



Task-dependent Activity and Connectivity Predict Episodic Memory Network-based Responses to Brain Stimulation in Healthy Aging

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ABSTRACT

Background: Transcranial magnetic stimulation (TMS) can affect episodic memory, one of the main cognitive hallmarks of aging, but the mechanisms of action remain unclear.

Objectives: To evaluate the behavioral and functional impact of excitatory TMS in a group of healthy elders.

Methods: We applied a paradigm of repetitive TMS – intermittent theta-burst stimulation – over left inferior frontal gyrus in healthy elders ($n = 24$) and evaluated its impact on the performance of an episodic memory task with two levels of processing and the associated brain activity as captured by a pre and post fMRI scans.

Results: In the post-TMS fMRI we found TMS-related activity increases in left prefrontal and cerebellum-occipital areas specifically during deep encoding but not during shallow encoding or at rest. Furthermore, we found a task-dependent change in connectivity during the encoding task between cerebellum-occipital areas and the TMS-targeted left inferior frontal region. This connectivity change correlated with the TMS effects over brain networks.

Conclusions: The results suggest that the aged brain responds to brain stimulation in a state-dependent manner as engaged by different tasks components and that TMS effect is related to inter-individual connectivity changes measures. These findings reveal fundamental insights into brain network dynamics in aging and the capacity to probe them with combined behavioral and stimulation approaches.

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Introduction

Episodic memory is one of the cognitive domains that is most affected by aging [1], and is accompanied by volumetric changes in brain structures, white and gray matter changes and dopamine receptors depletion [2].

Repetitive transcranial magnetic stimulation (rTMS) is able to modulate cortical excitability and produce cognitive [3] and motor [4] changes. Previously, we observed improvements in a face-name memory task after prefrontal rTMS applied to older subjects which was accompanied by increased recruitment of right prefrontal and bilateral posterior areas [5]. Cognitive improvements after transcranial stimulation have also been shown in mild cognitive impairment and Alzheimer's disease populations [6–8]. However,

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Conflicts of interest: Dr. Pascual-Leone serves on the scientific advisory boards for Nextstim, Neuronix, Starlab Neuroscience, Neuroelectrics, and Neosync; and is listed as an inventor on several issued and pending patents on the real-time integration of transcranial magnetic stimulation (TMS) with electroencephalography (EEG) and magnetic resonance imaging (MRI).

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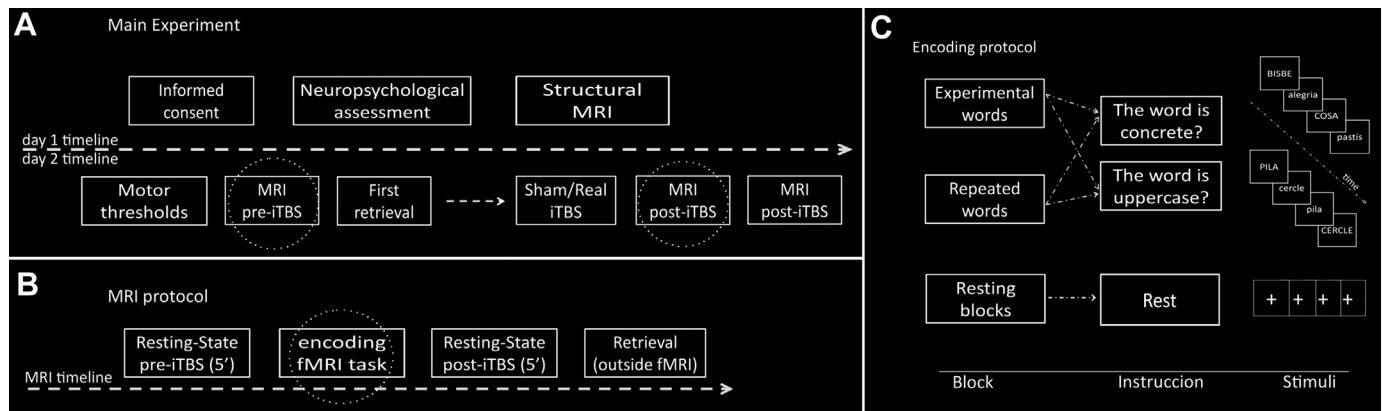


Figure 1. Schematic view of the experiment with A) timeline of the whole experiment, B) the MRI acquisition protocol, and C) the encoding protocol realized inside the MRI. Circled boxes in section A) are detailed in section B); circled boxes in section B) are detailed in section C).

mechanisms underlying cerebral and behavioral responses to rTMS remain unclear.

A mechanism that modulates TMS effects is the state-dependent phenomenon [9–11]. That is, TMS can induce changes revealing the potential to interact with ongoing cognitive processing or physiological states. At a functional level, state-dependency has shown to be related to both, regional activity [11], and connectivity [12–14], therefore representing relevant variables that can help to understand TMS variability, together with other factors such as age [15], genetics [16], technical aspects [17] or anatomical characteristics [18]. Neuroimaging techniques, such as functional magnetic resonance imaging (fMRI), have become a powerful tool to reveal shifts in connectivity and regional activity and it is increasingly being used together with TMS [19,20].

Recently, new patterned protocols of stimulation have emerged from animal studies, such as theta-burst stimulation (TBS) [21]. Applied in an intermittent fashion (iTBS), it enhances cortical excitability, while continuous TBS (cTBS) produces inhibitory post-effects. When applied to prefrontal areas, TBS has been shown to affect various cognitive functions, such as working memory [12,22], speech repetition [23] and emotional control [24].

The left prefrontal cortex (PFC) is a region that has consistently been implicated in the encoding of verbal material. TMS studies have causally shown the involvement of the PFC during episodic memory formation, both in the left dorsolateral prefrontal cortex [25–27] (DLPFC) and left inferior frontal gyrus [28–30] (IFG). Neuroimaging evidence also supports left PFC involvement in semantic encoding, compared to shallower encodings [31–33]. These findings can be contextualized into a classical psychological theory of level of processing (LoP). That is, different LoP at encoding, such as semantic or perceptual analysis of the incoming information, result in differentially durable traces, therefore affecting the probability of a successful retrieval [34,35]. Although there is some evidence of age affecting LoP [36–38], this phenomenon has not been thoroughly investigated in aging. Importantly, it seems that if appropriate support is given during encoding phases (i.e. semantic elaboration), aging effects on memory performance can be minimized [36,39].

In the present study, we applied excitatory TMS (iTBS) in combination with fMRI acquisitions at rest and during an encoding memory task with two levels of processing in a sample of elderly volunteers. The main objectives of the study were: 1) to investigate whether iTBS compared to sham stimulation could result in a transient improvement in memory performance, 2) to study the brain networks that support encoding processes and TMS effects on them and 3) to study state-dependent effects of iTBS.

Material and methods

Subjects

Twenty-four healthy older adults, between 61 and 80 years, were recruited (mean age = 71.75 y.o.; standard deviation [SD] = 6.81). Participants had a normal cognitive profile with MMSE scores ≥24 and performances not below 1.5 SD according to normative scores (adjusted for age, gender and education [40,41]) on a neuropsychological evaluation that covered the major cognitive domains (including verbal memory: Rey auditory verbal learning test; visual memory: Rey-Osterrieth complex figure; language: Benton naming test; semantic and phonetic fluencies; frontal/executive functions: direct and inverse digits, symbol digits modalities test, trail making test, Stroop test, London tower test; visuospatial: line orientation, and visuoperceptive: Poplereuter's embedded figures test). All participants were right-handed and none of them had any neurological or psychiatric disorder or any contraindications for TMS [42]. All subjects gave informed consent and the protocol was approved by local ethical committee. Subjects were randomly assigned to either the sham or experimental group as described below, although neuroimaging analysis was carried out with 10 subjects in the sham group, due to MRI acquisition problems.

Design and procedure

All subjects previously underwent a neuropsychological assessment and a structural MRI acquisition for subsequent TMS neuronavigation. The main part of the study consisted of two MRI acquisitions, before and after subjects received a real or sham iTBS session (Fig. 1A). In each MRI session subjects underwent an episodic memory encoding session in-between two resting-state fMRI acquisitions (Fig. 1B). After a wash-out period (≈ 1 h), subjects received real or sham iTBS and performed an equivalent fMRI encoding session. After each scanning session, subjects performed a memory retrieval task outside the MRI.

MRI acquisition

All subjects were examined on a 3T MRI scanner (Magnetom Trio Tim, Siemens Medical Systems, Germany). A high-resolution 3D structural dataset (T1-weighted magnetization prepared rapid gradient echo [MPRAGE], sagittal plane acquisition, TR = 2300 ms, TE = 2.98 ms, 240 slices, slice thickness = 1 mm, FOV = 256 mm, matrix size = 256 × 256) was acquired before the main

experimental day. fMRI sets of images consisting of 150 and 312 volumes for resting and task runs were also acquired (T2*-weighted GE-EPI sequence, TR = 2000 ms, TE = 16 ms, 40 slices per volume, slice thickness = 3 mm, interslice gap = 25%, FOV = 240 mm, matrix size = 128 × 128).

Memory task

In each MRI session subjects completed a word encoding memory task followed by a recognition test designed with Presentation software (Presentation v10.1 Neurobehavioral Systems). Four block-designed encoding batteries were generated with LEXESP [43], although subjects completed two encoding batteries (words from the non-presented batteries were used as new words during the retrieval). The presentation of batteries and the button response were counterbalanced. Each encoding battery consisted of 8 fixation, 8 novel words and 8 repeated words 24s-blocks, in which 4 words were constantly repeated. In word blocks, 12 words were presented for 2s, half of them in uppercase and the other in lowercase, while in fixation blocks a white cross was presented. Instructions were presented for 2s asking subjects to rest or to answer according to either deep-semantic (concrete/abstract) or shallow-perceptual judgments (uppercase/lowercase; Fig. 1C). Both batteries and within-battery blocks were equivalent according LEXESP normative data. The retrieval memory task started 15 min after the encoding and consisted on a recognition task (old/new decision) in which all the encoded words were presented mixed with new words from a non-presented battery (half new).

Transcranial magnetic stimulation

Magnetic pulses were delivered using a MagPro X100 (Mag-Venture, Denmark) with an eight-figure coil. Resting and active motor threshold (RMT; AMT) were determined for the right first dorsal interosseous (FDI) muscle over the left M1. RMT was acquired according to published protocols [44] while AMT was defined as the minimum stimulus intensity that elicited at least 6 of 10 consecutive MEPs of 200- μ V during FDI contraction.

iTBS was applied according to the protocol described by Huang et al. [21]. Bursts consisted of 3 pulses of 50 Hz at an intensity of 80% AMT, repeated every 200 ms during 2''. These trains were repeated once every 10'' for a total of 20 repetitions (600 pulses - 190''). Based on a fMRI verbal encoding meta-analysis we selected a region (MNI (x,y,z): -42,14,30) in the left IFG as stimulation point [45]. Neuronavigated stimulation with stereotactic registration was used while sham device was employed for sham iTBS. iTBS was applied in a room next to the scanner and immediately after the stimulation, subjects did the second MRI acquisition.

Data analysis

Behavioral data

To examine any possible effect of iTBS on memory recognition, 2*2*2 repeated-measures ANOVA for accuracy was performed, including Group (sham/real iTBS), Time (pre/post stimulation) and Level of Processing (deep/shallow) as independent variables. Accuracy was defined as ([Hits-False Alarms]/ \sum encoding words) and the range of the index was between -1 and 1, where 1 was an optimal encoding.

Sociodemographic and neuropsychological data

Unpaired *t*-tests and Chi-square tests were performed when appropriate both for behavioral and sociodemographic data. Tests were performed using the PASW 18.0 (Statistical Package for Social

Science, USA). When no specified data is presented as mean (SD); error bars represent standard errors of mean.

MRI analyses

MRI analysis was performed using tools from FSL (<http://www.fmrib.ox.ac.uk/fsl/>) and AFNI (<http://afni.nimh.nih.gov/>). Registration of functional images to a 3 mm standard template was performed always immediately before group analyses using a two-step linear registration [46].

fMRI data preprocessing included removal of the first 5 volumes, motion correction, skull stripping, spatial smoothing (full width at half maximum [FWHM] = 6 mm), grand mean scaling and filtering. Task-related dataset was filtered with a high-pass filter of 150'', while resting data were both high-pass and low-pass filtered (0.1 and 0.01 Hz).

Resting-state analyses

From the resting preprocessed dataset, both an independent component (ICA) and an amplitude of low frequency fluctuation (ALFF) analysis were performed to assess any iTBS-related changes produced either in the connectivity of resting-state networks (RSN) or in spontaneous brain activity respectively.

Independent component analysis

A data-driven temporal concatenation ICA approach [47] as implemented in MELODIC followed by a dual-regression algorithm [48] was used to study iTBS effects on RSN connectivity. MELODIC uses probabilistic ICA to decompose 4D data into an estimated number of spatial and temporal components [49,50]. Eight components were selected as reflecting spontaneous brain fluctuation while the remaining ones were considered artifactuals after comparison with existing RSN reported in the literature (Biswal, 2010; Smith, 2009): the anterior default mode network (DMN), the posterior DMN, the cerebellar network, the frontal executive network, the left and right frontoparietal networks, the sensorimotor network and a visual network [51,52].

Selected components were introduced into a dual-regression analysis involving a spatial and a temporal regression for each session. A subtraction between post-iTBS and pre-iTBS was performed to obtain one map reflecting differences between sessions. Maps were registered to a template and entered into a group analysis. Comparisons were made using a voxel-wise nonparametric permutation testing [53] (5000 permutations). Threshold-free cluster enhancement correction [54] was used and maps were thresholded at $P < 0.05$ family-wise error (FWE).

ALFF

An analysis based on the ALFF, thought to be a measure of spontaneous intrinsic brain activity [55], was performed with resting data. Preprocessed datasets [56] were transformed to frequency domain by a fast Fourier transform in order to calculate the power spectrum. ALFF is then computed as the square root of the band-pass filtered power spectrum, and the index arises from the mean amplitude within the frequencies of interest for each voxel. Fractional ALFF [57] (fALFF), was computed by dividing the ALFF index for the sum of amplitude of the entire frequency range (0–0.25 Hz). Both ALFF and fALFF values were Z-standardized and introduced in the same two-step pipeline as that described in the Independent component analysis section.

Task-related fMRI analysis

Functional task-related images were analyzed with FEAT. After the abovementioned preprocessing, a three-level general linear

model (GLM)-based statistical analysis was performed for all the fMRI-task sessions.

For assessing task-related iTBS changes, we modeled the encoding deep (EncD), repeated deep (RepD), encoding shallow (EncS) and repeated shallow (RepS) task blocks as first-level regressors, which were convolved. The regressors, their temporal derivatives and realignment motion parameters were also entered into the GLM for each session [58]. In the second-level fixed-effect analysis, pre-iTBS contrasts of interest resulting from the first-level analysis (Memory Effect [Mem > Rep], LoP [Deep > Shallow] and Interaction [(EncD > RepD)>(EncsS > RepS)]) were subtracted from post-iTBS contrasts for every subject. Finally, a third-level mixed-effect group analysis was performed [59]. This analysis allowed the study of an iTBS state-dependent effect over Memory, Level of processing, and the interaction of Memory*LoP, focused on assessing the rTMS effect over Deep Encoding. As we found iTBS effect over Interaction contrast, the model was re-run to explore the iTBS effect on the EncD > EncS and EncD > RepD first-level contrasts, that is, separating the Interaction contrast into two simpler first-level contrasts to gain further insight in the results.

Additionally baseline, pre-stimulation, patterns of task-related activation were analyzed to investigate the specific BOLD patterns of activation of every task. First-level pre-stimulation contrasts were entered in a matrix and mixed-effects analysis was performed. In both analyses, corrections for multiple comparisons were made at cluster level using Gaussian random field theory ($\text{min } Z > 2.3$; cluster significance $P < 0.05$).

PPI

A post-hoc connectivity analysis was performed to test whether there was a task-dependent change in connectivity between the stimulation coordinates and the regions in which iTBS effect was found. We hypothesized that state-dependent iTBS-induced effects on deep encoding would be related to a task-dependent shift in connectivity in the pre-stimulation encoding. Psychophysiological interaction (PPI) [60] allows the study of regions that differ in connectivity by context or condition. In this regard, applying this technique, we expected increased connectivity between posterior and IFG regions during (pre-stimulation) semantic encoding as well as a correlation of the connectivity shift (PPI measure) with distal rTMS effects. For the PPI, we established five psychological regressors, consisting of the convolved task conditions plus a resting condition spanning all the experimental time [61]. In addition, a physiological BOLD signal regressor from a ROI was created in the stimulated area (5 mm-radius sphere). Finally five PPI variables were created by multiplying a vector of each psychological condition with the physiological regressor. We generated PPI maps by

Table 1

Mean sociodemographic variables (standard deviations), motor threshold intensities and neuropsychological memory test scores (Rey Auditory Verbal Learning Test (RAVLT) and Rey-Osterrieth Complex Figure Test (ROCF) both assessed at 30 min for real and sham iTBS group.

	Real iTBS (n = 12)	Sham iTBS (n = 12)	t/χ (P)
Age	73.00 (6.28)	70.08 (7.15)	1.06 (0.300)
Education	0:5:5:2	0:4:2:6	3.40 (0.183)
Sex	6:6	6:6	0.00 (1.000)
RMT	57.75 (7.45)	53.08 (6.95)	1.59 (0.127)
AMT	52.83 (7.23)	48.80 (6.06)	1.47 (0.156)
RAVLT	7.67 (3.80)	8.08 (3.55)	-0.28 (0.784)
ROCF-30'	17.68 (5.27)	18.18 (3.55)	0.29 (0.776)

Education and Sex had been tested by Chi-square tests while for the other measures unpaired t-tests were used. Education levels are classified as basic:primary:secondary:superior whereas Sex levels are men:woman.

Table 2

Behavioral descriptive results from the recognition test assessed after each MRI encoding session.

	Real iTBS (n = 12)	Sham iTBS (n = 12)
Pre-stimulation retrieval		
Deep accuracy	0.32 (0.19)	0.38 (0.16)
Shallow accuracy	0.10 (0.09)	0.12 (0.11)
Post-stimulation retrieval		
Deep accuracy	0.31 (0.14)	0.32 (0.14)
Shallow accuracy	0.04 (0.09)	0.14 (0.15)

Statistical comparisons are given in the main text.

testing the same contrasts as those mentioned in the task-related GLM analysis using instead the PPI regressors. We created a 5 mm-ROI around the peak activation of the task-related Interaction contrast (MNI (x,y,z): -6,-82,-16) and examined ROI-to-ROI task-dependent change in connectivity. Finally, a correlation between pre-stimulation PPI measures and iTBS posterior changes in BOLD activity was performed to establish a relationship between both measures.

Results

The sham and real iTBS groups did not differ statistically in age, gender, education, motor thresholds or performance on neuropsychological memory tests ($P > 0.05$; Table 1).

Behavioral analysis

Mean memory performance was 0.21 (0.11). The three-way repeated-measures ANOVA to assess effects on retrieval accuracy only revealed main effects of LoP ($F = 143.78, P < 0.001$) being the semantic encoded material more easily recognized than the perceptual one. No main effects of Time nor Group were found ($F = 1.37, P = 0.258$; $F = 1.22, P = 0.281$). Concerning iTBS effects, neither Time*Group ($F = 0.83, P = 0.776$) nor Time*Group*LoP interaction ($F = 3.22, P = 0.087$) effects were found, indicating that iTBS had no impact on the main behavioral memory measures (Table 2; Fig. 2).

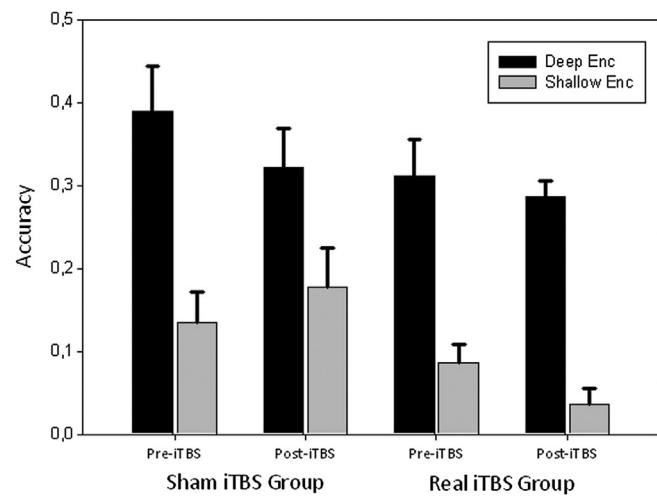


Figure 2. Accuracy in the recognition memory task. Only significant main effect of level of processing was found significant (Deep > Shallow accuracy; $F = 143.780, P < 0.001$). Error bars represent standard error of mean.

Table 3

Baseline task-related activations for the main contrasts investigated and the whole sample of subjects ($N = 22$; see also Fig. 3).

Task	Region	Location (x,y,z)	mm^3	Z-max
Mem > Rep	Cerebellum/OC	14, -98, 0	115,748	5.02 (25.80)
	Cerebellum/OC	-44, 28, -14	21,856	4.97 (7.53)
Rep > Mem	Right AG	36, -68, 38	4596	4.02 (1.66)
	Left PFC/PAC	-55, 22, 0	42,984	5.39 (13.70)
Deep > Shallow	Right cerebellum	34, -78, -40	10,084	4.41 (4.30)
	Left TOC	-60, -52, -2	3940	4.19 (1.62)
(EncD > RepD) >	Left IFG	10, 10, 60	5068	3.58 (1.73)
(EncS > RepS)	SMA/SFG	-52, 16, 18	4264	3.67 (1.40)

OC = occipital cortex; AG = angular gyrus; PFC = prefrontal cortex; PAC = paracingulate cortex; TOC = temporoccipital cortex; IFG = inferior frontal gyrus; SMA = supplementary motor area; SFG = superior frontal gyrus. Z-max = $(-\log_{10}(P))$

Coordinates are referred in MNI coordinates system.

Baseline fMRI task-related analysis

The Memory network (Mem > Rep) included activation of cerebellum, occipital cortex (OC), orbitofrontal cortex and left IFG and deactivation of right angular gyrus. LoP (Deep > Shallow) activation was mostly localized in the left PFC including the IFG, the middle and the superior frontal gyrus (SFG). The paracingulate cortex (PAC) and right cerebellum were also found to be implicated in the network. The Interaction contrast ([EncD > RepD] > [EncS > RepS]); also referred as deep encoding contrast) resulted in activation patterns in the left IFG and the dorsomedial PFC, encompassing the supplementary motor area and the SFG (Table 3; Fig. 3).

Pre- vs. post-iTBS analyses

The following analyses were carried to test iTBS impact over neuronal networks both in task and rest context.

Resting fMRI, ICA and ALFF analysis

In the eight RSN networks extracted from ICA, the FWE-corrected analysis did not reveal any significant clusters that indicated iTBS effects on the functional architecture of the brain. Even at an uncorrected level ($P < 0.001$) no relevant clusters emerged from the analysis. Results of the ALFF analyses did not demonstrate any effect of iTBS on FWE-corrected maps neither at an uncorrected level ($P < 0.001$).

Task-related fMRI analysis

Task-related analysis was initially focused on studying the effect of iTBS on Memory, LoP and Interaction BOLD contrasts. Results from these analyses would indicate a state-dependent effect of iTBS for the specific contrast (i.e. results on memory contrast would reflect a specific effect of iTBS during memory compared to repeated condition). Only in the Interaction contrast a cluster emerged encompassing primary visual areas, lateral OC, ventral occipitotemporal areas and the cerebellum (Table 4, Fig. 4). In other

words, iTBS compared to sham, induced increased activation specifically for deep encoding (LoP*Memory Interaction).

We additionally explored iTBS effect over EncD > RepD and EncD > EncS contrasts to confirm a more specific involvement of EncD condition in the interaction contrast (LoP*Memory) as opposite of an effect related to RepS condition. Congruently, similar clusters emerged in posterior areas for both contrasts. Additionally, the EncD > EncS contrast showed an additional cluster in the left IFG, the area underlying stimulation (Table 4, Fig. 4). These results indicate that iTBS had an effect on brain networks specifically when subjects were performing a deep encoding task, both in local and distal areas that belong to memory encoding network. As we wanted to gain some insight regarding the mechanisms underlying rTMS modulation over posterior areas, we performed a post-hoc connectivity analysis.

PPI – relationship between baseline task-dependent connectivity and iTBS effects

PPI ROI-to-ROI analysis revealed significant changes in connectivity during the pre-iTBS encoding, in a task-dependent fashion ((EncD > RepD) > (EncS > RepS)), between the stimulated region and the region in which maximum effects of iTBS during deep encoding were observed ($t = 2.53$, $P = 0.029$). Hence, coupling between both areas was greater when subjects performed a deep encoding than in the other ‘psychological’ states. To note, during pre-stimulation encoding, posterior ROI was more coupled with left IFG ROI in semantic condition even when no BOLD changes were observed in posterior areas for this specific contrast in the former area (see Fig. 3). Finally, PPI changes were associated with an iTBS effect on the BOLD signal in this posterior ROI ($r = 0.63$, $P = 0.028$) in the active group (Fig. 5), but not in the sham group ($r = -0.22$, $P = 0.551$). In other terms, greater task-dependent shifts in coupling between both areas in the pre-stimulation encoding correlated with greater state-dependent iTBS BOLD modulation in distal areas after stimulation.

Discussion

We applied real or sham iTBS over the left IFG in healthy elders in order to study behavioral and brain functional changes during an episodic memory task. Main conclusions could be summarized as: 1) iTBS did not produce changes in performance in the memory task. 2) Functional brain TMS-induced changes were found specifically when subjects were performing a deep encoding task in local (left IFG) and distal areas (OC and cerebellum). 3) Areas where TMS effects were found belong to memory encoding networks. 4) TMS effects correlated with task-related connectivity shifting measures at pre-iTBS encoding task. Finally, 5) when subjects were at “resting-state” there were no stimulation changes in connectivity or in spontaneous brain activity measures.

iTBS does not produce behavioral changes in memory retrieval

Although behavioral changes were hypothesized in accordance with existing literature, lack of cognitive effect of the stimulation in our study can be explained by a number of factors. First, most of the TMS protocols reporting effects on memory employed on-line protocols [30], while off-line protocols usually involve stimulation over a number of days [3]. Second, elderly people may be more resistant to show behavioral effects. Bihemispheric [5] or contralateral stimulation may be needed in the elderly to induce behavioral effects in accordance with literature on cognitive aging compensation processes [2,62,63]. Third, functional increases in OC and cerebellum may be unrelated to behavioral improvements

Table 4

Brain regions where iTBS effects (Time*Group interaction) were found (see also Fig. 4).

Task	Region	Location (x,y,z)	mm^3	Z-max
((EncD > RepD) > (EncS > RepS))	Cerebellum/OC	-6, -82, -16	15,532	3.87 (5.44)
EncD > RepD	Cerebellum/OC	-20, -82, -16	15,720	3.98 (6.53)
EncD > EncS	Cerebellum/OC	6, -88, -30	22,692	3.84 (8.13)
	Left IFG	-46, 34, 10	6668	3.42 (2.80)

OC = occipital cortex; IFG = inferior frontal gyrus. Z-max = $(-\log_{10}(P))$

Coordinates are referred in MNI coordinates system.

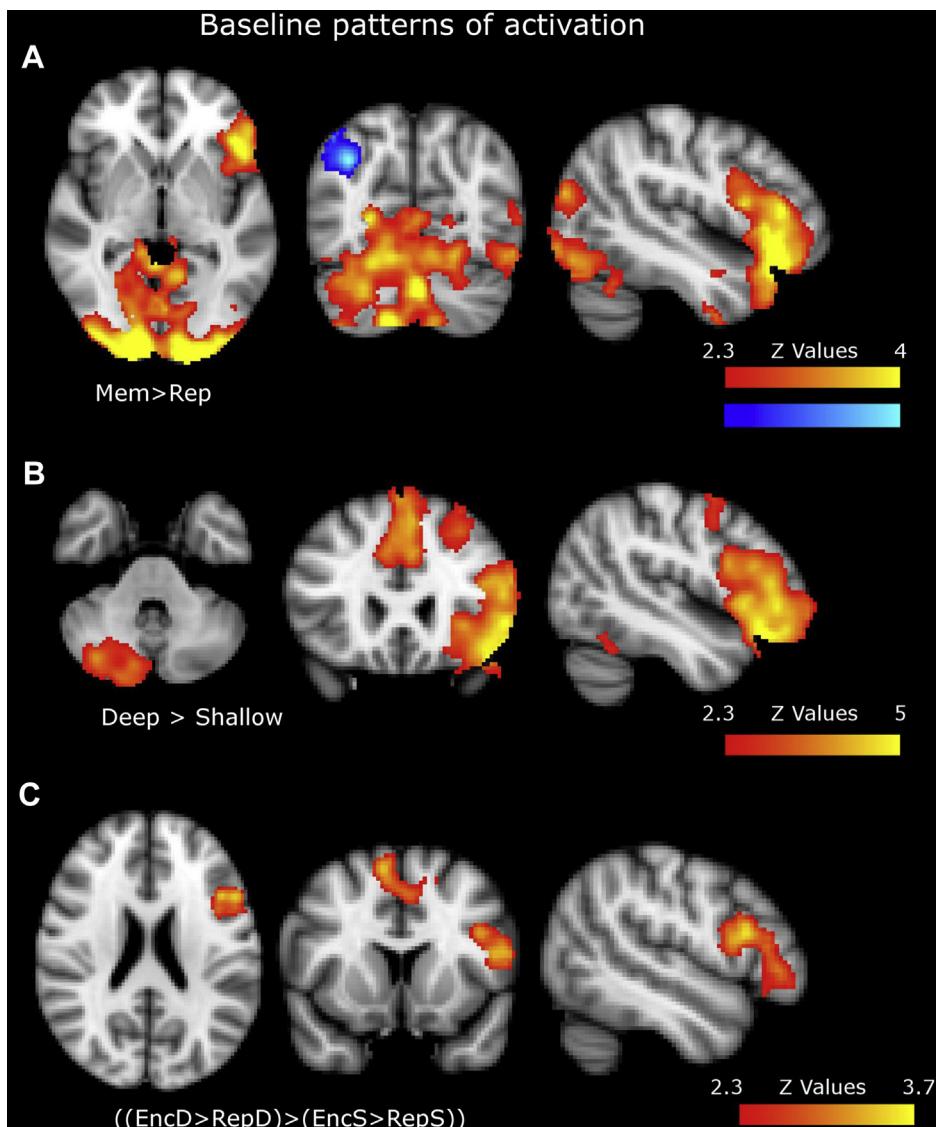


Figure 3. Baseline patterns of activation for A) Memory, B) LoP, and C) Interaction contrast task contrasts (images shown in radiological convention). For precise anatomical localizations, see Table 3.

since magnitude of activation is not fundamental in remembered items, compared to forgotten ones [45,63]. Four, mechanisms modulated by rTMS in the left IFG may be more related to encoding processes that do not strongly influence subsequent retrieval in terms of recognition accuracy [29,30]. Although unexpected, absence of behavioral changes allows us to interpret brain function avoiding complications of interpreting neural changes associated to behavioral modifications [10,64,65].

iTBS did not induce resting-state brain network changes in connectivity or in spontaneous brain activity measures

Our results show that the functional architecture of the brain as measured by resting fMRI was not modified by iTBS in contrast with published literature [66–69]. However, only two previous studies examined TMS effects over large-scale RSN [67,69] both modulating DMN connectivity. As the stimulated area in the present study was not clearly part of DMN or any well-established large-scale RSN, it is possible that effect of stimulation could be quite inconsistent due to subjects variability in its connectivity patterns and, thus, difficult to

assess with group analysis. Other methodological approximations, though, such as graph-theory methods [70], and seed-based analyses [71] could be more sensitive to reveal connectivity changes in such conditions. ALFF analyses also failed to detect TMS effects on spontaneous activity during the resting state. Similarly, other studies that used MRI techniques failed to detect changes of activity at rest after PFC TBS [72], suggesting that TBS may have a greater impact during a task than during resting-state conditions.

iTBS induced specific changes in BOLD signal during deep encoding task in local and distal related areas

Results strongly indicate that iTBS modulated brain network expression in a task-dependent manner. Specifically, we found that stimulation only produced differences in BOLD activity when subjects were performing a semantic encoding task while brain networks remained unaltered when subjects were at rest or doing a perceptual encoding task. Hence, LoP modulated LIFG stimulation effects in a state-dependent fashion similarly to other paradigms in TMS literature [10,73]. This task-dependent effect might be related

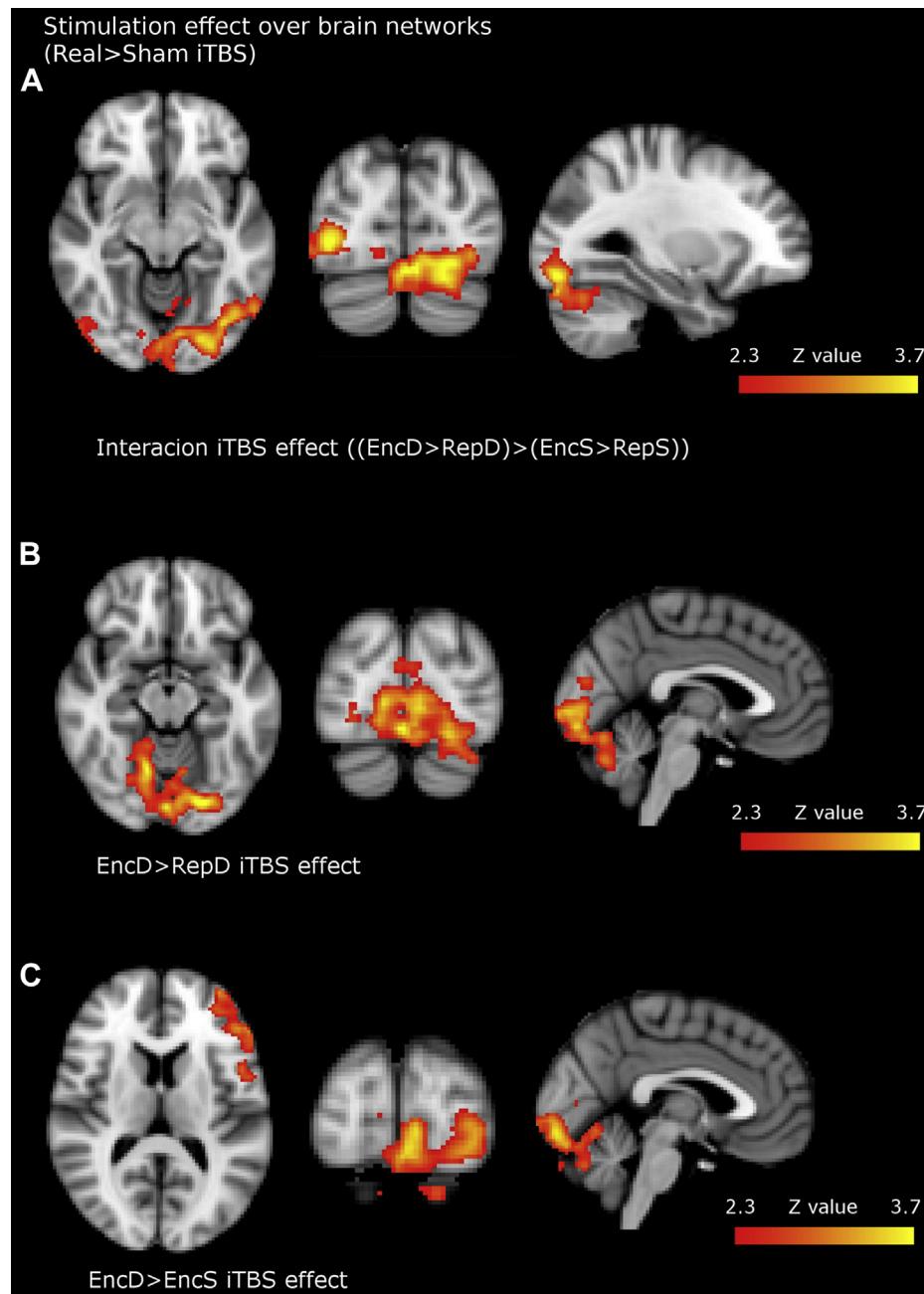


Figure 4. Brain regions where iTBS effects (Time*Group interaction) were found after unpaired two sample *t*-tests. All contrasts showed increased BOLD activity of real compared to sham group. A) Depicts increased activity for Interaction (Memory*LoP) first-level contrast, namely increased activity specifically for deep encoding. B) and C) show increased activity after real iTBS for EncD > RepD and EncD > EncS task contrasts respectively (images shown in radiological convention). For precise anatomical localizations, see Table 4.

to the regional state [31–33] of the targeted area and its functional implication during semantic encoding tasks [10,72–74] and it can be linked with recent TMS findings on the LoP theory [27]. Innocenti et al. found that deep encoding processes were interfered by the application of on-line interfering TMS over left PFC while shallow encoding processes remained unaffected during a memory task. This suggested that left PFC is a node engaged during long-term memory and crucial for semantic processing, and that TMS methods can selectively interact with semantic encoding networks. However the targeted area differed in both studies, being left DLPFC in the previous study and left IFG in ours. It has been proposed that DLPFC may be implicated in executive-monitoring processes [75] while left IFG seems to be specifically involved in

phonological and semantic control [76] and semantic elaboration processes [30].

Our results are in good agreement with a role of semantic control of left IFG, suggesting that this area may selectively exert top-down modulation over posterior areas. rTMS modulations were observed in the ventral visual stream, from primary visual areas to the ventral occipitotemporal cortex (see Fig. 4A), while areas included in the semantic network, such as the anterior temporal lobe [76,77], remained unaffected. Moreover, modulation was observed in relatively unspecific areas, hierarchically located before visual areas that are selectively involved in word and semantic recognition [78,79] such as the visual word form area. However, early visual activity has been shown to be modulated by semantic

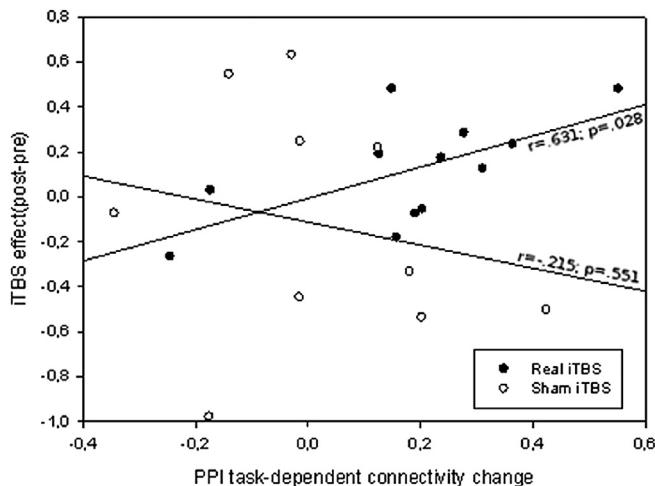


Figure 5. Correlation between PPI task-dependent connectivity changes at baseline and the iTBS-induced effects. PPI values reflect a deep encoding specific increased connectivity (positive values) between stimulated area and a ROI localized in the area where maximum iTBS effects were found. iTBS effect reflects relative change of signal in this area induced by stimulation (arbitrary units). See main text for ROI and contrast definitions.

properties such as non-predictive semantic cues [80], semantic priming paradigms [81], bilingual literacy [82], age of acquisition [83], or shifting in attention to semantic category [84]. Since these areas do not specifically respond to semantic properties of the stimuli, results were generally interpreted as evidences of top-down modulations. Further, EEG studies reported early sensitivity of posterior areas to semantics [85,86] before the widely described N400 event-related potential linked to semantic processing emerges [87]. However, off-line TMS and fMRI does not allow extracting conclusions of such temporal resolution, so we cannot ascertain whether IFG modulation over posterior regions reflects an early attentional shift toward facilitating deep encoding, such as the ones proposed by cuing paradigms or instead it reveals a continuous feed forward network that leads to enhanced recognition during semantic encoding [83]. Involvement of left IFG in encoding during a wide temporal window [29,30,88] in chronometric TMS approaches suggest a continuous involvement of prefrontal areas during semantic processing.

Interindividual changes in network connectivity with increasing task demands at baseline predict iTBS modulation of deep memory encoding networks

Our results showed a correlation of IFG-posterior coupling shifts toward deep encoding condition and task-dependent rTMS modulation. This result strengthens the idea of a semantic-selective top-down modulation of IFG to posterior areas probably through inferior fronto-occipital fascicle [89,90], a bundle that connects both areas. Relevance of connectivity parameters as a factor of variability in rTMS has been observed in several studies [14]. Both, connectivity from targeted region to rTMS distal modulations and brain intrinsic connectivity dynamics have been shown to modulate stimulation responses [10,12,13,91]. In our study, the PPI analyses revealed that the amount of posterior modulation is mediated by individual's subject capacity to shift between psychological contexts. The influence of IFG to posterior areas is not static and fixed but dynamically changes with different task conditions (in our study, depending on semantic and encoding demands) as suggested in other elegant studies that modulated activity in visual processing areas after IFG stimulation [65,92,93] in a content and context

specific manner. PPI analysis does not measure coupling but instead examines connectivity shifts in interaction with different psychological contexts. Although “absolute” connectivity patterns have been usually used in conjunction with rTMS, PPI measures may represent an appropriate approximation when considering task-dependent modulations of TMS. However, more research is needed in order to know whether absolute or relative patterns better predict TMS effect [36,39,94].

Regarding aging, the recruitment of networks were highly constrained by the specific task-demands on each condition which probably eliminated a differential engagement (compared to young subjects) of effective learning strategies which are known to be affected during intentional encoding in aging [36,39]. Experimentally establishing encoding strategies, has shown to minimize memory decrements in aging. Also, age-related functional changes seem to consist on task-related decreased deactivations and over-recruitment of additional areas while role of primary cognitive networks (those engaged in young subjects) usually remains partially preserved. Still, it is not possible to rule-out the possibility that age-related changes over networks are conditioning our results, similarly to other paradigms [26,95]. In the future, a young group and an intentional encoding condition should be considered, as well as stimulation over overrecruited areas, to fully explore the role of left IFG over memory encoding and its subsequent age-related changes. Our results, in conjunction with Innocenti et al. [27], highlight the relevance of combining stimulation within a specific strategy of encoding in order to obtain functional modifications of memory networks. These results have to be seriously taken into account in future studies involving both cognitive and transcranial stimulation. In conclusion, these results highlight the role of the left IFG in semantic encoding, probably by exerting top-down modulation effects, enforce the idea of task-dependency for higher cognitive functions, and emphasize the role of connectivity in order to understand TMS-induced changes.

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