Vagus nerve stimulation (VNS) has been tested for treatment of various neurological and psychiatric disorders for over 25 years. So far, it is approved as a treatment of drug-resistant epileptic seizures. Proven effectiveness and long clinical experience of VNS brought attention of many researchers into other potential applications. Among the most promising directions are areas of cognitive disorders and memory processing. Vagus nerve stimulation can be performed directly via surgically implanted stimulator (invasive VNS) or non-invasively via a clip attached to the auricular concha (transcutaneous VNS through the auricular branch of the vagal nerve).

The aim of our review was to present the published evidence regarding the impact of vagus nerve stimulation (VNS) on cognition, in particular on the processes of memory formation. Performing a meta-analysis is not a subject of this paper. Most of the data were obtained from patients receiving VNS due to epilepsy. However, studies on healthy individuals and animals were also analyzed.

Studies show that vagal stimulation has a positive effect on enhancement of memory processes. The underlying mechanism for the memory-enhancing effect of VNS remains uncertain and requires further investigations. Based on many observations and studies on patients undergoing this procedure, we conclude that vagus nerve stimulation is a promising therapeutic option for many cognitive disorders.

MeSH Keywords: Cognition • Memory • Vagus Nerve Stimulation

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Vagus nerve stimulation (VNS) was introduced for the first time and presented to patients in 1988. The European Community in 1994 and the Food and Drug Administration (USA) 3 years later (1997) approved VNS as an additional treatment option in patients suffering from epilepsy, whose seizures are refractory to antiepileptic medications [1]. Vagus nerve stimulation can be performed in 2 different ways: by direct invasive stimulation or indirect (non-invasive) stimulation. Invasive VNS (iVNS) requires surgical implantation of a pulse generator subcutaneously in the left thoracic region. The device is connected to electrodes attached to the left cervical vagus nerve. In contrast, transcutaneous VNS (tVNS) is non-invasive and does not require any surgical procedure; the stimulator is usually attached to the auricular concha via ear clips and delivers electrical impulses at the subcutaneous course of the afferent auricular branch of the vagus nerve [2–5]. Based on many observations in epileptic patients undergoing VNS, this procedure has been also considered a promising treatment of various neurological and psychiatric disorders [6,7].

Many trials have been performed, both on animals and humans, proving the positive influence of VNS on cognitive functions. The vagus nerve (VN) is a main part of the parasympathetic nervous system. It carries both afferent and efferent fibers. Most sensory fibers deliver stimulation to the nucleus of the solitary tract (NTS) [8]. VN also stimulates other brain structures [9,10], including hippocampus, which is the primary structure responsible for memory processing.

VNS improves cognitive function in animals after brain injury [11] and is involved in formation of hippocampal long-term potentiation (LTP) [12,13]. The memory-improving effect of VNS was proven in animal models [14,15].

Traditionally, the vagus nerve was considered a parasympathetic efferent nerve, controlling and regulating autonomic functions, such as heart rate and gastric tone. This view of the vagus nerve changed in 1938, with the observation that VNS resulted in changes in EEG, and it is now accepted that it is a mixed nerve, with 80% of the fibers carrying afferent (sensory) information and 20% carrying efferent (motor) information [16–18].

The Underlying Mechanism for Memory Enhancing Effect of VNS

As many times in history of clinical psychiatry and neurology underlaying physiological mechanism of clinically efficient method remains unknown and same is in VNS case. However, some clues could be obtained from existing studies showing that VNS changes different neurotransmitters levels in hippocamp [19,20]. Most important from the perspective of this paper effect on memory processing could be related to the increase of excitation of hippocampal neuronal network and the generation of local theta rhythm [21,22]. VNS has been also shown to increase the levels of free GABA in the cerebrospinal fluid [23].

Several studies examining the impact of vagus nerve stimulation (VNS) on cognition and memory were conducted (Table 1).

Vagus Nerve Stimulation (VNS) and Verbal Memory

Verbal memory is a memory of words and other abstractions involving language. It can be conscious declarative memory or unconscious procedural memory.

In 1999, Clark et al. reported enhanced verbal recognition memory in 10 patients with epilepsy after the application of short-term VNS. Their study was a randomized, double-blind, clinical trial to assess and evaluate enhanced recognition after VNS in epileptic patients. Four experimental sessions were performed. The results showed that moderate vagus nerve stimulation of 0.5 mA significantly improves word recognition (the mean increase in percentage terms totaling 35.6%). In contrast, when stimulation intensity was between 0.75 and 1.50 mA, which is more typical for the intensity effective in epilepsy treatment, the recognition performance was slightly impaired (decrease by 10%). Based on these data, the authors hypothesized that the effect of memory enhancement corresponds to the inverted U-shape function of current VNS intensity. Vagus nerve stimulation (VNS), applied at the stage of memory consolidation, brings enhanced performance of word recognition, which depends on the intensity value, with optimal stimulation being 0.5 mA, which is at the low end of the range of clinically effective doses for suppression of seizures [1,24].

Experimental data of Helmstaedter et al. (2001) indicated a negative effect of short-term VNS on memory performance. The researchers assessed memory and decision-making time by using 2 computerized memory tasks in 11 patients with epilepsy. The participants had to memorize a list of words during 3 learning trials. All the patients underwent VNS with current intensity greater than 1 mA, whereas the patients in a study by Clark et al. were treated with lower current intensities. Moreover, in contrast to the findings of Clark et al., VNS was applied during both learning and recall. Normative data from 3 tests, according to baseline sham conditions, were collected from 20 healthy individuals for the purposes of performance evaluation. The study revealed significant and fully reversible impairment of figural recognition memory when high values of VNS intensity were applied during learning and retrieval...
processes. The time required to make a decision regarding recognition of the verbal target items demonstrated significant acceleration during vagus nerve stimulation and reduction at the baseline level following stimulation. This suggests that VNS has a positive impact on arousal and attention [1,25].

Ghacibeh et al. (2006) examined which stage of the process of memory formation is affected by VNS. In their study, VNS was applied during 2 diverse stages of memory processing: learning consolidation and retrieval. They examined 10 epileptic patients with an implanted stimulator of the vagus nerve. Three parallel versions of the Hopkins Verbal Learning Test (HVLT) were used in the study. A list of 12 words was read out loud to the patients during the learning phase, followed by true (0.5 mA, 30 s) or sham (0.0 mA) stimulation. True or sham VNS was again applied immediately before the recall stage and immediately before recognition. In one version of HVLT, VNS was delivered only at the learning phase (stim-sham condition), and in another version of HVLT, VNS was used only during the retrieval phase (sham-stim condition). During the third version of HVLT, sham stimulation was applied both in the learning phase and in the retrieval phase (sham-sham condition). The results obtained indicated that retention of information is affected only when VNS is delivered immediately after the learning phase, but not directly before recall. The study revealed no impact of VNS on learning, but it enhances consolidation of memory, which leads to and results in improved retention performance [1,26].

The Impact of Vagus Nerve Stimulation (VNS) on Other Cognitive Functions and Quality of Life

The purpose of a study conducted by Ghacibeh et al. (2006) was to find out whether VNS had an influence on creativity...
and cognitive flexibility. The design of the study was the same as described above. Ten patients in whom vagus nerve stimulators had been implanted for the treatment of intractable seizures were asked to do 2 parallel versions of the creativity test (the Abbreviated Torrance Test for Adults) as well as a cognitive flexibility test (solving anagrams) during sham (0.0 mA) and true stimulation (0.5 mA, 30 s). The results of the study provided evidence for the impairment of creativity and cognitive flexibility following the application of VNS [1,27].

Martin et al (2004) performed an experimental study in which the impact of VNS on the process of making decisions was investigated using a counterbalanced design. Eight epileptic patients with implanted left vagus nerve stimulators were asked to do the Iowa Gambling Task in the conditions where low iVNS (0.5 mA) was delivered, and during sham stimulation (0.0 mA). The Gambling Task is sensitive to real-life decision-making deficits. Improved performance was confirmed by the fact that the participants made more advantageous choices in the stimulated as opposed to non-stimulated conditions. The results were significant irrespective of whether the comparisons were conducted for the same individual or between different patients [1,28].

Klinkenberg et al (2012) examined the influence of long-lasting VNS on cognitive status, mood, and quality of life among patients with refractory epilepsy. After neuropsychological testing, a vagus nerve stimulator was implanted in 41 patients. The testing was repeated 6 months after activation of the device (30 Hz, 0.5 ms, 30 s on, 5 min off). In 20% of the patients, seizure reduction by over 50% was observed after the treatment. There was also a significant increase in mood and quality of life scores. However, 6 months after VNS, there were no significant changes in cognition [1,29].

A study conducted by Sackheim et al. (2001) investigated whether VNS leads to impairment of cognition. Twenty-seven patients diagnosed with treatment-resistant chronic depression underwent neuropsychological testing, which evaluated different cognitive functions, before and after 10 weeks of VNS. Improvements in simple motor speed (finger tapping), psychomotor functioning (digit-symbol test), language (word fluency), and executive functioning (logical reasoning, working memory, response inhibition, and impulsiveness) were observed. These effects on neurocognitive functioning were significantly correlated with an improvement in depression scale scores but not with the output current of VNS. The authors concluded that vagus nerve stimulation in treatment-resistant depression may lead to enhanced cognitive functioning, primarily among patients who demonstrate clinical improvement. No evidence of deterioration in any neurocognitive measure was detected [1,30].

Dodrill and Morris (2001) enrolled 160 patients with partial seizures (pharmacologically resistant) for a double-blind multicenter efficacy trial. The aim of the study was to investigate the influence of chronic VNS on cognitive functioning and quality of life. The patients were randomly assigned to 1 of 2 groups (high and low stimulation). In the conditions of low stimulation, VNS was barely detectable for patients (1 Hz, 30 s on, 3 h off, 130 s pulse width), while in the group with high stimulation the parameters of VNS were ramped up to the tolerance level (30 s on, 5 min off, 30 Hz, 0.5 ms). Cognitive tests and questionnaires were repeated after 12–16 weeks of therapy with the application of fixed and unchanged stimulation. Overall, there were no significant changes between those 2 groups in the 2 investigated areas of cognition (attention and executive functioning) [1,31].

McGlone et al. (2008) made an attempt to avoid several limitations of previous VNS studies which investigated parameters such as quality of life or cognition. They did not perform the within-patient comparison because the patients served as their own control group; neither did they conduct any between-subject comparisons for low and high stimulation groups [1]. The researchers conducted a matched-case design study to compare VNS with different interventions. Three study groups were created: epileptic patients treated with iVNS (group 1), patients undergoing cerebral resective surgery (group 2), and patients receiving only antiepileptic drugs (group 3). The participants in each group underwent assessment before and after the intervention. The authors calculated the Reliable Change Index (RCI), which indicates the difference between pre-intervention and post-intervention scores in each patient, divided by the standard error of the difference. A group analysis showed and confirmed a substantial group effect. The patients who were under medical management and received only antiepileptic drugs (group 3) recorded higher scores with reference to memory indices than the patients after a resective surgery (group 2) or VNS implantation (group 1). A significant group × time interaction was observed for immediate memory and working memory indices. However, RCI revealed that more patients with VNS had better Auditory Recognition Index values as compared to the subjects undergoing an antiepileptic drug therapy. Additionally, after a follow-up of 12 months, more patients who had undergone resective surgery had decreased memory indices in comparison with the VNS patients [1,32].

Vagus Nerve Stimulation (VNS) in Patients with Alzheimer’s Disease (AD)

Sjögren et al studied whether VNS enhanced cognition in patients diagnosed with Alzheimer’s disease. Ten patients with AD (diagnosed according to NINCDS-ADRD A criteria) underwent cognitive screening (MMSE and ADAS-cog) before VNS
implantation, after 8 weeks of stable stimulation with the application of VNS (0.25–0.75 mA, 30 s on, 5 min off, 20 Hz, 0.5 ms), and during a follow-up after 6 months. In 4 out of 10 patients, an improvement was reported as early as during the recovery phase, before vagus nerve stimulation. This suggests a placebo effect connected with the VNS implantation procedure. Eight patients showed improvement of cognitive functions in ADAS-cog scores after 6 months as compared to the scores recorded during a follow-up at 3 months. This suggests that the positive effects on cognition remained stable or even improved with time. VNS seems to be a promising treatment option for AD patients [1,2,33].

A publication by Merrill et al. referred to a follow-up of over 1 year with reference to the study conducted by Sjögren et al.; 7 additional patients were included in the study. The researchers examined cerebrospinal fluid seeking for biomarkers, which may indicate that VNS improves not only the cognitive symptoms in AD, but also has a positive impact on the pathology of the underlying disease. The results revealed that about 70% of the patients presented an improvement or absence of decrease during cognitive screening after 6 months of stimulation. However, after 1 year of therapy, this value receded to 40%. Improvement at an early stage was ultimately followed by a gradual decrease, which may indicate delayed progression of the disease. An analysis of CSF biomarkers showed a tendency for a CSF tau level reduction and an insignificant increase in phospho-tau after 1 year of vagus nerve stimulation. Normalization of the pathological process may be suggested by the decline in total tau. Nevertheless, the increase of phospho-tau might indicate that the pathological process is accelerated. These contradictory findings make it impossible to draw firm conclusions [1,34].

The Influence of VNS on Cognitive Functions in Healthy Individuals

A recent study by Jacobs et al assessed healthy older individuals to investigate the effect of single-session transcutaneous VNS on associate memory performance, especially face-name associations, in healthy subjects. Thirty participants who had no evidence of cognitive deficits on neuropsychological screening, no history of neurological, psychiatric or cardiac disease, did not take psychoactive medications, did not abuse alcohol or drugs, were able to give informed consent, and used Dutch as their first language, took part in this single-blind, sham-controlled, randomized, crossover trial. The participants were asked to memorize the face-name association and to assess the gender of the person to keep them focused on the task. Transcutaneous stimulation was provided via an ear clip, with the following parameters: frequency of 8 Hz, electrical current of 5.0 mA, and pulse width of 200 ms. The experimental condition (VNS) was associated with higher scores than the condition with sham stimulation. There were no significant differences between the sham and the true stimulation conditions regarding the reaction times. Since the vagus nerve is associated with the maintenance of blood pressure, the authors performed a post hoc analysis in which they excluded participants taking antihypertensive drugs. This analysis revealed a slightly larger effect of stimulation compared with sham. The habituation effects are similar across the conditions but affected performance to a smaller extent in the tVNS condition. This could indicate that tVNS has a positive effect on learning and delayed recall performance of an episodic memory task. The modulating effect of tVNS on memory function is task-specific and does not transfer to other cognitive domains. Adverse effects were minimal and transient. These studies provided first-time evidence that tVNS can enhance associative memory performance in elderly people, even after a single session [35].

Conclusions

Current evidence does not allow researchers to reach an agreement about the underlying mechanism of the cognition modulating effect of VNS. Further research is warranted and needed. However, based on many observations and studies on patients undergoing this procedure, we can already conclude that vagus nerve stimulation is a promising tool in treatment of the cognitive dysfunction accompanying many neurodegenerative disorders. In particular, non-invasive methods could be widely used.

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