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Transcutaneous vagus nerve stimulation boosts associative memory in older individuals

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A B S T R A C T

Direct vagus nerve stimulation (dVNS) is known to improve mood, epilepsy, and memory. Memory improvements have been observed in Alzheimer's disease patients after long-term stimulation. The potential of transcutaneous vagus nerve stimulation (tVNS), a noninvasive alternative to dVNS, to alter memory performance remains unknown. We aimed to investigate the effect of a single-session tVNS on associative memory performance in healthy older individuals. To investigate this, we performed a single-blind sham-controlled randomized crossover pilot study in healthy older individuals ($n = 30$, 50% female). During the stimulation or sham condition, participants performed an associative face-name memory task. tVNS enhanced the number of hits of the memory task, compared with the sham condition. This effect was specific to the experimental task. Participants reported few side effects. We conclude that tVNS is a promising neuromodulatory technique to improve associative memory performance in older individuals, even after a single session. More research is necessary to investigate its underlying neural mechanisms, the impact of varying stimulation parameters, and its applicability in patients with cognitive decline.

1. Introduction

Memory is crucial to our identity. We draw on our past experiences to guide present and future decisions. Memory problems are the most often expressed complaints by older people. Of all memory systems, episodic memory, the encoding and retrieval of events embedded in their spatiotemporal context, shows the strongest decline with aging (Ronnlund et al., 2005). In particular, the ability of forming face-name associations declines with aging (James et al., 2008). The root causes of age-related memory decline are incompletely understood; however, evidence suggests involvement of a downregulated neuromodulatory system (McIntyre et al., 2012). Nonetheless, the older brain is also capable to reorganize itself adaptively (Duffau, 2006); therefore, strategies to enhance memory functions have gained popularity, also in nonclinical populations.

Direct vagus nerve stimulation (dVNS), an invasive stimulation technique, has received little attention in healthy aging and age-related cognitive decline. The idea of stimulating the vagus nerve to trigger the release of neuromodulators and modify brain activity has been pursued for more than a century (Groves and Brown, 2005). dVNS is an invasive surgical procedure in which a unidirectional wire is wrapped around the vagus nerve in the neck. This wire is connected to a subcutaneous battery implanted in the chest and sending an intermittently electrical current to the vagus nerve (George et al., 2000). The vagus nerve is the longest cranial nerve, and its fibers synapse bilaterally and topographically on neurons within the nucleus tractus solitarius, which in turn projects to the brainstem, in particular the locus coeruleus (McIntyre et al., 2012). Adrenergic activation of the vagus nerve is known to stimulate noradrenalin release from the locus coeruleus, which in turn activates several brain areas. Electrical stimulation of the vagus nerve through dVNS is believed to have specific effects on brain functioning through this pathway (McIntyre et al., 2012; Roozendaal and McGaugh, 2011).

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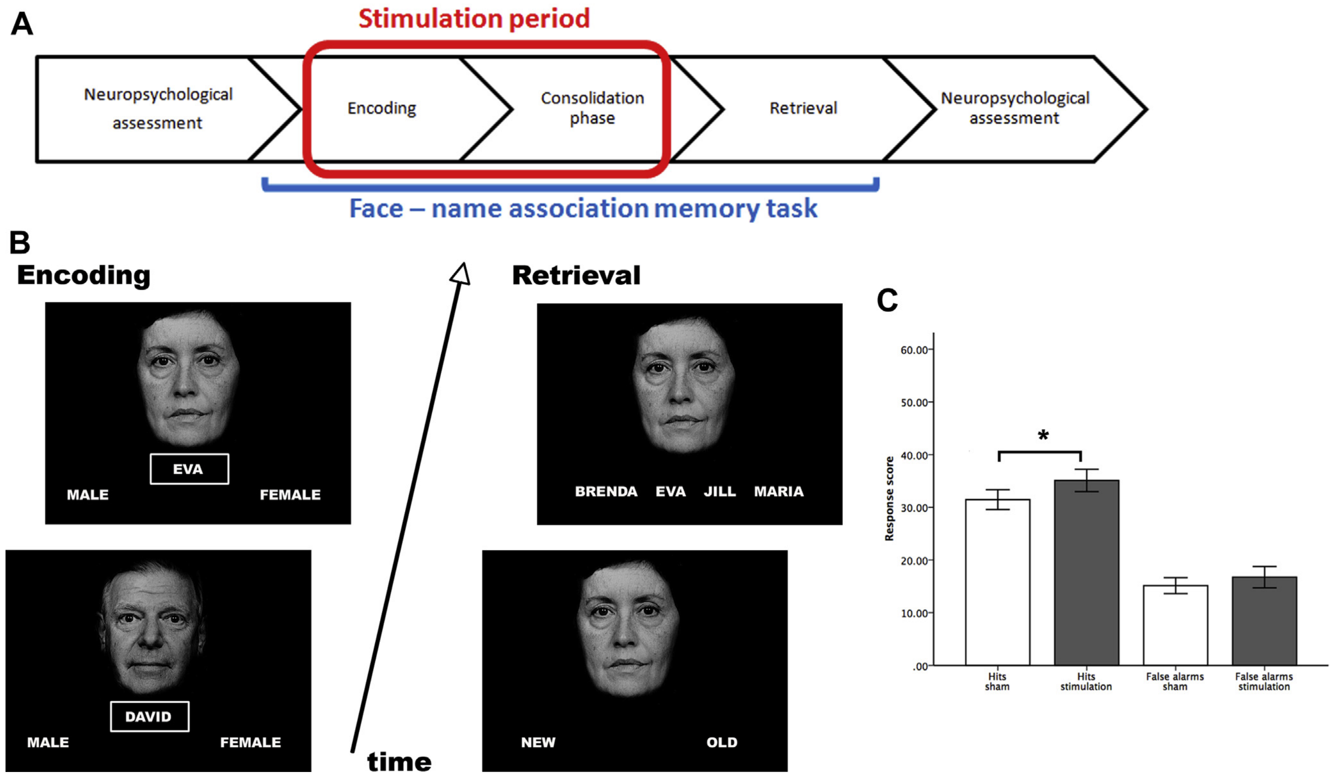

Fig. 1. Effect of transcutaneous vagus nerve stimulation on associative memory. (A) Study design. (B) Experimental paradigm. (C) Effects on associative memory performance: the number of hits (left) increased in the experimental (gray) compared with the sham (white) condition. There was no significant change in false alarm rate (right). Error bars represent 1 standard error, $^{*}p < 0.05$. (For interpretation of the references to color in this Figure, the reader is referred to the web version of this article.)

Although dVNS is successful in decreasing the frequency and activity of seizures (DeGiorgio et al., 2000) and improving depressive symptoms (Marangell et al., 2002), a concomitant improvement in cognitive functions has also been observed (Clark et al., 1999). As these cognitive effects might be related to the improvement of depressive symptoms, it is important to further examine this in animals or patients with cognitive decline. Previous work has now provided evidence for memory-enhancing effects after dVNS in rats (Clark et al., 1995, 1998). Furthermore, a small longitudinal study in Alzheimer's disease (AD) patients reported improvement or no decline in cognitive performance after 6–12 months of stimulation (Merrill et al., 2006; Sjogren et al., 2002). As this technique is invasive, only 10 patients could be included.

Transcutaneous vagus nerve stimulation (tVNS), a noninvasive alternative for dVNS, has shown similar positive effects in reducing the frequency of epileptic seizures and improving depressive symptoms (Kraus et al., 2007; Stefan et al., 2012). Furthermore, tVNS has also positive effects on pain perception and tinnitus severity (Busch et al., 2013; Vanneste and De Ridder, 2012). The potential of tVNS to modulate memory performance remains unknown. The goal of this study is to investigate for the first time the effect of tVNS on memory performance, in particular face-name associations, in healthy older persons as a proof of concept.

2. Materials and methods

2.1. Participants and cognitive assessment

Thirty participants (mean age, 60.57 [standard deviation {SD}, 2.54] years, 50% female), recruited from the community via local newspapers, participated in this single-blind sham-controlled randomized crossover design. All experiments were carried out at the Maastricht University, Faculty of Psychology and Neuroscience and the Faculty of Health, Medicine, and Life Sciences. The Ethical Review Board from the Faculty of Psychology and Neuroscience approved the study. Written informed consent was provided by all the participants. Participants were included if they met the following criteria: no evidence of cognitive deficits on neuropsychological screening, no presence of any neurological or psychiatric disease, no cardiac diseases (Kreuzer et al., 2012), no psychoactive medication use, no abuse of alcohol or drugs, Dutch as the mother tongue, and had to be able to give informed consent. Participants were invited twice at the same time of the day, separated by 7–10 days to avoid carryover effects. Each session was preceded and followed by a wide range of cognitive tests covering episodic memory (15-Word Learning Test [WLT]: learning and delayed recall) (Van der Elst et al., 2005), working memory (digit span forward and backward) (Bopp and Verhaeghen, 2005), language (verbal fluency) (Van der Elst et al., 2006c), attention (Concept Shifting Task) (Van der Elst et al., 2006a), information processing speed (Letter-Digit Substitution Test) (Van der Elst et al., 2006b), and executive functions (Stroop Color-Word Task) (Van der Elst et al., 2006d). All cognitive tests were presented in the same order for each participant, but different versions were applied to avoid practice effects. The Mini-Mental State Examination (Folstein et al., 1975) and the Hamilton Depression Rating Scale (Hamilton, 1960) were only assessed at the first meeting to check inclusion criteria.

2.2. Experimental paradigm

Between the cognitive assessments, participants performed a face-name association memory task. Figure 1 provides an overview of the design. Visual stimuli of this task were presented using