Towards rational use of cognitive training in those with mild cognitive impairment

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Abstract

The term cognitive training includes a range of techniques that hold potential for treating cognitive impairment caused by neurologic injury and disease. Our *central premise* is that these techniques differ in their mechanisms of action and therefore engage distinct brain regions (or neural networks). We support this premise using data from a single-blind randomized controlled trial in which patients with mild cognitive impairment were randomized to either mnemonic strategy training (MST) or spaced retrieval training (SRT) as they learned ecologically relevant object location associations. Both training approaches were highly effective in the short term, but MST demonstrated a clear advantage after days to weeks. MST also increased activation in and functional connectivity between frontal, temporal, and parietal regions as well as the hippocampus. In contrast, patterns of reduced activation and functional connectivity were evident following SRT. These findings support the rational development of cognitive training techniques.

1. Narrative

Cognitive training holds promise for treating cognitive deficits caused by neurologic injury and disease, including in those with mild cognitive impairment (MCI; [1, 2]). Multiple techniques are included under the general umbrella of *cognitive training*, all of which focus on improving or maintaining abilities using structured tasks [2, 3]. However, the current practice of lumping diverse techniques under this umbrella term may obscure meaningful differences between them and lead to suboptimal treatment. Our *central premise* is that these techniques differ in their "mechanisms of action" and engage distinct brain regions (or neural networks) as a result of the cognitive processes engaged. We support this premise using findings from a randomized controlled study and point to a future where providers will be able to rationally select specific cognitive training techniques that either re-engage dysfunctional brain regions (i.e., "restoration") or "compensate" using relatively preserved regions.

Our study randomized patients with MCI to either mnemonic strategy training (MST) or to a tightly matched active condition known as spaced retrieval training (SRT) while learning ecologically relevant object-location associations (OLA). MST enhances the depth of processing of the to-be-learned information by requiring the user to organize and elaborate on its "meaning" [3]. By providing general rules for patients to use across settings, MST may transfer to new information. Earlier studies showed that MST can improve memory for specific information (e.g., face-name or object-location associations learned using MST) [4-8]; the current study examined whether patients were able to independently use the mnemonic strategies during training and to then apply them to novel information. We and others have shown that MST increased activation in many brain regions that are affected in MCI, including the lateral prefrontal, parietal, and temporal cortices [4, 5, 7, 9, 10] as well as the hippocampus [11]. Such findings suggest that MST's beneficial effects arise from

increased cognitive control by neocortical regions (i.e., "top-down" processing), which restores the contributions of affected brain regions (e.g., hippocampus).

In contrast, SRT is a structured rehearsal technique in which delays between study and test are systematically increased [3]. An earlier review [12] found that SRT effectively teaches specific information (e.g., names of objects) as well as cue-behavior relationships (e.g., reducing inappropriate behaviors when a cue is presented) in those with dementia. SRT is also beneficial in those with MCI [13-15]. The mechanisms underlying SRT are not well established as we could not identify any neuroimaging studies in older adults. Since SRT relies on rehearsal, we hypothesized that activation-related changes would conform to well-established repetition suppression effects wherein activation is reduced in sensory cortical regions following multiple stimulus exposures, presumably due to increased efficiency of sensory processing [16].

Two primary findings from the current study directly support our central premise. First, both training approaches were highly effective at teaching specific information over the short term (~95% accuracy *during* training sessions), but only MST effects persisted and showed both physiological and cognitive evidence of near-transfer to novel stimuli. Second, functional magnetic resonance imaging (fMRI) demonstrated distinct patterns of change in brain activation and functional connectivity during encoding as a function of cognitive training technique. Specifically, MST increased activation in lateral and rostral prefrontal cortex as well as in the hippocampus whereas SRT reduced activation predominantly in sensory cortical regions (See Figures 2-5 and Supplemental Materials). Changes in the MST group are consonant with increased "top-down" processing since the (ventro)lateral prefrontal cortex is engaged during successful learning [17] as well as working memory [18], cognitive control [19], and semantic processing [20]. Additionally, the rostral prefrontal cortex is believed to shift attention and to coordinate distinct cognitive processes [21, 22]. The combination of these processes appears to support memory formation by re-engaging the hippocampus and other medial temporal regions, which are known to be vital for learning

and memory [23] but affected in those with MCI [24-26]. Our finding that MST increased hippocampal and larger network functional connectivity supports such integrative processing and, critically, expands earlier fMRI findings [4, 5, 7, 9, 11, 27]. Importantly, this increase appears to be restorative given our prior findings of reduced encoding-related activation [26] and connectivity [28] of such areas in those with MCI relative to cognitively intact controls. MST's apparent restorative effects are even more striking given the reduced activation shown by the SRT group in distinct brain regions that are generally less affected by Alzheimer's disease (i.e., primary motor, somatosensory, and visual cortices). Non-specific factors are highly unlikely to account for these neural changes given the tightly matched training conditions (e.g., both groups received the exact same number of training trials and reported comparable training experiences – Table 2) and comparable baseline neuropsychological profiles and brain volumes between the groups.

Pragmatically, such findings will ultimately help establish optimal treatment parameters for cognitive training techniques. For example, MST may be more appropriate when retention is needed for days to weeks or when transfer effects are desired. The fact that our participants successfully developed strategies for 82% of the stimuli suggests an relatively high level of skill was achieved during this relatively brief intervention (i.e., 405 total trials), which likely explains the observed near-transfer effects. Our imaging data also suggest MST will be most appropriate during earlier clinical/disease stages when the above-noted brain regions/networks are relatively preserved. In contrast, SRT and possibly other rehearsal-based approaches (e.g., see [11]) may be most appropriate for teaching specific information, especially when it is only needed in the short term (e.g., hours to days – such as when an individual is transitioning into a new living environment). The fMRI-related changes in typically preserved sensorimotor regions/networks suggest SRT may remain beneficial into more advanced clinical/disease stages. Thus, there may be a critical point in clinical progression when treatment should shift from MST to SRT (or other rehearsal based approaches).

Conclusions

The current findings reinforce our central premise that cognitive training techniques differ in their mechanisms of action but limitations and additional questions exist. We encourage the replication and extension of our findings to include other cognitive training approaches and more extensive mapping of the parameter space. Our data used a respectable sample size for this area of study and largely replicated and extended our earlier findings, though the number of participants is small for traditional clinical trial designs. While our fMRI analyses and associated time-courses replicate and extend our prior work, larger samples would enhance statistical confidence and enable correlational analyses between cognitive and neuroimaging changes. Other limitations include our use of a single task paradigm, loss of some outcome data, and need to evaluate transfer to everyday life. Future efforts should also clarify mechanisms of action and identify the optimal treatment parameters, especially as they relate to dose-response and patient-level factors (including biomarkers) for various cognitive training approaches. An intriguing but unanswered question emerges in whether the consistent re-engagement of the observed brain regions via MST could be leveraged to enhance everyday functioning through prolonged training like that used in computerized cognitive training approaches (e.g., 40+ hours of training instead of the ~3 hours in our studies) [29]. Careful consideration of such factors will ultimately allow clinicians to select the technique best suited for the patient's goals by engaging, or avoiding, regions affected by the underlying disease process. The clinical translation of cognitive training techniques will be improved through consistent use of our multi-stage process that establishes optimal conditions of use [3]. This translation-focused framework will be even more critical as disease-modifying (but not necessarily cognition enhancing) agents become available and commonplace in our treatment landscape.

2. Consolidated Results & Study Design

Participants: Fifty-nine right-handed participants with MCI were randomized to MST or SRT (1:1 ratio) using the sealed envelope method and were blinded to the other treatment condition. The study design is shown in Figure 1. The groups were not significantly different on demographic, neuropsychological performance, or key brain volumes at baseline (Table 1). Both the Emory University Institutional Review Board and the Atlanta VAMC Research and Development Committee approved the study. Participants provided informed written consent.

INSERT FIGURE 1

INSERT TABLE 1

Training procedures & outcome measures: Participants were randomized after the baseline fMRI session (see details below). We used the same study design [8, 9] and stimuli [8] as in our prior studies. During the 3 training sessions, each group received a total of 405 training trials during which they learned 45 OLAs from either List A or B (9 trials for each of 15 stimuli each session for 3 sessions). This list is referred to as the "trained" list; memory (in percent correct) for the OLAs on this list served as the primary outcome measure. The other list of OLAs was seen only post-training and provided a set of novel stimuli through which we examined training-related fMRI changes (secondary outcome used to evaluate physiological near transfer effects). The brief fMRI trials and supraspan nature of the task effectively evaluated activation change but were suboptimal for evaluating memory performance change [27]. Thus, we developed the object-location touchscreen test (OLTT; [30]), which served as our secondary cognitive outcome measure of near transfer and was performed outside the fMRI environment. The OLTT has several advantages relative to the in-scanner task since it uses a smaller number of stimuli, provides greater exposure time per object-location pair, has a more standard 15-minute delay, and uses a continuous measure of memory (i.e., distance from the target location) (see Section 3 and Supplemental Material for additional details).

MST required participants to use a 3-step process in which they 1) identified a salient feature, close to the object, within the room, 2) used a verbally-based "reason" that related the object to the specific feature, and 3) formed a corresponding mental image. Each subsequent "test" trial required the participant to recall, in order, the feature, reason, and location (from 5 options – each of which was a target location) so as to promote a specific series of steps that could be applied to other OLAs. In contrast, SRT required participants to recall the location of each object from among the 5 options following progressively longer delays of 0, 1, 2, 4, 8, 16, 32, 64, and 128 seconds. The correct OLA was shown following each trial for both groups (see Section 3 for more details).

fMRI scanning (sessions 1 & 5): Details for the sequences, paradigm, and analyses are provided below (see Section 3). Briefly, participants encoded either OLA List A or List B at baseline (which were novel since the stimuli had never been seen before) and were then trained on that list using the previously described methods. At post-training, participants again saw the trained list (that was novel at baseline) as well as the other list (which was novel). This design allowed us to directly compare change in encoding-related activation as a function of training-specific content (i.e., trained stimuli post > novel stimuli pre) as well as physiologic evidence of near-transfer (i.e., novel stimuli post > novel stimuli pre). fMRI changes for the trained stimuli presumably represent a mixture of cognitive training method as well as associated recall/re-encoding of those stimuli. In contrast, the novel stimuli provide a "process-pure" measure of the cognitive training condition. During these encoding runs, participants were instructed to remember each object's location and to push a button with their right index finger at the start of each trial to provide evidence of task engagement. fMRI encoding data were available from 21 MST and 18 SRT participants. Participants unable to complete fMRI underwent the same procedures in a quiet office.

One hour after the encoding fMRI session ended, participants completed the retrieval scan and selected the object's location from among 3 choices (retrieval data will be reported

separately). Each of the choices used during the retrieval phase was an actual target location within that room; a design intended to promote recollection over familiarity.

Imaging data analysis: To replicate our earlier findings [27], we used all previously described settings and analyses for BrainVoyager QX v21.4.0.4002, which is a software package for the analysis and visualization of functional and structural MRI datasets (Brain Innovation, Maastricht, The Netherlands) with a moving-target group-averaging cortex-based alignment procedure [31], which accounts for inter-individual variability in sulcal and gyral patterns (see Section 3 for details). Likewise, we applied the same hippocampal mask and small volume correction approach as in our earlier study [11], which had revealed increased hippocampal activation after MST. To further understand any treatment-induced effects, we then evaluated hippocampal functional connectivity using correlational psycho-physiological interaction (cPPI) following the methods described in the supplemental material (exploratory whole brain cPPI analyses are also provided in the supplemental materials).

Behavioral data analysis: Differences on the seven item post-training satisfaction Likert-style questionnaire were evaluated using the Mann-Whitney U. Using Stata,SE software (StataCorp LLC, College Station, Texas, v16.0) we set 2-tailed alpha to reject the null hypothesis at 0.05, with an emphasis on characterizing the observed effects in addition to reporting statistical significance for the primary and secondary (near-transfer) cognitive outcome measures. Consistent with our mixed-factorial experimental design, and continuously scaled outcomes, we utilized mixed-effects modeling to evaluate the effects of condition (MST, SRT) and time (Pre, Post, Follow-up) on our primary and secondary outcomes. Each model incorporated a random Y-intercept to accommodate the within-participants/longitudinal experimental design, using full information maximum likelihood estimation assuming compound symmetry variance-covariance structure of the random effects, and fixed-effects coefficients to evaluate the simple-interaction effects of treatment

by time, relative to pre-training. Exploratory analyses used mixed effects models that incorporated whether participants underwent fMRI scanning, which had no effect whatsoever as a main effect or interaction component with time, group, or the 3-way interaction term involving time, group, and fMRI status.

Behavioral findings (Table 2 & 3):

The general experience was comparable between the training groups as reflected by non-significant differences in their responses to the satisfaction survey (Table 2). During the training sessions, participants in the MST group were able to develop their own cues (i.e., "Feature" and "Reason" steps) on 82% of the trials and recalled the features (95.3% (SD=9.3)) and reasons (95% (SD=8.8)) on nearly all the trials. During the training sessions, participants in both groups remembered the target location of trained items on over 95% of the training trials (MST: 95.4% (SD=10.1); SRT: 95.8% (SD=6.1)), thereby demonstrating the short-term success of both training methods.

INSERT TABLE 2

As noted, outcomes were evaluated at baseline, 2 days after the final training session and about 1 month later, with omnibus interactions followed by simple-interaction contrasts comparing the Pre/Post and Pre/Follow-up changes by group. For our primary outcome measure of trained stimuli list accuracy (in percent correct; acquired in the fMRI scanner), the omnibus interaction was significant ($p<.001$) and simple-interactions revealed that the magnitude of improvement from baseline was significantly greater in the MST than the SRT group at both post-training (on average 18.47 (12.28-24.67 95% CI) units higher, $p<.001$) and at 1 month (on average 10.93 (4.57-17.29 95% CI) units higher, $p=.002$). There were no significant differences (omnibus $p=.56$) in memory test change (in percent correct) for the novel stimuli encountered during fMRI scanning post-training (on average 1.91 (-4.62 to 8.44 95% CI) units higher for MST, $p=.567$) or at 1-month follow-up (on average 1.76 (-8.45 to 4.93 95% CI) units higher for SRT, $p=.607$) (though see below for fMRI based

changes). However, the omnibus interaction effects were significant for all portions of the OLTT (secondary outcome measure of near transfer collected outside the fMRI environment) (free recall p=.019, cued recall p=.015, recognition p=.002). Simple interactions revealed that there was greater improvement for the MST than the SRT group during cued recall (on average 2.33 (.75 to 3.91 95% CI) units better, p=.004) and recognition (on average 2.81 (1.3 to 4.32 95% CI) units higher, p<.001) components post-training as well as during free recall at 1 month (on average .40 (.12 to .69 95% CI) units better, p=.005).

INSERT TABLE 3

fMRI Findings (Figures 2-5):

For the trained stimuli (trained stimuli post > novel stimuli pre), which were initially novel at baseline, the MST group demonstrated increased task-related blood oxygen level dependent (BOLD) signal, post-training relative to the pre-training state, in the medial frontal and parietal regions of the left hemisphere as well as reduced BOLD in the occipital cortex bilaterally (Figure 2). This contrast and the associated findings presumably reflect the cognitive training approach as well as memory (or "re-encoding") of the trained OLA. In contrast, comparing activations pre- and post-training for the stimuli that were novel at each time point yields results that more directly reflect the cognitive training approach. For the trained stimuli, the MST group demonstrated increased activation in the superior and medial prefrontal cortex as well as the precuneus and posterior cingulate cortex of the left hemisphere. For the novel stimuli (near-transfer), the MST group again showed increased activation in the left superior prefrontal cortex as well as in the left lateral prefrontal (e.g., inferior frontal gyrus with extension to the depths of the inferior frontal sulcus and ventral middle frontal gyrus), lateral occipitotemporal cortex, and medial temporal cortex. Reduced activation was observed in the occipital cortex for both trained- and novel-stimuli. Across nearly all of these regions, the time-courses were highly similar for the trained and novel stimuli, which suggests comparable cognitive processes were engaged across stimuli. Whole brain exploratory cPPI analyses revealed net increased connectivity (ratio of

increased to decreased connections for trained stimuli (trained post > novel pre) was 18.56:1, and 10.21:1 for the novel fMRI stimuli (novel post > novel pre)), especially between the default mode and visual networks (see supplemental materials). Moreover, we found increased hippocampal activation in the head and body of the left hippocampus for both trained and novel stimuli. Hippocampal functional connectivity for the trained stimuli was also increased with nearly all major associative brain networks (p's $\leq$.024) surviving FDR correction, with especially robust results ($P_{obs} \geq .08$) for the dorsal attention, frontoparietal, and visual networks. Similar, albeit attenuated, results were found for the novel stimuli with dorsal attention, frontoparietal, and visual network connectivity all surviving FDR correction (p's $\leq$.004) (see Supplemental Materials).

INSERT FIGURE 2

In contrast, the SRT group (Figure 3) demonstrated reduced BOLD signal bilaterally for both the trained and novel stimuli in (mostly sensory) neocortical regions distinct from those showing change following MST. The time-course data for the trained and novel stimuli were highly similar, again suggesting training-induced changes regardless of stimulus type. Whole brain connectivity suggested net decreases (decreased to increased ratio of 4.36:1 for trained stimuli and 8.37:1 for novel stimuli; see Supplemental Materials). Although there were no significant hippocampal changes in activation or connectivity following SRT, a trend toward reduced connectivity with the visual network was evident for novel stimuli (see Supplemental Materials).

INSERT FIGURE 3

Interaction analyses (group x time; Figures 4 & 5) largely mirrored the changes found at the individual group level. In all areas showing such interaction effects, the MST group showed significantly greater BOLD change than did the SRT group. Changes in the left rostral superior frontal gyrus and inferior frontal gyrus were highly similar for both trained and

novel stimuli; again supporting that MST preferentially engaged these regions. Likewise, MST showed significantly greater hippocampal BOLD change for both the trained (bilateral anterior) and novel stimuli (left anterior). Relative to SRT, the change in hippocampal connectivity for trained stimuli was significantly greater with the dorsal attention, default mode, frontoparietal, and visual networks following MST (see Supplemental Materials). While similar differences were evident with the dorsal attention and visual networks for the novel stimuli, the findings did not survive FDR correction (likely due to our sample size).

INSERT FIGURE 4

INSERT FIGURE 5

3. Detailed Methods and Results

Participants: Of the fifty-nine right-handed participants, one in each group was excluded from the study because of an inability to comprehend training instructions, leaving 57 participants with data at the primary endpoint (session 5; 96.6% retention). Four participants (3 MST) were unable to return for the 1-month evaluation (89.8% overall retention). Results were unchanged when these dropouts were excluded from analyses.

Each participant was diagnosed with amnestic MCI according to Petersen's criteria [32] during a consensus clinical conference. The diagnosis required a subjective report of cognitive decline (provided by the patient or an informant) and objective evidence of memory impairment with generally preserved global cognitive functioning and instrumental activities of daily living. Each participant completed the measures in Table 1 at the time of enrollment. Participants were stable on all medications for at least 6 weeks prior to the study. The overall profile reflects learning and memory deficits within the context of preserved everyday functioning and is consistent with an underlying Alzheimer's disease etiology.

Exclusion criteria for all participants included a history of neurologic injury or disease such as dementia, stroke, epilepsy, or moderate-to-severe traumatic brain injury as well as

psychiatric disorders (e.g., major depressive disorder, bipolar disorder, schizophrenia) and current or recent alcohol or drug dependence.

Training procedures & outcome measures: Randomization effectively equated the groups, as evidenced by the comparable performances across all measures, including brain volumes, at baseline (Table 1). We used the same study design [8, 9] and stimuli [8] as in our prior studies, where participants completed 5 sessions within 2 weeks and then returned for a follow-up evaluation approximately a month later. fMRI scanning was performed during sessions 1 and 5; there were always 2 days between sessions 4 and 5. Following our earlier recommendation to refine dosing parameters [3], each group received a total of 405 training trials during which they learned 45 OLAs from either List A or B (15 stimuli per session for 3 sessions). This list is referred to as the "trained" list; memory for the OLAs on this list served as the primary outcome measure. The other list of OLAs was seen only post-training (sessions 5 and 6) and provided a set of novel stimuli through which we examined near-transfer/generalization fMRI effects. The OLTT [30] served as our cognitive measure of near transfer and provides 15 seconds of exposure to each of 15 stimuli, thereby creating the conditions under which participants could demonstrate their application of trained skills. Memory was evaluated after a 15-minute delay by measuring the distance (in cm) between the stated versus actual location of a given object under free recall (i.e., a blank screen that evaluated uncued spatial memory) and cued recall (i.e., a picture of the target room without any objects present) conditions. A 3-choice recognition test was then completed where each option was a target item within the room; an approach intended to facilitate recollection instead of mere familiarity. Software coding errors led to the loss of data for the first 15 participants (7 MST, 8 SRT), leaving data from 21 participants per group.

During the training sessions, each trial began by showing an object and requiring the participant to name it. Consistent with phase 2 of our model [3], we required participants to develop their own MST cues (see Supplemental Material for examples). Success was

recorded and assistance provided if participants encountered difficulty. Each subsequent "test" trial required the participant to recall, in order, the feature, reason, and location (from 5 options – each of which was a target location) so as to promote a specific series of steps that could be applied to other OLAs. The cues were provided in the event of an incorrect response (or inability to recall the information) and the location shown after each trial to ensure corrective learning. In contrast, SRT required participants to recall the location of each object from among the 5 options following progressively longer delays of 0, 1, 2, 4, 8, 16, 32, 64, and 128 seconds. Each of these delays were "empty" in that the computer screen was blank and the participant did not engage in any task (or conversation). The correct location was shown after each trial for both groups to reinforce the correct object-location association.

At the end of session 5, all participants completed a questionnaire focusing on their experience in the study, including the perceived usefulness of the training approach [8] (see Table 2).

fMRI scanning (sessions 1 & 5) was performed, for MRI-eligible participants, on a Siemens Trio 3T MRI scanner (Siemens Medical Solutions, Malvern, PA), using a 12-channel head coil. Participants unable to undergo fMRI due to contraindications (e.g., tattoos, metallic implants, claustrophobia) or poor pre-training data quality (e.g., excessive motion) (7 MST, 11 SRT) followed the same procedures in a quiet office setting (as in [6, 8, 9, 27]). For blood oxygenation level-dependent (BOLD) contrast, T2*-weighted functional images were acquired using a single-shot, gradient-recalled, echo-planar imaging (EPI) sequence with the following parameters: repetition time (TR) 2000 ms, echo time (TE) 30 ms, field of view (FOV) 220 mm, flip angle (FA) 90°, 33 axial slices of 3.5 mm thickness, in-plane resolution 3.4×3.4 mm, and in-plane matrix 64×64. High-resolution anatomic images were acquired using a 3D MPRAGE sequence (TR 2300 ms, TE 3.9 ms, TI 1100 ms, FA 8°) consisting of

176 sagittal slices of 1 mm thickness (FOV 256 mm, in-plane resolution 1×1 mm, in-plane matrix 256×256).

During encoding, stimuli were presented in 5 functional runs, each consisting of seven 20 second rest blocks that alternated with six 32 second active blocks. Each active block consisted of three 10 second trials in which the object was shown for 1 second and then the object in location for 9 seconds. Trials were separated by a 1 second interstimulus interval. The order of blocks was randomized prior to the start of the study but then fixed within a given protocol to create 5 distinct "orders". These orders were randomized for each person across the 5 functional runs. At baseline, participants were shown a total of 45 novel stimuli (3 blocks per functional run, each with 3 stimuli) from either List A or B (based on randomization and counterbalancing for treatment group) as well as 45 repeated stimuli (i.e., two additional OLAs alternated during the block as in our earlier studies [9, 26, 27]). The structure of the post-treatment encoding scan was identical except that stimuli now consisted of the 45 trained stimuli (i.e., the novel stimuli from baseline that were used during Sessions 2-4) and 45 novel stimuli (i.e., the untrained List). In this way, we were able to directly compare change in encoding-related activation as a function of training-specific content (i.e., trained stimuli post > novel stimuli pre) as well as near-transfer (i.e., novel stimuli post > novel stimuli pre). The retrieval scan was performed one hour later, results of which will be reported separately. Participants unable to complete fMRI underwent the same procedures in a quiet office.

Additional Imaging data preprocessing details: Functional runs were motion-corrected in real time using Siemens 3D-PACE (prospective acquisition motion correction). For each subject, the functional images were realigned to the first image of the series using BrainVoyager QX v21.4.0.4002. Images were pre-processed using trilinear-sinc interpolation for additional motion correction, cubic spline interpolation for slice scan time correction, and high-pass temporal filtering to 2 cycles/run to remove slow drifts in the data. They were then co-

registered with anatomic images and transformed into Talairach space [33], which is standard in BrainVoyager.

To replicate our earlier findings [27], we used all previously described settings and analyses for BrainVoyager's moving-target group-averaging cortex-based alignment procedure [31], which accounts for inter-individual variability in sulcal and gyral patterns. All analyses were performed using random effects, general linear models (GLMs) for the aligned neocortical data. Resulting activation maps were corrected by imposing a cluster-volume threshold for contiguous vertices passing a vertex-wise significance threshold of $p < .05$ (500 iterations of a permutation test were performed), which is available in BrainVoyager and based on Monte Carlo simulations arising from prior work [34]. While this cluster-defining threshold (CDT – the initial voxel-level threshold at the p<.05 level) may be viewed as liberal relative to discussions around *observational* research [35], we felt it appropriate given our intent to *replicate* and extend our prior *intervention*-related findings [9, 11, 27]. Likewise, we applied the same hippocampal mask and small volume correction (with CDT p<.05) approach as in our earlier study [11], given those findings of increased hippocampal activation after MST. To further understand any treatment-induced effects, we then evaluated hippocampal functional connectivity using correlational psycho-physiological interaction (cPPI; implemented in SPM12) following the methods described in the Supplemental Material (exploratory whole brain cPPI analyses are also provided in the supplemental materials).

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Conflicts of Interest

All conflicts of interest have been reported and are on file.

Author Contributions

Each author provided significant intellectual contribution to warrant authorship and declares that he/she has seen and approved this manuscript.

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Table 1. Demographic and baseline neuropsychological test results for the MST and SRT groups. Standard deviations are provided in parentheses. Brain volumetrics are provided in percent of intracranial volume (% ICV). MMSE = mini-mental state exam; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; GDS = Geriatric Depression Scale; FAQ = Functional Activities Questionnaire. WAIS-III = Wechsler Adult Intelligence Scale 3rd edition. Degrees of freedom were 55 unless otherwise noted (+=52, ++=54, +++=48, ++++=37).

	MST (n=28)	SRT (n=29)	Pearson Chi^2	p-value
Sex (F/M)	10/18	14/15	.922	.424
			t(55)	**p-value**
Age (years)	72.7 (8.3)	70.5 (8.3)	.98	.33
Education (years)	15.8 (2.9)	15.9 (2.8)	.1	.92
MMSE (raw score)	27.2 (1.5)	27.8 (2.2)	.99	.33
WAIS-III Information (scaled score)	12.0 (2.5)	12.1 (2.5)	.11	.91
RBANS Indices (Standard Scores)				
Immediate Memory	87.7 (10.1)	88.3 (17.3)	.16	.88
Visuospatial/construction	96.0 (17.6)	95.4 (16.5)	.13	.90
Language	92.8 (11.1)	92.4 (18.4)	.11	.91
Attention	94.8 (11.7)	97.8 (17.1)	.79	.43
Delayed Memory	77.8 (19.6)	83.0 (18.3)	1.0	.31
Total Score	86.2 (8.8)	89.2 (14.1)	.97	.34
Trails A (T-scores)	47.8 (10.1)	47.5 (10.7)	.11	.91
Trails B (T-scores)+	48.3 (10.2)	49.5 (10.8)	42	.68
Wisconsin Card Sorting Test (Emory version)++				
Sorts completed (raw)	3.1 (1.8)	3.8 (1.4)	1.6	.11
Perseverative errors (raw)	6.5 (6.1)	4.5 (3.6)	1.51	.14
Set loss errors (raw)	1.8 (1.8)	1.5 (1.6)	1.55	.45
GDS (raw scores)	1.6 (1.4)	1.8 (2.0)	.17	.87
FAQ (raw scores)+++	3.7 (5.0)	3.0 (4.4)	.51	.61

Brain Volume (% ICV)[++++]				
Cortical gray matter	30.2 (2.3)	30.6 (2.1)	.51	.61
Total ventricular volume	3.4 (1.5)	3.5 (1.9)	.22	.83
Inferior lateral ventricles	.2 (.07)	.22 (.12)	.45	.66
Entorhinal cortex	.33 (.07)	.33 (.05)	.37	.71
Hippocampus	.43 (.08)	.43 (.08)	.27	.79
Parahippocampal gyrus	.29 (.03)	.28 (.03)	1.5	.15
Amygdala	.18 (.04)	.18 (.03)	.52	.61
Days between training sessions				
Sessions 1 & 2	1.75 (1.0)	2.7 (1.6)		
Sessions 2 & 3	3.8 (1.5)	3.3 (2.1)		
Session 5 & 1-month	31 (8.4)	30.5 (5.9)		

Table 2. Group medians (standard deviations in parentheses) for the post-training questionnaire that used a visual analogue scale (0=not at all, 5 = somewhat, 10 = extremely). Non-parametric tests (Mann-Whitney U) were used since some items did not meet the assumptions of normality and homogeneity of variance.

	MST	SRT	U	p-value
1) How useful was the training?	7.5 (1.79)	7.0 (1.61)	361	.462
2) How much do you feel the training improved your memory?	7.0 (1.64)	6.0 (1.77)	364	.494
3) How likely are you to use these strategies in your everyday life?	7.0 (2.15)	8.0 (2.21)	380.5	.679
4) How likely would you be to do a similar study?	8.0 (2.23)	7.0 (2.63)	371	.569
5) How likely would you be to refer a friend or family member for this study?	8.0 (2.31)	9.0 (2.52)	358	.430
6) How friendly was our staff (How well did we treat you)?	10.0 (0.39)	10.0 (1.0)	403.5	.952
7) How would you rate your overall experience in the study?	9.0 (1.48)	9.0 (1.74)	368	.528

Table 3. Group means (±95% CI) for outcomes measured Pre-training, Post-training, and 1 month later. Note that pre-training performance for the fMRI stimuli ("Trained" and "Novel" Lists) are the same since participants were randomized to one of two lists, which was novel at baseline but served as the training list during Sessions 2-4. Near transfer was evaluated using the OLTT, which was acquired in a quite office using novel stimuli outside of the fMRI environment. Omnibus interactions are reported in the text.*higher values indicate greater distance (in centimeters) from the actual target location, which reflects worse performance (OLTT Free Recall & Cued Recall).

	MST	SRT	Group x Time (relative to baseline) Simple Interaction Effects
Trained List (fMRI environment)			
Accuracy (percent correct)			
Pre-training	45.38 (40.19-50.57)	46.31 (41.25-51.36)	
Post-training	80.00 (74.86-85.14)	62.45 (57.40-67.51)	p < .001
1 month	54.37 (49.07-59.67)	44.37 (39.27-49.47)	p < .002
Novel List (fMRI environment)			
Accuracy (percent correct)			
Pre-training	45.38 (40.19-50.57)	46.31 (41.25-51.36)	
Post-training	45.71 (41.50-49.93)	44.68 (40.53-48.82)	p = .567
1 month	35.23 (30.82-39.63)	37.85 (33.65-42.05)	p = .607
Near Transfer (OLTT; office setting)			
Free Recall*			
Pre-training	11.64 (10.32-12.95)	9.81 (8.60-11.02)	
Post-training	9.55 (8.36-10.74)	8.88 (7.73-10.03)	p = .232
1 month	9.24 (8.03-10.46)	10.02 (8.80-11.24)	p = .005
Cued Recall*			
Pre-training	9.23 (7.93-10.53)	7.93 (6.64-9.24)	
Post-training	6.1 (4.80-7.40)	7.14 (5.84-8.44)	p = .004
1 month	7.07 (5.74-8.41)	6.91 (5.61-8.21)	p = .169
Recognition (Raw correct)			
Pre-training	7.9 (6.80-9.01)	9.43 (8.33-10.53)	
Post-training	10.57 (9.47-11.67)	9.29 (8.18-10.39)	p < .001
1 month	9.69 (8.56-10.83)	10.05 (8,.95-11.15)	p = .134

Figure Captions

Figure 1. Overall study design. Randomized participants completed 3 training sessions in which they learned a total of 15 stimuli each session using the designated approach (i.e., MST or SRT). Each stimulus was presented a total of 9 times during the session, with corrective feedback provided following each trial for both groups. Participants were trained using either List A or B, the "untrained" list was also used to evaluate fMRI-based evidence of transfer during post-training. Participants unable to complete fMRI scanning or with unusable data (MST n=7; SRT n=11) completed the same Post-training (session 5) procedures in a quiet office setting ("behavior only" in the Post-training box above). The 1-month follow up was behavior only and performed in a quiet office setting.

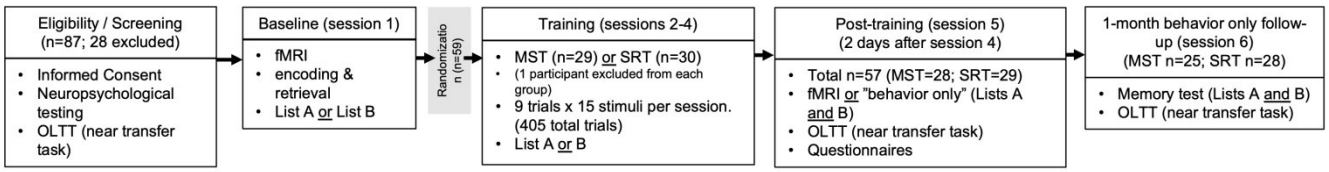


Figure 2. Changes in task-related BOLD signal for the MST group for the trained stimuli (left) and novel stimuli (right). Time courses are provided for an entire cluster for descriptive purposes. IFG = inferior frontal gyrus; mSFG = medial superior frontal gyrus; MTL = medial temporal lobe; PCu/PCC = precuneus/posterior cingulate cortex; pSTS= posterior superior temporal sulcus. Cooler colors (blue/green) show reduction while warmer colors (orange/yellow) show increased BOLD relative to pre-training.

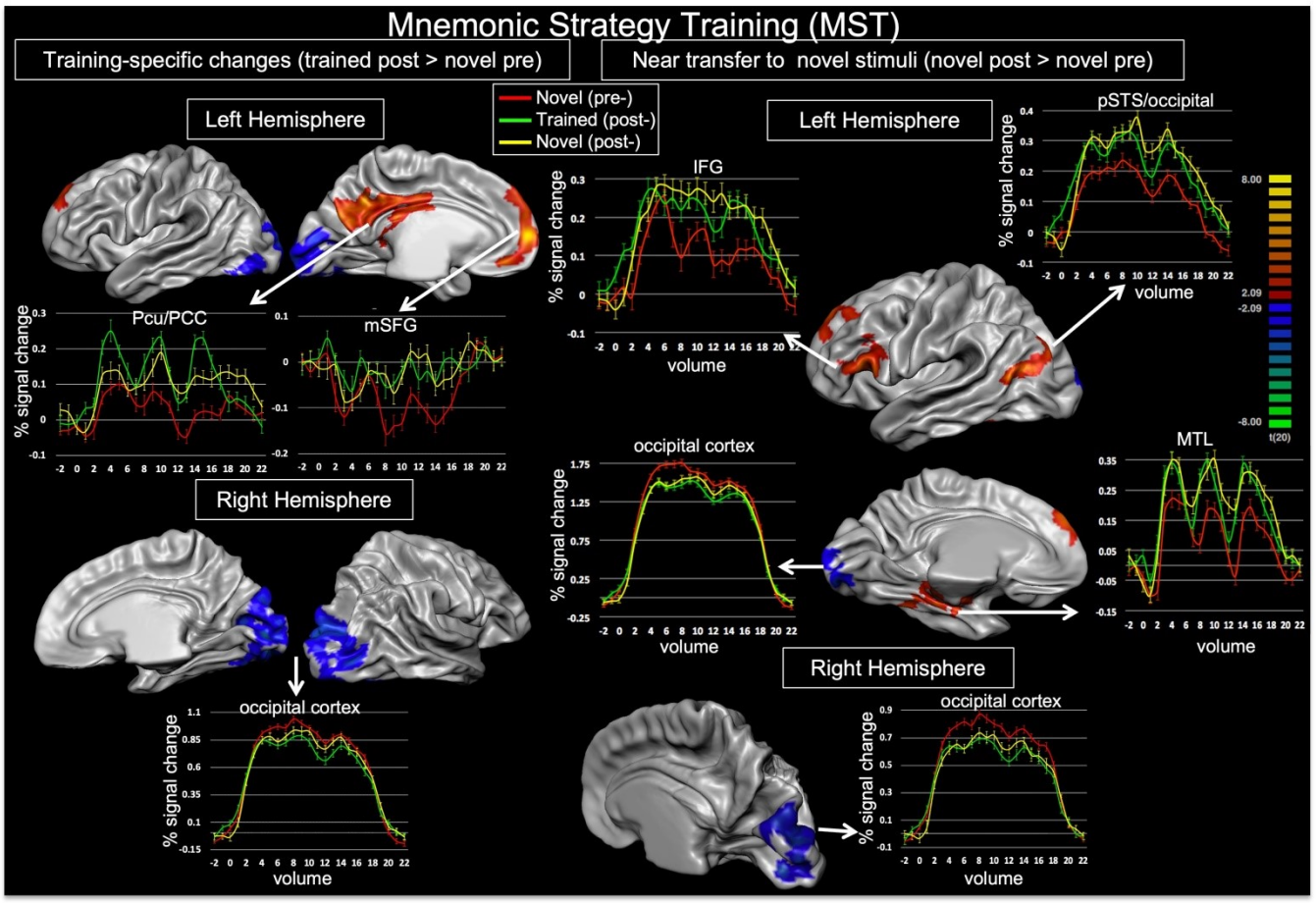


Figure 3. Changes in task-related BOLD signal for the SRT group for the trained stimuli (left) and novel stimuli (right). Time courses are provided for an entire cluster for descriptive purposes. AG = angular gyrus; ITG = inferior temporal gyrus; mSFG = medial superior frontal gyrus; pSTS= posterior superior temporal sulcus. Cooler colors (blue/green) show reduction while warmer colors (orange/yellow) show increased BOLD relative to pre-training.

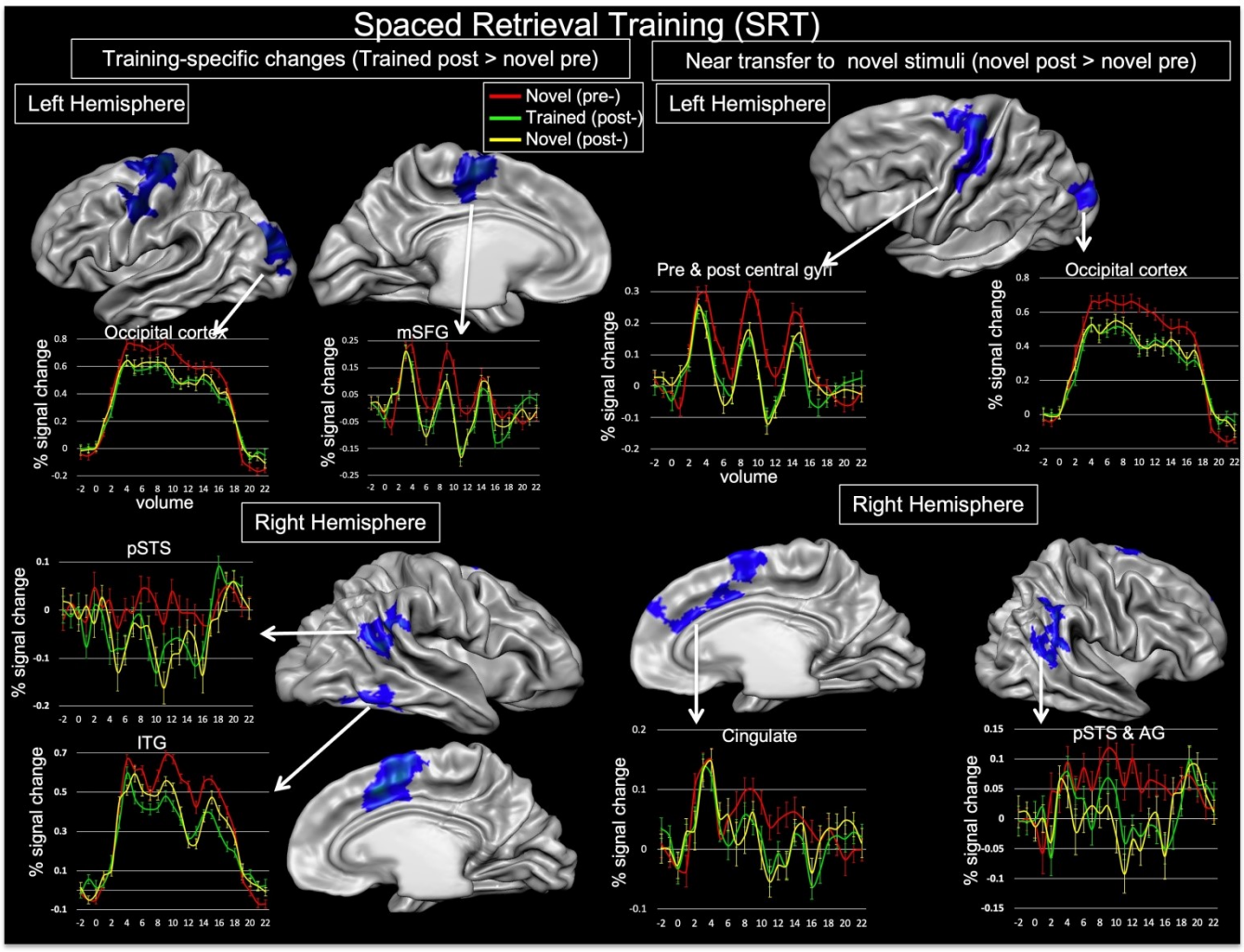


Figure 4. Changes in task-related BOLD signal for the interaction of group and time for the trained stimuli (left) and novel stimuli (right). Time courses are provided for an entire cluster for descriptive purposes. IFG= inferior frontal gyrus; IOS = intraoccipital sulcus; PCC/Pcu = posterior cingulate cortex / precuneus; SFS= superior frontal sulcus; STG = superior temporal gyrus. Warmer colors (orange/yellow) show increased BOLD in MST relavite to SRT for the post- > pre-training contrasts. There were no regions where SRT demonstrated greater activation than MST.

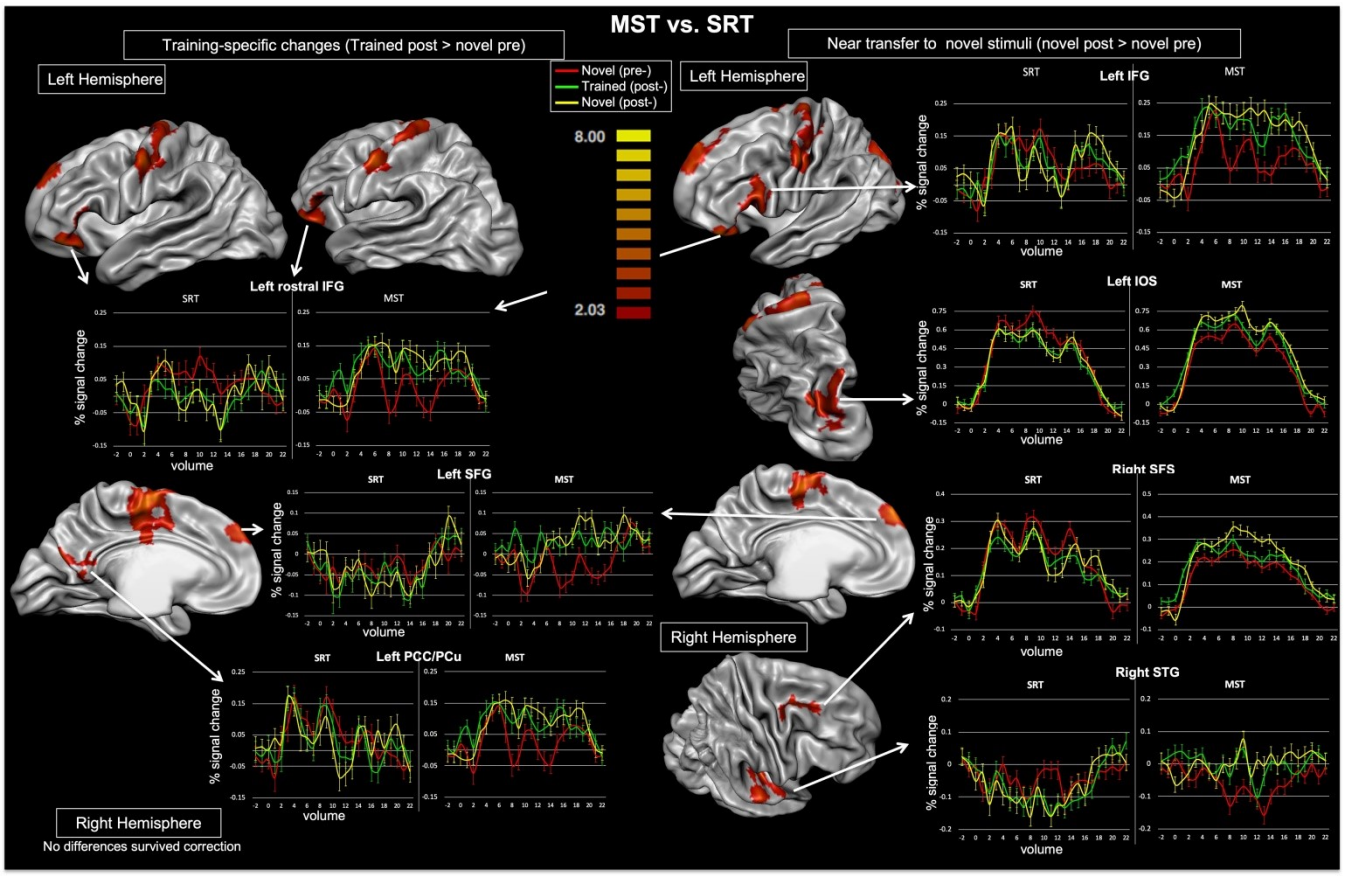
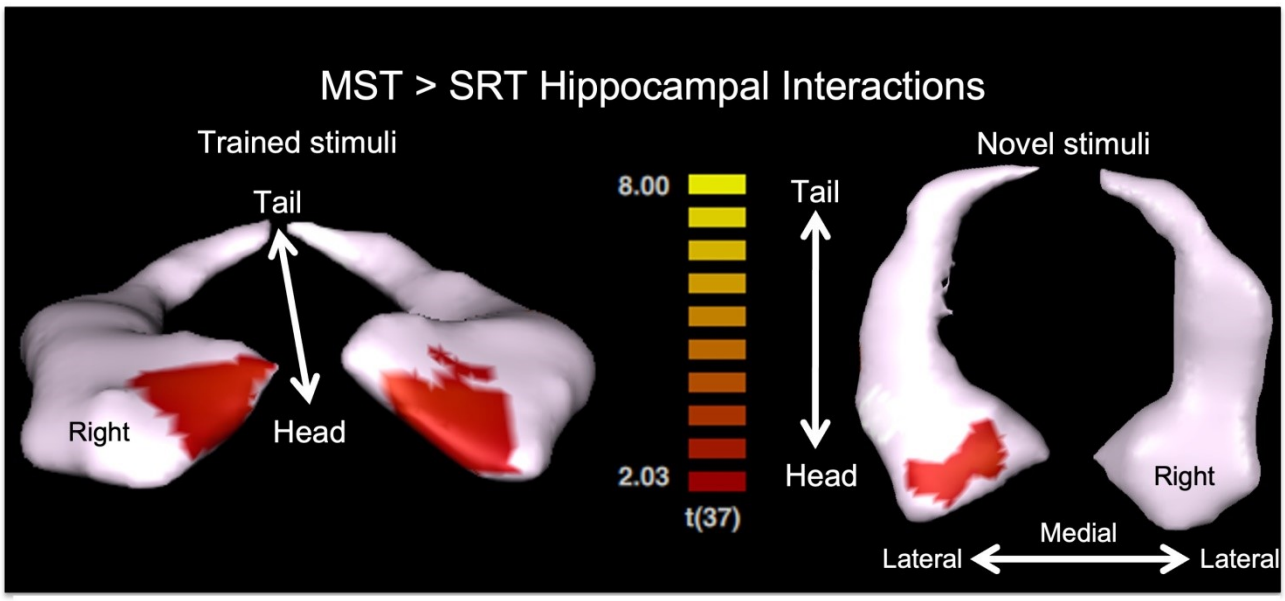
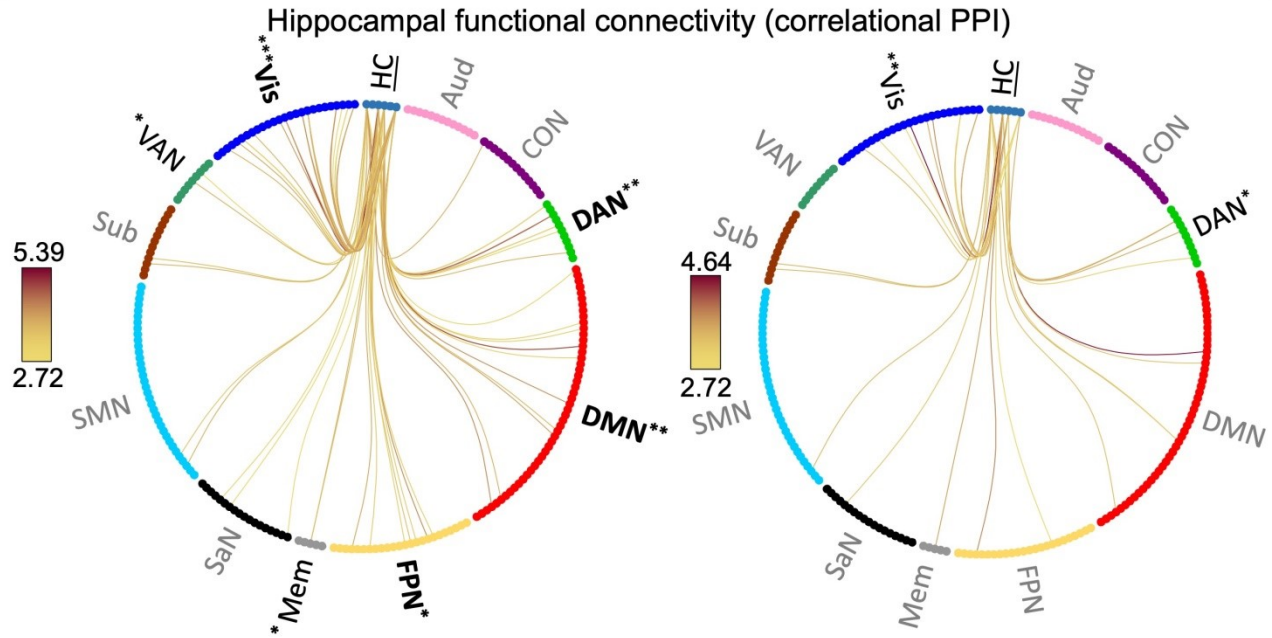


Figure 5. Relative to the SRT group, the MST group showed significantly greater hippocampal activation for both trained and novel stimuli (top row). Additionally, the MST group showed greater hippocampal connectivity change for the trained stimuli, especially with the visual, default mode, frontoparietal, and dorsal attention networks (bottom row). Similar differences were evident for the novel stimuli but only connectivity with the dorsal attention and visual networks survived FDR correction. Network names: Aud=auditory; CON = cingulo-opercular; DAN = dorsal attention network; DMN = default mode network; FPN = frontoparietal network; HC = hippocampus; Mem = memory; SaN = salience network; SMN = somatomotor network; sub = subcortical; VAN = ventral attention.





Research in Context

1. Systematic review: Literature review stemmed from consideration of articles on cognitive training for memory that were identified via multiple search engines (e.g., Web of Science, PubMed).
2. Interpretation: Our findings of greater cognitive improvement, brain activation, and functional connectivity following mnemonic strategy training relative to spaced retrieval training support our central premise that cognitive training techniques differ in their mechanisms of action. Only those trained using mnemonic strategies showed evidence of near-transfer, further reinforcing differences between training techniques.
3. Future directions: The study and implementation of cognitive training techniques should thoroughly consider the associated cognitive mechanisms of action and whether these processes rely on areas affected by, or resilient to, neurologic injury/disease. Future efforts should clarify the conditions under which techniques are

effective and consider a disease stage-specific approach as well as to clarify the impact of such techniques on tasks commonly performed in everyday life.