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Effect of vagus nerve stimulation on creativity and cognitive flexibility ☆

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Abstract

Objective. The purpose of this study was to determine whether vagus nerve stimulation influences cognitive flexibility and creativity.
Methods. Ten subjects, in whom vagus nerve stimulators had been implanted for the treatment of intractable seizures, performed tasks that assessed cognitive flexibility (solving anagrams), creativity (Torrance Test), and memory (Hopkins Verbal Learning Test) during actual and sham vagus nerve stimulation.
Results. Vagus nerve stimulation impaired cognitive flexibility and creativity, but these results could not be explained by the induction of a general encephalopathy because VNS did not impair learning and improved retention.
Conclusions. The means by which vagus nerve stimulation impairs cognitive flexibility and creative thinking is probably related to increased activity of the locus coeruleus–central adrenergic system that increases the signal-to-noise ratio and improves the brain's ability to attend to sensory input, but decreases its ability to recruit large-scale networks.

Keywords: Vagus nerve stimulation (VNS); Creativity; Cognitive flexibility; Central adrenergic pathways; Locus coeruleus

1. Introduction

Creativity has been defined as finding unity in what appears to be diversity [1], or the ability to understand, develop, and express, in a systematic fashion, novel orderly relationships [2]. Creative innovation is one of the most important functions of the human brain, but the means by which the brain develops innovative ideas is not well understood. Most investigators, however, believe that divergent thinking is a critical factor. Divergent thinking is important because creativity requires the novel understanding and expression of orderly relationships, and novelty requires that the creative person take a direction different from the prevailing modes of thought or expression. The concept of divergent thinking was put forth by William James who wrote [3]: "Instead of thoughts of concrete things patiently following one another in a beaten track of habitual suggestion, we have the most abrupt cross-cuts and transitions from one idea to another ... unheard of combination of elements. We seem suddenly introduced into a seething caldron of ideas ... where treadmill routine is unknown and the unexpected is the only law." James also suggested that the ability to switch strategies, cognitive flexibility, was critical to divergent thinking.

Little is known about the brain mechanisms underlying divergent thinking and cognitive flexibility. Cognitive flexibility encompasses the ability to inhibit strong preferences in order to explore alternative solution paths [4]. A handful of experiments have evaluated the effect of psychological and pharmacological manipulations on tests of creativity and cognitive flexibility. Performance on tests of creativity,

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[1] Basim Uthman has previously served as consultant and has received honoraria for speaking engagements from Cyberonics, Inc., manufacturer of the vagus nerve stimulator. The other authors have nothing to disclose.

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such as the Remote Associates Test, deteriorates during stressful conditions [5]. Propranolol, both a central and a peripheral beta blocker, improved performance of normal subjects on a word anagram test, whereas ephedrine worsened their performance [4], providing support for the postulate that brain norepinephrine (NE) influences cognitive flexibility. Furthermore, many of the greatest innovations came about when people were relaxing, resting, and drowsy. Many creative writers, artists, and composers suffer with depression or bipolar disorder [6–8]. During both relaxation and depression there is a decrease in brain NE. In contrast, during stress, there is an increase in brain NE.

Vagus nerve stimulation is an effective adjunct treatment for refractory partial epilepsy [9]. There has recently been interest in exploring other possible central nervous system (CNS) effects of vagus nerve stimulation, including a possible beneficial effect on chronic depression [10] and memory [11]. Although the exact mechanism by which vagus nerve stimulation helps reduce seizure frequency is still not fully known, the mechanism is most likely complicated and involves activation of several central pathways and neurotransmitter systems. There is some experimental evidence that this improvement might be partly related to activation of central adrenergic pathways [12,13]. Support for this postulate comes from studies performed in animal models of epilepsy in which treatment with adrenergic agents reduced seizure frequency [14].

In this experiment, we investigated the effects of vagus nerve stimulation on cognitive flexibility, creativity, and memory. We predicted a behavioral dissociation between mental flexibility–creativity and memory. Because vagus nerve stimulation may activate the neurons in the locus coeruleus (LC), which may result in increased release of brain NE, it should reduce creativity and cognitive flexibility, but because NE increases the brain's ability to process sensory stimuli (enhance signal-to-noise ratio), and enhances the response of specific cortical, thalamic, and hippocampal neurons to behaviorally salient stimuli, vagus nerve stimulation may improve some aspects of memory.

2. Methods

2.1. General design

To assess the effects of vagus nerve stimulation on creativity and cognitive flexibility, we used a within-subject double-blind design. Therefore, each subject received two equivalent versions of two different tests, each test assessing the two targeted cognitive functions. During one version of each test, subjects received real stimulation, and during the other, they received sham stimulation. During the entire testing session, both the examiner and the subjects were blinded to whether real or sham stimulation was being delivered. A third party, the "magnet operator," was responsible for administering the stimulation, but the magnet operator was limited to administering the stimulation and had no other interactions with either the examiner or the subjects.

2.2. Subjects

Ten patients, five women and five men, mean age 46.7 (range, 26 to 58), native English speakers, with medically intractable partial epilepsy, served as the experimental subjects. Vagus nerve stimulators (VNSs) had been implanted as adjunct treatment for epilepsy in all subjects. The devices had been implanted at least 3 months prior to testing to ensure stabilization of seizure control. Table 1 summarizes the characteristics and VNS settings of all subjects. None of the patients had a history or evidence of dementia (normal Mini-Mental Status Examination score), major head trauma, stroke, or learning disorder. Subjects were all medically stable, with no evidence of infection or progressive systemic illness that may interfere with testing. All subjects tolerated the VNS, with no major side effects. All patients exhibited significantly improved seizure control attributable to the VNS, and two subjects became completely seizure-free after implantation. All testing was performed in a single 4-hour session. The study was approved by the institutional review board of the University of Florida, and all subjects provided verbal and written informed consent.

2.3. Apparatus

The VNS is an electric stimulator implanted subcutaneously in the chest and connected, via subcutaneous electrical wires, to the cervical left vagus nerve. The VNS is programmed to deliver electrical stimulation at a set intensity, duration, pulse width, and frequency (*normal mode*). In addition, the VNS can be activated by holding a magnet against it for a few seconds (*magnet mode*). During the experiment, normal mode was turned off so that no spontaneous stimulation would occur outside the experimental protocol. The magnet mode was programmed to respond to the magnet

Table 1
Characteristics of subjects

Subject	Age	Gender	VNS settings			AED[a]	MMSE
			Amplitude (mA)	ON time (s)	OFF time (min)		
1	58	F	1.5	30	5	LTG, LVT	30
2	26	M	1.75	30	3	LTG, PGB, TGB	30
3	52	M	1.25	7	0.02	LVT	30
4	46	F	1.5	30	1.8	LTG	28
5[b]	51	M	0.75	30	3	LVT, PGB	30
6	51	F	1.25	30	5	GBP, CZP	25
7	40	M	2.75	30	5	PHE, LTG, LVT	27
8	47	F	1	30	5	ZSM, AZM	30
9	44	F	2.25	30	1.1	CBZ	29
10[b]	52	M	0.75	30	5	GBP, TPX	28

[a] LTG, lamotrigine; LVT, levetiracetam; PGB, pregabalin; TGB, tiagabine; GBP, gabapentin; CZP, chlorazepate; PHE, phenytoin; ZSM, zonisamide; AZM, alpraxolam; CBZ, carbamazepine; TPX, topiramate; MMSE, Mini-Mental Status Examination score.
[b] Subjects who were able to discriminate real from sham stimulation.