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Research report

Successful physiological aging and episodic memory: A brain stimulation study

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ABSTRACT

Functional neuroimaging studies have shown that younger adults tend to asymmetrically recruit specific regions of an hemisphere in an episodic memory task (Hemispheric Encoding Retrieval Asymmetry—HERA model). In older adults, this hemispheric asymmetry is generally reduced as suggested by the Hemispheric Asymmetry Reduction for OLDer Adults—HAROLD-model. Recent works suggest that while low-performing older adults do not show this reduced asymmetry, high-performing older adults counteract age-related neural decline through a plastic reorganization of cerebral networks that results in reduced functional asymmetry. However, the issue of whether high- and low-performing older adults show different degrees of asymmetry and the relevance of this process for counteracting aging have not been clarified.

We used transcranial magnetic stimulation (TMS) to transiently interfere with the function of the dorsolateral prefrontal cortex (DLPFC) during encoding or retrieval of associated and non-associated word pairs. A group of healthy older adults was studied during encoding and retrieval of word pairs. The subjects were divided in two subgroups according to their experimental performance (i.e., high- and low-performing). TMS effects on retrieval differed according to the subject's subgroup. In particular, the predominance of left vs. right DLPFC effects during encoding, predicted by the HERA model, was observed only in low-performing older adults, while the asymmetry reduction predicted by the HAROLD model was selectively shown for the high-performing group. The present data confirm that older adults with higher memory performance show less prefrontal asymmetry as an efficient strategy to counteract age-related memory decline.

1. Introduction

The ability to learn and remember new information declines with physiological aging [17]. In particular, older adults show impairments in episodic memory tasks [46], which involve encoding and retrieval of information concerning previously experienced events. These reductions in cognitive performance probably reflect age-related changes in the brain, which undergoes several structural and functional modifications [8]. Although some people also show pronounced cognitive deficits, others do not. Since demographic aging is proceeding rapidly, an increase in the mean age of the population will increase the number of people that will develop cognitive disabilities related to aging. Therefore, it is extremely important to identify effective interventions to reduce disabilities in older adults. Understanding the basis of minor vs. major age-related cognitive decline is also of great interest.

Several imaging studies have addressed the neural mechanisms underlying this memory decline in vivo. Modifications of prefrontal cortex (PFC) activation in older adults relative to younger adults have been frequently reported during encoding and retrieval of verbal [4,6,17,27,33] and visuo-spatial information [18,19,24]. Importantly, some studies showed that differences in neural activity between older and younger adults depended on the brain region studied [19,45] and that these changes involved both decrease and increase in neural activity. Age-related functional reductions seemed to occur primarily in the left PFC and temporo-occipital regions during encoding, but the right PFC was important for retrieval even if the performance reductions seemed to be more pronounced during encoding [6]. Conversely, increases of activity have also been found in insular regions during encoding and in the left PFC or cuneus/precuneus during retrieval. Based on these age-related changes, an amendment to the Hemispherical Encoding Retrieval Asymmetry (HERA) theory [47] was proposed for older adults. The HERA model predicts that the left PFC specializes in encoding and the right PFC specializes in retrieval. According to its most recent formulation [21], the HERA pattern is not absolute and can be affected by the nature of the presented material as well as memorization strategies, task difficulty, and item familiarity [2,31,38,48]. Functional neuroimaging studies [6] in older adults led to the creation of the Hemispheric Asymmetry Reduction in OLDer

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Adults (HAROLD) model [3]. Although activation of the right PFC during retrieval was less pronounced, a bilateral involvement of the PFC during both encoding and retrieval was found in healthy older adults.

Overall, the significance of these changes is intriguing because they could be caused either by an effective functional compensation strategy or by inadequate/less efficient processing in the contralateral hemisphere.

According to the compensation hypothesis [5], increased functional hemispheric symmetry in older adults could help counteract age-related neurocognitive deficits. Conversely, the dedifferentiation hypothesis explains the reduced asymmetry as a difficulty in recruiting specialized neural networks [26]. To compare these two hypotheses, several studies have investigated whether PFC functional symmetry is linked to reduced or increased performance.

A recent study that divided older adults into two groups (low- and high-performing) showed that preserved left frontal activity and enhanced right frontal activity during encoding was selectively present in high-performing older adults [40]. Furthermore, using a similar method, Cabeza and co-workers [5] provided support for the compensation hypothesis by showing that the right PFC was activated during a source memory task in younger and low-performing older adults, whereas bilateral PFC activation occurred in high-performing older adults. They concluded that high-performing older adults can "respond to the task demand" by recruiting bilateral PFC regions; therefore, reduced lateralization has advantageous effects on performance. Moreover, a PET study examined the correlations between regional cerebral blood flow and subject performance; the results suggested that increases in age-related cerebral activity may reflect the use of inadequate strategies in older adults (with regard to insular regions during encoding) or may signal beneficial compensatory activity (with regard to cuneus/precuneus and left PFC during recall) [4]. More recently, several fMRI studies have investigated the function of age-related cerebral changes, suggesting that bilateral PFC involvement during encoding could serve a compensatory role for age-related declines in medial–temporal functioning [10–12,20]. Altogether, these studies showed that a bilateral recruitment of the PFC during encoding was associated with successful memory performance, indicating that this shift may counteract age-related neurocognitive deficits.

Indeed, functional neuroimaging data cannot prove the necessary role of PFC activation in episodic memory because an activated area may simply be correlated with task performance rather than responsible for it. Repetitive transcranial magnetic stimulation (rTMS) can induce a temporary impairment of the performance only if the stimulated area is causally engaged in the task [32,49]. Based on this assumption, TMS has been used in many different cognitive domains to establish causality in brain-behavior relationships. Hemispheric specializations of the dorsolateral PFC (DLPFC) during episodic memory have been previously demonstrated by rTMS [14,37,41,44]. One study [43] used this technique to investigate the age-related reduction in DLPFC functional asymmetry during encoding and retrieval; the authors found a reduction of functional DLPFC asymmetry during retrieval but not encoding. However, differences in subject performance were not considered in that study, and no conclusions could be drawn about the functional role of the reduced hemispheric asymmetry [43]. Studying younger adults, Sandrini and co-workers [44] tested the influence of the material in the encoding as well as the retrieval of word pairs and found that the encoding of verbal material was disrupted by both right and left DLPFC stimulation. Retrieval, however, was only disrupted by right DLPFC stimulation. This result is in agreement with the "dual-coding theory" in which abstract nouns rely on verbal code representations (i.e., the left hemisphere only) whereas concrete nouns access a second mental image-based processing system (i.e., the right hemisphere). Several studies have shown that the ability to generate and manipulate mental images declines with age [13,23,35]. This decline seems to be mediated by a reduction in the volume of the DLPFC. In line with these data, we speculated that the stimuli used by Sandrini and co-workers [44] would result in a selective involvement of the left DLPFC in older adults (in line with the HERA model) because they can only use verbal code.

We used the same task previously used with younger adults [44] in the present study and aimed to verify DLPFC asymmetry during encoding and retrieval of related as well as unrelated word pairs in a group of healthy older adults. We wanted to examine the differential involvement of DLPFCs in high- and low-performing older adults to verify the validity of the compensation hypothesis. For this purpose, we directly compared TMS of the left and right DLPFCs during both encoding and retrieval in two subgroups of older adults divided according to their performance in a memory task. Based on previous imaging studies [5,7,40], we hypothesized that DLPFC hemispherical symmetry predicted by the HAROLD model would only be present in high-performing older adults, in line with the compensation hypothesis.

2. Materials and methods

2.1. Participants

Thirty-eight healthy, older adults (16 males) between 60 and 81 years old (mean age = 68.6 ± 5.9) took part in the experiment. All of the subjects were right-handed (Handedness Inventory = 96.8 ± 7.1) [1] and native Italian speakers. None of the participants had neurological, psychiatric, or other relevant medical problems, or any contraindication to TMS [42]. All participants gave written informed consent. The protocol was carried out in accordance with ethical standards and was approved by the local Ethical Committee at the IRCCS Centro San Giovanni di Dio – Fatebenefratelli, Brescia.

2.2. Neuropsychological evaluation

A detailed neuropsychological assessment allowed the exclusion of subjects who reported any dysfunction in linguistic, executive, memory, reasoning, attentive or constructional abilities. Neuropsychological testing was administered in a quiet room by an experienced examiner several days before the experimental phase. The examination included a screening test for dementia (mini-mental state examination, MMSE [15]), non-verbal reasoning (Raven Colored Progressive Matrices), verbal fluency (phonemic and semantic), memory (Story recall; Rey-Osterrieth Complex Figure, Recall; Serial Position Curve; Digit Span forward; Spatial Span), constructional and visuo-spatial abilities (Rey-Osterrieth Complex Figure, Copy), and attention and executive functions (Attentive Matrices; Trial-Making Test). All of the tests were administered and scored according to standard procedures [25].

2.3. Materials

A total of 96 pairs of nouns and 96 distracter words were used as stimuli in the experiment. Noun pairs were selected from a wider set of pairs in the PD/DPSS (Psycholinguistic Database/Dipartimento di Psicologia dello. Sviluppo e della Socializzazione-Developmental Psychology Department) psycholinguistics database [36]. The stimuli were then subdivided into two groups of 48 semantically related and 48 semantically unrelated pairs. Items belongings to the three groups (related, unrelated and distracter words) were balanced for word frequency [9], word length (2–4 syllables) and picture imageability scores (mean 5.95). The latter represents the easiness-of-imaging a stimulus word's referent and might influence the retrieval of word pairs associations.

2.4. Procedure

Subjects sat in a dimly lit room facing a computer monitor. The stimuli were presented using SuperLab (www.superlab.com) running on a personal computer with a 17-inch screen. The experiment included an encoding phase and a retrieval phase, and each phase included six experimental blocks.

Each encoding block included 16 words pairs randomly presented at the center of the screen: eight word pairs were semantically related (e.g., banana-monkey) and eight word pairs were unrelated (e.g., sling-shoe). Each pair of words was presented for 2000 ms and was preceded by a fixation point for 1500 ms. After the presentation of the words, a green circle appeared in the middle of the screen as a "go" signal, and each trial was followed, after the subject response, by a blank screen of 7000 or 8000 ms. During the encoding phase, the volunteers were asked to judge whether the two words were semantically related or not. After the presentation of the green circle, they were instructed to press one of the two buttons of a response box to

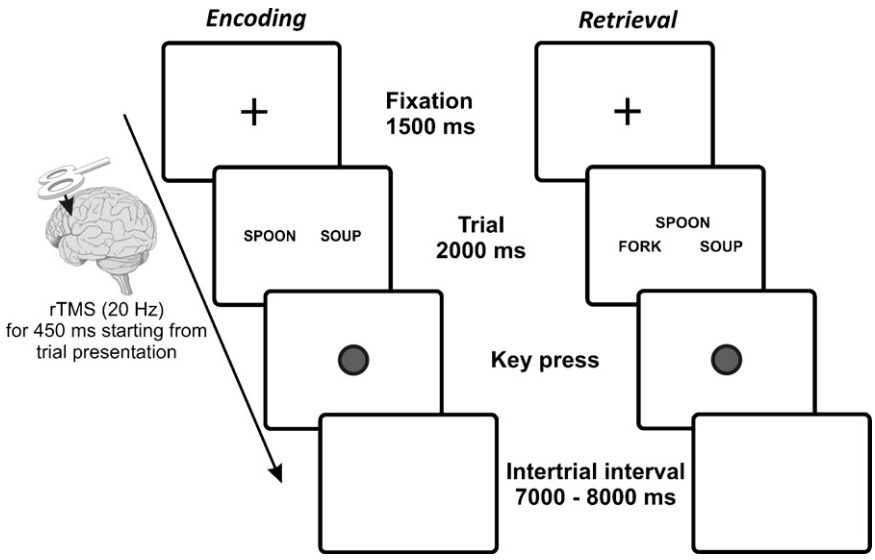

Fig. 1. Schematic representation of the experimental paradigm. Subjects fixated on a small cross at the center of the screen and monitored the appearance of target stimuli consisting of word pairs presented on the monitor for 2000 ms. Trains of rTMS were delivered, 10 pulses at 20 Hz, simultaneously with the word pair presentation to the left or right DLPFC as required. Participants had to identify related or unrelated word pairs in the encoding phase. One hour later, in the retrieval phase, they had to recognize words previously presented (tests) among new stimuli (distracters).

indicate their response. For half of the subjects, the left button was matched with semantically related pairs and the right button was matched with unrelated word pairs; this order was reversed for the other half. The encoding phase was followed by a 10-min delay before the retrieval phase. Critically, each encoding block had a corresponding retrieval block during the retrieval phase, and the order of encoding and retrieval blocks was fixed (i.e., the retrieval block corresponding to the first encoding block was the first retrieval block and so on).

Similar to the encoding blocks, each retrieval block included 16 trials (half of which involved related pairs). In each trial, the first word of each encoding pair was presented in red ink in the middle of the screen, flanked by two other words in black ink on each side. The latter included the target word presented alongside the red ink version in the encoding phase (target) and a novel word (distracter). Participants were instructed to determine which word they had previously seen together with the word in red ink as quickly as possible and respond by pressing the right or the left button accordingly. The position of the correct word was counterbalanced. See Fig. 1 for a summary of the experimental setting.

In both phases, accuracy and reaction times (RTs) were recorded.

2.5. TMS procedure

TMS was applied using a Magstim super rapid magnetic stimulator (50 Hz-biphasic, four boosters) and a figure-of-eight coil (custom double 70 mm; Magstim Company Limited, Whitland, UK). Before the experiment, individual resting motor excitability thresholds of stimulation were determined by stimulating the left motor cortex and inducing a contraction by a single TMS pulse in the contralateral first dorsal interosseous muscle. The threshold was defined as the minimum intensity that induced a visible contraction in the tested muscle, as agreed by two experimenters in at least three out of six trials. The stimulation intensity used during the experiment was set at 90% of each subject's threshold. Accordingly, the mean stimulation intensity was 57.4% (range: 43–75%) of the maximum stimulator output. During the experiment, rTMS was delivered using a ten-pulse train with a frequency of 20 Hz starting at trial onset. For each subject, a total of 640 real pulses were applied, which is within the safety guidelines for rTMS [42].

The stimulation site, Brodmann are a 46, was chosen according to previous studies [29,30,41,43,44] (Talairach coordinates $X = \pm 36$, $Y = 37$ and $Z = 39$). This site was localized on the subject's scalp using the softaxic evolution navigator system (www.emsmedical.net). The softaxic navigator system permits the computation of an estimated volume of MRIs of the subject's head to guide TMS coil positioning. The estimated volumes of MRIs are automatically calculated by a warping procedure using a generic MRI volume (template) based on a set of points digitized from the subject's scalp. The accuracy of this procedure has been evaluated on 28 healthy adults (mean age 35 years) using their own MRIs as a gold standard. In this evaluation, the TMS brain stimulation site was localized using both estimated MRIs and the subject's own MRI while the TMS coil was kept fixed to the subject's scalp. The results indicated a mean error of 2.11 mm with a standard deviation of 2.04 mm, which was lower than TMS spatial resolution. Using this system, we localized the left and right DLPFC of each subject. The subjects wore a close-fitting skullcap on which these positions were reproduced. To stimulate the DLPFC, we placed the junction of the two coil wings above this location. The coil was placed tangential to the scalp with the handle oriented to the midline (i.e., CZ in the electrodes location 10/20 system). To create a sham stimulation (in which no real stimulation reaches the cortex), the 70 mm placebo coil (Magstim Company Limited, Whitland, UK) was used. In the sham condition, the placebo coil was located on the left DLPFC during encoding and the right DLPFC during retrieval.

We combined the stimulation conditions used during encoding with those applied during retrieval so that a block associated with a real stimulation in one phase had no stimulation in the other. Using this rule, we obtained six experimental conditions: R-Enc (right rTMS in encoding, no stimulation in retrieval); L-Enc (left rTMS in encoding, no stimulation in retrieval); R-Ret (no stimulation in encoding and right rTMS in retrieval); L-Ret (no stimulation in encoding and left rTMS in retrieval); sham (left sham rTMS in encoding and right sham rTMS in retrieval) and baseline, which served as a further reference condition and consisted of no stimulation in encoding or retrieval.

3. Results

Out of the 38 subjects, 7 were excluded (6 men) because one or more pathological scores were found during the neuropsychological evaluation, or because they achieved a performance lower than 69% during the control conditions of the experimental task (mean between sham stimulation and baseline). See Table 1 for sample characteristics.

Since there was no significant difference (related: $t = 0.61$, $p > 0.05$; unrelated: $t = -1.37$, $p > 0.05$) between sham and baseline conditions, the performance at baseline was merged with that acquired during sham stimulation to obtain a general experimental performance index. We used a median split method to divide subjects into two groups according to the general performance index: high (HP, $n = 14$) and low (LP, $n = 17$) performers (see Table 1). *T*-tests were conducted to evaluate demographic and neuropsychological differences between the two groups, and no differences were found regarding demographics or cognitive performance ($p > 0.05$). The two groups only differed in their performance of the experimental task (performance index), in which HP participants performed better than LP subjects [HP: $92.0 \pm 5.6\%$, LP: $78.9 \pm 10.1\%$; $t(29) = 7.45$, $p < 0.0001$]. See Table 1 for details.

Following this subdivision, a two (process: encoding or retrieval) by two (stimulated hemisphere: right or left) by two (relatedness: related or unrelated word pairs) by two (groups: HP or LP) repeated-measures ANOVA was conducted for both accuracy and reaction times (RTs).

We did not find any significant differences in RTs.

Table 1
Demographic characteristics, neuropsychological and experimental assessment of the older adult group as a whole and of high- and low-performing groups separately.

Demographic characteristics	All group ($n = 31$)	High-performing ($n = 14$)	Low-performing ($n = 17$)		p (high vs. low-performing)
Age (years)	68.0 ± 5.8	68.3 ± 6.7	67.8 ± 5.1		ns
Education (years)	12.2 ± 3.9	11.7 ± 3.8	12.6 ± 4.0		ns
Gender (female/male)	22/9	13/1	9/8		
Edinburgh Handedness Inventory	96.3 ± 7.6	96.0 ± 8.3	96.5 ± 7.2		ns
Motor Threshold (MT)	64.3 ± 8.1	63.2 ± 6.6	65.1 ± 9.3		ns
Neuropsychological and experimental assessment	All group	High-performing ($n = 14$)	Low-performing ($n = 17$)	Cut-off	p
MMSE	29.1 ± 0.9	29.1 ± 0.8	29.0 ± 1.0	>24	ns
Raven (CPM 0-36)	30.6 ± 3.4	30.4 ± 3.7	30.8 ± 3.1	>17.5	ns
Trail making test A	43.3 ± 11.9	42.6 ± 13.8	44.0 ± 10.4	>93	ns
Trail making test B	99.0 ± 34.7	111.7 ± 35.9	87.2 ± 30.0	<282	ns
Trail making test B−A	62.5 ± 33.1	69.4 ± 27.3	56.1 ± 37.5	<186	ns
Attentional matrices	55.7 ± 3.1	55.1 ± 3.7	56.4 ± 2.4	>30	ns
Rey-Osterrieth Figure, Copy	31.2 ± 2.8	31.5 ± 3.0	31.0 ± 2.6	>28.87	ns
Memory for prose	15.0 ± 3.9	15.9 ± 4.6	14.2 ± 3.2	>7.5	ns
Rey-Osterrieth Figure, Recall	13.1 ± 6.7	11.3 ± 5.5	14.8 ± 7.4	>9.46	ns
Digit Span (forward and backward, WAIS)	10.2 ± 1.2	10.6 ± 1.4	9.9 ± 0.8	>9	ns
Spatial Span	5.4 ± 0.7	5.5 ± 0.9	5.3 ± 0.6	>3.5	ns
Serial curve position					
Primacy	19.7 ± 6.6	20.2 ± 7.3	19.3 ± 6.1	>4.5	ns
Recency	20.1 ± 4.5	21.5 ± 4.4	18.8 ± 4.3	>7.5	ns
First item	5.8 ± 1.9	5.5 ± 1.3	6.1 ± 2.3	>0	ns
Fluency (phonological cue)	37.5 ± 10.4	38.2 ± 12.9	36.9 ± 7.8	>16	ns
Fluency (semantic cue)	44.7 ± 9.1	45.1 ± 11.2	44.4 ± 7.2	>24	ns
Word pairs association retrieval (correctness, %)					
Related pairs, left stimulation during encoding	83.4 ± 4.5	86.6 ± 4.8	80.1 ± 4.4		
Related pairs, right stimulation during encoding	84.0 ± 4.0	89.3 ± 4.1	78.7 ± 3.7		
Related pairs, left stimulation during retrieval	83.3 ± 3.6	85.7 ± 3.8	80.9 ± 3.5		
Related pairs, right stimulation during retrieval	81.1 ± 3.9	82.1 ± 4.1	80.1 ± 3.7		
Related pairs, no stimulation	87.7 ± 3.8	93.8 ± 3.9	81.6 ± 3.8		
Related pairs, sham	89.4 ± 4.0	92.0 ± 4.0	86.8 ± 4.0		
Unrelated pairs, left stimulation during encoding	74.8 ± 4.9	85.7 ± 5.2	64.0 ± 4.6		
Unrelated pairs, right stimulation during encoding	80.5 ± 3.4	83.0 ± 3.6	77.9 ± 3.3		
Unrelated pairs, left stimulation during retrieval	81.4 ± 3.6	81.3 ± 3.8	81.6 ± 3.5		
Unrelated pairs, right stimulation during retrieval	77.1 ± 4.3	77.7 ± 4.5	76.5 ± 4.1		
Unrelated pairs, no stimulation	84.9 ± 4.2	91.1 ± 4.1	78.7 ± 4.2		
Unrelated pairs, sham	79.8 ± 4.3	91.1 ± 4.0	68.5 ± 4.6		
Performance index	85.5 ± 5.8	92.0 ± 5.6	78.9 ± 6.1		<0.0001

p: p-value; ns: not significant.

For accuracy measures, we included in the analysis the percentage of the effect of real rTMS relative to performance without real rTMS. To obtain these indices, the mean between the percentage achieved during sham and baseline conditions was subtracted from the percentage of correct responses in the real stimulation condition and the result was divided by the mean between sham and baseline and then multiplied by 100 [43]. Significant effects were found during the analysis of these data. The interaction between process and hemisphere was significant ($F_{1,29} = 4.15$, $p = 0.05$). Post hoc analyses (LSD Fisher) revealed that the interference caused by left DLPFC stimulation was higher when applied during encoding compared to retrieval ($p = 0.047$). Interestingly, the interaction between process, hemisphere, relatedness and group was marginally significant ($F_{1,29} = 4.01$, $p = 0.054$). Post hoc analyses (LSD Fisher) showed that no differences were present among the HP group, but some effects were present in the LP group. Moreover, the unique significant effects shown by these analyses were only observed with unrelated word pairs. The analysis showed significant differences when comparing right DLPFC stimulation effects with left DLPFC stimulation during encoding ($p = 0.001$). There were also significant differences between left DLPFC stimulation applied during encoding and left DLPFC stimulation applied during retrieval ($p = 0.00008$). No other effects reached statistical significance. These results (summarized in Fig. 2) highlight that a functional asymmetry with a predominance of the left DLPFC was only present in the LP group. Furthermore, this effect selectively applied to encoding.

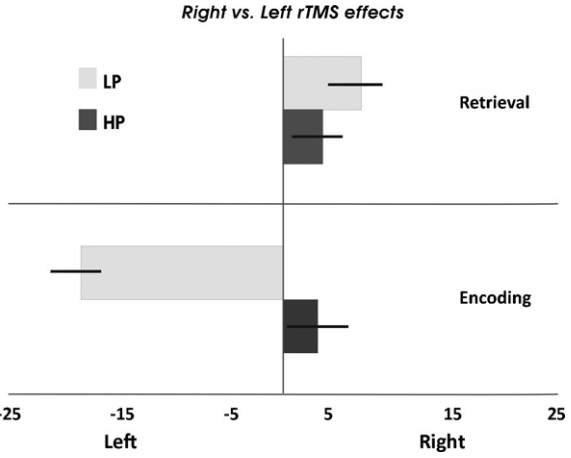

Fig. 2. The effects of differences between left and right DLPFC rTMS on subject accuracy. Accuracy effects are shown as a percentage with respect to unstimulated conditions. Only data obtained by applying rTMS during retrieval and encoding of unrelated word pairs are displayed. Subjects are divided into high- (HP, dark grey) and low-performers (LP, light grey). The distance between the bars and the ordinate axis indicates the difference in the effects of left and right DLPFC stimulation (i.e., a greater distance means a greater difference).

4. Discussion

In our study, we used TMS to establish the relationship between activity in the DLPFCs and the behavior of healthy, high- or low-performing older adults during encoding or retrieval of word pairs.

A previous study that used the present paradigm on younger adults [44] found a bilateral involvement of the DLPFCs during encoding. According to the "dual-coding" theory [34], the authors speculated that because subjects had to encode concrete nouns, they had to use a mixture of verbal as well as non-verbal strategies. The non-verbal strategies would employ an image-based processing system that would include the right DLPFC [29]. Regarding older adults, several studies have shown that the ability to generate and manipulate mental images declines with age [13,23,35], and this decline seems to be mediated by a reduction in the volume of the DLPFC [39]. Furthermore, the decrease of mental image production with age, possibly caused by more general and less specific images, seems to influence final recall [35]. Consequently, we expected to find a selective involvement of the left DLPFC during encoding in older adults (in line with the HERA model) because only verbal code could be used.

Our data showed that the asymmetry between left and right DLPFC during encoding, predicted by the HERA model, was selectively observed in low-performing older adults. The asymmetry reduction predicted by the HAROLD model was observed in high-performing participants during encoding and in both groups during retrieval. To date, only one other study has examined rTMS data from older adults [43]; their results seem to generally agree with the present findings. Rossi et al. [43] proved that there was an age-related reduction of functional DLPFC asymmetry during retrieval but not encoding; however, they did not distinguish between high- and low-performing participants. Nevertheless, in the present work the subject sample was specifically selected and different type of material was used in comparison to Rossi et al. [43], respectively verbal vs. non-verbal, and these differences can explain incongruence's. Moreover it is also possible that, since in Rossi et al. [43] older adults were not divided following their performance, the lack of an asymmetry reduction during encoding could depend on the inclusion of a greater percentage of low-performing participants who continued to show DLPFC asymmetry and who could mask reductions in the asymmetry of other participants.

With regard to encoding data, our results seem to be in agreement with the compensation hypothesis [5], which postulates an increased hemispheric symmetry in older adults that could help counteract age-related cognitive deficits. In fact, our data show that rTMS effects on left and right DLPFC were similar only for HP participants. Indeed, stimulation of the left DLPFC during encoding in the LP group induced a greater interference compared to the right DLPFC stimulation. These results align with the previous fMRI study that evaluated the effects of performance on encoding activation in older adults. This study suggested that successful aging (as in high-performing older adults) would be characterized by preservation of left PFC activation and enhancement of right PFC activation, which would provide compensatory encoding resources [40]. However, this result does not seem to fit the dedifferentiation hypothesis [26]. If reduced lateralization was merely another example of the deleterious effects of aging on the brain, then it should have been found in the LP group of older adults because they display more pronounced age-related cognitive deficits; however, that was not the case. On the contrary, reduced lateralization was found in the group of high-performing individuals, suggesting that this feature might be considered a successful change.

Data on retrieval are not so clear-cut because a reduction of DLPFC asymmetry is present in both HP and LP older adults relative to younger adults. The apparent incongruence between our results and previous imaging data might be explained by the task used. The previous fMRI study that tried to evaluate the significance of the DLPFC asymmetry reduction in retrieval in two groups of older adults (HP and LP) suggested that successful asymmetry reduction was selectively shown by HP subjects in source-memory retrieval [5]. However, the researchers showed that this functional asymmetry difference between HP and LP older adults was detectable in source memory but not in a recall task. Because the recall task of that study was a word pairs recall similar to that used in the present study, the absence of a DLPFC asymmetry in our study does not differ from previous fMRI results. The results of a recall task showed that both HP and LP older adults show a functional DLPFC asymmetry reduction, as suggested by the HAROLD model [3] in comparison to younger adults. Following the compensation hypothesis, all older adults would try to counteract age-related functional brain loss by means of DLPFC asymmetry reduction. Nevertheless, the latter is only one possibility because the lack of difference between the two older-adult groups during retrieval does not allow us to discriminate between the compensation and dedifferentiation hypotheses. As suggested by a previous study [6], increased activation of different brain regions can have different implications, and it seems unlikely that all of these increases represent successful compensation strategies. In particular, Cabeza and co-workers [6] highlighted that age-related retrieval changes linked to PFCs are mainly produced by activity increases whereas encoding changes result from decreased activity. This could be the first possible explanation (alternative to a generalized compensation) for the lack of DLPFC asymmetry differences between HP and LP older adults. The mechanisms that induce hemispheric symmetry are opposite in the two phases, and it is possible that only one of these mechanisms represents a strategy. The useful strategy used exclusively by HP participants could be represented by a "reduction" of left DLPFC activity during encoding, while the higher activity of the left DLPFC that leads to a symmetry during retrieval could be a non-strategic age-related modification observed in both HP and LP older adults. An alternative explanation for the lack of DLPFC asymmetry differences between the two groups concerns the techniques used. To date, this was the first study to use rTMS to investigate "causal" functional DLPFC asymmetry during retrieval in HP and LP older adults. Behavioral effects are only induced by rTMS if the stimulated area is crucially required for the selected task. It is possible that the increased left DLPFC activity observed during retrieval in older adults is a secondary effect rather than evidence for a causal role in retrieval processes.

An interesting point in our sample regards gender differences. An higher concentration of females in the high-performing group and an higher percentage of excluded males participants, due to one or more pathological scores or to a low experimental performance, suggest that women memory performances are higher than men's one. Gender differences have been examined in a variety of cognitive domains and there is emerging evidence for females advantage in a number of cognitive abilities and particularly in episodic memory [22]. Even if all gender differences diminished with advancing age, females continue to show persistent episodic memory advantage [28] and this reports are in line with our data that show an higher percentage of females included in the high-performance sample. Our data are also in line with the general higher longevity that characterized females when compared to males [16].

In summary, LP older adults recruited DLPFCs asymmetrically (left > right) during encoding, whereas HP older adults engaged DLPFC regions bilaterally. Additionally, both HP and LP older adults showed DLPFC symmetry during retrieval, which differs from younger adults. These results suggest that HP older adults counteract age-related neural decline by reorganizing brain functions whereas LP older adults, at least during encoding, recruit a similar network of brain regions as young adults but use them inefficiently.

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