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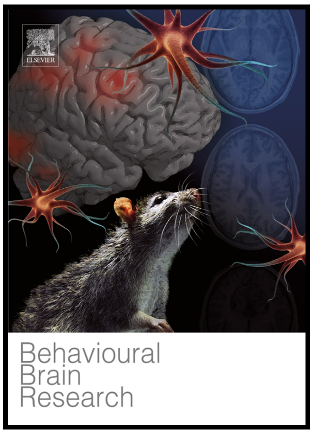

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The Effect of Non-Invasive Vagus Nerve Stimulation on Memory Recall in Reading: A Pilot Study

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Highlights

- taVNS was applied to the left posterior tragus during reading of short passages.
- The active taVNS group exhibited better passage recall than sham taVNS.
- taVNS was not associated with better performance on comprehension questions.
- Baseline memory was significantly correlated with memory recall performance.

Abstract

Expert reading acquisition is marked by fluent, effortless decoding and adequate comprehension skills and is required for modern daily life. In spite of its importance, many individuals struggle with reading comprehension even when decoding skills are adequate. Unfortunately, effective reading comprehension interventions are limited, especially for adults. A growing body of research suggests that non-invasive transcutaneous stimulation of the auricular vagus nerve (taVNS) may drive neural plasticity for low-level reading skills such as speech sound perception and letter-sound learning, but it is unknown whether taVNS can improve higher level skills as well. Thus, the current pilot study was designed to evaluate the effect of taVNS paired with passage reading on reading comprehension performance. Twenty-four typically developing young adults were recruited and screened for baseline reading and working memory skills. Participants received either sham or active taVNS while reading short passages out loud. Immediately following each passage, participants answered a series of test questions that required either direct recall of passage details or more complete comprehension of the passage content. While taVNS did not improve the mechanics of reading (e.g., reading rate or accuracy), there was a significant effect of active taVNS on test performance. This effect was driven by significant improvement on accuracy for memory questions while there was no effect of taVNS on comprehension question accuracy. These findings suggest that taVNS may be beneficial for enhancing memory, but its efficacy may be limited in higher cognitive domains.

Keywords: reading errors; fluency; current intensity; inference; taVNS; comprehension

1. Introduction

Fluent reading is a necessary skill in the developed world but despite adequate education and intelligence, up to 10% of children fail to acquire reading comprehension skills [1]. Reading comprehension requires a reader to both fluidly decipher print and extract meaning [2,3]. To comprehend meaning, a reader must both recall the printed information and draw inferences for information not explicitly stated in the passage [4]. Difficulty in reading comprehension causes significant hardship not only with respect to self-esteem, but also to academic and vocational outcomes [5]. For example, students at all levels of education are required to read and comprehend material in textbooks, during lectures, and on assignments and exams. While reading and comprehension skills are essential, acquiring these skills takes years of practice and instruction. The long trajectory required for reading acquisition is partially due to the neural plasticity required to support reading [6,7] and partially due to the large number of lower-level skills that support reading comprehension, such as word reading fluency and language comprehension [8]. Thus, to support children and adults in acquiring and optimizing their reading comprehension abilities, clinicians must focus on several low-level reading skills as well as the reader's ability to keep recently read text in their working memory. Given the large number of related skills, determining the best intervention approach for each individual can be challenging.

Currently, several reading comprehension interventions exist, but they are time consuming and not effective for all users, especially those targeted at adults. For example, while a vocabulary-based training improved reading fluency in adults learning English as a second language, it did not improve comprehension [9]. Researchers have also developed a reading comprehension intervention that focuses on strategies during pre-reading, reading, and post-reading to improve comprehension skills in young adults [10]. In the reading comprehension strategy intervention, participants are taught to preview headings of passages, reread highlighted portions of passages, and write summaries of what they read. While this approach can be effective, it is also a time-consuming exercise and busy adults may be less likely to persist in practicing this approach. Further, while interventions that are effective in children (such as Corrective Reading, RAVE-O, and Guided Repeated Reading) can improve reading comprehension in adults, they require at least 10-18 weeks of intervention [11]. Thus, while these interventions are somewhat effective in adults, they exhibit three main limitations: (1) they require many weeks of intervention, (2) they do not fully address executive functions implicated in reading comprehension, such as working memory, and (3) they are not effective in all cases. Thus, the goal of the current study was to investigate whether a novel non-invasive neurostimulation approach can improve reading comprehension in young adults.

Neuromodulation is a popular technique for enhancing or driving neural plasticity and a number of these techniques have been evaluated for reading. Examples include transcranial direct stimulation (tDCS), transcranial magnetic stimulation (TMS), and vagus nerve stimulation (VNS). Previous data have suggested that tDCS applied to the left inferior parietal lobe aided in letter-sound pairings, but this effect was stronger for those with lower, compared to higher, baseline reading skills [12]. Additionally, in a sample of individuals with dyslexia, tDCS applied to the left parietotemporal region led to better reading accuracy [13] and reading efficiency up to six months after treatment [14]. These studies show the efficacy of tDCS as a neuromodulator in the reading realm, but this technique also comes with limitations. Specifically, tDCS (a) has shown more success in readers with dyslexia than typical readers, (b) can be difficult to administer in a setting outside the laboratory, and (c) can have some discomfort during and after stimulation. Compared to tDCS, VNS offers some additional benefits, such as portability and reduced discomfort for the wearer. Thus, we utilized vagus nerve stimulation in the current pilot study.

Cervical vagus nerve stimulation (cVNS) involves the release of norepinephrine and acetylcholine, neurotransmitters implicated in learning and memory [15,16]. Importantly, key neurotransmitter systems must be intact to ensure effectiveness of cVNS [17,18]. In the sensory domain, cVNS paired with an external stimulus, such as a tone, leads to significant and long-lasting neural plasticity in the rodent primary auditory cortex [19]. cVNS paired with training has also improved motor function recovery in stroke-induced rats and driven neural plasticity in motor cortex [20,21]. In humans, active cVNS led to higher rates of recognition memory of highlighted words in a passage [22], decreased errors in a delayed recall task [23], and better performance on a verbal fluency task [24], when compared to sham cVNS. To date, cVNS has been FDA approved for individuals with treatment resistant epilepsy and depression, and as of this writing, is in active clinical trials for stroke and tinnitus. However, cVNS implantation requires an expensive and invasive procedure, which makes it an impractical intervention for reading skills.

Transcutaneous auricular vagus nerve stimulation (taVNS) activates similar deep-brain structures as cVNS (e.g., nucleus tractus solitarius), without the need for an invasive, expensive surgery, by applying low-level electrical stimulation to the left outer ear [25,26,27]. Growing evidence supports the hypothesis that taVNS drives similar neural plasticity as the more invasive cVNS. For example, taVNS paired with physical therapy increases post-stroke motor function recovery performance [28] and alleviates symptoms of tinnitus [29]. In the language and reading domains, taVNS improves learning of novel letter-sound pairings [30] and novel Mandarin speech sound categories [31]. This approach also increases performance on a face-name association task in healthy older adults [32], suggesting its effectiveness in higher cognitive domains. Previous evidence has shown that taVNS increases performance in lower-level reading skills like letter-sound learning [30]. We evaluated whether administration of active taVNS, compared to sham taVNS, is associated with higher reading comprehension performance, a skill requiring both reading and memory.

2. Materials and Methods

2.1 Participants

Fifty-five young adults were screened for eligibility from an online participant pool at a southern university. All potential participants completed a short online background survey covering personal history of reading and motor development, diagnoses, medications, and family history. Participants then completed several baseline assessments including: a non-verbal IQ measure (the matrices subtest of the KBIT-2) [33], timed single-word reading (the Sight Word Efficiency and Phonemic Decoding Efficiency subtests from the TOWRE-2) [34] and untimed single-word reading (Word Identification and Word Attack subtests from the WRMT-3) [35]. To qualify as a typical reader, participants needed to (a) be a native English speaker, (b) be between the ages of 18-35, (c) achieve a standard nonverbal IQ score of 85 or higher, (d) achieve standard scores of 90 or higher on all four reading measures, and (e) have no medical implants. Participants that reported diagnoses (e.g., depression, anxiety, ADHD) or medications (e.g., Prozac, Zoloft) were also excluded. These diagnoses and classes of medications significantly impact the function of neurotransmitter systems critical for VNS [17,18,36]. Thus, we excluded these individuals to ensure all participants had, to the best of our knowledge, typical neurotransmitter function to minimize any potential interaction with stimulation.

In addition to inclusion testing, participants also completed additional reading measures, including Passage Comprehension and Oral Fluency (WRMT-3) [35] and Rapid Digit and Letter Naming (i.e., naming a nine-by-four grid as quickly and accurately as possible; CTOPP-2) [37]. Finally, we also administered assessments of learning and memory utilizing four subtests of the WRAML-2 [38]. The Design Memory Core subtest required participants to reproduce images after viewing them and a short delay. The Verbal Learning Core subtest included four trials of hearing a long list of words and then immediately repeating as many as possible. In the Number-Letter subtest, participants listened to combinations of letters and numbers, progressing in difficulty, and immediately repeated them verbatim. The Design Memory Recognition subtest probed the participant's memory of the shapes viewed in the Design Memory Core subtest. Finally, the Verbal Learning Recall subtest asked participants to name as many words as possible from the Verbal Learning Core after a 10-minute delay. Assessments were only used for screening and not readministered after the study.

Of the participants who completed screening, 11 were excluded for low reading scores, five for low IQ, six for exclusionary medications or diagnoses, three for safety concerns related to the placement of the taVNS device, two for scheduling conflicts, and four did not complete the study due to non-response or withdrawal. Thus, the final sample included 24 typically developing young adults (descriptive statistics of standard scores are presented in Table 1). Eligible participants were randomized into a sham taVNS (n = 12) or active taVNS (n = 12) group. The decision to use these two groups was based off previous work in our lab [30] that compared a training only group, a sham taVNS group, an earlobe stimulation group (region not innervated by the vagus nerve), and an active taVNS group, in a between-groups design. In this prior study, analyses showed that active taVNS outperformed all the control groups, but the device sham group was closest in performance to the active taVNS group. Thus, we decided to incorporate a sham taVNS group as this group seemed most likely to demonstrate a placebo effect, if one were to occur.

While we originally planned to recruit a larger sample size in the study, recruitment was terminated due to safety concerns regarding in-person research and potential confounds during the COVID-19 pandemic. Each experimental group consisted of ten participants that completed the study using a Parasym taVNS device (Parasym, Ltd., London, UK) and two additional participants that completed the study using the TENS7000 transcutaneous electrical nerve stimulation (TENS) device (TENS7000, Middleburg Heights, OH). The TENS device participants completed the study first, while we waited for the Parasym devices to arrive at the lab, for use in this study. To ensure that the difference in stimulation device did not impact the results, we conducted a confirmatory analysis in the sample trained using only the Parasym device. Given the lack of differences, we combined the groups to increase statistical power in this pilot study. However, future research is needed with larger sample sizes using a consistent paradigm to replicate this study.

All participants were compensated with course credit, and the study was approved by the Texas Christian University Institutional Review Board. All participants provided written informed consent prior to enrollment.

2. 2. Materials and Procedures

2. 2. 1. taVNS device, settings, and procedures

Most participants ($n_{sham} = 10$, $n_{active} = 10$) received taVNS from the Parasym device (Figure 1A), which utilizes a one-quarter inch diameter gold-plated copper electrode. For a subset of participants ($n_{sham} = 2$, $n_{active} = 2$), taVNS was administered using the TENS7000 device (Figure 1B). This device utilized an earpiece linked to an electrode with a separate grounding pad placed behind the ear. Regardless of device, the stimulating electrode was positioned at the posterior tragus of the left ear to stimulate the auricular branch of the vagus nerve [25,27]. Identical parameters were used across devices such that current was delivered as square, biphasic pulses with a 200 µs pulse width, and 5 Hz frequency [30]. During the testing session, stimulation onset and offset were controlled manually by a trained researcher. Stimulation was delivered only during oral reading to model previous research suggesting that VNS efficacy relies heavily on pairing stimulation with the external training stimulus, such as a tone [19] or movement [40,41].

Each participant received a stimulation at a customized intensity level to ensure comfort, as stimulation was given above sensory threshold. This intensity level was determined for each participant during a short thresholding procedure (Table 2). A trained researcher acquired two measurements at each participant's absolute minimum threshold and two measurements at the upper level of comfort, prior to the onset of pain [27,30]. The average of these four measurements was then used as the participant's stimulation current throughout the study. The average current threshold across the entire sample was (N = 24; 2.03 ± .10 mA), with the sham taVNS group exhibiting marginally higher thresholds (2.23 ± .11 mA) than the active taVNS group (1.84 ± .16 mA; unpaired two-tailed t-test, t (22) = 2.69, p = .057, d = .83). Participants using the TENS device had thresholding intensities that ranged from 1 mA to 3 mA, and participants using the Parasym device had thresholding intensities that ranged from 1.1 mA to 2.7 mA.

2. 2. 2. Reading comprehension measure

To evaluate the effect of taVNS on reading comprehension, participants read passages from both forms of the GORT-5 [42] in a counterbalanced order. For each form, passage 6 was administered as a practice passage, and passages 11-16 were administered as test passages. Test passages ranged from 131 to 284 words (179.42 ± 44.12 words). Passages were presented in white font on a black background using custom code in PsychoPy [43]. For each passage, participants read the text out loud at their normal pace and pressed a button when finished, which removed the passage from the screen (Figure 2A). Stimulation was manually controlled by an experienced researcher from behind a barrier and was turned on at the initiation of each passage and turned off as soon as the participant finished reading. For those in the sham condition, the device remained off throughout the session without the participants' knowledge. To quantify any effect of taVNS on reading mechanics, we calculated average reading errors per passage [44] and average reading rate per passage [45,46]. Reading errors were calculated as the total number of deviations from print per passage (e.g., mispronounced words, added words, omission of words, and changes in the order of words). Reading rate was calculated as the number of words read per minute (wpm) per passage. As there was no effect of test form on percent of test questions correct (paired two-tailed t-test; t (23) = .20, p = .84), both forms were combined for subsequent analyses.

Immediately after reading each passage, a researcher asked the accompanying five test questions as provided in the GORT-5 (Figure 2B) [42]. To score the test questions, correct answers were awarded one point, and incorrect answers were given zero points, with no partial credit given. Raw scores out of 60 possible questions were converted to a percent correct for further analysis. To ensure accuracy of scoring, two trained researchers each scored participant responses, and discrepancies were resolved by coming to a consensus. No adverse events occurred during the session.

To analyze performance, authors VJT and AD classified each test question as a memory question (i.e., the answer being explicitly stated in the passage, such as recalling the name of a character in the passage) or a comprehension question (i.e., the reader must have an understanding beyond what is explicitly stated in the passage, such as inferring the attitude of the writer of the passage). There were minimal discrepancies, which were resolved by author TMC. In total, 45 questions were classified as memory questions (75% of total questions) and 15 questions as comprehension (25% of total questions). Classification of each individual question is provided in Table S1.

2. 3. Blinding procedure for stimulation sessions

During the reading paired with stimulation, the stimulation device was hidden behind a barrier, so that the participant could not see it. Those participants randomized into the sham taVNS group underwent the same thresholding procedure as those in the active taVNS group. Participants were told that each person may experience the stimulation differently and that some may not even detect the stimulation during training. At the end of the study, participants were debriefed, during which they were told about the existence of a control group and then asked to guess which group they were randomized to. Given the suprathreshold stimulation, we were not surprised to see a majority (83%) of participants in the active taVNS group guessed their group assignment. Importantly participants in the sham group were at chance level at detecting their group assignment (50%), suggesting the blinding procedure was effective.

2. 4. Statistical analysis plan

Two-tailed, independent-samples *t*-tests were used to compare the sham taVNS and active taVNS groups on standard English assessments and evaluate any differences in baseline reading abilities. Descriptive statistics for participant age and standard scores on assessments are presented as M ± SD (Table 1).

To investigate the effect of taVNS on reading, we used two-tailed, independent-samples *t*-tests on each of the key dependent variables, unless otherwise noted. All descriptive statistics for outcome measures are reported as the M ± SEM.

Pearson's *r* was used to determine if variability in individual current intensity was related to comprehension performance in the active taVNS group. Finally, we used Pearson's *r* to quantify the relationships between two verbal memory measures and comprehension performance. The Bonferroni correction was used to correct for multiple comparisons. All data were analyzed using custom scripts in MATLAB (MathWorks, Portola Valley, CA).

3. Results

3. 1. Significant effect of taVNS on recall of read content

We first evaluated whether active taVNS was associated with changes in reading accuracy or reading rate. Given prior reports that another form of neuromodulation, repetitive transcranial magnetic stimulation (TMS), can improve performance on these reading metrics [44], we tested the hypothesis that reading mechanics may also benefit from taVNS. In terms of accuracy, there was no group difference between sham (3.26 ± .51 errors per passage) and active taVNS (2.53 ± .46 errors per passage; t (22) = 1.12, p = .28; Figure 3A). In terms of average reading rate (words per minute; wpm), there was also no difference between sham (144.38 ± 6.78 wpm) and active taVNS (147.73 ± 4.97 wpm; t (22) = .42, p = .68; Figure 3B). These results suggest that unlike other forms of non-invasive stimulation, taVNS may not influence the mechanics of reading within the session.

We next evaluated the effect of taVNS on comprehension. There was a significant effect of stimulation across all test questions (t (22) = 2.59, p = .017, d = 1.06; Figure 4A) such that participants receiving active taVNS achieved higher scores compared to those receiving sham taVNS. To determine whether this effect was driven by performance on a specific question type, we evaluated whether active taVNS was associated with improved performance on the subsets of memory and comprehension questions separately. There was a significant group difference on memory questions such that the active taVNS group (49.63 ± 3.47%) significantly outperformed the sham taVNS group (37.04 ± 3.47%; t (22) = 3.00, p = .007, d = 1.23; Figure 4B). This result survived correction for multiple comparisons. There was no difference between the sham taVNS (35.55 ± 5.24%) and active taVNS group (39.44 ± 4.06%) on the comprehension questions (t (22) = .61, p = .54; Figure 4C).

Since each participant received a custom current level, we evaluated the relationship between current intensity and memory performance in the active taVNS group using Pearson's r correlations to determine if current intensity influenced outcomes. Across the entire active taVNS group (n = 12), there was no significant relationship between current intensity and percent correct (r = .27, p = .40). Due to subtle differences in current output across devices, we replicated this analysis in the participants that received stimulation from the Parasym device (n = 10). There was again no significant relationship between current intensity and percent correct (r = .33, p = .35; Figure 5), suggesting that current intensity did not influence taVNS efficacy in this sample.

3. 2. No effect of stimulation device on outcome measures

Most participants completed the study using the Parasym taVNS device (n = 20), while a small subset of participants completed the study using a TENS7000 device (n = 4). To ensure that the stimulation device used did not impact the findings, we repeated our analyses in the participants that received stimulation from the Parasym device and replicated our findings. In this subsample, there was no benefit of active taVNS on reading accuracy (t (18) = .13, p = .90) or on reading rate (t (18) = .17, p = .87). With respect to test performance, there was a significant benefit of taVNS on memory questions (t (18) = 2.33, p = .03) but there was no group difference on comprehension questions (t (18) = .19, p = .86). This consistent pattern of results suggests that stimulation device differences did not impact the efficacy of posterior tragus stimulation of the auricular vagus nerve on our dependent measures.

3. 3. Relationships between verbal working memory and performance on test questions

Prior evidence suggests that comprehension abilities require working memory skills [2]. To investigate whether taVNS influenced this relationship, we next utilized Pearson's *r* to evaluate the relationships between verbal working memory and performance on memory questions in each experimental group separately. In the sham taVNS group, there was no relationship between Verbal Learning Core standardized scores (WRAML-2) [38] and performance on memory questions ($r = .05$, $p = .88$). However, there was a significant positive correlation between these metrics within the active taVNS group, which survived correction ($r = .65$, $p = .023$). Similarly, in the sham taVNS group, there was no significant relationship between Verbal Learning Recall standardized scores (WRAML-2) [38] and performance on memory questions ($r = -.39$, $p = .24$), but there was a significant, positive relationship in the active taVNS group, which survived correction ($r = .65$, $p = .021$).

At baseline, participants also completed an additional verbal short-term working memory task in which strings of numbers and letters were read by a researcher and then repeated immediately by the participant. The active taVNS group exhibited higher scores on this measure compared to the sham taVNS group. Thus, we evaluated the relationship between performance on this measure and the memory recall scores across the entire sample using Pearson's *r*. There was no significant relationship between Number-Letter working memory scores and performance on memory-based questions ($r = .13$, $p = .54$).

3. 4. Stimulation dosage was not related to memory performance

Since stimulation duration was determined by reading speed, some participants may have received more time receiving stimulation than others. In the current pilot study, however, duration of stimulation did not differ between the sham taVNS (80.83 ± 4.21 seconds per passage) and active taVNS (78.33 ± 2.81 seconds per passage) groups (unpaired, two-tailed *t*-test: $t\ (22) = .52$, $p = .61$. Further, there was no significant relationship between duration of stimulation and memory performance in the active taVNS group ($r = .15$, $p = .65$).

4. Discussion

The goal of the current pilot study was to evaluate the effect of taVNS on reading comprehension in a sample of typically developing young adult readers. Our results demonstrate, for the first time, that active taVNS, compared to sham taVNS, paired with reading is associated with increased performance on memory-based recall of previously read material, a higher-level reading skill. However, there was no effect of taVNS on comprehension question performance or on the mechanics of oral reading (e.g., reading accuracy and reading rate). These findings support our prior work demonstrating that taVNS is associated with improved reading skills [30] but indicate that the efficacy of taVNS may be limited to tasks relying on sensory plasticity and memory of explicitly trained materials [17,18,19,20,21], rather than inference.

4.1. Comparison to behavioral reading comprehension interventions

Vagus nerve stimulation, when paired with sensory stimuli or motor movements, leads to enhanced learning and measurable neural plasticity in both the animal model and in humans [17,28,32,36]. A growing body of work suggests that taVNS may be as effective in these paradigms as cVNS [28,47], providing a non-invasive option for sensitive populations. In the current pilot study, we observed robust effects of taVNS on memory questions in a single session of stimulation, which suggests the addition of taVNS may accelerate the benefits of traditional behavioral interventions which require weeks to months of consistent training. For example, previous randomized controlled trials of classroom interventions, such as *Let's Know!* [48,49,50,51] required multiple sessions per week for several weeks to produce significant improvement in reading comprehension. In the current pilot study, we attempted to bypass this long training time by pairing taVNS with a single session of real-time reading. While our initial findings are encouraging and support the use of this approach for sensory and motor deficits, previous studies also suggest that VNS may be limited in its ability to improve generalized learning. For example, cVNS and taVNS paired with physical therapy increase post-stroke motor function recovery [28,52], but those benefits were specific to the movements taught in training and did not generalize to untrained skills.

It is possible that extended and generalizable benefits could be observed in other training domains since long-term sensory plasticity has been reported in both the rodent model up to three weeks after auditory therapy [19] and in humans between three- and six-months after movement therapy [36]. Future research should investigate the generalizability of taVNS for reading comprehension to determine whether stimulation also increases performance on untrained passages. Importantly, comprehension questions are often more difficult than memory recall questions, since additional information must be extracted from what the student has read or studied. Given our observation that pairing stimulation with reading was not sufficient to improve comprehension performance, it is important for future research to investigate whether other forms of stimulation (e.g., timing, type of passage used, etc.) may improve this skill.

Finally, interventions [53] administered to struggling readers have improved reading comprehension skills. The current pilot study was conducted on typically developing young adults with average or above-average low-level reading skills, and it is currently unknown whether taVNS is effective in those with reading disorders. Individuals with dyslexia exhibit deficits in a variety of lower-level reading skills, such as decoding [54], phonological awareness [55,56,57], and automaticity [58,59,60]. Those who struggle with these low-level reading skills are often forced to focus their cognitive resources on the mechanics of reading rather than on absorbing the content of a passage. It is therefore possible that a taVNS intervention for dyslexia would require a focus on the mechanics of reading rather than on comprehension. While our prior work [30] demonstrated benefits of taVNS on automaticity and decoding in letter-sound learning, it is unknown whether this approach is effective in individuals with dyslexia.

4. 2. Baseline verbal memory skills influence reading comprehension

Reading comprehension is a complex process that requires multiple lower-level skills working together. In addition, readers must extract meaning from text beyond information that is explicitly stated, referred to as comprehension (understanding the text) and inference (making conclusions that go beyond the states text). Since our data suggest no benefit of taVNS on comprehension questions, future research should examine other parameters or paradigms to investigate if taVNS can improve these skills. For example, one taVNS study employed stimulation during encoding (training) and a brief consolidation period in a face-name association task [32]. Their results suggest that pairing with training and during consolidation does yield a significant benefit in face-name association learning, which is also a memory task. A second study stimulated participants after they read passages and then probed recall of highlighted words, with positive results [22]. While there is an abundance of evidence that stimulation during training is effective in driving neural plasticity [19,28], there is inadequate taVNS research that compares stimulation during training with stimulation during training and consolidation. Given the importance of comprehension skills, future work is needed to explore whether changes to the stimulation protocol can elicit a taVNS effect on memory recall and comprehension, rather than just memory recall.

Surprisingly, we observed significant, positive correlations between baseline verbal working memory tasks (learning and recall) and performance on memory questions in the active taVNS group, but not in the sham taVNS group. Executive functions, such as updating and shifting, contribute to reading comprehension (see [61] for a review) and working memory is essential for retaining and integrating information from text [62]. Additional findings have corroborated these relationships between memory skills and reading comprehension with other verbal memory tasks (e.g., sentence span; [63]) and in individuals with inadequate reading skills [64]. One meta-analysis reported that higher executive functions (e.g., reading span, counting span, digit span) were significantly correlated with increased reading comprehension, even after accounting for several covariates, such as age or type of assessment used [65]. Collectively, these data suggest that regardless of age, memory consistently plays a significant role in comprehension ability and supports the link between verbal working memory and reading comprehension.

While the relationship between working memory and reading comprehension is expected, we were surprised to find that the relationship between verbal working memory and comprehension was significant only in the active taVNS group. Given that this relationship was present in the active group but not the sham group, it is possible that some aspect of the taVNS mechanism interacts with the neural circuitry subserving these existing skills to boost performance. Thus, we hypothesize that pairing stimulation with reading takes advantage of existing neural circuitry, in this case that which supports verbal working memory, to enhance memory for read content. Given that vagus nerve stimulation relies on precisely timed release of neurotransmitters such as norepinephrine and acetylcholine, we suggest that these chemicals act by strengthening existing synapses in the typically developing brain rather than encourage the formation of new connections [19,66]. However, future mechanistic research is needed to determine whether this is in fact the case, whether changes in stimulation parameters have a different effect, and additional translational work is needed to determine whether these mechanisms are consistent in the brains of those with dyslexia.

4. 3. No effect of current intensity on taVNS efficacy

Previous work investigating the impact of current intensity on cVNS efficacy in the rat model [39] and in humans [22] reported that moderate stimulation intensities were more effective than higher stimulation intensities [39]. A similar effect was reported in humans such that moderate intensities were more effective than higher current intensities for improvement on a recognition memory task [22]. Contrary to this evidence from the cVNS literature, we observed no relationship between taVNS current intensity and performance on comprehension. It is possible that taVNS exhibits a different dose-response curve with respect to current intensity compared to invasive vagus nerve stimulation. One study reported that taVNS delivered at intensities below sensory threshold can selectively enhance speech sound categorization of Mandarin tones [31]. Studies conducted above sensory threshold have also reported a benefit of taVNS, in cognitive tasks such as face-name association [32] and novel letter-sound learning [30]. The presence of a stimulation effect at a variety of intensities suggests that current intensity may be less important in taVNS protocols than in cVNS protocols. However, it is important to note that no study to date has explicitly manipulated current intensity or systematically investigated potential relationships between current intensity, learning, and retention. The taVNS current intensity parameter must be explored systematically to optimize future clinically relevant stimulation protocols targeting a variety of tasks.

4. 4. Limitations

There are four key limitations in the current study. First, it is important to note that our choice of the GORT-5 as our measure of reading comprehension carries its own caveats. For example, most questions (45) were classified as memory-based questions, and only 15 of the questions were classified as comprehension questions. Thus, we may have been underpowered to detect an effect of taVNS on this type of measure. In addition, it is important to note that performance on the task was quite low overall, perhaps because our passages included many low-frequency words. Given the added pressure of reading out loud, participants may have spent more cognitive effort focusing on decoding of these words rather than processing meaning. Future research should investigate if similar results are found in passages with high-frequency words, such that participants may need less effort to decode unfamiliar words. Findings from such a study would suggest that readers, when not pressured to focus on decoding low-frequency words, can still maintain enhanced comprehension when paired with taVNS.

Second, participants were recruited from an online participant pool. In our case, this pool of participants is generally made up of individuals from mid- to high socioeconomic (SES) backgrounds, limiting our ability to generalize these findings. Previous research suggests that home environment and SES strongly influence future reading ability [67,68,69,70]. Specifically, children from a low SES background have more phonological deficits than those from higher SES homes, and phonological skills are necessary for successful reading [67]. Future research should replicate the current methodology in a sample that comes from a wider range of SES backgrounds to determine whether the biological impact of a lower SES upbringing impact the efficacy of taVNS, as lower SES has been linked to lower white matter tracts [71,72] suggesting the growing importance of SES in white matter development [73]. Further, lower SES has been associated with higher levels of norepinephrine [74], which would likely impact the efficacy of vagus nerve stimulation [17,18,36].

Third, our sample size was underpowered due to the forced discontinuation of in-person research during the COVID-19 pandemic. A post-hoc analysis (d = 1.23, α = .05, n_{sham} = 12, n_{active} = 12) yielded a power of .82, confirming we did meet adequate power and these data should thus be interpreted with caution, as a pilot study. Future research is needed to replicate these findings in a larger and more diverse sample.

Fourth, previous research has also suggested that oral language measures, such as syntax and vocabulary, are related to reading comprehension skills [75], and these were not measured as part of the standard English assessments testing eligibility. An assessment was added to the full study after these pilot data were collected, but then the onset of COVID-19 led to data collection being terminated for this study. Future studies evaluating taVNS and reading comprehension should be sure to include such measures.

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Conflicts of Interest

The authors have no conflicts of interest to declare.

CRediT Author Statement

Vishal J. Thakkar: methodology, software, formal analysis, investigation, data curation, writing, **Zoe A. Richardson:** data curation, writing, **Annie Dang:** data curation, **Tracy M. Centanni:** conceptualization, methodology, software, data curation, writing, supervision, project administration

References

1. Landi N, Ryherd K. Understanding reading comprehension deficit: A review. Lang Linguistics Compass. 2017;11(2):e12234. https://doi.org/10.1111/lnc3.12234

2. Cain K, Oakhill J, Bryant P. Children's reading comprehension ability: Concurrent prediction by working memory, verbal ability, and component skills. J Educ Psychol. 2004;96(1):31-42. https://doi.org/10.1037/0022-0663.96.1.31

3. Landi N, Frost SJ, Mencl WE, Sandak R, Pugh KR. Neurobiological bases of reading comprehension: Insights from neuroimaging studies of word-level and text-level processing in skilled and impaired readers. Read Writ Q. 2013;29:145-67. https://doi.org/10.1080/10573569.2013.758566

4. Kendeou P, McMaster KL, Christ TJ. Reading comprehension: Core components and processes. Policy Insights from the Behav Brain Sci. 2016;3(1):62-9. https://doi.org/10.1177%2F2372732215624707

5. Imam OA. Effects of reading skills on students' performance in science and mathematics in public and private secondary schools. J Educ Learn. 2016;10(2):177-86.

6. Centanni TM, King LW, Eddy MD, Whitfield-Gabrieli S, Gabrieli, JDE. Development of sensitivity versus specificity for print in the visual word form area. Brain Lang. 2017;170:62-70. http://dx.doi.org/10.1016/j.bandl.2017.03.009

7. McCandliss BD, Cohen L, Dehaene S. The visual word form area: Expertise for reading in the fusiform gyrus. Trends Cogn Sci. 2013;7(7):293-9. https://doi.org/10.1016/S1364-6613(03)00134-7

8. Kim Y-SG. Developmental, component-based model of reading fluency: An investigation of predictors of word-reading fluency, text-reading fluency, and reading comprehension. Read Res Q. 2015;50(4):459-81.

9. Oliver R, Young S. Improving reading fluency and comprehension in adult ESL learners using bottom-up and top-down vocabulary training. Stud Second Lang Learn Teach. 2016;6(1):111-33. https://doi.org/10.14746/ssllt.2016.6.1.6

10. Griffiths GG, Sohlberg MM, Kirk C, Fickas S, Biancarosa G. Evaluation of use of reading comprehension strategies to improve reading comprehension of adult college students with acquired brain injury. Neuropsychol Rehabil, 2016 ;26(2) :161-90. https://doi.org/10.1080/09602011.2015.1007878

11. Sabatini JP, Shore J, Holtzman S, Scarborough HS. Relative effectiveness of reading intervention programs for adults with low literacy. J Res on Educ Effect. 2011;4:118-33. https://doi.org/10.1080/19345747.2011.555290

12. Younger JW, Booth JR. Parietotemporal stimulation affects acquisition of novel grapheme-phoneme mappings in adult readers. Front Hum Neurosci. 2018;12:109: https://doi.org/10.3389/fnhum.2018.00109

13. Costanzo F, Varuzza C, Rossi S, Sdoia S, Varvara P, Oliveri M, Koch G, Vicari S, Menghini D. Reading changes in children and adolescents with dyslexia after transcranial direct current stimulation. NeuroReport. 2016;27:295-300. doi: 10.1097/WNR.0000000000000536

14. Costanzo F, Rossi S, Varuzza C, Varvara P, Vicari S, Menghini D. Long-lasting improvement following tDCS treatment combined with training for reading in children and adolescents with dyslexia. Neuropsychologia. 2019;130:38-43. https://doi.org/10.1016/j.neuropsychologia.2018.03.016

15. Picciotto MR, Higley MJ, Mineur YS. Acetylcholine as a neuromodulator: Cholinergic signaling shapes nervous systems function and behavior. Neuron. 2012;76(1): 116-29. https://doi.org/10.1016/j.neuron.2012.08.036

16. Tully K, Volshakov VY. Emotional enhancement of memory: How norepinephrine enables synaptic plasticity. Mol Brain. 2010;3:15. https://doi.org/10.1186/1756-6606-3-15

17. Hulsey DR, Hays SA, Khodaparast N, Ruiz A, Das P, Rennaker RL, Kilgard MP. Reorganization of motor cortex by vagus nerve stimulation requires cholinergic innervation. Brain Stimul. 2016;9:174-81. http://dx.doi.org/10.1016/j.brs.2015.12.007

18. Hulsey DR, Shedd CM, Sarker SF, Kilgard MP, Hays SA. Norepinephrine and serotonin are required for vagus nerve stimulation directed cortical plasticity. Exp Neurol. 2019;320:112975. https://doi.org/10.1016/j.expneurol.2019.112975

19. Engineer ND, Riley JR, Seale JD, Vrana WA, Shetake JA, Sudanagunta SP, Borland MS, Kilgard MP. Reversing pathological neural activity using targeted plasticity. Nature. 2011;470:101-106. https://doi.org/10.1038/nature09656

20. Khodaparast N, Hays SA, Sloan AM, Hulsey DR, Ruiz A, Pantoja RL, Kilgard MP. Vagus nerve stimulation during rehabilitative training improves forelimb strength following ischemic stroke. Neurobiol Disease. 2013;60:80-88. doi: 10.1016/j.nbd.2013.08.002

21. Porter BA, Khodaparast N, Fayyaz T, Cheung RJ, Ahmed SS, Vrana WA, Rennaker RL, Kilgard MP. Repeated pairing vagus nerve stimulation with a movement reorganizes primary motor cortex. Cereb Cortex. 2012;22:2365-74. doi:10.1093/cercor/bhr316

22. Clark KB, Naritoku DK, Smith DC, Browning RA, Jensen RA. Enhanced recognition memory following vagus nerve stimulation in human subjects. Nat Neurosci. 1999;2(1):94-8. https://doi.org/10.1038/4600

23. Sun L, Perakyla J, Holm K, Haapasalo J, Lehtimaki K, Ogawa KH, Peltola J, Hartikainen KM. Vagus nerve stimulation improves working memory performance. J Clin Exp Neuropsychol. 2017;39(10):954-64. https://doi.org/10.1080/13803395.2017.1285869

24. Sackeim HA, Keilp JG, Rush AJ, George MS, Marangell LB, Dormer JS, Burt T, Lisanby SH, Husain M, Cullum CM, Oliver, N., & Zboyan, H. The effects of vagus nerve stimulation on cognitive performance in patients with treatment-resistant depression. Neuropsych, Neuropsychol, and Beh Neurol. 2001;14(1):53-62.

25. Badran BW, Dowdle LT, Mithoefer OJ, LaBate NT, Coatsworth J, Brown JC, DeVries WH, Austelle CW, McTeague LM, George MS. Neurophysiologic effects of transcutaneous auricular vagus nerve stimulation (taVNS) via electrical stimulation of the tragus: A concurrent taVNS/fMRI study and review. Brain Stimul. 2018;11:492-500. https://doi.org/10.1016/j.brs.2017.12.009

26. Frangos E, Ellrich J, Komisaruk BR. Non-invasive access to the vagus nerve central projections via electrical stimulation of the external ear: fMRI evidence in humans. Brain Stimul. 2015;8(3):624-36. https://doi.org/10.1016/j.brs.2014.11.018

27. Yakunina N, Kim SS, Nam E-C. Optimization of transcutaneous vagus nerve stimulation using functional MRI. Neuromodulation. 2016;20(3):290-300. https://doi.org/10.1111/ner.12541

28. Redgrave JN, Moore L, Oyekunle T, Ebrahim M, Falidas K, Snowdon N, Ali A, Majid A. Transcutaneous auricular vagus nerve stimulation with concurrent upper limb repetitive task practice for poststroke motor recovery: A pilot study. J Stroke Cerebrovasc Dis. 2018;27(7):1998-2005. https://doi.org/10.1016/j.jstrokecerebrovasdis.2018.02.056

29. Yakunina N, Kim SS, Nam E-C. BOLD fMRI effects of transcutaneous vagus nerve stimulation in patients with chronic tinnitus. PLoS ONE. 2018;13(11):e0207281. doi: https://doi.org/10.1371/journal.pone.0207281

30. Thakkar VJ, Engelhart AS, Khodaparast N, Abadzi H, Centanni TM. Transcutaneous auricular vagus nerve stimulation enhances learning of novel letter-sound relationships in adults. Brain Stimul. 2020;13(6):1813-1820. https://doi.org/10.1016/j.brs.2020.10.012

31. Llanos F, McHaney JR, Schuerman WL, Yi HG, Leonard MK, Chandrasekaran B. Non-invasive peripheral nerve stimulation selectively enhances speech category learning in adults. NPJ Sci Learn. 2020;5:12. https://doi.org/10.1038/s41539-020-0070-0

32. Jacobs HIL, Riphagen JM, Razat CM, Wiese S, Sack AT. Transcutaneous vagus nerve stimulation boosts associative memory in older individuals. Neurobiol Aging. 2015;36:1860-7. http://dx.doi.org/10.1016/j.neurobiolaging.2015.02.023

33. Kaufman AS, Kaufman NL. K-BIT: Kaufman brief intelligence test. (2nd ed.). 2004; Bloomington, MN: Pearson.

34. Torgesen J, Wagner R, Rashotte C. Test of word reading efficiency (2nd ed.). 2012; Austin, TX: ProEd, Inc.

35. Woodcock, RW. Woodcock reading mastery tests. (3rd ed.). 2011;Bloomington, MN: American Guidance Service Circle Pines.

36. De Ridder D, Vanneste S, Engineer ND, Kilgard MP. Safety and efficacy of vagus nerve stimulation paired with tones for the treatment of tinnitus: A case series. Neuromodulation. 2013;17:170-9. https://doi.org/10.1111/ner.12127

37. Wagner RK, Torgesen JK, Rashotte CA. CTOPP-2: Comprehensive test of phonological processing. (2nd ed.). 2013;Austin, TX: ProEd, Inc.

38. Sheslow D, Adams W. Wide range assessment of memory and learning. (2nd ed.). 2009;Austin, TX: ProEd, Inc.

39. Borland MS, Vrana WA, Moreno NA, Fogarty EA, Buell EP, Sharma P, Engineer CT, Kilgard MP. Cortical map plasticity as a function of vagus nerve stimulation intensity. Brain Stimul. 2016;9:117-23. http://dx.doi.org/10.1016/j.brs.2015.08.018

40. Pruitt DT, Schmid AN, Kim LJ, Abe CM, Trieu JL, Choua C, Hays SA, Kilgard MP, Rennaker RL. Vagus nerve stimulation delivered with motor training enhances recovery of function after traumatic brain injury. J Neurotrama. 2016;33:871-9. https://doi.org/10.1089/neu.2015.3972

41. Morrison RA, Danaphongse TT, Pruitt DT, Adcock KS, Mathew JK, Abe ST, Abdulla DM, Rennaker RL, Kilgard MP, Hays SA. A limited range of vagus nerve stimulation intensities produce motor cortex reorganization when delivered during training. Behav Brain Res. 2020;391:112705. https://doi.org/10.1016/j.bbr.2020.112705

42. Wiederholt JL, Bryant BR. Gray oral reading tests. (5th ed.). 2012;Austin, TX: ProEd, Inc.

43. Peirce J, Gray JR, Simpson S, MacAskill M, Hochenberger R, Sogo H, Kastman E, Lindelov, JK. PsychoPy2: Experiments in behavior made easy. Behav Res Methods. 2019;51(1):195-203. https://doi.org/10.3758/s13428-018-01193-y

44. Costanzo F, Menghini D, Caltagirone C, Oliveri M, Vicari S. How to improve reading skills in dyslexics: The effect of high frequency rTMS. Neuropsychologia. 2013;51:2953-59. http://dx.doi.org/10.1016/j.neuropsychologia.2013.10.D18

45. O'Brien BA, Mansfield JS, Legge GE. The effect of print size on reading speed in dyslexia. J Res Read. 2005;28(3):332-49. https://doi.org/10.1111/j.1467-9817.2005.00273.x

46. O'Brien BA, Wallot S. Silent reading fluency and comprehension in bilingual children. Front Psychol. 2016;7:1265. doi: 10.3389/fpsyg.2016.01265

47. Lehtimaki J, Hyvarinen P, Ylikoski M, Bergholm M, Makela JP, Aarnisalo A, Pirvola U, Makitie A, Ylikoski J. Transcutaneous vagus nerve stimulation in tinnitus: A pilot study. Acta Oto-Laryngol. 2013;133:378-82. https://doi.org/10.3109/00016489.2012.750736

48. LARRC. Learning to read: Should we keep things simple?. Read Res Q. 2015;50(2):151-69. https://doi.org/10.1002/rrq.99

49. LARRC, Chiu YD. The simple view of reading across development: Prediction of grade 3 reading comprehension from prekindergarten skills. RASE. 2018;39(5):289-303. https://doi.org/10.1177/0741932518762055

50. LARRC, Pratt A, Logan J. Improving language-focused comprehension instruction in primary-grade classrooms: Impacts of the Let's Know! experimental curriculum. Educ Psychol Rev. 2014;26:357-377. https://doi.org/10.1044/2019_JSLHR-L-19-0015

51. Clarke PJ, Snowling MJ, Truelove E, Hulme C. Ameliorating children's reading-comprehension difficulties: A randomized controlled trial. Psychol Sci. 2009;21(8):1106-16. https://doi.org/10.1177/0956797610375449

52. Dawson J, Pierce D, Dixit A, Kimberley TJ, Robertson M, Traver B, Hilmi O, McLean J, Forbes K, Kilgard MP, Rennaker RL, Cramer SC, Walters M, Engineer N. Safety, feasibility, and efficacy of vagus nerve stimulation paired with upper-limb rehabilitation after ischemic stroke. Stroke. 2016;47:143-50. https://doi.org/10.1161/STROKEAHA.115.010477

53. Martins LZ, Cárnio MS. Reading comprehension in dyslexic schoolchildren after an intervention program. CoDAS. 2020;32(1):e20180156. https://doi.org/10.1590/2317-1782/20192018156

54. Lyon GR, Shaywitz SE, Shaywitz BA. A definition of dyslexia. Ann Dyslexia, 2003;53:1-14. http://dx.doi.org/10.1007/s11881-003-0001-9

55. Bradley L, Bryant PE. Difficulties in auditory organization as a possible cause of reading backwardness. Nature. 1978;271:746-47. https://doi.org/10.1038/271746a0

56. White S, Milne E, Rosen S, Hansen P, Swettenham J, Frith U, Ramus F. The role of sensorimotor impairments in dyslexia: A multiple case study of dyslexic children. Dev Sci. 2006;9(3):265-269. https://doi.org/10.1111/j.1467-7687.2006.00483.x

57. Zuk J, Perdue MV, Becker B, Yu X, Chang M, Raschle NM, Gaab N. Neural correlates of phonological processing: Disrupted in children with dyslexia and enhanced in musically trained children. Dev Cogn Neurosci. 2018;34:82-91. https://doi.org/10.1016/j.dcn.2018.07.001

58. Norton ES, Wolf M. Rapid automized naming (RAN) and reading fluency: Implications for understanding and treatment of reading disabilities. Annu Rev Psychol. 2012;63:427-52. https://doi.org/10.1146/annurev-psych-120710-100431

59. Pennington BF, Bishop DVM. Relations among speech, language, and reading disorders. Annu Rev Psychol. 2009;60:283-306. https://doi.org/10.1146/annurev.psych.60.110707.163548

60. Wolf M, Obregón M. Early naming deficits, developmental dyslexia, and a specific deficit hypothesis. Brain Lang. 1992;42:219-47. https://doi.org/10.1016/0093-934X(92)90099-Z

61. Butterfuss R, Kendeou P. The role of executive functions in reading comprehension. Educ Psychol Rev. 2018;30(3):801-826. https://doi.org/10.1007/s10648-017-9422-6

62. Spencer M, Richmond MC, Cutting LE. Considering the role of executive function in reading comprehension: A structural equation modeling approach. Sci Stud Read. 2020;24(3):179-99. https://doi.org/10.1080/10888438.2019.1643868

63. Daneman M, Carpenter PA. Individual differences in working memory and reading. J Verbal Learn Verbal Behav. 1980;19:450-66. https://doi.org/10.1016/S0022-5371(80)90312-6

64. Peng P, Barnes M, Wang C, Wang W, Li S, Swanson HL, Dardick W, Tao S. A meta-analysis on the relation between reading and working memory. Psychol Bull. 2018;144(1):48-76. http://dx.doi.org/10.1037/bul0000124

65. Follmer DJ. Executive function and reading comprehension: A meta-analytic review. Educ Psychol. 2018;53(1):42-60. https://doi.org/10.1080/00461520.2017.1309295

66. Hays SA, Rennaker RL, Kilgard MP. Targeting plasticity with vagus nerve stimulation to treat neurological disease. Prog Brain Res. 2013;207:275-299. https://doi.org/10.1016/B978-0-444-63327-9.00010-2

67. Bowey JA. Socioeconomic status differences in preschool phonological sensitivity and first-grade reading achievement. J Educ Psychol. 1995;87(3):476-87. https://doi.org/10.1037/0022-0663.87.3.476

68. Bradley RH, Corwyn RF. Socioeconomic status and child development. Annu Rev Psychol. 2002;53:371-399. doi: 10.1146/annurev.psych.53.100901.135233

69. Cheng Y, Wu X. The relationship between SES and reading comprehension in Chinese: A mediation model. Front Psychol. 2017;8:672. https://doi.org/10.3389/fpsyg.2017.00672

70. Kieffer MJ. Socioeconomic status, English proficiency, and late-emerging reading difficulties. Educ Res. 2010;39(6):484-86. https://doi.org/10.3102/0013189X10378400

71. Ozernov-Palchik O, Norton ES, Wang Y, Beach SD, Zuk J, Wolf M, Gabrieli JDE, Gaab N. The relationship between socioeconomic status and white matter microstructure in pre-reading children: A longitudinal investigation. Hum Brain Mapp. 2019;40(3):741-54. doi: 10.1002/hbm.24407

72. Ursache A, Noble KG. Socioeconomic status, white matter, and executive function in children. Brain Behav. 2016;6:e00531. https://doi.org/10.1002/brb3.531

73. Giedd JN. Structural magnetic resonance imaging of the adolescent brain. Ann N Y Acad Sci. 2004;1021(1):77-85. https://doi.org/10.1196/annals.1308.009

74. Cohen S, Doyle WJ, Baum A. Socioeconomic status is associated with stress hormones. Psychosom Med. 2006;68(3):414-20. doi: 10.1097/01.psy.0000221236.37158.b9

75. Foorman, BR, Petscher Y, Herrera S. Unique and common effects of decoding and language factors in predicting reading comprehension in grades 1-10. Learn Individ Differ. 2018;63:12-23. https://doi.org/10.1016/j.lindif.2018.02.011

Table 1

Participant characteristics and standard assessment scores (M ± SD) by stimulation group. Two-tailed, independent-samples *t*-tests were used to investigate group differences on standard assessments. * = $p < .05$.

Assessment	Sham taVNS	Active taVNS	T-Statistic
Sample Size (# Females)	12 (8)	12 (9)	N/A
Age	20.50 ± 2.48	19.17 ± .88	1.74
KBIT-2 Matrices	100.08 ± 9.07	104.33 ± 10.99	1.03
TOWRE-2 Sight Word Efficiency	106.58 ± 12.13	106.75 ± 14.81	.03
TOWRE-2 Phonemic Decoding Efficiency	109.17 ± 7.07	111.25 ± 7.75	.69
WRMT-3 Word Identification	103.25 ± 7.15	108.08 ± 10.25	1.34
WRMT-3 Word Attack	103.75 ± 10.96	102.67 ± 6.46	.30
WRMT-3 Passage Comprehension	99.25 ± 9.33	103.42 ± 11.41	.98
WRMT-3 Oral Fluency	109.50 ± 8.63	111.58 ± 8.07	.61
CTOPP-2 Rapid Digit Naming	11.33 ± 1.50	11.08 ± 1.08	.47
CTOPP-2 Rapid Letter Naming	10.92 ± 1.38	10.67 ± 1.23	.47
WRAML-2 Verbal Learning Core	10.08 ± 2.31	11.25 ± 2.26	1.25
WRAML-2 Number-Letter	10.25 ± 2.77	12.75 ± 2.38	2.37*
WRAML-2 Verbal Learning Recall	9.55 ± 3.53	10.67 ± 2.53	.88

Note. KBIT = Kaufman Brief Intelligence Test, 2nd Edition; TOWRE-2 = Test of Word Reading Efficiency, 2nd Edition, WRMT-3 = Woodcock Reading Mastery Test, 3rd Edition; CTOPP-2 = Comprehensive Test of Phonological Processing, 2nd Edition, WRAML-2 = Wide Range Assessments of Memory and Learning, 2nd Edition.

Table 2

taVNS thresholding measurements. Two measurements were taken at the lower end of sensation and two measurements were taken at the upper end of comfort. The average of these measurements was the customized current intensity used during training.

Value	Question	Intensity (mA)
1	"Tell me when you feel anything unusual in your left ear."	
2	"Tell me when the stimulation feels uncomfortable, but not painful."	
3	"Tell me when you cannot feel any stimulation in your left ear."	
4	"Tell me when the stimulation feels uncomfortable, but not painful."	
	Average of Values 1-4	

Figure Captions

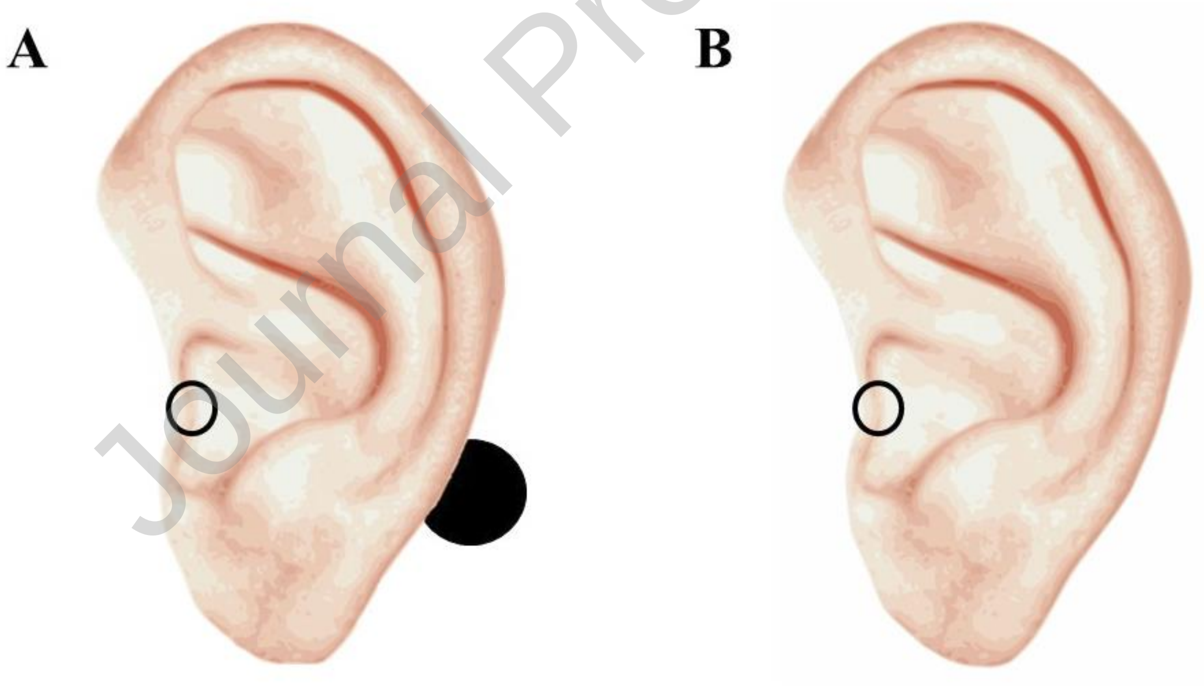

Figure 1. Electrode Placement of Each taVNS Device. (**A**) Four total participants completed the study on a TENS7000 device with an electrode (smaller black circle) placed on the posterior side of the left tragus and a ground placed behind the left ear (larger black circle). (**B**) Twenty total participants completed the study on a Parasym device, where an electrode (smaller black circle) was positioned on the posterior side of the left tragus.

A

There are sundry definitions of jazz, all of them vague. Their vagueness seems imperative, however, if they are to accommodate the custom of jazz to appropriate everything in sight. This receptivity to sources derives from a dominant feature of jazz: improvisation. The emphasis on improvising entails an openness to the entire legacy of diverse musical elements. Although formulating the content of jazz is not feasible, there is little difficulty in pinpointing the group that spawns the music. Jazz musicians have always constituted a subculture of music, a cultish but scarcely organized body of instrumentalists who rarely manage to eke out a livelihood from their music. Until recently they have been unschooled in their chosen music, except as they have imitated recordings of other musicians. Never accepted by academics, only partially accepted by the public, jazz musicians comprise a closed community in which innovation and experimentation are more valued than tradition.

B

Question	Correct Responses	Classification
What does the story state as to why jazz is difficult to define?	Tends to absorb other types of music; composed of different elements; jazz appropriates everything in sight	Memory
Why are jazz musicians probably less organized than other musicians?	Jazz is individualistic; no set rules; music is improvised	Comprehension
According to the last sentence of this story, what two elements do jazz musicians value more than tradition?	Innovation and experimentation	Memory
In the story, what one word described a dominant feature of jazz?	Improvisation	Memory
According to this story, what group has never accepted jazz?	Academics	Memory

Figure 2. Example of Passage and Associated Test Questions Administered during Reading Session. (**A**) Participants read two practice passages and twelve test passages from the standardized GORT-5 assessment (Weiderholt & Braynt, 2012) out loud to a researcher and pressed a button when they finished reading. Passages were presented one at a time in white font on a black background. (**B**) Immediately after reading, a researcher asked five associated test questions about the passage, and participants provided answers out loud.

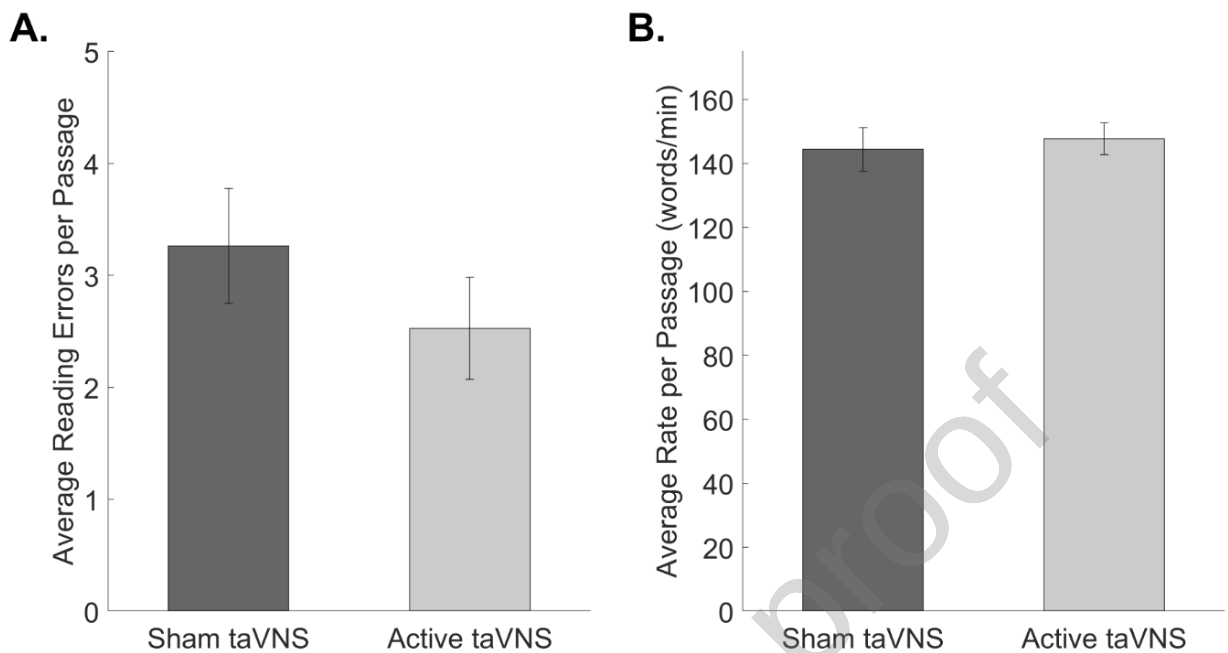

Figure 3. No Benefit of taVNS on Oral Reading Mechanics. We quantified the average errors made per passage and average reading rate per passage (words/min) while participants read out loud. There was no difference between the active taVNS group and the sham taVNS group on average errors during reading (**A**) or reading rate (**B**). Error bars represent standard error of the mean (SEM).

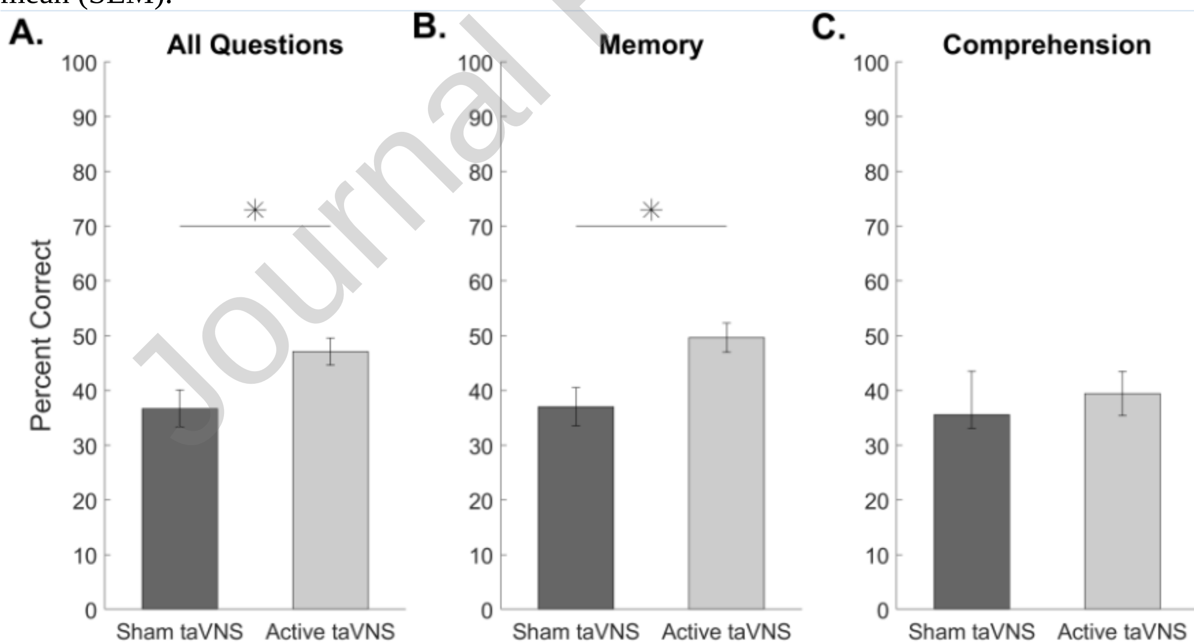

Figure 4. Performance on Test Questions. (**A**) There was a significant benefit of active taVNS compared to sham taVNS across all test questions. (**B**) This effect was driven by a significant benefit of active taVNS on memory questions. (**C**) There was no benefit of taVNS on comprehension questions. Error bars represent standard error of the mean (SEM). * $p < .05$

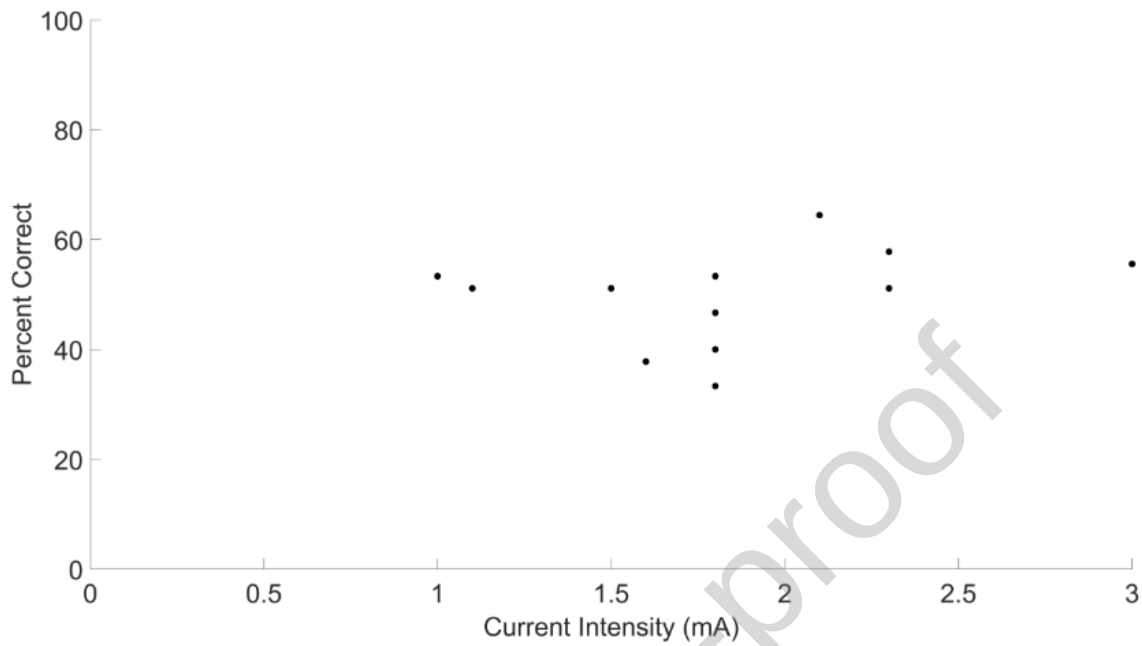

Figure 5. Relationship between Current Intensity and Performance on Memory Questions in Participants Receiving Active taVNS. There was no significant relationship between taVNS current intensity and percent correct on memory questions (r = .27, p = .35) in participants receiving active taVNS (n = 12).