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RESEARCH ARTICLE

Mnemonic strategy training modulates functional connectivity at rest in mild cognitive impairment: Results from a randomized controlled trial

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Abstract

Introduction: Mnemonic strategy training (MST) has been shown to improve cognitive performance and increase brain activation in those with mild cognitive impairment (MCI). However, little is known regarding the effects of MST on functional connectivity (FC) at rest. The aim of the present study was to investigate the MST focused on face-name associations effect on resting-state FC in those with MCI

Methods: Twenty-six amnestic MCI participants were randomized in MST (N = 14) and Education Program (active control; N = 12). Interventions occurred twice a week over two consecutive weeks (ie, four sessions). Resting-state functional magnetic resonance imaging was collected at pre- and post-intervention. Regions of interest (ROIs) were selected based on areas that previously showed task-related activation changes after MST. Changes were examined through ROI-to-ROI analysis and significant results were corrected for multiple comparisons.

Results: At post-intervention, only the MST group showed increased FC, whereas the control group showed decreased or no change in FC. After MST, there was an increased FC between the left middle temporal gyrus and right orbitofrontal cortex. In addition, a time-by-group interaction indicated that the MST group showed greater increased FC between the right inferior frontal gyrus and left brain regions, such as fusiform gyrus, temporal pole, and orbitofrontal cortex relative to controls.

Discussion: MST enhanced FC in regions that are functionally relevant for the training; however, not in all ROIs investigated. Our findings suggest that MST-induced changes are reflected in task-specific conditions, as previously reported, but also in general innate connectivity. Our results both enhance knowledge about the mechanisms underlying MST effects and may provide neurophysiological evidence of training transfer.

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aging, cognitive rehabilitation, functional connectivity, functional magnetic resonance imaging, memory training, mild cognitive impairment, mnemonic strategy, neuroimaging, resting-state

1 | INTRODUCTION

The accelerated growth of age-related conditions such as Alzheimer's disease (AD) and related dementias[1] is challenging for health systems and economies worldwide. Considering this scenario there is an increasing interest in non-pharmacological cognition-oriented treatments for individuals at high risk for dementia, because such treatments may enhance cognitive performance and protect against disease-related decline.[2-9] Application of these treatments is especially appropriate for individuals with amnestic mild cognitive impairment (aMCI), which present episodic memory deficit but minimal impairment of instrumental activities of daily living,[10-13] reflecting the "transitional" state between normal aging and dementia, particularly due to AD.[12,14,15]

Cognitive training has been recognized as a valid method to promote brain plasticity and reduce cognitive impairment in aMCI.[16] Among training protocols for aMCI, a promising approach is mnemonic strategy training (MST),[4-6,9,17] which teaches cognitive "tools" that facilitate the association and organization of new information and require deeper information processing,[4] processes known to benefit memory functioning.[18] Additionally, MST requires the user to actively hold and manipulate to-be-learned information, processes that engage cognitive control mechanisms such as working memory.[9] In particular, MST has enhanced learning and memory in individuals with aMCI for meaningful information like faces and names,[16,19-24] which are vital for social interactions and a frequent cognitive complaint in older adults.[25,26] Moreover, face-name memory is sensitive to AD pathology (ie, cortical amyloid beta deposition),[27] suggesting that this is an appropriate target for individuals at risk for dementia.

To evaluate the neurophysiological mechanism of MST, studies typically investigate changes in blood oxygen level–dependent (BOLD) signals using functional magnetic resonance imaging (fMRI), and have revealed increased "activation" after MST,[9] in contrast to nominal change or even decreased activation after repeated exposure of stimuli[28] or "placebo" intervention.[19,20] Our previous works focused on associative memory for face-name and showed that memory gains were accompanied by increased activation in frontoparietal regions associated with attention and cognitive control as well as in temporal areas relevant for semantic memory, social cognition, and emotional/face processing.[19,20] Our findings were consistent with the other evidence that MST (re)engages brain regions associated with executive functions, cognitive control, and memory.[16,22,29-31]

Despite the evidence supporting task-based changes after MST in aMCI, little is known about its effects on functional connectivity (FC) at rest, which could indicate a general mechanism of training transfer by showing changes in "innate" synchrony between brain regions. Training transfer can be defined as the transfer of training-based gains beyond the specific confines of the training situation, which can occur in tasks with similar training content (ie, content-transfer) or to a different context such as everyday life (ie, context-transfer).[32] Currently, only two cognitive training studies involving MCI investigated changes in FC at rest.[33,34] These programs, focused on executive functions[33] and attention/speed,[34] applied a rehearsal-based approach, which relies on repetition practice without involving learning mnemonic strategies as in MST. The results indicated that training induced increase[33] or maintenance[34] of FC in the default-mode network, but no changes in networks associated with cognitive control. These results are in line with a study on healthy aging that found increased within-network FC after multi-domain cognitive training.[35] While these studies demonstrate training-related changes on resting-state, no work has examined the comparable effects following MST in MCI.

To examine the underlying mechanism of MST in aMCI, the present study investigated changes in FC at rest after MST focused on associative memory for faces and names. A Brazilian sample of aMCI was randomized to MST or education program (EP), which served as an active control condition. We present analyses of between- and within-group changes in FC after MST and EP considering neuroanatomic regions-of-interest (ROIs) that showed increased brain activation after MST.[19,20] We hypothesized that these ROIs would demonstrate greater FC after MST, thereby indicating that the benefits of MST extend beyond the task-specific training condition. Such findings would clarify the mechanisms underlying training effects while also suggesting training transfer outside the task-specific conditions.[33,35] In contrast, we did not predict changes associated with the control intervention (EP).[34,36]

2 | METHODS

2.1 | Design

Data were collected as part of a single-blind randomized controlled trial, the primary results of which were previously reported.[19,20] In brief, our previous reports refer to the training gains and transfer effects considering changes in neuropsychological measures and activation-fMRI changes. Methods are summarized as study details can be found in prior publications. Participants were randomly assigned by an independent researcher to two interventions programs (MST or EP). The study design and participant selection are presented in Figure 1, following the CONSORT (Consolidated Standards of Reporting Trials) guidelines.[37] After the screening session, participants underwent neuropsychological evaluations and MRI exams at pre- and post-intervention.

2.2 | Participant and selection criteria

The present study used resting-state fMRI data from 26 of the 30 previously reported participants.[19,20] The resting-state fMRI data from the remaining four individuals were unusable (details below). Participants (age range 62–82 years; education range 4–18 years) were recruited through community announcements and health professional referrals. All participants were volunteers and provided written informed consent, in accordance to the Declaration of Helsinki. The study was approved by the Ethics Committee of the Medical School of University of São Paulo and registered at ClinicalTrials.gov (NCT01978353).

At baseline, participants completed medical and neuropsychological evaluations. Inclusion criteria required participants to be 60 years or older, right-handed, native Portuguese speaker, at least 4 years of education, normal or corrected vision and hearing, and diagnosis of aMCI according to Petersen's criteria,[11] as detailed previously.[19] Participants were excluded if they present MRI contraindication, history or presence of central nervous system condition (not related to aMCI; eg, stroke, traumatic brain injury, brain cancer), major ongoing psychiatric condition (eg, psychosis, bipolar disorder, attention-deficit hyperactivity disorder, major depression and anxiety disorders, alcohol/drug dependence or abuse), and pharmacological treatment that could affect cognition (eg, benzodiazepines and chemotherapy). Participants under antidepressant drugs were accepted if doses were stable for at least 6 months, and with significant depressive symptoms.

2.3 | Clinical and neuropsychological evaluation at baseline

The instruments used in the baseline assessments were described previously,[19] and are listed here: Cambridge Examination for Mental Disorders of Older People; Hamilton Anxiety Rating Scale; Montgomery–Åsberg Depression Rating Scale; Informant Questionnaire on Cognitive Decline in the Elderly; Bayer Activities of Daily Living Scale; Multifactorial Memory Questionnaire; Montreal Cognitive Assessment; Vocabulary, Matrix Reasoning, and Digit Span from the Wechsler Adult Intelligence Scale Third edition; Short Cognitive Performance Test - SKT; Stroop Test; Phonemic and Semantic Fluencies; Boston Naming Test, Rey Complex Figure Test; Hopkins Verbal Learning Test; Logical Memory and Faces from the Wechsler Memory Scale Third Edition. IQ was calculated based on Vocabulary and Matrix Reasoning scores.

2.4 | MRI acquisition

To assess training effects, MRI sessions were scheduled approximately 1 month before the intervention, and approximately 1 week after finishing the programs, similar to a previous work.[16] MRI scanning was performed on a 3T Philips Achieva MR system at the Institute of Radiology of the Faculty of Medicine, University of São Paulo. The resting-state protocol adopted was previously used by our group.[38] In brief, we used a T2*-weighted echo planar imaging sequence including the following parameters: TE 30 ms, TR 2000 ms, flip angle 80, field of view 240 × 240, matrix 80 × 80, slice thickness 4 mm (voxel size 3 × 3 × 4 mm), number of slices 31–32, gap 0.5 mm, Sense 2.5, Softone 3.7—acoustic noise reduction.[39] Participants were instructed to keep their eyes open looking at a fixation cross. In total, 204 volumes were acquired in 6 minutes and 48 seconds. During the image acquisition, four electrocardiogram electrodes were affixed to the participants' chest and a respiration band placed at the abdomen to collect signals

RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed the literature using traditional (eg, PubMed) sources, and relevant citations are appropriately cited. Mnemonic strategy training (MST) has been shown to improve cognitive performance and increase brain activation in those with mild cognitive impairment (MCI). However, little is known regarding the effects of MST on functional connectivity at rest, which can elucidate additional underlying mechanisms of MST.
2. **Interpretation**: Our findings that MST-induced changes also occur in innate connectivity at rest extend previous findings from task-specific conditions. Our results both enhance knowledge about the mechanisms underlying MST effects and may provide neurophysiological evidence of training transfer.
3. **Future directions**: Brief MST may alter innate functional connectivity, at least temporarily. Future studies should examine the duration of this effect and additional evidence of training transfer, particularly in real-life contexts.

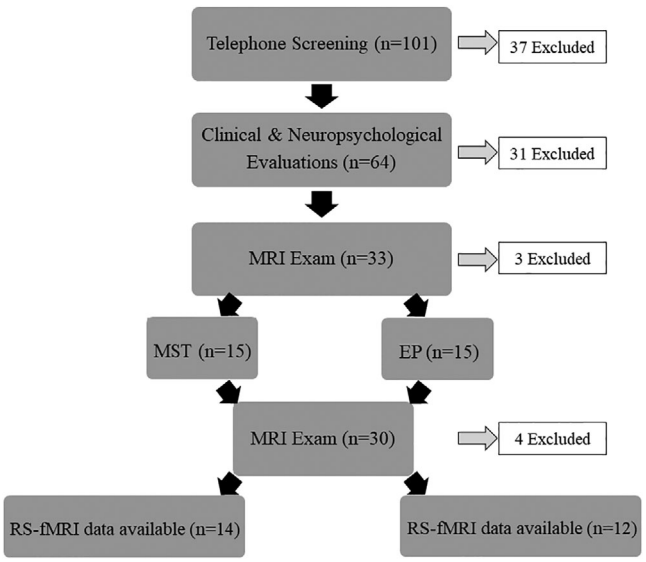

FIGURE 1 Participants' selection flowchart

from the heartbeats and respiratory movements (sampled at 500 Hz). The resting-state fMRI acquisition was performed at the beginning of the MR session, immediately after the reference scan and thus no cognitive tasks or tests were administered before the resting-state sequence on the day of the MRI exam. An anatomical 3D T1-weighted scan of the whole brain was acquired immediately after the resting-state fMRI acquisition. The T1 parameters comprised TR 7 ms, TE 3.2 ms, flip angle 8o, Sense 1.5, field of view 240 × 240, matrix 240 × 240, 180 slices of 1 mm each with no gap, yielding a voxel size of 1 × 1 × 1 mm. In addition, we acquired sequences of Axial Fluid-Attenuated Inversion Recovery scan and susceptibility-weighted (principles of echo-shifting with a train of observations [PRESTO]), which together with T1 acquisition, were used to identify brain alterations. All images followed a quality control protocol and were inspected by a neuroradiologist.

2.5 | Interventions

Intervention procedures can be found in detail in our previous reports.[19,21] Both interventions were administered individually, face to face, with participants attending four 1-hour sessions, twice a week, over two consecutive weeks.

2.5.1 | Mnemonic strategy training: associative memory for face-name

The goal of training was to alter the way in which participants attempted to learn and subsequently recall the targeted information. The mnemonic strategy was trained in 36 face-name pairs (12 new pairs in each of the three first sessions, and a review of all pairs in the last session). Our approach followed the "feature-reason-image" (FRI) process in which they were directed to a salient facial feature ("feature"), learned a "nickname" linking the facial feature to the name ("reason"), and were instructed to create a mental image that integrated the visual and verbal cues ("image").[28] The reason cues rhymed with or were phonologically similar to the actual name. On each training trial, participants were required to first recall the feature, second the reason, and then the corresponding name on up to 10 training trials. After the training, participants underwent a review of the 12 pairs trained during the session, using the same step-by-step process ("same day review"). The following training session began with the review of all 12 pairs trained in the previous session ("delayed review"), and then a new set of 12 pairs were trained. The last session was a review of all 36 pairs.

Additionally, participants were asked to complete the ecological "generalization step" to enhance comprehension and transfer to their everyday life.[19] The participants had to apply the methodology considering real people they knew but whose name they had trouble recalling. Participants were asked to imagine the person's face, describe it out loud, and then apply the FRI methodology, creating their own associations. Participants trained one real-life example in each session and were actively encouraged to use the associative methodology in their life.

2.5.2 | Education program

In each session, age-relevant topics were discussed, such as: healthy aging, memory functioning, aspects that can interfere in memory, risks and protective factors related to AD, and information on MCI and AD. Similar to the MST group, review periods were integrated to reinforce the contents, and in the last session there was an overall review.

2.6 | Resting-state functional connectivity analysis

Based on our previous findings of task-related changes in activation,[19,20] we selected 17 ROIs (Table S1 in supporting information) considering both hemispheres and subdivisions of nine brain regions, as follows: inferior frontal gyrus (IFG), orbitofrontal cortex (OFC), fusiform gyrus, anterior and posterior cingulate cortex (PCC), precuneus, temporal pole, middle temporal gyrus (MTG), and superior temporal gyrus.

The FC analysis was performed with the CONN-fMRI FC toolbox v18b[40] in conjunction with SPM 12 (Wellcome Department of Imaging Neuroscience, London; http://www.fil.ion.ucl.ac.uk/spm/), running in MATLAB R2015 environment (The MathWorks, Inc., Natick, Massachusetts). We used the CONN toolbox because it allows seed-based correlation analysis according to the low-frequency, temporal fluctuations of BOLD signals. As in a previous study,[41] all structural and functional sequences (pre- and post-intervention) were preprocessed using the CONN's default pipeline for volume-based analysis following eight steps: (1) functional realignment and unwarping (subject motion estimation and correction); (2) functional center to (0,0,0) coordinates (translation); (3) functional slice-timing correction using ascending order (correction for inter-slice differences in acquisition time); (4) functional outlier detection (ART-based identification of outlier scans for scrubbing), using conservative settings, that is, 95th percentile in normative sample in functional outlier detection system with Global-signal z-value threshold = 3 and Subject-motion mm threshold = 0.5); (5) functional direct segmentation (simultaneous gray and white matter/cerebrospinal fluid [CSF]) and normalization to Montreal Neurological Institute (MNI) adopting default Tissue Probability Maps with target resolution = 2 mm; (6) structural center to (0,0,0) coordinates (translation); (7) structural segmentation (simultaneous gray and white matter/CSF) and normalization to MNI space adopting default Tissue Probability Maps with target resolution = 1 mm; and (8) functional smoothing (spatial convolution with 8 mm full width half maximum Gaussian kernel filter). After pre-processing, four participants were excluded due to insufficient amount of valid scans (less than 3 min of total scans)[42] to ensure data quality.

Similar to previous works,[41,43] the first four volumes of functional sequences were excluded from analysis (dummy scans), therefore T1 magnetization could reach steady state and patients could adapt to

the MRI scanner noise. Subsequently, BOLD data underwent a denoising process with a CompCor method, which reduces physiological and movement effects without removing the global signal,[44] applying a band-pass filter (0.008 to infinite Hz), using a simultaneous band-pass approach[45] to reduce both noise effects and low frequency drift, and linear regression of the following confounding effects: CSF and white matter (5 parameters each), realignment (12 parameters), and artifact scrubbing (113 parameters).[40] Further, the region-wise BOLD time-series was processed based on CONN's default atlas (132 ROIs), to conduct the seed-based ROI-to-ROI analysis to create the FC maps. Of note, the CONN's default atlas includes cortical and subcortical ROIs referred to the Harvard Oxford atlas,[46] and cerebellar ROIs according to the Automated Anatomical Labeling atlas.[47]

In the ROI-to-ROI FC analysis, individual correlation maps throughout the whole brain were computed extracting the mean BOLD time-course from each single seed and calculating the correlation coefficients with the BOLD time-course of all other CONN's default atlas brain regions. The correlations were obtained by applying General Linear Model and bivariate correlation analysis weighted for Hemodynamic Response Function: higher Z-scores represent positive correlations between ROIs (ie, increased FC reflected by increased BOLD signal time series synchronization), whereas lower Z-scores represent lesser correlations between ROIs (ie, decreased FC). Subsequently, Fisher's transformation was applied to all Z-scores derived from bivariate correlations, and correlation coefficients were converted into standard scores. Changes in the FC (post > pre; and pre > post) were examined within and between groups in the contrasts MST > EP and EP > MST. Time-by-group interactions were also examined. Results were corrected for multiple comparisons using false discovery rate (corrected threshold of $P < 0.05$ applied for all reported clusters).[48]

In addition, because our sample presented high variability in years of education (range of 4–18 years) and based on previous evidence showing that education can influence FC in healthy older adults[49] and AD,[50] we ran an additional analysis of the resting state functional connectivity (RSFC) changes controlling for education. For that, we extracted the FC values for each of the significant changes and ran analyses of covariance (ANCOVAs) considering the within-group changes and time-by-group interaction.

3 | RESULTS

3.1 | Participant characteristics

Demographic characteristics and neuropsychological performance of both intervention groups at baseline are shown in Table 1. No differences between groups were observed prior to interventions.

3.2 | Functional connectivity change

The interval between the end of the interventions and the second MRI exam occurred approximately 1 week after the end of interventions. The average of interval was 5.7 days (2.0) and range of 2 to 12 days. There was no difference in this interval between the groups ($P = .79$). For the MST group, the average interval was 5.4 days (range 2–12), and for EP group was 6.1 days (range 3–10).

3.2.1 | Within group

The ROI-to-ROI within-group analysis revealed a different pattern of RSFC change after each intervention: whereas there was an increase of FC after MST, we observed a decrease after the control intervention (EP; Table 2). Specifically, in the MST group there was an increase of FC between the left anterior MTG and right OFC (Figure 2). In the EP group, the IFG showed a decreased of FC with bilateral temporal pole and fusiform gyri. In addition, the PCC showed decreased of FC with left temporal pole and right anterior MTG (Figure 3). It is worth mentioning that considering the significant results uncorrected for multiple comparisons (Figure S1 in supporting information), the MST showed increased FC in several ROIs after the programs, while the EP group showed an extended pattern of decreased FC.

3.2.2 | Time-by-group interaction

The analysis revealed a time-by-group interaction indicating that the MST group showed greater increase of FC than controls between the right IFG pars triagularis and the three following ROIs on the left hemisphere: fusiform gyrus, temporal pole, and OFC (Figure 4). For additional details, see the uncorrected results in Table S2 in supporting information.

3.2.3 | Education as a covariate

The ANCOVAs revealed that after controlling for education, the within-group results did not remain significant ($Ps > .05$), while the interactions retained significance ($Ps = .01$; for details see Table S3 in supporting information). Of note, although the range of education was highly variable in each of the intervention groups (MST: 4–17 years; EP: 4–18 years), it was similar across groups.

3.3 | Exploratory analysis: brain-cognition correlations

An exploratory analysis was run to investigate correlations between change in RSFC and change in cognitive performance. For the RSFC data, we extracted the values of FC between the ROIs that showed significant change after MST or EP, and calculated change score (ie, post-pre). Regarding the cognitive data, we used the primary outcome of our study, the Face-Name Recognition Task (FNRT), which has been described elsewhere and showed transfer effects to untrained face-name pairs.[19,21] In brief, in the FNRT participants had to match names

TABLE 1 Characteristics of both intervention groups

	AMT (N = 14) M (SD)	EP (N = 12) M (SD)	*P*-value
Demographics			
Age (years) (range 62–82 years)	72.7 (5.6)	72.0 (6.7)	0.77
Education (years) (range 4–18 years)	11.4 (3.6)	13.5 (3.8)	0.17
Sex (women %)	71.4%	75%	1
Ethnicity, white (%)	50%	58.3%	.71
Clinical Characteristics			
MADRS	3.7 (3.6)	2.1 (2.7)	0.24
HAMA	2.7 (3.3)	1.4 (1.3)	0.20
IQCODE	3.1 (0.1)	2.9 (0.6)	0.25
B-ADL	1.6 (0.5)	1.5 (0.5)	0.68
MMQ - Contentment	32.7 (14.0)	36.6 (9.8)	.43
MMQ - Ability	48.5 (10.2)	54.7 (7.5)	.09
aMCI subtype (MD/SD)	9/5	9/3	.43
Neuropsychological Performance			
MoCA	24.2 (2.2)	24.5 (2.6)	0.75
Estimated IQ	97.6 (7.8)	98.6 (11.6)	0.79
COWAT (Letters FAS)	35.7 (10.2)	35.7 (12.1)	0.99
Semantic Fluency (Animal)	15.7 (3.7)	14.0 (3.0)	0.21
Boston Naming Test	54.5 (4.8)	52.0 (6.7)	0.28
Digit Span forward (WAIS-III)	7.5 (1.5)	8.4 (2.0)	0.23
Digit Span backward (WAIS-III)	4.3 (1.2)	5.2 (1.2)	0.08
Stroop (seconds on third plate)	34.5 (9.9)	38.2 (10.2)	0.35
SKT-Attention Score	1.7 (2.0)	2.3 (2.2)	0.49
SKT-Memory Score	0.5 (1.1)	0.6 (9.8)	0.82
HVLT-R Immediate recall	20.9 (2.9)	20.6 (3.2)	0.83
HVLT-R delayed recall	3.4 (2.9)	2.3 (1.9)	0.28
Faces Immediate recall (WMS-III)	33.0 (5.0)	34.3 (3.6)	0.45
Faces delayed recall (WMS-III)	31.2 (4.7)	33.1 (3.2)	0.31
LM Immediate recall (WMS-III)	19.1 (5.7)	23.2 (5.8)	0.08
LM delayed recall (WMS-III)	16.7 (5.7)	16.9 (7.9)	0.94
ROCF - Copy	29.8 (3.5)	27.7 (4.6)	0.18

Note: AMT, associative memory training; B-ADL, Bayer Activities of Daily Living Scale; COWAT, Controlled Oral Word Association Test; ED, education; HAMA, Hamilton Anxiety Rating Scale; HVLT-R Hopkins Verbal Learning Test Revised; IQ, intelligence quotient; IQCODE, Informant Questionnaire on Cognitive Decline in the Elderly; LM, logical memory; M, mean; MCI, mild cognitive impairment; MMQ: Multifactorial Memory Questionnaire; MADRS, Montgomery-Åsberg Depression Rating Scale; MoCA, Montreal Cognitive Assessment; ROCF, Rey-Osterrieth Complex Figure Test; SKT, Short Cognitive Performance Test; SD, standard deviation; WAIS, Wechsler Adult Intelligence; WMS, Wechsler Memory Scale. Performance in neuropsychological tests refers to raw data. MCI subtype: MD = Multiple Domain; SD = Single-Domain. Tests scores reflect raw scores.

and faces under a four-choice recognition task 30 minutes after having encoded face-name pairs in the scan. Scores regarding response accuracy and reaction time were calculated for each assessment endpoint as well as change score (post-pre). Our results revealed that only in the MST group was there a correlation between change in the RSFC and change in cognitive performance. Spearman's coefficients showed that the increase of FC (between left anterior MTG and right OFC) was correlated with increase of reaction time level ($r_s = .57$; $P = .03$; Figure 5A) and increase of accuracy for untrained face-name stimuli ($r_s = .51$; $P = .05$; Figure 5B).

4 | DISCUSSION

In the present randomized controlled study, we used resting-state fMRI to investigate the effects of MST on FC. Consistent with our hypothesis,

TABLE 2 Changes in resting state functional connectivity after the intervention

Seed ROI	ROI	T-test statistic	*P*-value Uncorrected	*P*-value corrected
Mnemonic Strategy Training (MST)				
Middle temporal gyrus L	Frontal orbital cortex R	T(24) = 3.69	.001	**.01**
Education Program (EP)				
IFG pars triangularis R	Temporal pole L	T(24) = −3.57	.001	**.02**
	Fusiform gyrus L	T(24) = −3.15	.004	**.02**
	Fusiform gyrus R	T(24) = −3.09	.005	**.02**
	Temporal pole R	T(24) = −2.84	.008	**.03**
PCC	Temporal pole L	T(24) = −3.87	.0007	**.01**
	Middle temporal gyrus R	T(24) = −3.23	.003	**.02**
Temporal pole L	PCC	T(24) = −3.87	.0007	**.01**
	IFG pars triangularis R	T(24) = −3.57	.001	**.01**
MST > EP				
IFG pars triangularis R	Fusiform gyrus L	T(24) = 3.09	.005	**.04**
	Temporal pole L	T(24) = 3.08	.005	**.04**
	Frontal orbital cortex L	T(24) = 2.91	.007	**.04**

Note. Correction refers to FDR procedure.
Abbreviations: FDR, false discovery rate; IFG, inferior frontal gyrus; PCC, posterior cingulate cortex

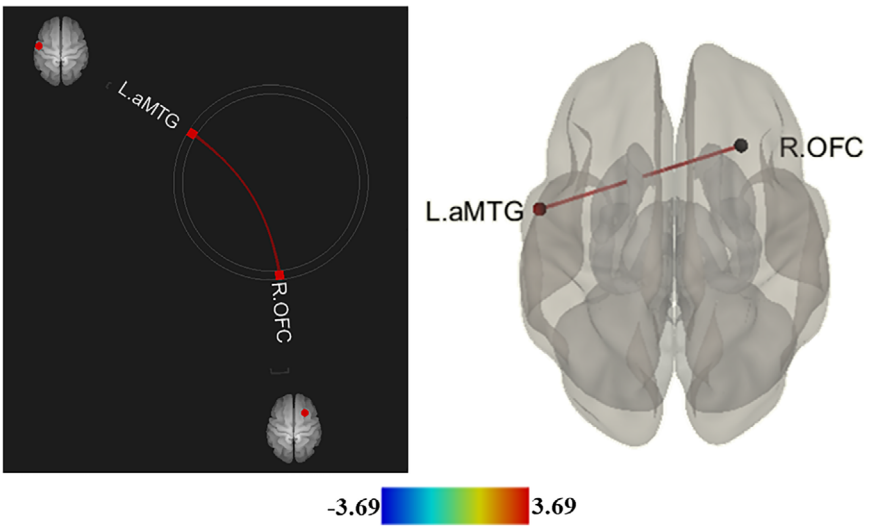

FIGURE 2 Region of interest (ROI)-to-ROI analysis showing increased resting-state functional connectivity in the mnemonic strategy training (MST) group. Right Inferior Frontal Gyrus - pars triangularis (R.IFG.tri) was positively correlated with left brain regions, such as temporal pole, orbitofrontal cortex (L.OFC), and temporal fusiform cortex (L.TFusC). Results remained significant after correction for multiple comparisons (FDR). Positive correlations are illustrated in red, and negative correlations are illustrated in blue

increased FC was observed after four sessions of MST, in comparison to the active control group focused on education. At post-intervention, there was an increase of FC only in the MST group, between the left anterior MTG and right OFC, while there was no FC change between these ROIs in the control group. Compared to the control group, the MST participants showed greater increase of FC between the right IFG pars triagularis—and left regions, such as temporal pole, temporal fusiform, and OFC. In contrast with our hypothesis, we found that MST-related FC increases were circumscribed in a set of ROIs, and the control group showed decreased FC between some of the ROIs. To the best of our knowledge, the current study is the first to show that MST alters brain dynamics at rest in aMCI, which extends our previous findings of training gains, transfer effects, and task-related increase activation after the same MST protocol.[19,20] In addition, our exploratory analysis revealed that RSFC were associated with cognitive change. Together, these findings and our previous reports[19,20] provide robust evidence of MST cognitive effects and its underlying brain mechanisms in individuals at high risk for dementia.

Changes within-group indicated that the MST led to greater increased FC between left anterior MTG and right OFC. Interestingly, both regions are implicated in semantic processing,[51-56] and particularly MTG is involved in semantic memory.[54-56] This finding extends our

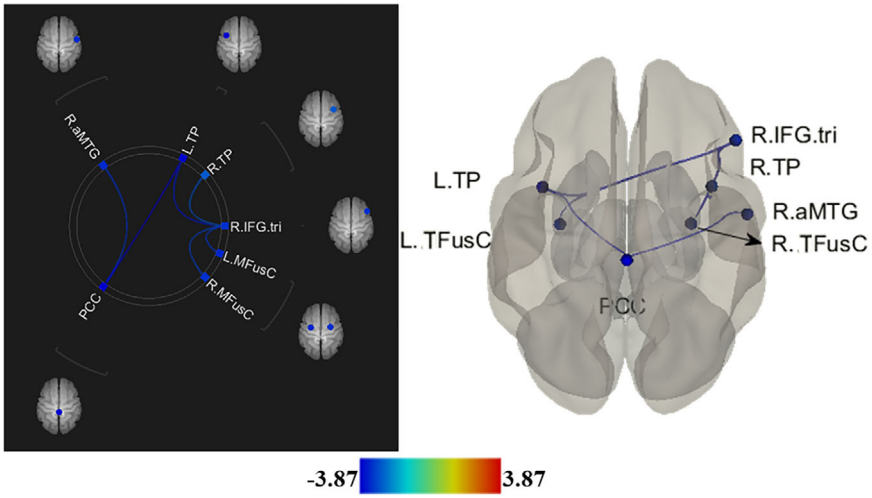

FIGURE 3 Region of interest (ROI)-to-ROI analysis showing decreased resting-state functional connectivity in the Education Program (EP) group (control intervention). Right Inferior Frontal Gyrus - pars triangularis (R.IFG.tri) was negative correlated with bilateral temporal pole (R.TP and L.TP, and bilateral temporal fusiform cortex (R.T.FusC and L.T.FusC). Posterior cingulate cortex (PCC) was negative correlated with left temporal pole (L.TP) and right middle temporal gyrus (R.MTG). Results remained significant after correction for multiple comparisons (false discovery rate). Positive correlations are illustrated in red, and negative correlations are illustrated in blue

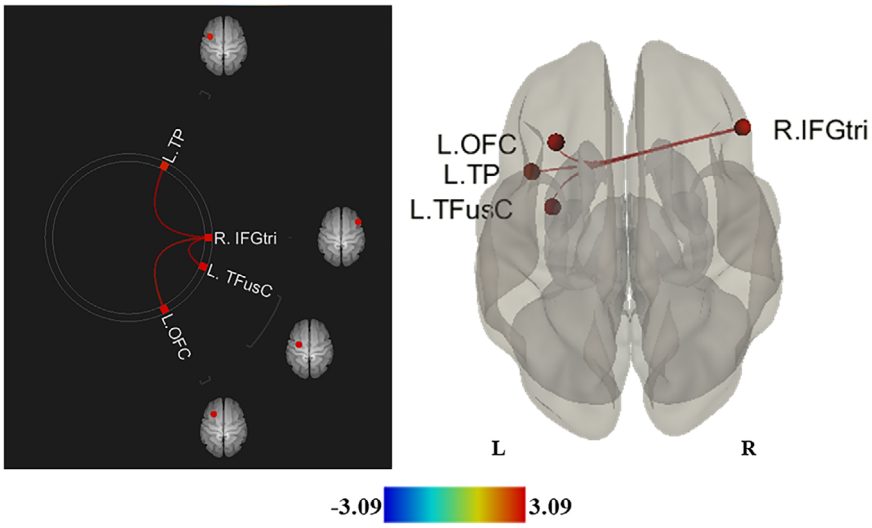

FIGURE 4 Region of interest (ROI)-to-ROI analysis showing time-by-group interaction in the contrast mnemonic strategy training (MST) > EP. MST group showed greater increased FC between the left anterior middle frontal gyrus (L.aMTG) and the right orbitofrontal cortex (R.OFC). Results remained significant after correction for multiple comparisons (false discovery rate). Positive correlations are illustrated in red, and negative correlations are illustrated in blue

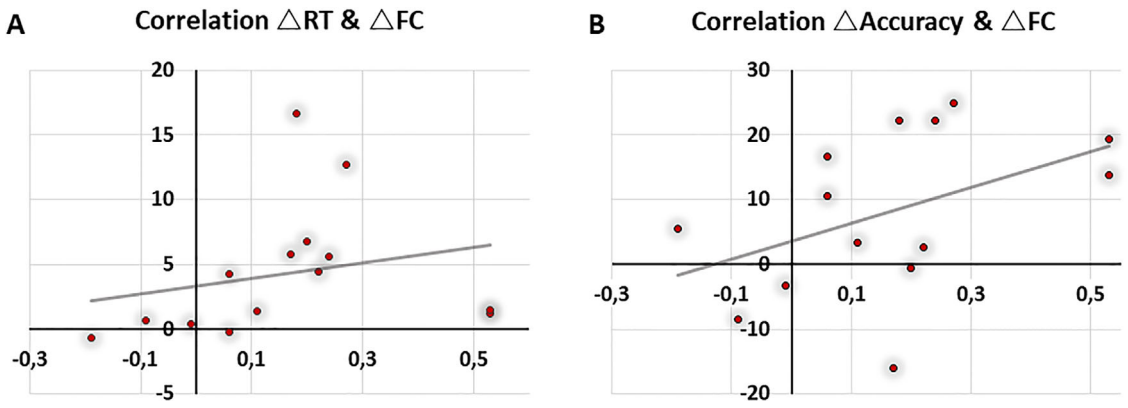

FIGURE 5 Correlations between resting state functional connectivity change and cognitive change. Only in the mnemonic strategy training group there was a correlation between change in functional connectivity (between aMTG left – OFC right) and change in accuracy and reaction time for untrained face-name stimuli in the Face-Name Recognition Task. X axis, Functional connectivity (FC) values; Y axis, Face-Name Memory Task raw score; △ = change (post-pre); RT = Reaction Time

previous observation that the anterior lateral MTG is a critical region underlying the training improvements.[19] The recruitment of regions relevant for semantic processing is consistent with our training procedure, in which participants were required to associate unrelated information (ie, faces and names) in a more strategic and meaningful way, rather than processing in a "automatic" manner. Therefore, our results suggest that a critical mechanism of our MST is the recruitment of semantic processing to enhance new learning/memory, in line with the observation than the relatively preserved semantic memory can serve as a compensation for impaired episodic memory in aMCI.[57] These results are reinforced by the fact that increased RSFC between the left MTG and right OFC was positively correlated with changes in cognitive performance (accuracy and reaction time) for untrained stimuli. The present findings are in line with our previous observation that MST induced greater accuracy and slower performance for untrained stimuli (in comparison to EP).[19] In addition, our previous work showed that increased accuracy was positively correlated with increased reaction time,[20] consistent with the inherently slower and more effortful nature of using mnemonic strategies.[4]

In conformity to our hypothesis, in the control group the RSFC between left MTG and right OFC remained stable. However, this group showed decreased FC between other ROIs (IFG and bilateral temporal pole, IFG and fusiform cortex, PCC and left temporal pole, and PCC and right anterior MTG). In retrospect, we observe that our findings are in line with others' results of increase of FC (within the default mode network) after cognitive training, but decrease of FC after a control intervention involving leisure engagement and social interaction in MCI.[33,34] In addition, our findings are consistent with a study that observed increased RSFC after multi-domain cognitive training but decreased FC associated with a wait-list control group (ie, no intervention) in healthy older adults.[35] Together, these results suggest that the cognitive programs proposed by these previous studies and ours might counteract decreased integration within network or RSFC between specific regions that may have occurred due to the aging process or underlying neurodegenerative disease. Such findings could also reflect habituation to the scanning environment. Nevertheless, it remains to be determined the FC changes associated with control interventions or absence of intervention; therefore, the inclusion of active and passive control groups in future studies may advance the field. In addition, future research should determine whether intervention effects are influenced by possible habituation to the scanning environment.

Moreover, the time-by-group interaction indicated that a central area with increased FC after MST was the IFG, known to be involved in several executive control processes, such as selective attention,[58] attention control,[59] working memory,[60] controlled memory retrieval,[61] and inhibition.[62] While the control group showed decreased or stable FC between the right IFG and all ROIs, the MST showed an increase of FC between right IFG and left temporal fusiform, a region implicated in high-level visual and face processing,[63,64] verbal semantic knowledge,[65] and semantic judgements.[66] Another ROI with increased FC with right IFG was the left temporal pole, known to be linked to social/emotional processing[67] and face-name associations, particularly retrieval of newly learned people's names from faces.[68,69] In addition, the right IFG showed increased FC with the left OFC mostly involved in language-related functions, such as semantic processing,[51-53] emotional salience,[70] face expression identification, and association learning.[71] The increased FC in these regions is in line with our training methodology, in which the patients learned to use explanations that linked the face feature, the reason, and the name using cues that were verbal/semantic (ie, semantic organization/elaboration) or emotional/social (eg, emotional expression of the face). In addition, our findings are in line with others reports of increased RSFC after cognitive interventions including MST in patients with Parkinson's disease[72] and multiple sclerosis.[73] However, this is the first study, to our knowledge, to show such effects in those with MCI.

It is worth mentioning that we did not find changes in all 17 ROIs examined and found different ROIs to be implicated in the within-group changes, and in the interaction. This yields multiple testable hypotheses for future studies. First, it is possible that the observed changes are "critical" relationships associated with treatment success. Second, many of these relationships may have existed at baseline but our sample may be insufficient to capture the magnitude of this change given the correction for multiple comparisons. This possibility highlights the challenges with intervention-related work and, perhaps, justifies reliance on effect-sizes more than *P*-values.[74] In addition, we observed differences in the within- versus between-group (interaction) analyses. These interaction effects can arise from one or a combination of within-group increased, decreased, or stable FC at the nodal level that may not be evident within a given group. It is possible that results were limited by the correction threshold adopted, because uncorrected results showed that more ROIs were connected. In addition, our results suggest that not all brain regions showing task-related change become more connected after MST, similar to a previous pilot study.[22]

An advantage of our study is that we were able to perform the post-intervention MRI approximately 1 week after the end of the protocols. This allowed us to observe an "acute" effect of the intervention, which may be dissipated after longer periods. Future studies should examine the duration of the effect observed. The change observed in the "innate" FC at rest suggests a general mechanism of transfer, because regions relevant for the strategies trained were in stronger synchrony after the intervention. The increase of resting-state FC only in the MST group is highly suggestive that our methodology alters the interaction between regions involved in learning and remembering new information beyond the task context, which was reinforced by the brain-cognition correlations. It is worth mentioning that our sample was relatively diverse regarding educational level (4–18 years), suggesting that our training is possibly beneficial to individuals with different reserve levels, an aspect that should be investigated in cognitive training studies. In addition, after controlling for education, the interactions remained significant although the within-group results did not retain significance. It is likely that these results were influenced by the fact that the range of education was highly variable within groups, although similar across groups. Future studies should examine the role of education and other reserve proxies on intervention effects.

The present findings should be interpreted in the light of our previous results showing near and far transfer effects to untrained stimuli and to a self-report measure of memory difficulties in everyday life,[19,20] indicating the ecological validity of our intervention. Despite the encouraging results, future evidence is necessary to confirm our findings, and we acknowledge the limitations of our study. First, the results rely on a modest sample size, which limits the power of analysis, and replication with larger samples is needed. However, this is the first study of its kind, providing an initial foundation on which future efforts can build. Second, we cannot totally rule out that the training effect observed is specific to MST and not to the "general" training procedure or face-name exposure, because we did not control for face-name exposure between groups. Despite that, our results are in line with a previous report that found additional benefits from a similar MST over matched-stimuli exposure group.[28] Third, the cognitive requirements differed, by nature, between the interventions so we cannot rule out the possibility that other strategy-based training would result in similar FC changes. However, the psychoeducation condition controlled for several aspects including expectations associated with a non-pharmacologic intervention, learning/memory for new information, social interaction with the therapist, and was matched for number and duration of sessions. Thus, the observed differences reflect training-induced effects. Similarly, our prior studies found significant task-related differences in neocortical[75] and hippocampal[31] BOLD signal after MST versus a repeated exposure training that provided the exact same number of trials, sessions, and session duration. Fourth, although we extensively describe the cognitive performance of participants, the current study did not estimate memory deficit accounting for the premorbid ability level (eg, education), because the norms available did not account for this aspect. Future studies should account for premorbid ability level when selecting aMCI participants. In addition, we included participants with either single- or multiple-domain aMCI, and this aspect may have influenced our findings (although groups were statistically similar in this regard). Fifth, although we previously reported that brain volumes (including hippocampus) of the aMCI participants were significantly smaller than those of a cognitively unimpaired control sample,[19] disease-specific biomarkers were not available. While reliance on the clinical phenotype of aMCI is well accepted, future studies should integrate biomarkers. It is worth mentioning there is a lack of AD biomarkers in non-pharmacologic intervention research and incorporating such data may be critical to inform the groups most likely to benefit from specific interventions, such as MST. In addition, future studies should compare intervention effects on MCI with a healthy control group, to better understand the specific RSFC effects on each population.

In conclusion, the present report extends literature showing that MST alter brain functioning[16] and is of benefit in those with aMCI,[16,19-24] a population at higher risk to develop dementia. We are the first to report that MST increase resting-state FC in aMCI, which was observed in regions associated with executive control and semantic processing, in line with the strategies trained. Critically, our findings suggest that MST may alter innate connectivity, at least temporarily, and enhance networks critical for learning and memory. Theoretically, such changes would result in transfer and should be examined in future studies, particularly in real-life contexts. Despite the encouraging results, our findings partially support our hypothesis because we found RSFC in a circumscribed set of ROIs and the results should be interpreted with caution due to the small sample size.

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CONFLICTS OF INTEREST

No author has any conflict of interest.

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