



Original Articles

Non-invasive Access to the Vagus Nerve Central Projections via Electrical Stimulation of the External Ear: fMRI Evidence in Humans



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ABSTRACT

Background: Tract-tracing studies in cats and rats demonstrated that the auricular branch of the vagus nerve (ABVN) projects to the nucleus tractus solitarius (NTS); it has remained unclear as to whether or not the ABVN projects to the NTS in humans.

Objective: To ascertain whether non-invasive electrical stimulation of the cymba conchae, a region of the external ear exclusively innervated by the ABVN, activates the NTS and the “classical” central vagal projections in humans.

Methods: Twelve healthy adults underwent two fMRI scans in the same session. Electrical stimulation (continuous 0.25ms pulses, 25Hz) was applied to the earlobe (control, scan #1) and left cymba conchae (scan #2). Statistical analyses were performed with FSL. Two region-of-interest analyses were performed to test the effects of cymba conchae stimulation (compared to baseline and control, earlobe, stimulation) on the central vagal projections (corrected; brainstem $P < 0.01$, forebrain $P < 0.05$), followed by a whole-brain analysis (corrected, $P < 0.05$).

Results: Cymba conchae stimulation, compared to earlobe (control) stimulation, produced significant activation of the “classical” central vagal projections, e.g., widespread activity in the ipsilateral NTS, bilateral spinal trigeminal nucleus, dorsal raphe, locus coeruleus, and contralateral parabrachial area, amygdala, and nucleus accumbens. Bilateral activation of the paracentral lobule was also observed. Deactivations were observed bilaterally in the hippocampus and hypothalamus.

Conclusion: These findings provide evidence in humans that the central projections of the ABVN are consistent with the “classical” central vagal projections and can be accessed non-invasively via the external ear.

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Introduction

The main visceral sensory nerve – the vagus – which innervates the esophagus, trachea, lungs, heart, pancreas, stomach, intestines, etc., projects to the nucleus tractus solitarius (NTS), the first central relay of vagal afferents [5,52,54]. The vagus nerve includes a

sensory “auricular” branch that innervates the external ear [5,48]. The cymba conchae of the external ear (Fig. 1A) is innervated exclusively by this branch; other regions of the external ear receive afferent innervation by this branch solely, or shared with other nerves, e.g., the posterior and inferior walls of the ear canal [13,56] and the cavity of the concha [48].

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and member of the Advisory Board of Cerbomed. EF received financial compensation from Cerbomed to support the fMRI data analysis. No contractual relations or proprietary considerations exist that restrict the dissemination of our findings.

Preliminary findings have been published abstract form [16–18].

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To our knowledge, there is no reported evidence in humans that the auricular branch of the vagus nerve (ABVN) projects to the NTS. However, neuroanatomical and brain imaging evidence suggests that this projection is plausible in humans. A tract-tracing study using horseradish peroxidase in cats provided evidence that the ABVN projects to the NTS, the spinal trigeminal nucleus, and other sensory nuclei within the brainstem. Primary afferent terminal labeling was observed specifically in the interstitial, dorsal, dorsolateral, and commissural subnuclei of the NTS [45]. A subsequent study in rats provided further evidence of a direct projection of the ABVN to the NTS [19]. Three functional MRI (fMRI) studies in humans investigating the effects of transcutaneous vagus nerve stimulation (t-VNS) via the external ear did not report activation of the NTS, possibly because of methodological differences or because different regions of the external ear other than the cyma conchae were stimulated and were not supplied or insufficiently supplied by the ABVN [11,35,36]. However, the brain regions that were significantly affected by the stimulation in those studies are consistent with primary and higher-order central projections of the vagus nerve. Functional MRI studies of invasive vagus nerve stimulation (VNS) also reported activity within afferent vagal projection sites [6,37,38,41,44]. The regions most commonly affected by t-VNS and VNS are the insula, thalamus, amygdala, hippocampus, postcentral gyrus, nucleus accumbens, hypothalamus, and brainstem.

In addition to the above neuroanatomical and brain imaging studies, there is evidence that t-VNS produces cognitive and behavioral effects that are also produced by VNS [7,10,22,29,41,43,53,55,57,58]. Based on conventional neuroanatomy, VNS would be expected to activate the vagal projections beginning centrally at the NTS; therefore, it is likely that t-VNS, via the ABVN, would also activate the NTS.

In the present study, we used functional MRI to test the following hypothesis: non-invasive electrical stimulation of the auricular branch of the vagus nerve (t-VNS) via the cyma conchae, exclusively innervated by the ABVN, will activate the NTS and the “classical” vagal projections. Brain regions that respond to electrical stimulation of the cyma conchae were compared to regions that respond to stimulation of the control region, the earlobe. The earlobe is innervated by the greater auricular nerve, which is a composite nerve of cervical spinal nerves 2 and 3 and projects to the nucleus cuneatus in the brainstem [48]. Preliminary findings have been published in abstract form [16–18].

Materials and methods

The study received approval from the Rutgers University Institutional Review Board, and the “Rutgers University Brain Imaging Center (RUBIC) Common Practices for fMRI” guidelines were strictly followed.

Research participants

Twelve healthy participants (9 females and 3 males; age range 21–71 years; mean $\pm$ SD age, 32.6 ± 13.8 years) were recruited for the study by word of mouth. Each person provided written informed consent and was compensated for participating in the study. Participants underwent two structural and functional magnetic resonance imaging scans in the same session and were instructed to remain alert and awake while viewing a sequence of still images of natural scenery (“travelogue” images) during each scan.

Stimulation procedure

Before each scan, participants were fitted with the Cerbomed NEMOS® device designed specifically for mild electrical stimulation of the cyma conchae of the external ear (Fig. 1A) via an adjustable earpiece containing two hemispheric titanium electrodes (Fig. 1D) connected to a battery-operated stimulator. The device was used to provide transcutaneous electrical stimulation of the *left* cyma conchae and the *left* earlobe (as a control). Control stimulation of the earlobe was conducted by positioning the earpiece upside down (Fig. 1B). Cyma conchae stimulation was conducted by positioning the earpiece upright, as designed to be used (Fig. 1C).

The battery-containing stimulator unit remained in the monitor room; the unshielded cable (7 m in length) attached to the earpiece electrodes was passed through a wave-guide to the participant in the scanner. The stimulus intensity was adjusted for each of the participants as they lay supine on the scanner gurney prior to each scan. The intensity was increased from 0.1 mA in 0.1 mA increments until a participant reported a “tingling” sensation that was below the intensity that produced a noxious “pricking” sensation [12]. The individual stimulation intensities that were selected in this way were 0.3–0.9 mA for the control (earlobe) stimulation condition (0.58 ± 0.19 mA; mean $\pm$ SD), and 0.3–0.8 mA for the cyma conchae stimulation condition (0.43 ± 0.14 mA; mean $\pm$ SD). The

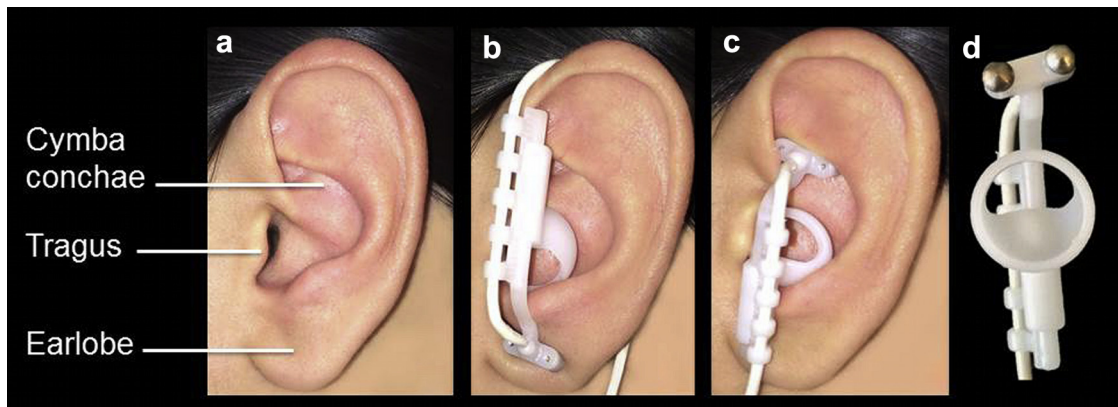


Figure 1. A. The left external ear indicating the regions referred to in the Introduction and Stimulation Procedure section; B. Position of the earpiece during the control condition (earlobe stimulation); C. Position of the earpiece during the experimental condition (cyma conchae stimulation); D. Detail of the earpiece and the pair of titanium electrodes.

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