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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.

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 Nexstim, 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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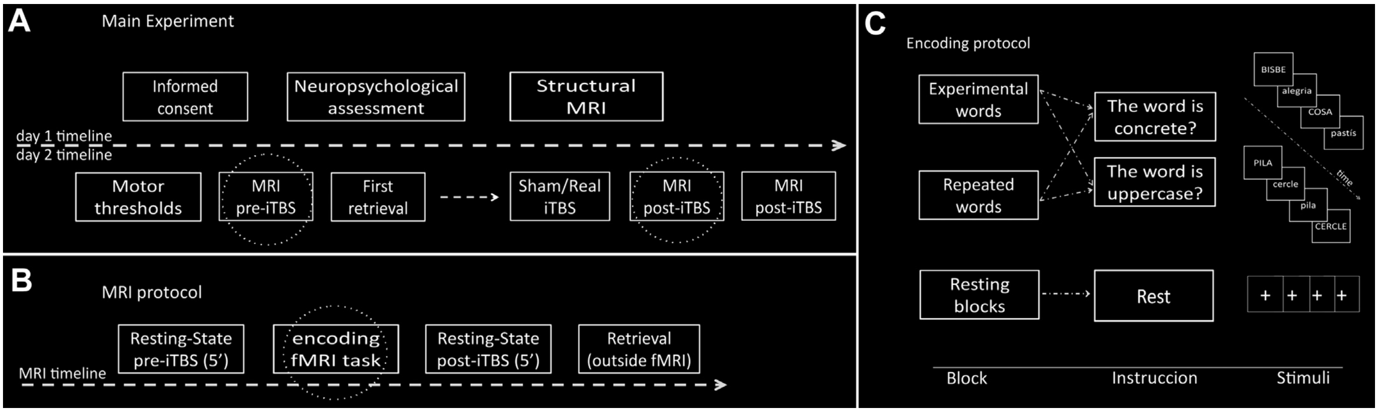

Figure 1. Schematic view of the experiment with A) timeline of the whole experiment, B) the MRI acquisition protocol, and C) the encoding protocol realized inside the MRI. Circled boxes in section A) are detailed in section B); circled boxes in section B) are detailed in section C).

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: Popplereuter'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