0.48 (0.82)			
Functional competence	Pre	64.80 (13.35)	61.19 (12.40)	18.65	0.001	0.313
	Post	77.61 (6.62)	61.06 (15.50)			

SD = standard deviation; η_p^2 = partial eta squared.

2.3. GM volume

No baseline differences in GM volume were found between groups. Repeated measures analyses (interaction effect group x time) revealed no significant results at the interaction level. Intragroup paired *t*-tests showed greater GM volume in the right temporal lobe (including the right inferior temporal gyrus, middle temporal gyrus, superior temporal gyrus, fusiform gyrus, temporal pole, and parahippocampal gyrus) in the REHACOP group at post-treatment compared to pre-treatment ($p < .05$ corrected) (see Table 3; Fig. 2). In contrast, the active control group

Table 1
Socio-demographic, clinical characteristics and behavioral data of the sample at baseline.

		REHACOP group (n = 27)		Active control group (*n* = 16)		*t/U/X2*	*p*
		Mean n (%)	SD	Mean n (%)	SD		
Age (years)		42.67	10.06	42.63	12.55	0.012	0.991
Education (years)		10.26	2.25	9.44	2.66	1.083	0.285
Gender	Males	24 (88.9 %)		15 (93.8 %)		0.281	0.596
	Females	3 (11.1 %)		1 (6.3 %)			
Handedness	Right-handed	20 (74.1 %)		11 (68.7 %)		3.637	0.162
	Left-handed	0 (0 %)		2 (12.5 %)			
	Mixed-handed	7 (25.9 %)		3 (18.8 %)			
Age of onset (years)		24.00	5.71	20.38	5.42	1.822	0.062
Illness duration		18.67	9.85	22.25	11.72	−1.075	0.289
Previous hospitalizations		5.12	3.62	7.50	7.75	200.00	0.685
Hospitalization status	Outpatients	16 (59.3 %)		9 (56.3 %)		0.04	0.847
	Inpatients	11 (40.7 %)		7 (43.8 %)			
Medication dosage		487.22	289.33	539.54	241.04	−0.608	0.546
Clinical symptoms							
Positive symptoms		9.85	4.54	9.44	2.94	214.00	0.960
Negative symptoms		26.52	15.34	36.81	12.10	2.292	0.027
Disorganization		7.00	3.10	7.94	2.64	−1.010	0.318
Excitement		7.63	3.77	7.38	3.59	210.00	0.879
Depression		6.56	1.93	6.00	2.61	0.741	0.428
Recognition memory paradigm: behavioral data							
Hits		82.28	15.52	71.43	26.21	179.50	0.353
Correct rejections		78.01	21.75	81.25	26.12	−189.00	0.490
False negatives		16.67	14.42	25.89	26.84	−195.00	0.592
False positives		19.68	19.66	15.63	18.11	192.50	0.548
Total intracranial volume (cm^3)		1.52	0.20	1.53	0.16	187.00	0.466

SD = standard deviation; *t* = *t*-test; *U* = Mann-Whitney *U*; X^2 = chi-squared; Medication dosage refers to chlorpromazine equivalent doses (mg/day). Negative symptoms were assessed by means of the BNSS. Behavioral data from the recognition memory paradigm are given in percentage scores.

Table 3
Gray matter (GM) volume changes in the REHACOP group (pre < post).

Anatomical brain regions included in a cluster	Cluster size (voxels)	FSL coordinates			*t*	*p*
		x	y	z		
Right inferior temporal gyrus, middle temporal gyrus, superior temporal gyrus, fusiform gyrus, temporal pole, parahippocampal gyrus	1702	21	62	16	5.72	0.002

Cluster size denotes the extent of the cluster of significant voxels. FSL voxel coordinates refer to the location of the most statistically significant voxel in the cluster. FSL voxel coordinate system indicates: x increases from left to right; y increases from posterior to anterior; and z increases from inferior to superior. The region in bold represents the maximum coordinate encompassed in the cluster.

showed no significant GM volume changes.

2.4. Cortical thickness

No baseline differences were found between groups regarding cortical thickness. Repeated measures analyses (interaction effect group x time) revealed no significant results at the interaction level. Intragroup analysis showed no significant results corrected at $p < .001$ in any of the two groups. However, intragroup analysis corrected at $p < .05$ showed that the REHACOP group showed greater cortical thickness in the right temporal lobe (including the right temporal pole, inferior temporal gyrus, middle temporal gyrus, superior temporal gyrus, and fusiform gyrus) at post-treatment compared to pre-treatment (see Table 4; Fig. 3). In contrast, the active control group showed no significant GM volume changes.

2.5. WM indexes

No baseline differences in WM indexes were found between groups. Longitudinal analyses showed no significant WM changes within or between groups at post-treatment.

2.6. Resting-state fMRI

No baseline differences were found between groups in the functional connectivity of any network during resting-state fMRI. In addition, no significant longitudinal changes in functional connectivity were found within or between groups during resting-state fMRI.

2.7. Memory fMRI paradigm

No baseline differences were found in brain activation during the learning and recognition memory fMRI tasks between groups. In addition, no significant longitudinal changes in brain activation were found within or between groups in the learning and recognition fMRI tasks.

2.8. Correlations between change in cognitive performance and brain

Correlation analyses between change in cognitive performance and change in GM volume and cortical thickness are detailed in Supplementary Material 2. No significant correlations were found between change in performance in the recognition memory paradigm, neurocognitive and social cognitive performance and GM volume and cortical thickness among patients from the REHACOP group.

3. Discussion

The main aim of this study was to explore the functional and structural brain changes after implementing an integrative cognitive remediation program (REHACOP) that combined training in neurocognition, social cognition, and social and functional skills among patients with schizophrenia. Although significant cognitive and functional changes were found, the results did not show significant brain changes associated

Table 4
Cortical thickness changes in the REHACOP group (pre < post).

Anatomical brain regions included in a cluster	Cluster size (mm^2)	Cluster maxima Talairach coordinates			*p*
		x	y	z	
Right temporal pole, inferior temporal gyrus, middle temporal gyrus, superior temporal gyrus, fusiform gyrus	3927.10	38.3	16.1	−32.8	0.000

Cluster size denotes the surface area (mm^2) of the cluster. Talairach coordinates indicate: x increases from left to right; y increases from posterior to anterior; and z increases from inferior to superior. The region in bold represents the maximum coordinate in the cluster.

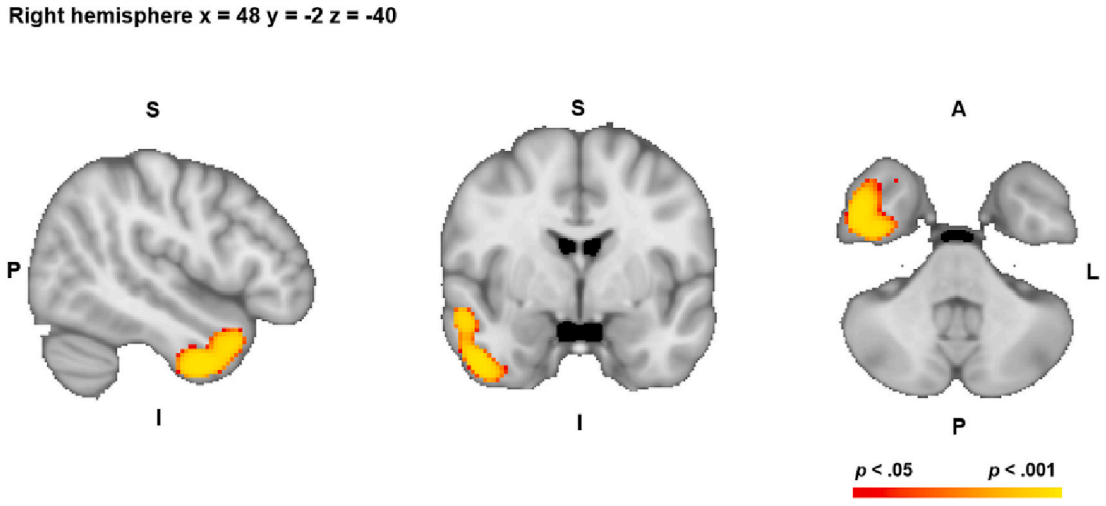

Fig. 2. Gray matter (GM) volume changes in the REHACOP group (pre < post).
This figure depicts longitudinal changes in gray matter (GM) volume in the REHACOP group (red-yellow). Results are corrected for Family-Wise Error (FWE) ($p < .05$). S = superior; I = inferior; A = anterior; P = posterior; L = Left; R = Right. Coordinates are shown in MNI (Montreal Neurological Institute) space. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

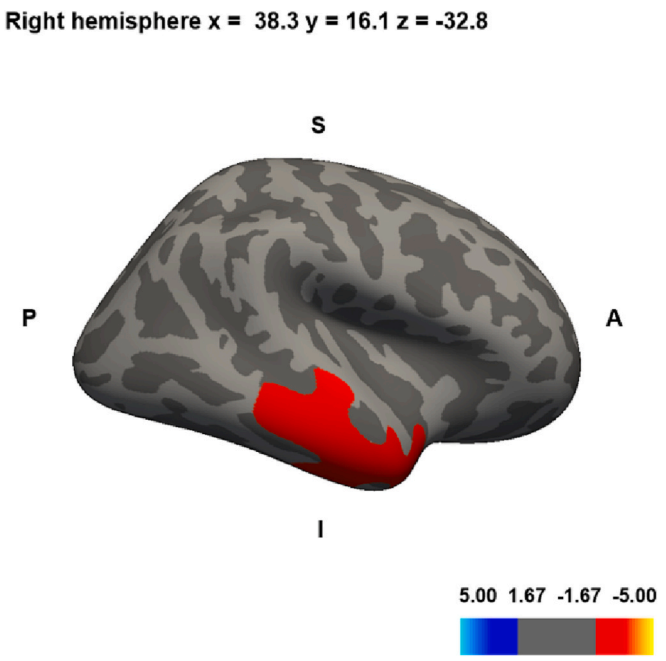

Fig. 3. Cortical thickness changes in the REHACOP group (pre < post).
This figure depicts longitudinal changes in cortical thickness in the REHACOP group. Color bars represent a scale of *t* values with cold colors representing thinning and warm colors thickening. Results were corrected for multiple comparisons at the cluster level using Monte-Carlo simulation ($p < .05$). S = superior; I = inferior; A = anterior; P = posterior. Coordinates are reported in Talairach space.

with cognitive remediation detectable by the MRI techniques used in this study. In contrast, exploratory paired *t*-tests did show that the REHACOP group had greater GM volume and cortical thickness at post-treatment. The absence of significant brain-level results associated with cognitive remediation may be due to the small sample size, which limited the statistical power to detect significant interaction effects. In addition, the possible associations between changes in cognitive performance and structural brain changes were analyzed, but not significant associations were found after correcting for multiple comparisons.

In line with results from Sampedro et al. (2021), significant neurocognitive, social cognitive, and functional improvements were found in the subsample of the present study after cognitive remediation. Previous studies have also found improvement in neurocognition, social cognition and functional outcome after an integrative cognitive remediation (Fisher et al., 2017; Hooker et al., 2012; Peña et al., 2016). In contrast, no significant interaction effect was found in the behavioral data of the recognition memory fMRI task. Nevertheless, intragroup analysis did show a better performance of the memory task at post-treatment in the REHACOP group. Although patients from the REHACOP group improved cognitive functioning, this may not have been reflected in the single task used in the fMRI, which is performed in a more stressful situation (within the scanner) as opposed to the neuropsychological assessment.

Contrary to what was expected, no changes were found either in functional connectivity during resting-state or in brain activation during memory fMRI paradigm after cognitive remediation. In contrast, numerous studies have reported increased activation and functional connectivity after cognitive remediation in multiple regions such as the prefrontal cortex and thalamic regions (Donohoe et al., 2018; Eack et al., 2016; Fan et al., 2017; Keshavan et al., 2017; Penadés et al., 2013; Ramsay et al., 2017b; Subramaniam et al., 2014; Vianin et al., 2014). The lack of significant results in brain function of patients from this study may be partly due to the small sample size used, or to the kind of activities performed by the active control group. In some studies, the control group performed psychoeducational sessions or treatment as usual (Eack et al., 2016; Fan et al., 2017; Keshavan et al., 2017; Vianin et al., 2014) rather than occupational activities, unlike in this study. Moreover, the task performed in the fMRI involved a different cognitive domain than the one in other studies, which included working memory (Donohoe et al., 2018; Ramsay et al., 2017b; Subramaniam et al., 2014).

With regard to WM integrity, no significant longitudinal changes were found in WM indexes. Only two studies have analyzed this issue in schizophrenia (Matsuoka et al., 2019; Penadés et al., 2013) and in contrast to our results, these studies found increased FA, RD, and MD in the anterior part of the genu of the corpus callosum, the right posterior thalamic radiations, and the left posterior cerebellum (Matsuoka et al., 2019; Penadés et al., 2013). Nevertheless, considering the small number of studies available, more research is needed to better understand the possible effect of cognitive remediation on WM integrity. Moreover, a recent study carried out with individuals at ultra-high risk for psychosis (Kristensen et al., 2020) also found no WM changes after cognitive remediation.

Regarding GM changes, repeated measures analyses showed no significant differences in GM volume and cortical thickness associated with integrative cognitive remediation. However, intragroup analyses indicated an increase in GM volume and cortical thickness of regions from the right temporal lobe (including the right inferior temporal gyrus, middle temporal gyrus, superior temporal gyrus, fusiform gyrus, temporal pole, and parahippocampal gyrus) in the REHACOP group. There have been few studies that have analyzed GM structural changes after cognitive remediation in schizophrenia (Eack et al., 2010; Morimoto et al., 2018; Ramsay et al., 2017a). Two studies that analyzed this issue reported GM volume changes mainly in the right and left temporal lobes after cognitive remediation (Eack et al., 2010; Morimoto et al., 2018). Specifically, Eack et al. (2010) found greater preservation of GM volume in the left hippocampus, fusiform gyrus, and parahippocampal gyrus, and increased left amygdala GM volume after an integrative cognitive remediation. Morimoto et al. (2018) found greater GM volume in the right hippocampal region after cognitive remediation. Ramsay et al. (2017a) reported no interaction (group x time) effect on GM subcortical volume related to cognitive remediation in early schizophrenia, but the cognitive remediation group that had showed cognitive improvement showed increases in left thalamic volume. The greater right temporal lobe volume and cortical thickness found in the REHACOP group at post-treatment were in line with the changes found in the temporal lobe in the studies by Eack et al. (2010) and Morimoto et al. (2018). However, since we did not find a significant interaction effect, our findings cannot be attributed to cognitive remediation. The lack of an interaction effect may be partly due to the small sample size, as well as to the kinds of activities performed by the active control group, different to those in the other studies (Eack et al., 2010; Morimoto et al., 2018). Moreover, the study by Eack et al. (2010) included a 2-year integrative cognitive remediation program, in contrast to the 20-weeks program implemented in the study described here.

In these studies mentioned above (Eack et al., 2010; Morimoto et al., 2018; Ramsay et al., 2017a), changes in GM volume were associated with changes in cognition. However, in the present study no significant correlations were found between changes in temporal GM volume and cortical thickness and changes in cognitive performance among patients from the REHACOP group after correcting for multiple comparisons. This may be partly due to the small sample size of the REHACOP group ($n = 27$).

In addition to the factors mentioned above (e.g., sample size, active control group, etc.), some individual and illness-related features may also be relevant for inducing statistically significant neural plasticity. Indeed, some of the previous studies obtaining both structural and functional brain changes after cognitive remediation (Eack et al., 2010; Morimoto et al., 2018; Penadés et al., 2013) included a younger sample with a shorter illness duration compared to the sample of the present study. Nevertheless, the absence of studies analyzing predictors of brain

changes after cognitive remediation does not allow us to draw clear conclusions. Meta-analyses and systematic reviews analyzing predictors of cognitive and functional improvements (Lejeune et al., 2021; Seccomandi et al., 2020) have not found baseline clinical symptoms or age to influence cognitive and functional outcomes, but Lejeune et al. (2021) did found that chronicity of the disease explained larger improvements on functional outcome. Therefore, it may also be the case that the fact that the active control group had slightly, although not significantly, longer disease duration may have influenced the lack of statistically significant results at the brain-level. However, factors that influence cognitive and functional change may not influence in the same way or with the same strength as factors that influence brain-level changes and vice versa, so more research is needed to clarify this idea.

The fact that previous studies have found changes mainly in temporal regions suggests that this lobe could play a key role in the restoration and improvement of cognitive functioning. Furthermore, in the studies by Eack et al. (2010) and Morimoto et al. (2018), as in this study, memory was one of the cognitive domains trained in the intervention, which is highly associated with the temporal lobe (Bonner-jackson et al., 2015). In addition, Eack et al. (2010) included integrative cognitive remediation combining both neurocognition and social cognition, with the latter also being associated with the temporal lobe (Carrington and Bailey, 2009; Lee et al., 2016; Schurz et al., 2014). Interestingly, increased right temporal volume in the hippocampus was also found in healthy adults after a 14-week intensive learning program (Koch et al., 2015). Morimoto et al. (2018) suggested that changes in temporal lobe volume after cognitive remediation could be associated with an increase in brain-derived neurotrophic factor (BDNF), since BDNF seems to be related to the maintenance of the volume of regions involved in memory processes such as the hippocampus and parahippocampal areas (Miranda et al., 2019). Specifically, cognitive remediation has been shown to increase the serum levels of BDNF in patients with schizophrenia (Fisher et al., 2016; Vinogradov et al., 2015). Nevertheless, caution must be exercised in this respect and further research is needed.

Furthermore, it has been suggested that cognitive remediation could have both a neuroprotective or regenerative effect on the brain of patients with schizophrenia (Eack et al., 2010; Morimoto et al., 2018). However, the exact mechanism underlying the improvements following cognitive remediation (e.g., stability, regeneration or both) remains unclear, so future studies should try to clarify this idea. In the case of the present study, no conclusions can be drawn on this question, but it seems unlikely that regeneration of the cerebral GM could have taken place in a sample of chronic patients with an average age of over 40 years and in a 20-week treatment interval.

This study has several limitations. First, sample size was small, which may have limited the significance of the results. Second, as expected, the sample was skewed toward men, but there were no sex differences between both groups. Third, patients were not blind to the treatment they were receiving. Nevertheless, they were instructed not to mention what type of treatment they would receive or had received during evaluations. Four, several patients dropped out and some intervention sessions had to be temporarily suspended due to the COVID-19 pandemic, although they were successfully resumed at a later stage. Finally, the cortical thickness results only appeared to be significant at a threshold of $p < .05$ corrected for multiple comparison, instead of at a threshold of $p < .001$, so results should be interpreted with caution.

In summary, the present study did not find longitudinal brain structural and functional changes related to cognitive remediation. However, GM volume and cortical thickness increases at post-treatment were found in the right temporal lobe in the cognitive remediation group. Although the structural changes found in this study cannot be attributed to the cognitive remediation program, the scant literature available (Eack et al., 2010; Morimoto et al., 2018; Ramsay et al., 2017a) suggests that cognitive remediation could have an effect on the brain structure of patients with schizophrenia. Specifically, the temporal lobe may be a key region involved in the cognitive improvement following cognitive remediation in schizophrenia. Nonetheless, this idea must be considered with caution, given the small number of studies available. More research is needed to better understand the neural underpinnings of cognitive remediation in schizophrenia. It would also be interesting to study the long-term brain changes identified and whether short-term brain changes are maintained. Furthermore, future studies should combine MRI data with BDNF measures.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2023.03.021.

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CRediT authorship contribution statement

Authors NO, NIB, JP, and PS designed the study and wrote the protocol. Authors AS, PS, ACZ, NIY, MTE, and CP performed the clinical and neuropsychological evaluations. AS, AGG, NIB, and JP managed the literature searches and undertook the statistical analysis. AS and JP wrote the first draft of the manuscript. All authors contributed to the writing and revision of the manuscript. All authors have approved the final manuscript.

Declaration of competing interest

NO and JP are co-authors and copyright holders of the REHACOP cognitive remediation program, published by Parima Digital, SL (Bilbao, Spain).

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