Transcranial brain stimulation studies of episodic memory in young adults, elderly adults and individuals with memory dysfunction: A review

Rosa Manenti [a], Maria Cotelli [a], Ian H. Robertson [b], Carlo Miniussi [a,b,c,*]

[a] Cognitive Neuroscience Section, IRCCS Centro San Giovanni di Dio Fatebenefratelli, Brescia, Italy
[b] Trinity College Institute of Neuroscience and School of Psychology, Trinity College Dublin, Dublin, Ireland
[c] Department of Biomedical Sciences and Biotechnologies, National Institute of Neuroscience, University of Brescia, Brescia, Italy

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ABSTRACT

Transcranial magnetic and electric stimulation studies examining episodic memory in young participants have established the role of the left prefrontal cortex during encoding and the right prefrontal cortex during episodic retrieval. Furthermore, these techniques have been used to verify the reduction in functional asymmetry in the prefrontal cortex that occurs with ageing, at least during encoding, suggesting the existence of compensatory adjustments for the structural and neurotransmitter loss that occurs with physiological ageing. Nevertheless, it has been shown that several factors can modulate performance based on the type of material or strategy used. It is important to note that although numerous studies have addressed the role of the prefrontal cortex in episodic memory, a number of studies have also demonstrated the involvement of a more distributed neural network sustaining this function involving the temporal lobes and parietal cortices. Finally, it is evident that the use of transcranial stimulation techniques might represent a powerful tool not only for investigating the involvement of cerebral areas in a specific cognitive task but also for designing interventional therapies for individuals with memory impairment.

Introduction

Episodic memory, or the ability to remember names, places, specific events, situations and experiences taking place in the course of daily life, is a fundamental form of cognition that creates the history of a human being and guides our present and future behaviour. Specifically, episodic memory is a category of long-term memory that involves the conscious recollection of a unique past event that was personally experienced [1]. Tulving describes episodic memory as a system that "receives and stores information about temporally dated episodes or events and temporal-spatial relations between them" [1]. Precisely defining and understanding the neural basis of episodic memory have proven to be problematic. One of the reasons for this is that to correctly remember information, good encoding and successful retrieval of the information are crucial. The relevance of these two different processes in episodic memory is now well established (see Refs. [2,3]).

Functional neuroimaging studies have repeatedly provided evidence of hemispheric asymmetry in memory encoding and retrieval in healthy young participants, as suggested by the hemispheric encoding-retrieval asymmetry model (HERA) [4]. According to this model, the left prefrontal cortex (PFC) is involved in the encoding of novel events, whereas the right PFC is involved in the retrieval of information from the episodic memory. Although the HERA model was limited to verbal materials in its original proposal, the model was later extended to non-verbal materials by Nyberg and coworkers [2,5]. Nevertheless, the HERA model is not based on clear-cut results, and several studies suggest that the type of material, rather than the nature of the process, accounts for the observed lateralisation (e.g. Refs. [6,7]).

Recently, the use of non-invasive brain stimulation (NIBS) to study memory has gained popularity as a complementary method to functional neuroimaging (for a review see Refs. [8]). By bypassing the correlative approaches of standard imaging techniques, it is possible to establish a causal relationship between brain areas and a specific process of cognition. In fact, functional neuroimaging data cannot demonstrate the necessary role of PFC activation in episodic memory because an activated area may simply be correlated with task performance, rather than being responsible for it. NIBS can induce a temporary modification of performance only if the

stimulated area is causally engaged in the task [9–11]. Analogous to lesion studies, NIBS can provide information about where and when a particular process occurs [10,12]. Based on this assumption, NIBS has been used in many different cognitive domains to establish causality in brain–behaviour relationships. Specifically, NIBS techniques include transcranial magnetic stimulation (TMS) or repetitive TMS (rTMS) and transcranial electric stimulation (tES). Among tES techniques, the most widely used to date is transcranial direct current stimulation (tDCS). TMS and tDCS techniques have the potential to transiently influence behaviour by altering neuronal activity, which may have facilitatory or inhibitory behavioural effects [13]. TMS has been shown to transiently modulate neural excitability in a manner that is dependent on the frequency of stimulation (high vs. low). The mechanism underlying tDCS is a change in neuronal membrane potentials that is dependent on the direction of current flow (anodal vs. cathodal). Nevertheless, the final effects induced by TMS or tDCS depend on the technical parameters used during stimulation, such as the intensity of stimulation, coil orientation, site of the reference electrode and time of application as well as the possible interactions between these factors and the physiological and cognitive state of the subject [14–16]. An example of the complexity of the approach can be found in the effects of TMS on priming. Priming is a form of implicit memory that is accompanied by reductions in neural activity when an experience is repeated. Combining imaging and rTMS, Thiel and collaborators [17] and Wig et al. [18] highlighted that the left inferior frontal gyrus in not only involved in word processing, but is also essential for repetition priming since the facilitation linked to repeated words was abolished (interference) when rTMS was applied over this area. Another form of priming is perceptual priming that is induced by the presentation of visual stimuli (prime) that can improve the probability of detecting a subsequent stimulus (probe) with similar features. Campana and coworkers [19] showed the TMS applied over the extrastriate motion area V5/MT, during the interval between prime and probe, can abolish perceptual priming. A similar negative effect was found on spatial priming by O'Shea et al. [20] stimulating the left but not right frontal eye fields, highlighting the functional specialization of left frontal eye fields for priming (see also [21]). In all these experiments TMS interfered with priming effects in a specific way depending on the type of task and stimulated site. Nevertheless, it has been showed that TMS can actually prime the system and induce a facilitation in the task execution (e.g. [22]). Abrahamyan and colleagues [22] applied TMS at different intensities over V1 to concurrently measure the threshold for plaid detection. It was found that, at intensities below the phosphene threshold (weak signal), TMS significantly improved the performance when compared with the control condition, while higher TMS intensity (above the phosphene threshold) increases visual threshold [22]. Therefore, brain stimulation can interfere with priming or may prime the system itself, by modulating the cortical excitability or the threshold response. In this context the task instructions, timing and eventually intensity of stimulation are fundamental aspects for the final effect.

NIBS and episodic memory in healthy young participants

Several studies have used rTMS to investigate the role of the dorsolateral PFC (DLPFC) in the encoding and retrieval of information (see Table 1). It has been established that episodic encoding of verbal [23–26] or verbalisable [27] material critically depends on the left or bilateral [28] PFC, whereas encoding of non-verbalisable material [29] depends on the right PFC.

A relevant issue in the study of episodic encoding is the type of encoding required by an experimental task. In this vein, a recent study by Innocenti and coworkers [30] investigated whether deep and shallow encoding share the same cortical networks and how these networks contribute to the level of the processing effect. To investigate the brain areas involved in this phenomenon, the authors applied rTMS during two kinds of encoding: deep (semantic) and shallow (perceptual) encoding of words. The results indicated that only rTMS applied to the left DLPFC abolished the beneficial effect of deep encoding, both in terms of accuracy and reaction times. This finding highlights the specific role of the left DLPFC and suggests that it represents a crucial node responsible for the improved memory performance induced by semantic processing [30].

However, other studies have evaluated the role of the DLPFC in the retrieval phase [24,27,28] and have reported involvement of the right DLPFC related to verbal or verbalisable stimuli. In particular, Sandrini and coworkers [28] addressed the role of the DLPFC with respect to semantically related or unrelated word pairs to assess the effect of stimulus novelty on the same experimental paradigm (see also Ref. [31]). Importantly, involvement of the DLPFC was shown only for unrelated word pairs, suggesting that the DLPFC would be engaged for encoding and retrieval only during the elaboration of novel material [28,31]. Overall, these results strongly indicate that the nature of the material to be remembered interacts to a great extent with the encoding-retrieval DLPFC asymmetry and that the role of the DLPFC is mainly evident in the processing of novel stimuli. Similarly, other variables, such as individual strategies, seem to influence DLPFC asymmetry during retrieval. In particular, recent imaging studies have emphasised the role of memory strategies in influencing cerebral activity during episodic retrieval [32,33]. Because the DLPFC constitutes a specialised region involved in monitoring of self-ordered and externally ordered responses [34,35], these regions would be more engaged related to paradigms that require retrieval strategies. A recent rTMS study investigated the effect of episodic memory strategies on DLPFC asymmetry during the retrieval of novel face-name pairs [36]. At the end of the experimental task, the authors asked the participants to report their use of memory strategies to encode and retrieve the pairs. Accordingly, the subjects were subdivided into two groups: strategy users (SU) and no-strategy users (NSU). The results showed that the difference in the use of memory strategies resulted in different rTMS-induced interference effects: the SU group showed a selective interference effect after right DLPFC stimulation, while the NSU group showed a reduced performance after left DLPFC stimulation. Importantly, the overall performance of these two groups was comparable. These researchers suggest that during memory retrieval, the left DLPFC might be recruited when the subject does not deliberately apply a retrieval strategy, whereas there is a shift to the right DLPFC if cognitive control processes engaged by strategies are needed to guide episodic retrieval [36].

It is important to note that, despite numerous studies that have investigated the role of the DLPFC in episodic memory, neuroimaging studies have clearly demonstrated the involvement of a more distributed neural network sustaining this function. This memory network includes the DLPFCs, the medial-temporal lobes, the parietal cortices (PARCs) and the precuneus [3,6,37–40]. The first rTMS study to investigate the role of the parietal cortices in the encoding and retrieval of visual scenes [41] concluded that the activity of the intraparietal sulci, as shown in several functional neuroimaging studies on memory, was not causally engaged in memory encoding and the retrieval of visual scenes. In a recent study, Manenti and colleagues [24] investigated the role of the DLPFC and the PARC in young participants through combining rTMS and fMRI during a word encoding and retrieval task. These researchers introduced a single-subject analysis that was able to directly correlate fMRI activation and rTMS effects on an individual basis to deeply investigate the role of these two activated

Table 1
Brain stimulation in healthy young individuals.

Study	Number of Participants	Stimulation technique	Target area	Stimulated cognitive process	Outcome	Results
repetitive Transcranial Magnetic Stimulation (rTMS)						
[27]	13	High-frequency rTMS	Right or left DLPFC	Encoding or retrieval of pictures	Picture retrieval	Encoding: ↓ picture retrieval after left DLPFC stimulation Retrieval: ↓ picture retrieval after right DLPFC stimulation
[29]	10	High-frequency rTMS	Right or left DLPFC	Encoding of pictographs and unfamiliar patterns	Association retrieval	↓ association retrieval after right DLPFC stimulation
[23]	16	High-frequency or low-frequency rTMS	Right or left DLPFC	Working or logical memory, verbal fluency	Working verbal memory, logical memory, phonetic verbal fluency	High-frequency rTMS over left DLPFC: ↓ logical memory
[28]	12	High-frequency rTMS	Right or left DLPFC	Encoding or retrieval of word pairs	Word-pair retrieval	Encoding: ↓ word-pair retrieval during left and right DLPFC Retrieval: ↓ word-pair retrieval during right DLPFC
[26]	15	High-frequency rTMS	Right or left PFC	Encoding of words and abstract shapes	Retrieval of words and abstract shapes	↓ word retrieval after left DLPFC stimulation ↓ shape retrieval after left DLPFC stimulation
[25]	12	High-frequency rTMS	Right or left lPFC and left parietal cortex	Encoding of words	Word recognition	↑ word recognition after left lPFC stimulation
[41]	42	High-frequency rTMS	Right or left DLPFC, right or left parietal cortex	Encoding or retrieval of pictures	Picture retrieval	Encoding: ↓ picture retrieval after left DLPFC stimulation Retrieval: ↓ picture retrieval after right DLPFC stimulation
[30]	18	High-frequency rTMS	Right or left DLPFC	Deep or shallow encoding of words	Retrieval of words	No benefits of deep encoding after left DLPFC stimulation
[36]	14	High-frequency rTMS	Right or left DLPFC	Retrieval of face-name associations	Retrieval of face-name associations	↓ associations retrieval after right DLPFC in strategy users and after left DLPFC in no-strategy users
[24]	11	High-frequency rTMS	Right or left DLPFC, right or left parietal cortex	Encoding or retrieval of words	Words retrieval	Retrieval: ↓ words retrieval after right DLPFC, right and left DLPFC stimulation
transcranial Direct Current Stimulation (tDCS)						
[44]	30	Left atDCS and right ctDCS or left atDCS	Anterior temporal lobe	False memory task	Number of false memories, veridical memories	↓ false memories during left atDCS and right ctDCS and during left atDCS compared with the placebo
[47]	36 (12, 12, 12)	Right atDCS and left ctDCS or left atDCS and right ctDCS	Anterior temporal lobes	Encoding and retrieval of pictures	Pictures recognition	Right atDCS and left ctDCS: ↑ pictures recognition
[42]	20	atDCS, ctDCS	Right or left DLPFC	Auditory word encoding	Word retrieval	Left ctDCS: ↓ short-term word retrieval
[43]	19	atDCS, ctDCS	Left PFC	Associative verbal learning	Learning speed, learning success	Left atDCS: ↑ learning speed and success
[45]	32	atDCS, ctDCS	Left DLPFC	Encoding or recognition of words	Word recognition	Encoding: ↑ word retrieval after atDCS, ↓ word retrieval after ctDCS Retrieval: ↑ (trend) word retrieval after atDCS, ↓ word retrieval after ctDCS
[46]	12	Right atDCS and left ctDCS or left atDCS and right ctDCS	Fronto-temporal areas	Encoding of pleasant or unpleasant figures	Pleasant and unpleasant figures retrieval	Right atDCS and left ctDCS: ↑ pleasant figures recall Left atDCS and right ctDCS: ↑ unpleasant figures recall

DLPFC = Dorsolateral Prefrontal Cortex; lPFC = Inferior Prefrontal Cortex; PFC = Prefrontal Cortex; rTMS = repetitive Transcranial Magnetic Stimulation; atDCS = anodal transcranial Direct Current Stimulation; ctDCS = cathodal transcranial Direct Current Stimulation; ↑ = improvement; ↓ = worsening.

loci (i.e. the DLPFC and the PARC) during both encoding and retrieval. This method showed not only the usual crucial involvement of the right DLPFC but also the involvement of the bilateral PARC during word retrieval, demonstrating that an fMRI-guided rTMS approach could represent a more powerful tool to investigate the neural underpinnings of cognitive functions more precisely [24].

In the last several years, the role of the different cortical areas involved in episodic encoding and retrieval has been investigated in studies using tDCS (see Table 1). Most of these studies have focused on the cerebral areas involved during the encoding of verbal

material. Elmer and colleagues [42] studied the effects of anodal or cathodal tDCS over the left and right DLPFC during the encoding of words. The authors concluded that only cathodal stimulation of the left DLPFC, among all of the tested conditions, resulted in decreased subsequent retrieval accuracy. These data confirmed the selective role of the left DLPFC during word encoding that was previously hypothesised based on rTMS studies. Floel and coworkers [43] investigated the relevance of the left PFC during an associative verbal learning task. These authors applied anodal or cathodal tDCS over the posterior part of the left peri-sylvian area and compared the effects of this treatment with sham stimulation. A significant

Table 2
Brain stimulation in healthy elderly individuals.

Study	Participants	Stimulation technique	Target area	Stimulated cognitive process	Outcome	Results
repetitive Transcranial Magnetic Stimulation (rTMS)						
[57]	37 young adults, 29 elderly adults	High-frequency rTMS during encoding or retrieval of pictures	Right or left DLPFC	Encoding or retrieval of pictures	Picture retrieval	**Young Adults** Encoding: ↓ picture retrieval, left more than right DLPFC Retrieval: ↓ picture retrieval, right more than left DLPFC **Elderly Adults** Encoding: ↓ picture retrieval, left more than right DLPFC Retrieval: ↓ picture retrieval, right same as left DLPFC
[64]	38 elderly adults	High-frequency rTMS during encoding or retrieval of word pairs	Right or left DLPFC	Encoding or retrieval of word pairs	Word-pair retrieval	**Low-performing (N = 14)** Encoding: ↓ word-pair retrieval, left more than right DLPFC Retrieval: ↓ word-pair retrieval, right same as left DLPFC **High-performing (N = 17)** Encoding: ↓ word-pair retrieval, right same as left DLPFC Retrieval: ↓ word-pair retrieval, right same as left DLPFC

RC = Randomised Controlled Study; DLPFC = Dorsolateral Prefrontal Cortex; rTMS = repetitive Transcranial Magnetic Stimulation; ↑ = improvement; ↓ = worsening.

improvement in associative learning performance was found only after anodal tDCS. A subsequent study compared three conditions during a false word memory task: bilateral stimulation [anode over the left anterior temporal lobe (ATL) and cathode over the right ATL], unilateral stimulation (anode over the left ATL) and sham stimulation [44]. The data showed that there was a reduction in false memories following both the uni- and bi-lateral stimulation treatments compared with the sham stimulation, which suggests a role of the left ATLs during verbal learning [44].

Only one study has evaluated the role of the DLPFC in verbal retrieval using tDCS. Consistent with previous data on verbal encoding, a recent study [45] administered anodal or cathodal tDCS over the left DLPFC (compared with the sham stimulation and stimulation of the motor cortex) during the encoding or recognition of words. With respect to encoding, the data show that only anodal stimulation over the left DLPFC improved memory, whereas cathodal stimulation of the same area resulted in memory impairment. Regarding recognition, cathodal stimulation of the left DLPFC impaired recognition, while anodal stimulation was associated with a trend towards improving recognition. These data essentially support the role of the left DLPFC during both the encoding and retrieval of words, emphasising the importance of the material used in the task.

Considering non-verbal stimuli, a recent study investigated the effects of bilateral tDCS (left cathodal and right anodal or left anodal and right cathodal or sham) over fronto-temporal cortical areas during the encoding of images characterised by different levels of affective arousal and valence [46]. The results indicated that left cathodal and right anodal stimulation facilitated the recall of pleasant images, whereas the opposite pattern of stimulation facilitated the recall of unpleasant images. The authors noted that these data support the specific-valence hypothesis of emotional processes, which assumes that there is specialisation of the right hemisphere in processing unpleasant stimuli and of the left hemisphere in processing pleasant stimuli. Moreover, the data suggest a relevant role of fronto-temporal areas during the encoding of images [46].

Chi and coworkers [47] investigated the cerebral areas involved in memory related to visual stimuli. The authors applied bilateral tDCS (left cathodal and right anodal, left anodal and right cathodal, or sham) to the ATLs in three groups of participants during the encoding and subsequent retrieval of a set of pictures. The data showed that there was a selective improvement of visual memory during left cathodal and right anodal stimulation, indicating the critical role of the temporal lobes during this task [47].

Nevertheless, it is important to note that because in this last study, tDCS was applied during both encoding and retrieval, a clear-cut conclusion regarding the timing of the induced effect (i.e. during encoding or during retrieval) could not be made.

NIBS and episodic memory in healthy elderly participants

Only two studies have used rTMS to study changes in episodic memory due to normal physiological ageing (see Table 2). No study has yet been published examining episodic memory in ageing using tDCS. We know that the ability to learn and remember new information declines with physiological ageing [48]. This reduction in cognitive performance probably reflects age-related changes in the brain, which undergoes a number of structural and functional modifications [49].

Several neuroimaging studies have addressed the neural mechanisms underlying episodic memory declines in vivo. Modifications of PFC activation in older adults relative to younger adults have been frequently reported during the encoding and retrieval of verbal [48,50–53] and visuo-spatial information [7,54,55]. Age-related functional declines occur primarily in the left PFC and temporo-occipital regions during encoding, whereas increases in activity have been observed in insular regions during encoding and in the left PFC or cuneus/precuneus during retrieval [51]. Based on these age-related changes, an amendment to the HERA theory [4] was proposed for older adults, as healthy older adults exhibited bilateral involvement of the PFC during both encoding and retrieval. These data have been summarised in the hemispheric asymmetry reduction in older adults (HAROLD) model [50,56].

Based on imaging data, rTMS was applied in a group of healthy elderly individuals to verify the HAROLD model by Rossi and colleagues [57]. These researchers investigated the role of the left and right DLPFC during the encoding and retrieval of complex figures using the same paradigm that demonstrated the role of the left DLPFC during encoding and the right DLPFC during retrieval in young participants [27]. The authors found a reduction in functional DLPFC asymmetry during retrieval, but not encoding, thus supporting the HAROLD model, at least for episodic retrieval processes [57].

A relevant issue when studying episodic memory changes during healthy ageing is that decreased performance is not evident in every participant. Although some individuals show pronounced cognitive deficits, others do not. Therefore, it is important to identify whether there is a relationship between subject performance and the structures engaged during episodic memory tasks. Moreover,

understanding the neural basis of minor vs. major age-related cognitive declines is of great interest, as demographic ageing is proceeding rapidly. An increase in the mean age of the population will increase the number of people who will develop age-related cognitive disabilities. Identifying changes/alterations in brain activity might help to guide effective interventions aimed at reducing memory disabilities in older adults.

Overall, the significance of the functional changes revealed by researchers using imaging and rTMS is intriguing because these changes could be caused either by an effective functional compensation strategy or by inadequate or less efficient processing in the contralateral hemisphere. According to the compensation hypothesis [58], increased functional hemispheric symmetry in older adults could help counteract age-related neurocognitive deficits. Conversely, the de-differentiation hypothesis explains the reduced asymmetry as a difficulty in recruiting specialised neural networks [59]. To compare these two hypotheses, imaging studies have investigated whether PFC functional symmetry is linked to reduced or increased performance, suggesting that bilateral PFC involvement during encoding could play a compensatory role with respect to age-related declines in medial-temporal functioning [60–63]. Based on these imaging studies, rTMS can be a powerful tool to demonstrate the crucial involvement of the left or right PFC during encoding and retrieval in high- or low-performing older participants.

Recently, Manenti and coworkers [64] employed the same task previously used with younger adults [28] to verify the HAROLD model and the compensation hypothesis in high- and low-performing older adults. For this purpose, the authors directly compared rTMS of the left and right DLPFCs during encoding and retrieval in two subgroups of older adults divided according to their behavioural performance in a word pairs memory task. The results indicated that low-performing older adults recruited the DLPFCs asymmetrically (left > right) during encoding, whereas high-performing older adults (i.e. those with scores similar to younger adults) engaged DLPFC regions bilaterally. Additionally, both groups showed DLPFC symmetry during retrieval, which differs from what is observed in younger adults. Briefly, the reduction of asymmetry predicted by the HAROLD model was observed in high-performing participants during encoding and in both groups during retrieval. These results suggest that high-performing older adults counteract age-related neural declines by reorganising brain functions, whereas low-performing older adults recruit a network of brain regions similar to that recruited in young adults but use it inefficiently, at least during encoding [64]. These data are partially in line with the compensation hypothesis, although further studies will be required to fully investigate the functional differences in these two groups of healthy ageing individuals.

NIBS and episodic memory in mild cognitive impairment and Alzheimer's disease patients

Since the introduction of NIBS techniques, it has become evident that the modulatory effects of cortical stimulation may outlast the immediate stimulation period, with effects of repeated sessions lasting over days and weeks. This finding has generated interest in the possibility of improving deficits in the cognitive domain [65–71]. Recently, few studies applied rTMS or tDCS to improve memory deficits in elderly individuals with memory impairment, patients with amnesic mild cognitive impairment (aMCI) and with Alzheimer's Disease (AD). The potential for therapeutically improving memory in subjects with deficits and the possibility that such effects may be long lasting could lead to the development of completely new therapeutic approaches (see Table 3).

Regarding elderly participants with memory deficits, Solé-Pedullés and coworkers [72] demonstrated a beneficial role of high-

Table 3
Brain stimulation intervention in patients with Alzheimer's disease and individuals with mild cognitive impairment.

Study	Participants	Stimulation technique	Target area	Study design	Frequency/Duration	Outcome	Follow-up	Results
repetitive Transcranial Magnetic Stimulation (rTMS)								
[71]	39 elderly adults with memory impairment	high-frequency rTMS (20 participants), placebo rTMS (19 participants)	bilateral prefrontal	RC	one 50-min session	associative memory	none	↑ associative memory
[69]	1 MCI	high-frequency rTMS	left parietal	U	ten 25-min sessions (5/week)	associative memory, reasoning, language, learning, short- and long-term memory, praxis, attention, executive functions	24 weeks	at end and FU: ↑ associative memory, long-term memory
transcranial Direct Current Stimulation (tDCS)								
[74]	10 AD	atDCS, ctDCS or ptDCS	bilateral temporo-parietal	WS	three 30-min sessions (2 mA)	long-term memory, attention	none	atDCS: ↑ long-term memory, ctDCS: ↓ long-term memory
[70]	10 AD	atDCS vs. ptDCS	left DLPF, left temporal	WS	three 30-min sessions (2 mA)	executive functions, memory	none	atDCS: ↑ long-term memory
[75]	15 AD	atDCS–ptDCS or ptDCS – atDCS	bilateral temporal	RC	five 30-min sessions over 5 days (2 mA)	language, praxis, long-term memory, attention	4 weeks	atDCS at end and FU: ↑ long-term memory

RC = Randomised Controlled Study; U = Uncontrolled pre-post study; WS = Within-Subject study; FU = Follow-up after end of treatment; AD = Alzheimer's Disease patients; MCI = Mild Cognitive Impairment patients; DLPF = Dorsolateral Prefrontal; atDCS = anodal transcranial Direct Current Stimulation; ctDCS = cathodal transcranial Direct Current Stimulation; ptDCS = placebo transcranial Direct Current Stimulation; rTMS = repetitive Transcranial Magnetic Stimulation; ↑ = improvement; ↓ = worsening.

frequency rTMS applied over the left and right PFC in associative memory. This study combined rTMS and fMRI, and the participants exhibited a behavioural improvement in a face-name association memory task following a single session of real (not sham) off-line stimulation. This improvement was associated with the recruitment of the right PFC and bilateral posterior cortices, as shown by fMRI [72]. Furthermore, a recent study by Cotelli and collaborators [69] assessed whether daily application of high-frequency rTMS to the left parietal area for two weeks could lead to significant improvements in memory related to face-name associations in an individual with aMCI [73,74]. A significant improvement was observed, providing evidence for a putative role of the left parietal area in associative memory as well as the possibility of an associative memory' enhancement by rTMS [69].

With respect to AD patients, three tDCS studies have been conducted. First, Ferrucci and collaborators [75] found that after a single session of anodal tDCS over the bilateral temporo-parietal areas in AD patients, word recognition memory task accuracy increased. Moreover, in two subsequent studies, Boggio and Colleagues [70,71] investigated the effects of anodal tDCS on long-term memory performance among AD patients. First, Boggio et al. [70] applied a single session of anodal tDCS over the left DLPFC or over the left temporal cortex and detected a subsequent improvement in recognition memory evaluated with the Visual Recognition Memory task. Subsequently, Boggio and coworkers [76] demonstrated that repeated sessions of anodal tDCS applied bilaterally over the temporal areas resulted in an improvement in performance for a group of AD patients in a visual recognition memory task. Importantly, this effect was still observed after four weeks of treatment [76]. It should be noted that a recent review concluded that stimulation techniques appear to be safe in AD patients [77], opening the door to new possibilities in the memory rehabilitation field.

Conclusion

In summary, NIBS techniques have elucidated the role of the left DLPFC during episodic encoding and the involvement of the right DLFPC during episodic retrieval in young participants. NIBS studies point to a crucial involvement of the DLPFC in processes required for optimal encoding and retrieval in episodic memory and in the location of appropriate working memory resources [30,78—81]. These techniques have been useful also in verifying the reduction in DLPFC functional asymmetry with ageing, showing that recruitment of both the left and right DLPFCs may be a strategy used to compensate for structural loss, at least during encoding. Moreover, it has become evident that the use of NIBS techniques might represent a powerful tool not only for investigating the involvement of cerebral areas in a specific cognitive task but also in designing interventional therapies for individuals with memory impairment. Further studies will be required to identify the optimal responders to specific NIBS treatments [13,82]. However, the reviewed studies indicate that although randomised placebo-controlled studies are still needed, these interventions can significantly contribute to the improvement and provision of care for people with memory deficits.

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