NON-INVASIVE VAGUS NERVE STIMULATION IMPROVES LANGUAGE AND COMPREHENSION: EMPIRICAL EVIDENCE AND A REVIEW OF READING SKILLS

by

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Vidya dadati vinayam vinayad yati patratam |
Patratvad dhanam apnoti dhanad dharmam tatah sukham ||

Education leads to sensibility, sensibility attains character and qualification, from that comes wealth, and from wealth, one does good deeds, from that comes joy.
-Hitopadesha, Text 6

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Non-Invasive Vagus Nerve Stimulation Improves Language and Comprehension: Empirical Evidence and a Review of Reading Skills

There are many reasons adults may wish to learn new languages or improve their reading skills. For example, the hospitality industry often encourages workers to know more than one language, to aid in communication with tourists or other non-local visitors. Second, the business world has become increasingly international. Professionals often must travel overseas for integral meetings or read documents written in their non-native language. Third, military personnel are often deployed to unfamiliar regions, and familiarity with the local language is beneficial in communicating with civilians and reading local signs for quick reaction in hostile situations. Fourth, in immigrant families, subsequent generations may lose touch with their family's native language. In turn, they may lose contact with historical scriptures, legal documents, and methods of communication in their home country as well. For these reasons, effective training programs are essential for teaching language and reading skills to adults. The goal of the current dissertation work was to study the effects of transcutaneous auricular vagus nerve stimulation (taVNS) on improving language and reading skills in young adults.

While learning such skills in adulthood is often necessary, it is significantly more difficult to acquire speech, language, and reading skills after the respective sensitive period closes. There are three critical milestones for speech, language, and reading acquisition. Each skill has a sensitive period, in which the brain optimally acquires the skill and after which, learning becomes more difficult (Abadzi, 1996; Abadzi, 2012; Johnson & Newport, 1989; Thomas & Knowland, 2009; Werker & Hensch, 2015). The first of these windows is specific to speech sound categorization, which closes in the first two years of life (Kuhl, 1979; Kuhl et al., 1992; Kuhl, Tsao, & Liu, 2003; Thomas & Knowland, 2009; Werker & Hensch, 2015). The second sensitive period is specific to oral language skills, such as vocabulary and grammar, and closes around the time of puberty (Johnson & Newport, 1989; Lenneberg, 1967; Long, 1990, but see Birdsong & Molis, 2001). The third sensitive period is specific to orthography acquisition and closes around the age of 18 or 19 (Abadzi, 1996; Abadzi, 2012). While learning of new language skills outside of these sensitive windows is possible, individuals almost never achieve native-like fluency.

Programs such as Rosetta Stone and DuoLingo are popular for novel language and orthography learning. However, such training approaches require many days of training to gain familiarity and some level of fluency (e.g., Abadzi, 2012). Further, without consistent practice and instruction, people fall back to a level of inexperience (Nielson, 2011). Therefore, there is a need for a novel method for achieving fluency, as well as retention, of language and reading skills. A growing body of evidence suggests that non-invasive neuromodulation techniques, such as taVNS, may provide an additional benefit of neural plasticity in addition to computer-based learning programs.

Mechanisms of Vagus Nerve Stimulation

The vagus nerve (cranial nerve X) has connections to a variety of bodily systems, but its most well-known role is in the fight-or-flight response. During a life-threatening or otherwise dangerous event, this nerve releases key neurotransmitters critical for the formation of a lifelong emotional memory, designed to protect the individual in future similar situations. Artificial stimulation of the vagus nerve is thought to drive plasticity for non-emotional stimuli by stimulating the release of the same key neurotransmitters that aid in learning and memory. Vagus nerve stimulation (VNS) activates the nucleus tractus solitarius (NTS). In turn, the NTS has projections to two key deep brain structures, the nucleus basalis (NB) and locus coeruleus (LC), which respectively release acetylcholine (ACh) and norepinephrine (NE). Acetylcholine and norepinephrine have been regarded as pro-plasticity neurotransmitters and are implicated in learning and memory (Picciotto, Higley, & Mineur, 2012; Tully & Volshakov, 2010).

To date, implantable cervical vagus nerve stimulation (cVNS) has been FDA approved for individuals with treatment-resistant depression (Sackeim et al., 2001) and epilepsy (DeGiorgio et al., 2000; Morris et al., 1999). Further, implantable cVNS is currently in clinical trials for other conditions, such as tinnitus (De Ridder, Vanneste, Engineer, & Kilgard, 2013) and motor recovery after stroke (Dawson et al., 2016) and is being studied in humans for other conditions such as inflammation and rheumatoid arthritis (Koopman et al., 2016) and anxiety (George et al., 2008). A growing literature on implantable cVNS (see, Hays, Rennaker, & Kilgard, 2013, for a review) has reliably demonstrated that pairing accurate timing of stimulation with an external stimulus (e.g., a tone at a specific frequency or a particular movement, such as reaching to grasp an item) drives long-lasting and meaningful neural plasticity (Borland et al., 2016; Engineer et al., 2011; Khodaparast et al., 2013; Khodaparast et al., 2014; Porter et al., 2011; Shetake et al., 2012). For example, when cVNS was paired with a tone, plasticity specific to the frequency of the paired tone was observed in primary auditory cortex (A1) in rodents (Engineer et al., 2011). Rats that received active cVNS during frequencies not specific to noise-induced tinnitus exhibited fewer tinnitus-like symptoms, as measured through a Turner gap detection task, as well as normalization of the neural reorganization to model that of a healthy rat (Engineer et al., 2011). cVNS is now in clinical trials as a novel treatment for tinnitus in humans (De Ridder, Vanneste, Engineer, & Kilgard, 2014). Further, implantable cVNS is also capable of driving meaningful plasticity in the motor cortex in traumatic-brain injury induced in rats (Pruitt et al., 2016), in stroke models of rats (Khodaparast et al., 2013; Khodaparast et al., 2014; Porter et al., 2011), and in humans undergoing motor recovery after ischemic stroke (Dawson et al., 2016).

Beyond the sensory and motor modalities, implantable cVNS also improves skills in the cognitive domain (Clark et al., 1999; Sackeim et al., 2001; Sjogren et al., 2002; Sun et al., 2017). Epilepsy patients were more accurate at recalling highlighted words in a paragraph after receiving active stimulation compared to passages in which they received sham stimulation (Clark et al., 1999). When instructed to remember the orientation of a previously seen triangle, participants being treated for epilepsy with implantable cVNS were more accurate when receiving active stimulation compared to sham stimulation (Sun et al., 2017). Patients with depression receiving stimulation exhibited improved performance on digit-symbol matching and verbal fluency tasks (Sackeim et al., 2001). Further, active cVNS in patients with Alzheimer’s disease significantly improved performance on memory assessments such as the Mini-Mental Status Exam (Sjogren et al., 2002). These findings collectively suggest that implantable cVNS is capable of improving symptoms in a variety of conditions and also improves performance on a number of cognitive tasks. Therefore, this approach may be applicable to other cognitive tasks, such as language and comprehension skills. However, cVNS is both an expensive and invasive procedure, and is therefore not be a practical option for interventions in cognition and reading.

The auricular branch of the vagus nerve (ABVN) runs through the outer ear and can be accessed noninvasively (Yu, Zhao, Guo, & Rong, 2016) through low-level electrical stimulation at the cymba concha region of the pinna (Frangos, Ellrich, & Komisaruk, 2015; Redgrave et al., 2018; Yakunina, Kim, & Nam, 2016) or the posterior side of the tragus (Badran et al., 2018). Studies using functional magnetic resonance imaging (fMRI) have established that transcutaneous auricular vagus nerve stimulation (taVNS) activates similar deep brain and medullary structures as implantable cVNS, without the need for invasive surgery (Frangos, Ellrich, & Komisaruk, 2015; Yakunina, Kim, & Nam, 2016). For example, 25 Hz stimulation to the cymba concha region of the left ear aids in motor control recovery after stroke in human participants (Redgrave et al., 2018). Benefits of taVNS in humans are also reported in epilepsy (Stefan et al., 2012), tinnitus (Ylikoski et al., 2017), chronic migraine (Straube et al., 2015), and inflammation and atrial fibrillation (Stavrakis et al., 2017). In the language domain, taVNS paired with training selectively increased learning of speech sound categories of Mandarian tones (Llanos et al., 2020). Further, work in our lab supports the benefit of taVNS in novel orthography acquisition (Thakkar et al., 2020). Typically developing young adults that received active taVNS exhibited significantly faster completion times on a rapid naming task after training and a higher percent correct on a timed decoding task, than did individuals in the control groups, after only five days of training (Thakkar et al., 2020). Based on prior studies of taVNS in language and letter-sound learning, it is likely that taVNS paired with training can reopen sensitive windows to aid in acquisition after the sensitive windows close. In addition to speech sound categorization and letter-sound correspondence learning, individuals need to acquire adequate vocabulary, language, and reading comprehension skills to fully gain a language. Thus, in the current dissertation, we evaluated effects of taVNS on vocabulary learning (Aim 1) and reading comprehension (Aim 2) skills in typically developing young adults. Finally, we present a literature review (Aim 3) describing two skills often measured in studies of reading acquisition, which discusses the need for clarity in the definition of these terms. We hope that such clarity will facilitate future taVNS work aimed at improving these skills.

Aim 1

High Frequency taVNS Increases Memory of Novel Vocabulary Words in Young Adults

Although language acquisition is relatively easy for children, it becomes significantly more difficult after puberty, with extensive training required for adults to reach fluency (Johnson & Newport, 1989; Lenneberg, 1967; Long, 1990, but see Birdsong & Molis, 2001; Hartshorne, Tenenbaum, & Pinker, 2018). Although both children and adults are able to learn novel pseudowords, children exhibit better memory than adults, even after a short delay (Bishop, Barry, & Hardiman, 2012), supporting the idea that plasticity for second language (L2) acquisition decreases across the lifespan. In spite of the increased difficulty, learning of a second language is often important for older children and adults for a variety of personal and vocational reasons. There is also evidence that language acquisition can improve one's career income (McManus, Gould, & Welch, 1983) and overall health (Bialystok, Craik, & Luk, 2012), including a potential neuroprotective effect of bilingualism (Bialystok, Craik, & Freedman, 2007, but see Van den Noort et al., 2019). Given an increased need for L2 acquisition and fluency in adulthood, more efficient and successful methods for improving vocabulary memory are needed. In the current study, we investigated the use of a novel approach to enhance learning of novel vocabulary words and memory after a delay in young adults.

Current approaches to second language learning consist largely of in-person classroom options, one-on-one tutoring, and automated computer programs (e.g., DuoLingo and Rosetta Stone; Lu, 2008), using strategies such as recall and restudy (Krishnan, Watkins, & Bishop, 2017). While in-person coursework is a common choice for adolescents and young adults, more adults are turning to computer programs and apps for their language learning needs. For example, DuoLingo reported a large user base of 300 million active users in 2020 (duolingo.com). In spite of the popularity of this approach, the time required to make progress is significant and the effectiveness of this method is impacted by motivation to study consistently (Loewen et al., 2019). Even in those with a high degree of motivation, the retention of learned material after studying ends is quite poor (Nielson, 2011). One study investigated retention via a recall and recognition test in teaching Spanish-English word pairs and found that recall tests were harder than recognition tests, and shorter intersession intervals led to worsened performance compared to longer intersession intervals (Bahrick & Phelps, 1987). This increased difficulty in novel language acquisition for older children and adults may be due to a variety of factors (for a review, see Birdsong, 2018) including decreasing plasticity with age (Hurford, 1991), changes in myelination (Long, 1990), age-related cognitive decline (Lee, 2004), or variable differences in education and motivation (Vanhove, 2013). Regardless of the reason, data suggest that failures in language learning are likely due to poor retention of learned information rather than a deficit in initial learning. Although performance on vocabulary recognition tends to be high immediately after training (Brown et al., 2012), performance significantly decreases as the testing delay increases (e.g., Salavati & Salehi, 2016). Thus, improvement of retention is critical for designing more effective language learning programs.

Poor retention may be driven by a number of cognitive factors related to developmental plasticity changes and baseline skills in the native language that impact the degree to which words in the novel language are retained. Working memory (e.g., Kim, 2017; for a review, see Archibald, 2017) and short-term memory (Majerus, 2013) skills have both been evaluated in vocabulary learning and memory. Working and short-term memory play important roles in encoding and consolidation, since associations between the written and verbal parts of a word need to be correctly stored for access in the future. For example, working memory skills are significantly correlated with performance on word learning and retrieval tasks (Hazrat, 2015), and performance on a letter/digit span task is a strong predictor of L2 learning rate (Atkins & Baddeley, 1998). This suggests that various memory systems work together to increase vocabulary learning and retention, and verbal short-term memory may be a stronger predictor than verbal working memory in children learning L2 (Verhagen & Leseman, 2016). Thus, if memory skills are critical for language learning, a method for reliably and quickly improving verbal memory would be beneficial in a wide array of language learning applications.

One promising method for driving such long-lasting neural plasticity is vagus nerve stimulation (VNS). A growing body of evidence suggests that stimulation of the afferent branch of the vagus nerve drives significant and long-lasting neural plasticity in sensory (Engineer et al., 2011), motor (Khodaparast et al., 2013; Porter et al., 2012), and cognitive (Clark et al., 1999; Sackeim et al., 2001; Sun et al., 2017) domains. Stimulation of this nerve is possible non-invasively by targeting the auricular branch of the vagus nerve (ABVN) at either the cymba concha (Redgrave et al., 2018; Thakkar et al., 2020) or the posterior side of the tragus (Badran et al., 2018). Stimulation of the ear at these locations leads to increased activation in deep brain structures shown to be critical for effective vagus nerve stimulation (Frangos, Ellrich, & Komisaruk, 2015; Yakunina, Kim, & Nam, 2016). taVNS paired with training drives significant neural plasticity in a variety of domains, including post-stroke motor function recovery (Redgrave et al., 2018) and tinnitus (Yakunina, Kim, & Nam, 2018). In the cognitive domain, taVNS paired with training increased performance on a face-name association task (Jacobs et al., 2015), during speech sound category learning (Llanos et al., 2020), and during novel letter-sound learning (Thakkar et al., 2020). Previous studies have successfully utilized a variety of stimulation frequencies, including 1 Hz (Straube et al., 2015), 5 Hz (Thakkar et al., 2020), 8 Hz

(Jacobs et al., 2015), 10 Hz (Stefan et al., 2012), or 25 Hz (Llanos et al., 2020; Redgrave et al., 2018; Ylikoski et al., 2017). Vagus nerve stimulation may therefore be effective in aiding the learning and memory of vocabulary words in a novel language.

The current study was designed to answer two specific research questions. First, we investigated if taVNS is capable of improving learning and memory of novel words in young adults. Second, given the range of stimulation intensities utilized in the literature, we investigated whether stimulation frequency impacts efficacy. We evaluated the efficacy of sham taVNS versus low (5 Hz) or high (25 Hz) frequency taVNS on young adults' ability to learn and remember vocabulary words in a novel language.

Method

Participants

We recruited and screened 84 undergraduate students using an initial one-hour eligibility session. This screening session included a short online survey about personal history of reading and motor development, diagnoses, medications, and family history. We then tested nonverbal IQ and reading through five standardized assessments (Appendix A). The matrices subtest of the KBIT-2 (Kaufman & Kaufman, 2004) was utilized as a measure of nonverbal IQ. To evaluate baseline reading ability, we administered the Sight Word Efficiency and Phonemic Decoding Efficiency subtests of the TOWRE-2 (Torgesen, Wagner, & Rashotte, 2012) and the Word Identification and Word Attack subtests of the WRMT-3 (Woodcock, 2011). Since the training program required participants to read both English and Palau words on a screen with a time limit, we excluded participants with low baseline reading scores. To be eligible for the study (i.e., a typically developing young adult), participants had to: (a) be a native English speaker, (b) be between the ages of 18 and 35, (c) have a standard score of 85 or higher on nonverbal IQ, (d) have standard scores of 90 or higher on each of the four reading measures listed above, and (e) have no prior experience with Palau, the language to-be-taught during training. All participants in all groups scored a 0% on a cued-recall pre-test, confirming that everyone had no prior knowledge of to-be-trained words. 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 (De Ridder et al., 2013; Hulsey et al., 2016; Hulsey et al., 2019). Thus, we excluded these individuals to ensure all participants had, to the best of our knowledge, typical neurotransmitter function.

Of the 84 participants who were screened for eligibility, two participants were excluded for low IQ, 23 for low reading scores, 19 for exclusionary medications or diagnoses, and four for issues in scheduling or withdrawing from the study. Seven additional participants were unable to complete the study due to the onset of the COVID-19 pandemic. Thus, the final sample included 29 typically developing young adults (Table 1).

A number of descriptive assessments were also administered but were not used to determine eligibility. These additional assessments included the Rapid Digit Naming and Rapid Letter Naming subtests of the CTOPP-2 (Wagner, Torgesen, & Rashotte, 2013) and the Design Memory Core, Verbal Learning Core, Number-Letter, Design Memory Recognition, and Verbal Learning Recall subtests of the WRAML-2 (Sheslow & Adams, 2009). Two researchers scored each assessment independently and resolved discrepancies in scoring by discussion and consensus. Final raw scores were then converted to age-normed standard scores. The study was approved by the Texas Christian University Institutional Review Board, and all participants provided written informed consent prior to beginning the study.

Table 1

Participant Characteristics and Standard Assessment Scores (M ± SD) by Experimental Group for Participants in Aim 1

Assessment	Sham taVNS	5 Hz taVNS	25 Hz taVNS	F-Statistic
Sample Size (# Females)	11 (10)	8 (5)	10 (2)	N/A
Age	19.76 ± 1.47	19.19 ± .71	19.41 ± .58	.73
KBIT-2 Matrices	108.45 ± 13.17	101.38 ± 14.17	105.90 ± 8.91	.79
TOWRE-2 Sight Word Efficiency	109.36 ± 11.17	112.50 ± 10.04	110.40 ± 11.14	.20
TOWRE-2 Phonemic Decoding Efficiency	110.82 ± 6.63	110.38 ± 4.00	111.90 ± 7.40	.14
WRMT-3 Word Identification	111.27 ± 4.92	106.00 ± 7.33	107.50 ± 9.03	1.39
WRMT-3 Word Attack	104.27 ± 5.97	108.50 ± 9.10	102.80 ± 7.89	1.32
CTOPP-2 Rapid Digit Naming	11.36 ± 1.36	12.00 ± 1.41	11.70 ± 2.95	.22
CTOPP-2 Rapid Letter Naming	10.82 ± 1.83	11.25 ± 1.83	10.40 ± 3.10	.29
WRAML-2 Design Memory Core	9.09 ± 2.07	8.38 ± 2.33	10.50 ± 1.35	2.88
WRAML-2 Verbal Learning Core	11.27 ± 2.57	11.38 ± 2.45	11.70 ± 1.95	.09
WRAML-2 Number-Letter	12.27 ± 2.00	13.00 ± 1.69	11.80 ± 2.49	.72
WRAML-2 Design Memory Recognition	9.82 ± 2.04	9.50 ± 2.45	11.70 ± 2.45	2.56
WRAML-2 Verbal Learning Recall	11.18 ± 2.48	10.50 ± 2.33	11.90 ± 2.51	.73

Note. KBIT-2 = 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.

Materials and Procedures

taVNS Device and Procedures. Transcutaneous auricular vague nerve stimulation (taVNS) was administered using the ParaSym device (https://www.parasym.co/index.html), which delivers current through a small, circular, ¼ inch in diameter gold-plated copper electrode, placed at the posterior tragus (Figure 1). This stimulation location was chosen to ensure activation of the auricular branch of the vagus nerve, which innervates the nucleus tractus solitarius (NTS; Badran et al., 2018; Yakunina, Kim, & Nam, 2016). In the two active stimulation groups, current was delivered as square, biphasic pulses with 200 µs pulse width. Stimulation frequency varied by group assignment and was either set at 5 Hz stimulation (*n* = 8) or at 25 Hz stimulation (*n* = 10). In the sham stimulation group (*n* = 11), the device was turned off without participant knowledge. Stimulation was delivered to the left outer ear, as prior VNS research has suggested that stimulation of the right branch results in more bradycardia than does stimulation of the left branch (see Butt et al., 2020; Yuan & Silberstein, 2015, for reviews).

Figure 1. Visual depiction of electrode placement. In Aim 1 and Aim 2, participants were randomized into one stimulation groups. Regardless of aim and group, the stimulating electrode was always placed at the posterior side of the left tragus, a region innervated by the vagus nerve, Stimulation was delivered with a 200 µs pulse width, and as square, biphasic pulses.

All participants, regardless of group assignment, completed a thresholding procedure to determine the appropriate amount of current for each individual prior to the training session. To determine this customized current level, a trained researcher recorded two measurements at the participant's absolute minimum threshold of sensation and two measurements at the upper end of comfort, prior to the onset of pain (Thakkar et al., 2020; Yakunina, Kim, & Nam, 2016; Table 2). Thresholding was completed using 5 Hz for the sham taVNS and 5 Hz taVNS groups, while the 25 Hz taVNS group was evaluated at 25 Hz. Thresholding current intensities were significantly lower in the 25 Hz taVNS group (1.96 ± .13 mA) compared to the 5 Hz taVNS group (2.33 ± .11 mA; two-tailed, unpaired t-test; *t* (16) = 2.22, *p* = .04).

Table 2

taVNS Thresholding Measurements

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	

Palau Vocabulary Training Program. Eligible participants completed a one-hour associative learning training session in which they learned 30 novel vocabulary words in Palau, a language which utilizes the Latin alphabet, and corresponding English translations (Table 3). Since the training program included visual text and images without any auditory stimuli, we chose Palau as the training language so as to avoid any confounds caused by learning a language with an unfamiliar orthography. The training program was designed to mimic the presentation of novel vocabulary in existing commercial programs, such as DuoLingo (Duolingo, Pittsburgh, PA; https://www.duolingo.com/) and Rosetta Stone (Rosetta Stone, Arlington, VA; https://www.rosettastone.com/), with alternating blocks of exposure and knowledge checks. Stimulation was turned on during exposure blocks and turned off during knowledge checks, with onset/offset being manually controlled by a trained researcher from behind a barrier.

During each exposure block, a total of 25 trials were presented, each consisting of a Palauan noun, its associated English translation, and an image representing the word’s meaning (Figure 2A). Each trial was presented for four seconds and each block contained a randomized set of five words, each presented five times in pseudorandom order so that no word was presented twice in a row. Each exposure block lasted 100 seconds. Following each exposure block, stimulation was turned off and participants completed a short testing block (knowledge checks) to evaluate attention during training and familiarity with the words learned in the preceding exposure block. In each knowledge check trial, participants saw a Palauan word and were instructed to pick the correct English translation out of four possible choices (Figure 2B). Each testing block included five trials of each of the most recently learned words for a total of 25 trials presented in a pseudorandomized order. Reaction time and accuracy data were also collected during knowledge check trials. The training session was presented using custom coding in PsychoPy (Peirce et al., 2019).

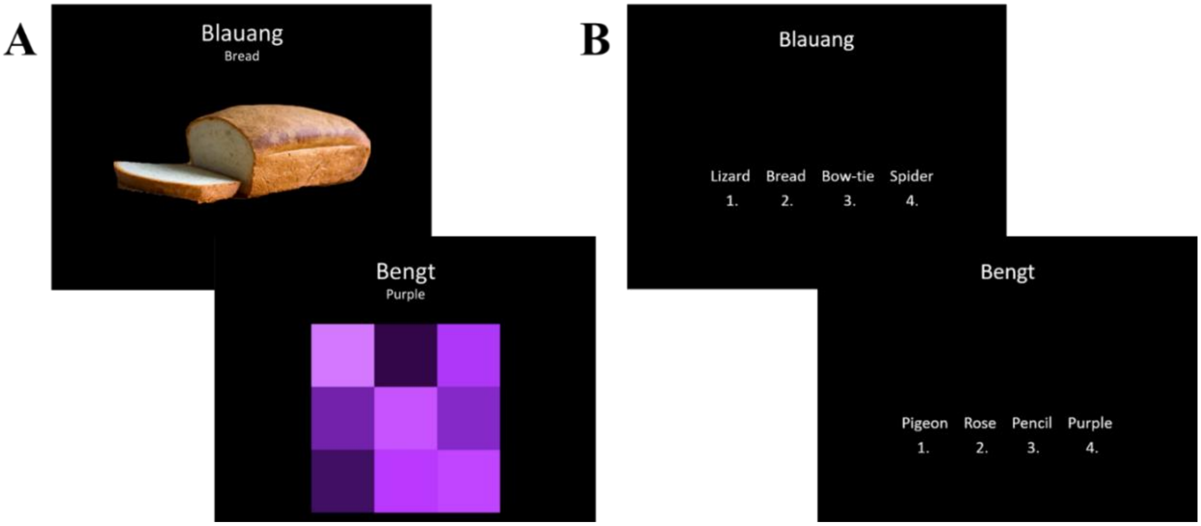


Figure 2. Procedure for exposure and knowledge checks during training. (**A**) During exposure paired with stimulation, participants saw a Palauan word, its English translation, and an image for four seconds on the screen, before seeing the next word. Each block of exposure paired with stimulation included five repetitions of each of five words, in a pseudorandomized order, and lasted 100 seconds. (**B**) During knowledge checks, participants saw a Palauan word with four English translations and selected the correct one. Accuracy and reaction time data were collected for each of the 300 trials.

Participants completed a total of 12 exposure blocks and 12 knowledge check blocks with an optional short break at the halfway point. In total, participants viewed each of the 30 words a total of 10 times. No adverse events occurred during training.

Table 3

Trained Palauan Words with Corresponding English Translations

Block	Palau Word	English Translation
1	Blauang	Bread
	Bengt	Purple
	Olbiungel	Necklace
	Bangikoi	Butterfly
	Buil	Moon
2	Bilis	Dog
	Haburas	Toothbrush
	Terebel	Stairs

	Orrekim	Rainbow
	Berebur	Lizard
3	Chedeng	Shark
	Chirt	Spoon
	Rois	Mountains
	Bubuu	Spider
	Olechukl	Camera
4	Iaes	Fly
	Uos	Horse
	Buk	Plate
	Kingall	Chair
	Baror	Lamp
5	Chudel	Grass
	Sisiak	Magnet
	Belochel	Pigeon
	Tuangel	Door
	Chiekl	Worm
6	Bara	Rose
	Rrat	Bicycle
	Cheedarullekl	Bowtie
	Oluches	Pencil
	Tuu	Banana

Palau Cued-Recall Translation Assessment. To assess learning and memory of trained words, participants completed a cued-recall assessment immediately following training (i.e., post-training) and after a seven-day delay. Participants were presented with the thirty trained words, cues, and instructed to provide the correct English translation associated with each word. The assessment was administered through Qualtrics (Qualtrics, Provo, UT), with the 30 test words presented in a randomized order. There was no time limit on this task. The assessment was scored such that each correct translation earned one point, and each incorrect translation earned zero points. Raw scores out of thirty possible points were converted to percent correct.

Statistical Analysis Plan

All data were analyzed using custom scripts in MATLAB (MathWorks, Natick, MA). A one-way between-groups ANOVA was used to ensure groups were matched on baseline assessments of nonverbal IQ, reading, memory, and attention (Table 1). Descriptive statistics for standard assessment scores are presented as M ± SD. A mixed-design ANOVA of stimulation group (sham taVNS, 5 Hz taVNS, vs. 25 Hz taVNS) and test time (post-training and seven-day delay) was used to evaluate cued-recall translation performance. Significant main effects were followed up with post-hoc *t*-tests. Descriptive statistics for outcome measures are presented as M ± SEM (Table 4). All *t*-tests were unpaired and two-tailed unless otherwise noted.

Given the significant difference in thresholding current intensities between the two active stimulation groups, we applied partial correlations, controlling for stimulation frequency, to evaluate whether stimulation intensity was significantly correlated with performance outcomes. Additional Pearson's correlations were used to evaluate relationships between baseline verbal learning scores and performance on the cued-recall assessments separately for each experimental group. The Bonferroni correction was applied to adjust for multiple comparisons.

Results

Experimental Groups were Matched on Standard Assessments

Participants completed a series of baseline assessments of nonverbal IQ, reading ability, memory, and attention to prior to enrollment in the study. Twenty-nine typically developing young adults were enrolled, and descriptive statistics are provided in Table 1. One-way between-groups ANOVAs first established that the groups did not statistically differ on chronological age (*F* (2, 26) = .73, *p* = .49) or nonverbal IQ (*F* (2, 26) = .79, *p* = .47). Performance also did not differ on each of four reading measures: the TOWRE-2 Sight Word Efficiency (*F* (2, 26) = .20, *p*

= .82), the TOWRE-2 Phonemic Decoding Efficiency (*F* (2, 26) = .14, *p* = .87), the WRMT-3 Word Identification (*F* (2, 26) = 1.39, *p* = .27), and the WRMT-3 Word Attack (*F* (2, 26) = 1.32, *p* = .28). In addition to measures assessed for inclusion criteria, participants completed additional descriptive measures. The three groups did not differ on any assessment, including measures of Rapid Digit Naming (*F* (2, 26) = .22, *p* = .80) and Rapid Letter Naming (*F* (2, 26) = .29, *p* = .75). Finally, the groups also did not differ on measures of memory and attention in the WRAML-2, including the Design Memory Core (*F* (2, 26) = 2.88, *p* = .07), Verbal Learning Core (*F* (2, 26) = .09, *p* = .91), Number-Letter (*F* (2, 26) = .72, *p* = .50), Design Memory Recognition (*F* (2, 26) = 2.56, *p* = .10), and Verbal Learning Recall (*F* (2, 26) = .73, *p* = .49).

Higher Frequency taVNS Improved Cued-Recall Performance after Seven-Day Delay

We next analyzed accuracy and reaction time data during knowledge checks to evaluate attention and learning over the course of the training program using one-way ANOVAs (Table 4). There was no main effect of group on accuracy during training (*F* (2, 26) = .49, *p* = .62, η^2 = .04; Figure 3A). There was also no main effect of group on reaction time (*F* (2, 26) = 1.56, *p* = .23, η^2 = .11; Figure 3B). Importantly, accuracy performance in all groups was close to the ceiling and confirmed that participants were paying attention and gained familiarity with novel vocabulary words throughout the training session. This result was corroborated by a significant Shapiro-Wilk test, *W* (29) = .77, $p \leq .001$, suggesting that accuracy scores during training were not normally distributed. Further, tests of skewness (-1.39) and kurtosis (1.15) suggest that more participants’ scores were clustered at the higher end, around 100% accuracy, confirming that performance was at ceiling in all groups.

Table 4

Descriptive Statistics (M ± SEM) for Outcome Measures during Training and on the Cued-Recall Translation Assessment

Outcome Variable		Sham taVNS	5 Hz taVNS	25 Hz taVNS
Knowledge Checks During Training	Percent Correct	99.50 ± .21%	99.57 ± .14%	99.72 ± .15%
	Reaction Time	1.60 ± .11 s	1.37 ± .09 s	1.63 ± .14 s
Palau Cued-Recall Translation	Post-Training	77.27 ± 7.48%	82.50 ± 6.24%	90.67 ± 3.88%
	Seven-Day Delay	36.97 ± 7.11%	41.25 ± 8.05%	64.33 ± 7.89%

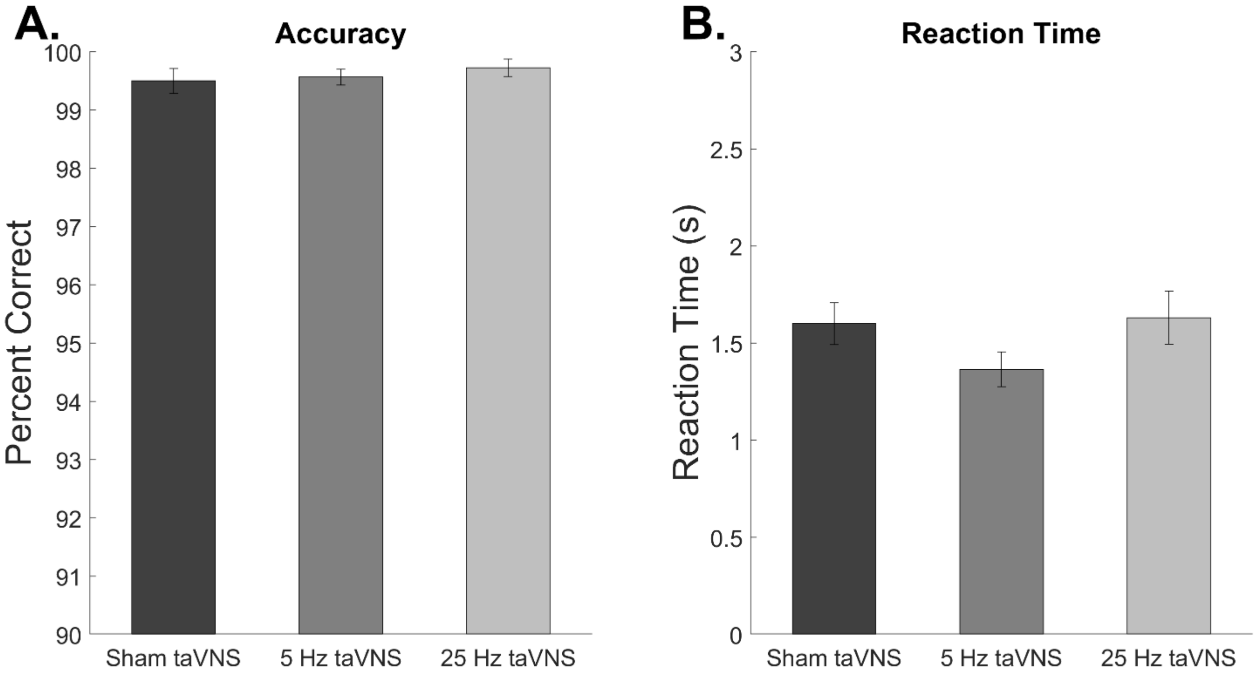


Figure 3. Data from knowledge checks during training. Participants completed 300 knowledge checks during training where they saw a Palauan word and selected the best of four English translations. Accuracy and reaction time were collected for each knowledge check trial. Separate one-way between-groups ANOVAs showed that there was no effect of stimulation group on accuracy during training (**A**) or average time to respond to a knowledge check (**B**).

We next analyzed performance on the cued-recall translation tests immediately after training and after a seven-day delay. There was a significant main effect of test time (*F* (1, 26) =

117.20, $p \leq .001$) and a marginal main effect of stimulation group (*F* (2, 26) = 3.36, $p = .05$). There was no interaction between stimulation group and test time (*F* (2, 26) = 2.16, $p = .14$; Table 4). Post-hoc *t*-tests revealed there was no effect of taVNS at post-training (Figure 4A). There were no differences between the sham taVNS and 5 Hz taVNS groups (*t* (17) = .54, $p = .60$), between the sham taVNS and 25 Hz taVNS groups (*t* (19) = 1.62, $p = .12$), or between the 5 Hz and 25 Hz taVNS groups (*t* (16) = 1.23, $p = .24$). However, after a seven-day delay, the 25 Hz taVNS group outperformed both the sham taVNS group (*t* (19) = 2.72, $p = .01$, $d = 1.19$) and the 5 Hz taVNS group (*t* (16) = 2.15, $p = .048$, $d = 1.02$; Figure 4B). There was no significant difference between the sham and 5 Hz taVNS groups (*t* (17) = .42, $p = .68$).

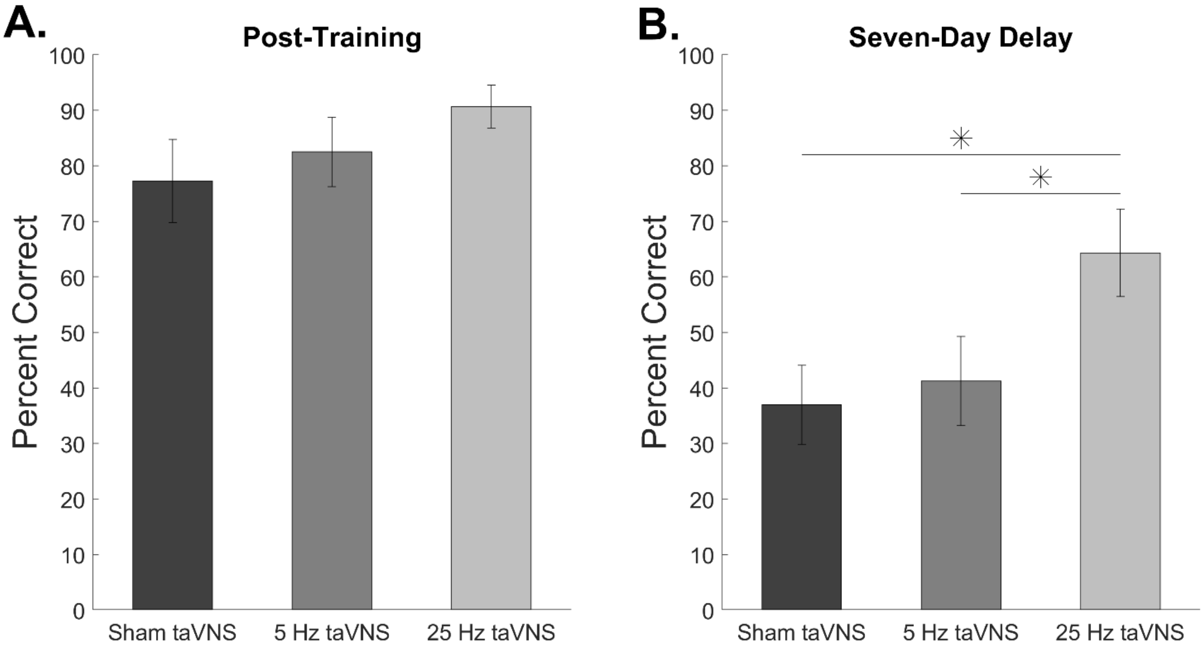


Figure 4. Performance on Palau-to-English translation test immediately after training and after a seven-day delay. Participants completed a cued-recall translation test of the 30 trained words after training and seven days later. Each of the Palauan words was provided, and participants entered the English translation. Accuracy was recorded and converted to a percent correct. Post-hoc tests were used to follow up a mixed-design ANOVA of stimulation group and test time. (**A**) There was no effect of stimulation group on performance after training. (**B**) Seven days after training, the 25 Hz taVNS group outperformed both the sham and 5 Hz taVNS groups. * signifies $p < .05$.

No Effect of Stimulation Intensity on taVNS Efficacy

Since there was a significant difference in the thresholding intensity in each stimulation group, we evaluated whether the effect of stimulation frequency on performance after a seven-day delay was driven by differences in current intensity. Partial correlations, controlling for stimulation frequency, were not significant after a seven-day delay ($r = .27$, $p = .17$; Figure 5). These results suggest that stimulation current intensity did not impact performance and that stimulation frequency did not influence this finding.

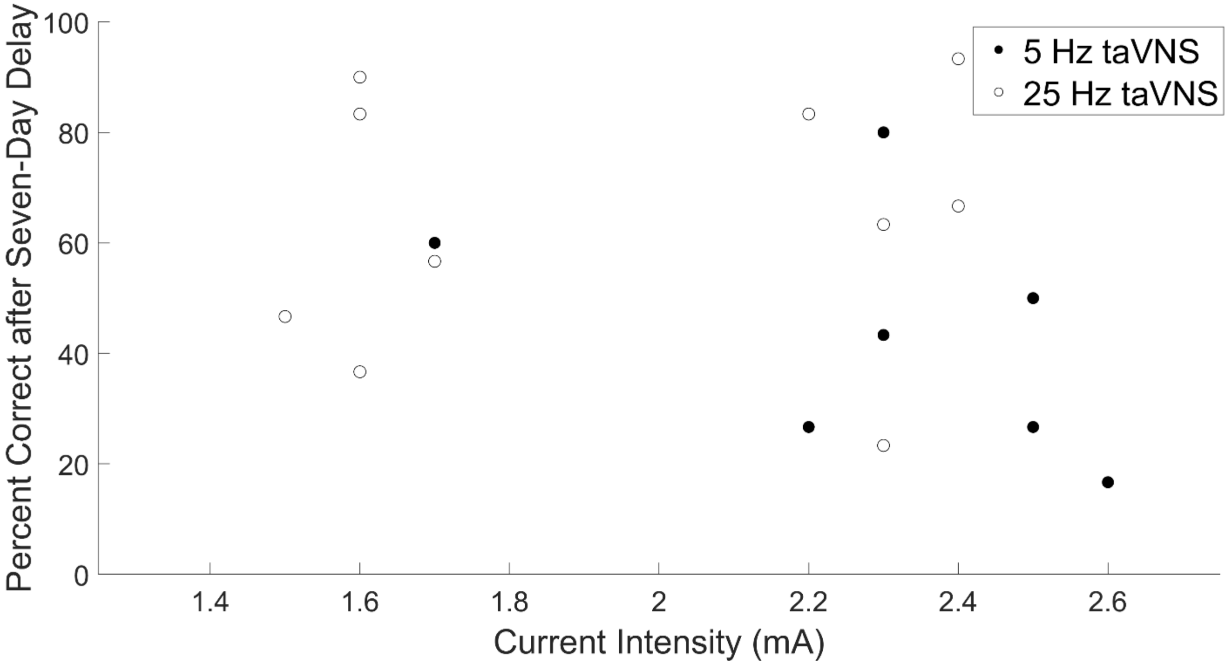


Figure 5. Current intensity does not correlate with performance after seven-day delay. Partial correlations found no relationship between thresholding current intensity and performance after a seven-day delay when controlling for stimulation frequency.

Verbal Memory Ability Predicts Performance after Seven-Day Delay in the 25 Hz taVNS Group

The ability to acquire knowledge of vocabulary words in a novel language requires a variety of baseline skills, including working memory (Atkins & Baddeley, 1998). To evaluate whether verbal working memory skills provided an advantage to participants, we used Pearson's *r* to quantify the relationships between two Verbal Learning subtests of the WRAML-2 (Core and Recall) and cued-recall performance. During the Core subtest, participants listened to a list of words and immediately repeated as many as they could remember, in any order. This list was read and repeated four times in succession. There were no significant relationships between the standard scores on the Verbal Learning Core and post-training performance within the sham taVNS (r = .49, p = .13; Figure 6A), the 5 Hz taVNS (r = .02, p = .96; Figure 6B), and the 25 Hz taVNS groups (r = .11, p = .37; Figure 6C). There were also no significant relationships between Verbal Learning Core and seven-day delay scores within the sham taVNS (r = .13, p = .70; Figure 6D), the 5 Hz taVNS (r = .01, p = .99; Figure 6E), and the 25 Hz taVNS groups (r = .18, p = .61; Figure 6F). The lack of any relationship between Verbal Learning Core and outcomes was likely due to the fact that this assessment evaluates short-term (10-30 seconds) memory, while language learning requires consolidation, especially for long-term memory of newly learned words.

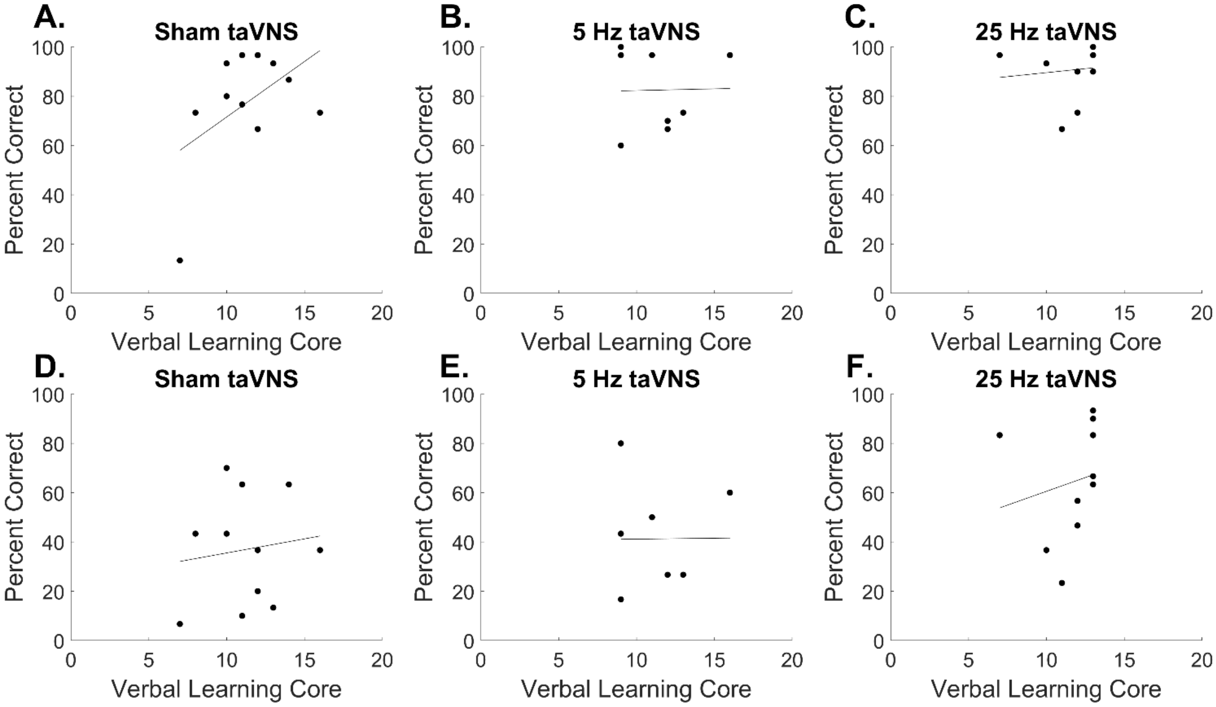


Figure 6. Relationship between verbal learning core and performance by stimulation group. Results suggested that were no relationships between performance on the Verbal Learning Core measure and performance on cued-recall translation at post-training within the sham taVNS (**A**), 5 Hz taVNS (**B**), and 25 Hz taVNS (**C**) groups. Similar results were seen seven days later within the sham taVNS (**D**), 5 Hz taVNS (**E**), and 25 Hz taVNS (**F**) groups.

Thus, we next evaluated whether a longer-term verbal working memory task, the Verbal Learning Recall task, was a better predictor of performance. This subtest includes a 10-15-minute delay between initial presentation of a word list and the prompt for free-recall assessment. There were no significant relationships between this measure and post-test performance in either the sham taVNS (*r* = .30, *p* = .37; Figure 7A) or 5 Hz taVNS (*r* = -.17, *p* = .70; Figure 7B) groups. However, there was a significant, positive relationship in the 25 Hz taVNS group (*r* = .79, *p* = .007; Figure 7C), such that higher scores on verbal recall correlated with better post-training performance, though this finding did not survive correction. After the seven-day delay, there was no significant correlation between Verbal Learning Recall and performance in the sham taVNS (*r* = .20, *p* = .56; Figure 7D) or the 5 Hz taVNS (*r* = -.17, *p* =

.69; Figure 7E). There was a significant, positive relationship between Verbal Learning Recall and performance within the 25 Hz taVNS group (*r* = .72, *p* = .018; Figure 7F), but this finding also did not survive correction.

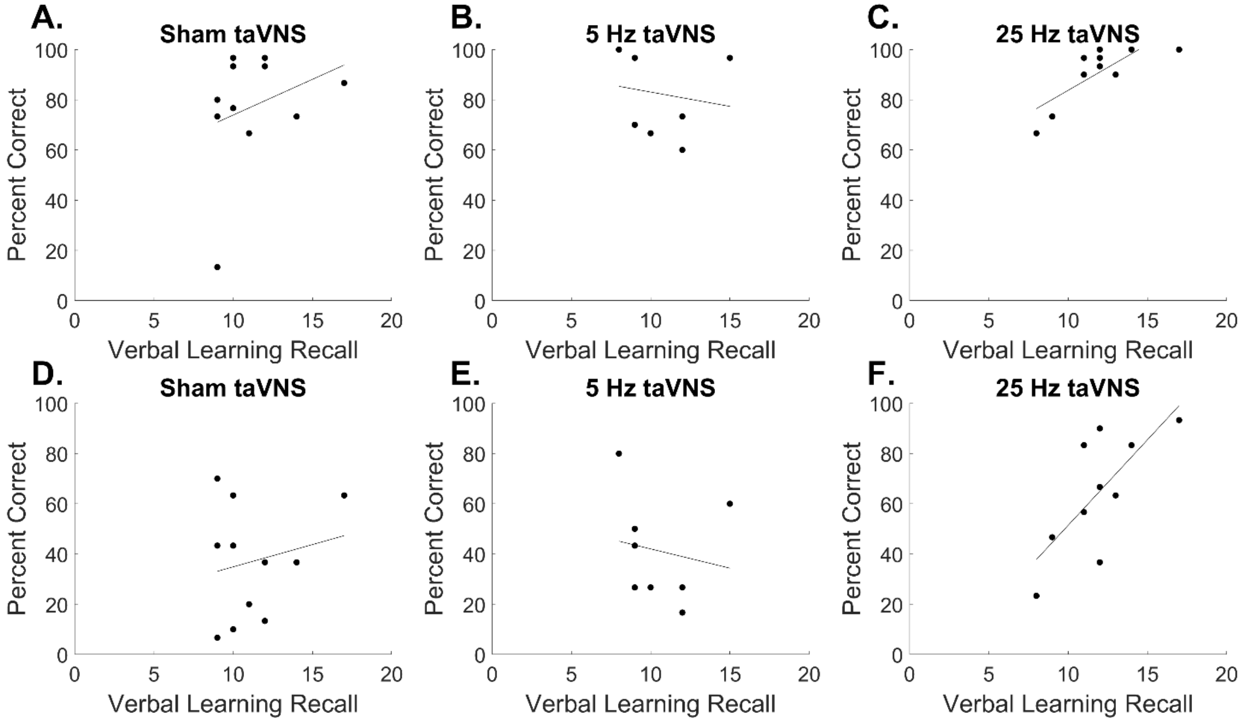


Figure 7. Relationship between verbal learning recall and performance by stimulation group. Pearson's correlations suggested that there was no significant relationship between verbal learning recall and cued-recall translation test performance at post-training for the sham taVNS (**A**) and 5 Hz taVNS (**B**) groups. Similar results were seen for the sham taVNS (**D**) and 5 Hz taVNS (**E**) groups after a seven-day delay. There was a significant, positive correlation for the 25 Hz taVNS group at both post-training (**C**) and after a seven-day delay (**F**).

Discussion

The goal of Aim 1 was to investigate the effectiveness of taVNS on typically developing young adults' ability to learn and remember vocabulary words in a new language and whether stimulation frequency and/or intensity influenced performance. We observed no effect of taVNS on learning of words immediately after training, but a significant benefit of 25 Hz stimulation emerged on learned words after a seven-day delay period. Importantly, while frequency of stimulation influenced efficacy, there was no effect of stimulation intensity on performance. These findings demonstrate, for the first time, that taVNS paired with training can aid in memory of novel vocabulary words and that stimulation frequency may be an important parameter to consider when designing future taVNS protocols.

The Effects of taVNS on Learning and Memory after Training

While previous taVNS studies have shown significant effects after training (e.g., Llanos et al., 2020; Redgrave et al., 2018), our results suggest that there is no benefit of taVNS during initial vocabulary acquisition, but significant findings emerged at the seven-day delay session. Learning during training was measured by accuracy and reaction time during the 300 knowledge check trials. It is likely that the null effect of taVNS on acquisition during training was due to the close temporal proximity between exposure to the new words and the knowledge checks pertaining to those words. Participants in all groups performed at ceiling levels on these knowledge checks, leaving little room to detect any benefits of taVNS. Since the acquisition task was designed to mimic well-known language learning approaches, such as those used by DuoLingo and Rosetta Stone, it is possible that the training approach was maximally effective.

To investigate potential effects of taVNS during training, future research should utilize a training program lasting multiple days, utilize a drop-out training method, or restructure the training program to increase difficulty of knowledge checks. A drop-out training method, as used in Swahili-English learning, only has participants restudy and tested on words that are not learned over the course of the task, and words not correctly remembered would be maintained in the task (Pasqualotto, Kobanay, & Proulx, 2015). This procedure for knowledge checks may detect potential taVNS benefits more accurately, since words learned well are dropped from the training program. Words that are not learned well continue to appear so that participants receive extra practice with those words. In such an experiment, data could be analyzed as number of required to learn the new word consistently. Another potential approach could be to redesign the knowledge checks in a more difficult format (e.g., written free-recall, matching, or verbal free-recall), to further probe the potential effects of taVNS during initial learning. Using these methods makes it less likely that participants will exhibit performance at ceiling during training. Alternatively, to further mimic previously used computer-training programs, such as DuoLingo, knowledge checks could be administered in a matching format. For example, multiple novel words or pictures can be listed in one column with corresponding translations in another column, and participants would have to correctly match novel word or picture to English translation. An extra layer of difficulty could be added if words presented were a combination of words from the current and previous training blocks.

A second suggestion to probe the potential effects of taVNS during training would involve restructuring the training program format. In Aim 1, participants saw five repetitions of five words and then completed knowledge checks on the words they had just seen. Another approach to address this could be that participants see ten words per block to increase the information they need to remember for subsequent knowledge check trials. Given the previous research suggesting the importance of memory skills in vocabulary learning (e.g., Wojcik, 2013), increasing the number of words to be remembered may help detect potential benefits of taVNS. Despite a null finding during training, the ceiling effect does demonstrate the feasibility of the training program, since all participants in all groups gained familiarity with novel word associations in a single training session.

Immediately after training and seven days after training, participants completed a cued-recall test, which is more difficult than a multiple-choice knowledge check, of trained stimuli by providing English translations to the Palauan words. We observed no effect of taVNS on the cued-recall assessment that occurred immediately after training. This finding poses the question about the effect of taVNS on overall learning after training (see Colzato & Beste, 2020, for a review). For example, a cross-sectional study comparing young adults to older adults found no benefit of taVNS to the cymba conchae on verbal memory learning in either age group, both during the study (analogous to knowledge checks in Aim 1) and after the study (analogous to the post-training cued-recall test in Aim 1; Mertens et al., 2020). In another study, taVNS applied to the posterior tragus led to higher performance in association memory in older adults ten minutes after a single session (Jacobs et al., 2015). The delay between training and testing supports the hypothesis that vagus nerve stimulation strengthens memory for learned associations. Collectively, these studies may suggest that taVNS may have stronger effects after a period without training, rather than during the course of training.

taVNS Efficacy is Impacted by Stimulation Frequency but Not Intensity

While a number of prior taVNS studies have demonstrated significant effects by utilizing a range of stimulation frequencies, no taVNS study to date has systematically compared multiple stimulation frequencies within the same paradigm. Aim 1 is the first to show that frequency of stimulation may influence its efficacy on language learning. We directly compared multiple frequencies, which were chosen based on prior successes in reading and language at both 5 Hz (Thakkar et al., 2020) and 25 Hz (Llanos et al., 2020). In Aim 1, we observed a significant benefit of 25 Hz stimulation, but not 5 Hz stimulation, on vocabulary recall performance seven days after training. Although this result provides support for 25 Hz as an effective stimulation frequency, it is important to emphasize that our findings do not suggest that 25 Hz should be used in all future taVNS studies. Similarly, while Aim 1 did not show a benefit at 5 Hz, we do not suggest that researchers abandon this frequency, as our prior work did demonstrate significant benefits of 5 Hz stimulation on automaticity (i.e., rapid naming) and decoding (i.e., timed pseudoword reading), in typically developing young adults learning novel letter-sound relationships in Hebrew, a more transparent orthography (Thakkar et al., 2020). One potential reason for a benefit only observed in the 25 Hz taVNS group is that higher frequencies are needed in order to sufficiently activate all of the different fibers that form the vagus nerve. For example, one study in healthy humans found that 100 Hz stimulation led to significantly higher brainstem responses, as compared to frequencies of 2 Hz, 10 Hz, and 25 Hz (Sclocco et al., 2020). Specifically, the vagus nerve is comprised of A-fibers, B-fibers, and C-fibers, and each has a respective threshold to be activated. It is possible that activation of each fiber can vary as a function of stimulation frequency or current intensity (Groves & Brown, 2005; Jiao et al., 2015).

There are also a number of possible reasons for the discrepancy in the 5 Hz taVNS effect across our prior study and Aim 1. First, the stimulation location differed across studies, as our prior study stimulated the cymba concha region of the left ear (Thakkar et al., 2020) and we stimulated the posterior tragus of the left ear for Aim 1. This change was due to availability of stimulation devices rather than a methodological choice and suggests that additional research is needed to determine whether stimulation to the posterior tragus or the cymba concha impacts efficacy. Location of stimulation may inform on future taVNS protocols, especially because previous research has studied the distribution of innervation of auricular regions. Specifically, when considering the auricular branch of the vagus nerve, a study on human cadavers found that the cymba conchae region has more innervation from the vagus as compared to the tragus (Peuker & Filler, 2002). Thus, a lower current frequency may be sufficient to activate the targeted nerve fibers in the cymba.

Second, the two studies differ in the number of pairings per stimulus, which refers to the number of times a stimulus is presented or taught when paired with stimulation. It is possible that there is a threshold of minimum number of pairings necessary for taVNS to be rendered effective, and previous protocols have varied in the number of pairings used (Borland et al., 2016; Engineer et al., 2011; Redgrave et al., 2018). While cVNS and taVNS are both well-supported through multiple studies, many pairings between stimulus and stimulation are needed to drive behavioral benefits and neural plasticity. In Aim 1, we taught 30 English-Palau associations with ten pairings per word, which is significantly below the number of pairings reported in other studies. For example, auditory plasticity was observed in the rodent model after 300 cVNS-tone pairings per day for twenty days (Borland et al., 2016; Engineer et al., 2011), and motor function was recovered in post-stroke patients after receiving 30-50 repetitions of each motor movement paired with taVNS (Redgrave et al., 2018). Further, our prior study taught 16 consonant-vowel combinations with approximately 60 pairings per combination (Thakkar et al., 2020). Therefore, future research is needed to replicate our paradigm with additional pairings to evaluate whether a greater taVNS effect is possible.

A third possibility is the type of content being learned. In our letter-sound learning study (Thakkar et al., 2020), we utilized an audio-visual stimulus where participants mapped a visual grapheme to a corresponding sound, whereas in Aim 1 we taught vocabulary words where participants mapped printed words to corresponding pictures with no auditory stimulus component. Based on the type of content being learned, it is possible that information was processed or modulated through different neural circuits. Future research is needed to elucidate the impacts of stimulation location (posterior tragus vs. cymba concha), training length (number of pairings per stimulus and number of sessions in training), and frequency (low, moderate, vs.

high) interact, all of which will be critical for designing optimal protocols utilizing this technology.

To date, cVNS is FDA approved at frequencies in the 20-30 Hz range for individuals with treatment resistant depression or epilepsy (Howland, 2014; Jiao et al., 2015). In a rat model, researchers suggest that higher rates of VNS efficacy in decreasing epilepsy occur at higher frequencies, increasing beyond 130 Hz. However, it is important to note that researchers also speculate that frequencies above 50 Hz can cause irreversible damage in humans (Groves & Brown, 2005). As such, there is still a lot of speculation regarding optimal stimulation frequencies for VNS. We can speculate that frequencies in the 20-30 Hz range for humans may be most optimal, given the abundance of research yielding significant results at those frequencies. As mentioned above, it is possible that these higher frequencies are necessary to adequately activate all fibers that comprise the vagus nerve. While it is unknown whether activation of all fibers is needed to observe VNS benefits, we hypothesize that lower frequencies may not sufficiently activate all fibers of the vagus nerve, potentially explaining some null results seen in Aim 1. However, we did find a benefit of 5 Hz taVNS in our letter-sound learning work (Thakkar et al., 2020), so it is possible that frequency and number of pairings interact in some way. While studies in the rodent model help understand the threshold of pairings needed, future research should be conducted in human participants with manipulated pairings per stimulus in language and reading domains.

In addition to stimulation frequency, another parameter of interest evaluated in this study was the relationship between current intensity and performance in each of the active taVNS groups. In the current study, we found no effect of current intensity on cued-recall performance at post-training or after a seven-day delay. Previous research using the invasive cVNS in a rodent model compared various stimulation frequencies and found that moderate intensities of stimulation led to more neural reorganization in auditory cortex than did higher intensities of stimulation (Borland et al., 2016), and these results were confirmed in similar studies of plasticity in the motor cortex (Morrison et al., 2020; Morrison et al., 2021). This influence of intensity was also observed in humans, where cVNS at moderate intensity yielded stronger effects than at higher intensity during a verbal memory task (Clark et al., 1999). These previous cVNS studies suggest that moderate current intensities are most effective (see Van Leusden, Sellaro, & Colzato, 2015, for a review), but little is known about whether intensity influences efficacy in taVNS. One prior study investigated the effects of subthreshold stimulation on categorization of speech sound categories in Mandarin. They reported that subthreshold taVNS selectively enhanced learning on certain categories (Llanos et al., 2020). This finding, in tandem with our taVNS effect using suprathreshold intensities, suggests that taVNS efficacy may rely more on the matching of frequency to the task at hand rather than matching stimulation intensity along an inverted-U function. Future research is needed, however, to systematically evaluate both the frequency and intensity parameters across a range of tasks (Groves & Brown, 2005).

Baseline Working Memory and Performance

Previous research has established the importance of memory skills in vocabulary learning and memory after training. In order to successfully acquire novel vocabulary words, a learner must associate a word with a form of meaning. Children are able to do this easily with mere exposure, but regardless of exposure or experience, we must remember these associations for the future (Wojcik, 2013). Previous work suggests that there is a definite connection between verbal short-term memory and novel word learning (Gupta & MacWhinney, 1997; Jarrold, Thorn, & Stephens, 2009; McGregor et al., 2017). Thus, we also evaluated the relationship between a subset of measures in the WRAML-2 (Sheslow & Adams, 2009) and performance on the translation tests, as verbal working memory has been linked to novel word learning in children (Hansson et al., 2004).

We observed a significant relationship between the Verbal Learning Recall measure and performance after the seven-day delay, specific to the 25 Hz taVNS group. This could be attributed to a compounding effect of verbal recall and stimulation. In Aim 1, we utilized two memory tasks to evaluate participants' ability to store word lists for immediate recall (Verbal Learning Core) or delayed recall (Verbal Learning Recall). Given our observation that individuals with higher scores on these tasks received a greater benefit of 25 Hz taVNS (as demonstrated by higher scores after a seven-day delay), it is possible that taVNS strengthens existing neural circuits already optimized for long term verbal recall. This hypothesis is supported by previous imaging work that found a significant association between higher performance on verbal learning tasks and greater activation of key brain regions (e.g., extrastriate area and left-lateralized parietal areas), some of which also overlap with the language network (Heinze et al., 2006). Future research should further investigate this relationship, including in populations of individuals with impaired memory skills.

Comparison with Other Neuromodulation Techniques

While the current study yielded significant results, not all individuals may benefit from taVNS intervention. There may be certain contraindications of treatment that prevent an individual from being able to use this technique (e.g., disrupted neurotransmitter systems important in VNS, injury to the left ear). Thus, it is important to compare the efficacy of taVNS with other techniques important in vocabulary learning. Collectively, non-invasive brain stimulation techniques have been shown to treat a variety of conditions and enhance learning and memory. For example, transcranial random noise stimulation (tRNS), enhanced acquisition of Swahili words in young adults when stimulation was applied to the posterior parietal cortex (Pasqualotto, Kobanbay, & Proulx, 2015). Another example of a non-invasive neuromodulation technique is transcranial direct current stimulation (tDCS) which is thought to enhance neural plasticity by priming neurons for learning via increased cortical excitability (Medeiros et al., 2012). When using tDCS, anodal stimulation to a specific region of interest (ROI) is used to increase excitability of underlying neurons, and cathodal stimulation to a specific ROI can decrease excitability. Prior studies using tDCS have found that anodal stimulation to the temporo-parietal cortex led to faster reaction times in retrieval after a word-picture training program (Perceval et al., 2017), and tDCS over Wernicke's area led to enhanced vocabulary learning (Floel et al., 2008). Anodal tDCS to the left inferior frontal gyrus (IFG) also yielded higher accuracy scores in a verb learning task in healthy young adults (Fiori et al., 2018).

In contrast to the tDCS influence on the underlying membrane potential, taVNS drives neural plasticity by releasing key neurotransmitters implicated in learning and memory by pairing stimulation with a particular external stimulus (Roosevelt et al., 2006). taVNS devices are smaller and more easily accessible compared to other non-invasive neuromodulation techniques, so the addition of taVNS is a more realistic addition to computer training programs in language learning. However, it is likely that taVNS may not be effective for all participants, and non-responders may benefit from another technique, such as tDCS. In our previous work (Thakkar et al., 2020) and in Aim 1, we only enrolled typically developing young adults so that there would be no concern of diagnoses such as depression or anxiety interfering with the efficacy of taVNS. There is inadequate research investigating the role of neurotransmitters or other baseline neural characteristics in tDCS, so this information would be beneficial in future research. We speculate that individuals that do not benefit from taVNS due to being diagnosed with certain conditions or report taking certain medications may still benefit from tDCS. To understand these techniques further, future research should compare various non-invasive neuromodulation techniques, such as taVNS, tRNS, and transcranial direct current stimulation (tDCS), since each operates through a unique mechanism.

Limitations

There are three main limitations to the current study. First, our sample size is smaller than we had anticipated. Unfortunately, our recruitment of participants was cut short by the COVID-19 pandemic, which created conditions that made in-person data collection unsafe. Thus, we have plans to replicate and extend these findings in a larger, fully powered study. An *a priori* power analysis ($f = .25$, $\alpha = .05$, power = .90, groups = 3, measurements = 2, correlation among repeated measures = .5) suggested that a total sample size of 54 participants would yield a significant effect and moderate effect size. Using the strongest effect after a seven-day delay, a post-hoc power analysis ($d = 1.19$, $\alpha = .05$, $n_{\text{sham}} = 11$, $n_{\text{high-frequency}} = 10$) suggested that a power of .73 was achieved, meaning that the analysis is underpowered (Faul et al., 2007).

A second limitation was a restriction on the type of words taught during training. We trained thirty concrete nouns in one training session. Concrete nouns were used so that a visual image could be provided with the translation. Prior research has also shown that concrete nouns are more easily remembered than abstract nouns (e.g., Fliessbach et al., 2006; Hamilton & Rajaram, 2001). This poses a limitation since vocabulary in language learning must also involve the learning of abstract nouns (e.g., loyalty, love, excitement), and not just concrete nouns (e.g., bread, spoon, rose), and it is currently unknown whether taVNS will be effective in enhancing learning for abstract vocabulary words. Additionally, proficiency in a language also requires knowledge of verbs, adjectives, and grammar skills, which were not taught in Aim 1.

A third limitation was the lack of neural recordings. Neuromodulation techniques, such as cVNS and taVNS, are designed to induce neural plasticity. There is well-documented evidence in cVNS leading to neural plasticity in the sensory and motor cortex (Engineer et al., 2001; Borland et al., 2016). While prior taVNS studies (e.g., Llanos et al., 2020; Redgrave et al., 2018; Thakkar et al., 2020) reported behavioral benefits, prior work did not observe significant neural plasticity as measured by EEG (Llanos et al., 2020). Thus, the lack of neural recordings in Aim 1 prevents us from drawing any conclusions about high frequency taVNS inducing neural plasticity and investigating if verbal memory truly does take advantage of preexisting neural circuitry to lead to behavioral benefits.

Aim 2

Improvement of Memory-Based Reading Comprehension Using Transcutaneous Auricular Vagus Nerve Stimulation

In order to achieve expertise in reading, individuals must acquire adequate knowledge of letter-sound relationships and vocabulary learning. Our previous work demonstrated that taVNS can enhance both rapid naming and timed decoding of learned letter-sound relationships (Thakkar et al., 2020) as well as the ability to remember novel vocabulary words after training (Aim 1). Knowledge of letter-sound relationships and vocabulary are only two of the skills needed to achieve reading mastery. Since these are lower-level skills, it is also essential to extend our knowledge of potential taVNS effects on higher-level reading skills, such as reading comprehension. Thus, Aim 2 was designed to evaluate the effect of taVNS on reading comprehension.

Fluent reading is a necessary skill in the developed world but in spite of adequate education and intelligence, up to 10% of children fail to acquire adequate reading comprehension skills (Snowling et al., 2009). Difficulty in reading comprehension causes significant hardship not only with respect to self-esteem, but also to academic and vocational outcomes. For example, students are required to read and comprehend material from textbooks and lecture slides, utilize the printed word for studying, and then for reading and completing exams. While reading and comprehension skills are essential, acquiring these skills takes years of practice and instruction. Currently, a number of reading comprehension interventions exist, but they are time consuming and not effective for all users, especially those targeted at adults. Thus, the goal of Aim 2 was to investigate a novel approach to improve reading comprehension scores in young adults.

A number of interventions aim to improve oral reading skills and reading comprehension skills. For example, in adult English as a Second Language (ESL) learners, a vocabulary-based training improved reading fluency, but not comprehension (Oliver & Young, 2016). As a second example, researchers adapted reading intervention programs that were effective in children (i.e., Corrective Reading, RAVE-O, and Guided Repeated Reading) and found that, in adults, these interventions can improve multiple skills, including comprehension, after 10-18 weeks of intervention (Sabatini et al., 2011). While these interventions show some promise, they exhibit three main limitations: 1) they take 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. A method to decrease intervention time would be incredibly valuable for individuals who need to improve their performance at school or at work.

Neuromodulation is a popular approach to enhance cortical connections and drive neural plasticity. One such method involves leveraging the role of the vagus nerve. Cervical vagus nerve stimulation (cVNS) involves the release of norepinephrine and acetylcholine, neurotransmitters implicated in learning and memory (Picciotto, Higley, & Mineur, 2012; Tully & Volshakov, 2010). Importantly, key neurotransmitter systems must be intact to ensure effectiveness of cVNS (Hulsey et al., 2016; Hulsey et al., 2019). 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 (Engineer et al., 2001). cVNS paired with training has also improved motor function recovery in stroke-induced rats and driven neural plasticity in motor cortex (Khodaparast et al., 2013; Porter et al., 2012). In humans, active cVNS led to higher rates of recognition memory of highlighted words in a passage (Clark et al., 1999), decreased errors in a delayed recall task (Sun et al., 2017), and better performance on a verbal fluency task (Sackeim et al., 2001), when compared to sham cVNS. To date, cVNS has been FDA approved for individuals with treatment resistant epilepsy and depression, and it 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 (Badran et al., 2018; Frangos, Ellrich, & Komisaruk, 2015; Yakunina, Kim, & Nam, 2016). 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 (Redgrave et al., 2018) and alleviates symptoms of tinnitus (Yakunina, Kim, & Nam, 2018). In the language and reading domains, taVNS improves learning of novel letter-sound pairings (Thakkar et al., 2020) and novel Mandarin speech sound categories (Llanos et al., 2020). This approach also increases performance on a face-name association task in healthy older adults (Jacobs et al., 2015), suggesting its effectiveness in higher cognitive domains. Given the previous evidence that taVNS increases performance in lower-level reading skills like letter-sound learning (Thakkar et al., 2020), we evaluated whether taVNS is capable of improving reading comprehension performance, a skill requiring both reading and memory, in typically developing young adults.

Method

Participants

Fifty-five young adults were screened for eligibility from an online participant pool at Texas Christian University in Fort Worth, Texas. 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 (Appendix A): a non-verbal IQ measure (the matrices subtest of the KBIT-2; Kaufman & Kaufman, 2004), timed single-word reading (the Sight Word Efficiency and Phonemic Decoding Efficiency from the TOWRE-2; Torgesen, Wagner, & Rashotte, 2012) and untimed single-word reading (Word Identification and Word Attack from the WRMT-3; Woodcock, 2011). 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 reading scores of 90 or higher on all four 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 (De Ridder et al., 2013; Hulsey et al., 2016; Hulsey et al., 2019). Thus, we excluded these individuals to ensure all participants had, to the best of our knowledge, typical neurotransmitter function.

In addition to inclusion testing, participants also completed Passage Comprehension and Oral Fluency (WRMT-3; Woodcock, 2011), Rapid Digit and Letter Naming (CTOPP-2; Wagner, Torgesen, & Rashotte, 2013), and the Design Memory Core, Verbal Learning Core, Number-Letter, Design Memory Recognition, and Verbal Learning Recall (WRAML-2; Sheslow & Adams, 2009) subtests.

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 withdrew partway through the study. Thus, the final sample included 24 typically developing young adults (age:

19.84 ± .40 years; 7 males and 17 females). To ensure that our participants had intact neurotransmitter systems, we only enrolled typically developing young adults to investigate the effectiveness of taVNS on reading comprehension. Eligible participants were randomized into a sham taVNS (*n* = 12) or active taVNS (*n* = 12) group (Table 5).

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 as a result of the COVID-19 pandemic. To maximize our statistical power in these circumstances, each experimental group consisted of twenty participants that completed the study using a Parasym taVNS device (https://www.parasym.co/index.html) and four additional participants that completed the study using the TENS7000 transcutaneous electrical nerve stimulation (TENS) device (https://tens7000.com/). To ensure that the difference in stimulation device did not impact the results, we conducted a confirmatory analysis in the sample trained using the Parasym device. 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.

Table 5

Participant Characteristics and Standard Assessment Scores (M ± SD) by Stimulation Group for Participants in Aim 2

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-2 = 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.

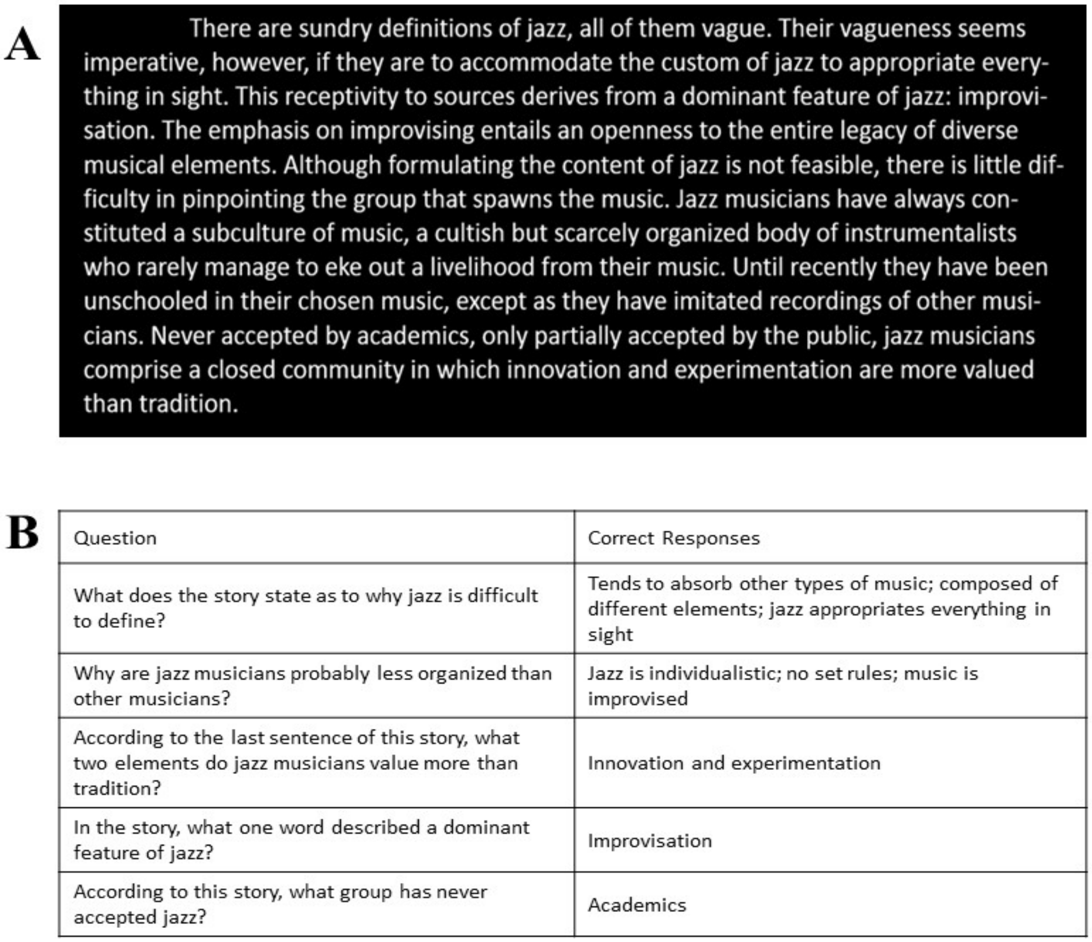
Materials and Procedures

taVNS Device, Settings, and Procedures. Most participants ($n_{\text{sham}} = 10$, $n_{\text{active}} = 10$) received taVNS from the Parasym device, which utilizes a one-quarter inch diameter gold-plated copper electrode. For a subset of participants ($n_{\text{sham}} = 2$, $n_{\text{active}} = 2$), taVNS was administered using the TENS7000 device. 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 (Badran et al., 2018; Yakunina, Kim, & Nam, 2016). Current was delivered with identical parameters across devices: as square, biphasic pulses with a 200 μs pulse width, and 5 Hz frequency (Thakkar et al., 2020). During the testing session, stimulation onset and offset were controlled manually by a trained researcher to ensure that stimulation was delivered only during active reading. Stimulation was only delivered during oral reading to model previous research suggesting that VNS efficacy relies heavily on pairing stimulation with the external stimulus, such as a tone (Engineer et al., 2011), movement (Pruitt et al., 2016; Morrison et al., 2020) or passage being read.

Custom stimulation intensity 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 (Thakkar et al., 2020; Yakunina, Kim, & Nam, 2016). The average current threshold across the entire sample ($N = 24$) was (2.03 ± .10 mA), with the sham group exhibiting marginally higher thresholds (2.23 ± .11 mA) than the active taVNS group (1.84 ± .16 mA; unpaired two-tailed *t*-test, $t\ (22) = 2.69$, $p = .057$, $d = .83$). In the subset of participants run on the Parasym device ($n = 20$), the sham taVNS group (2.27 ± .13 mA) exhibited significantly higher thresholds than did the active taVNS group (1.81 ± .12 mA; unpaired two-tailed *t*-test: $t\ (18) = 2.69$, $p = .02$, $d = 1.16$).

Reading Comprehension Outcome Measure: Administration and Data Coding. To evaluate the effect of taVNS on reading comprehension, participants read passages from both forms of the GORT-5 (Wiederholt & Bryant, 2012) in a counterbalanced order. For each form, passage 6 was administered as a practice passage, and passages 11-16 were administered as test passages. Passages were presented in white font on black background using custom code in PsychoPy (Peirce et al., 2019). 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 8A). 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 (Costanzo et al., 2013) and average reading rate per passage (O’Brien, Mansfield, & Legge, 2005; O’Brien & Wallot, 2016). 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 overall reading comprehension performance (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 8B; Wiederholt & Bryant, 2012). 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. Two researchers independently scored participant responses for accuracy, and discrepancies were resolved by coming to a consensus. No adverse events occurred during the session.



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.

Question	Correct Responses
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
Why are jazz musicians probably less organized than other musicians?	Jazz is individualistic; no set rules; music is improvised
According to the last sentence of this story, what two elements do jazz musicians value more than tradition?	Innovation and experimentation
In the story, what one word described a dominant feature of jazz?	Improvisation
According to this story, what group has never accepted jazz?	Academics

Figure 8. Example of a test passage and associated questions administered during reading session. Participants read two practice passages and twelve test passages from the GORT-5 (Weiderholt & Bryant, 2012) out loud to a researcher and pressed a button when they finished reading. (**A**) Passages were presented one at a time in white font on a black background. (**B**) Immediately after reading, a researcher asked five test questions about the passage, and participants provided answers out loud.

To analyze performance, two experienced researchers 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 named in the passage) or a comprehension question (i.e., a 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 a third researcher. 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 8 (Appendix B).

Data Analysis and Statistics. Two-tailed, independent-samples *t*-tests were used to compare the sham and active taVNS groups on standard English assessments and evaluate any differences in baseline reading abilities. Descriptive statistics are presented as M ± SD (Table 5). 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. To correct for multiple comparisons, the Bonferroni correction was applied.

Results

No Group Differences on Nonverbal IQ and Reading

Prior to enrollment in the study, all participants completed baseline assessments of nonverbal IQ, reading ability, rapid naming, and memory. Twenty-four typically developing young adults qualified for the study, and descriptive statistics for assessments are provided in Table 5. Two-tailed, between-groups *t*-tests were applied to analyze any group differences. Participants in the sham taVNS and active taVNS were matched by chronological age (t (22) = 1.74, p = .09) and nonverbal IQ (t (22) = 1.03, p = .31). Additionally, participants in the sham and active taVNS groups were matched on baseline reading ability, as measured by the TOWRE-2 Sight Word Efficiency (t (22) = .03, p = .98), the TOWRE-2 Phonemic Decoding Efficiency (t (22) = .69, p = .50), the WRMT-3 Word Identification (t (22) = 1.34, p = .19), and the WRMT-3

Word Attack (*t* (22) = .30, *p* = .77). In addition to assessments used to determine eligibility, participants completed additional descriptive measures. On these measures, participants were matched on more reading abilities, as measured by the WRMT-3 Passage Comprehension (*t* (22) = .98, *p* = .34), WRMT-3 Oral Fluency (*t* (22) = .61, *p* = .55), CTOPP-2 Rapid Digit Naming (*t* (22) = .47, *p* = .64), and CTOPP-2 Rapid Letter Naming (*t* (22) = .47, *p* = .64). Finally, we established no group differences on the Verbal Learning Core (*t* (22) = 1.25, *p* = .22) and Verbal Learning Recall (*t* (22) = .88, *p* = .39). There was a significant group difference on the Number-Letter task, such that the active taVNS group scored significantly higher than did the sham taVNS group (*t* (22) = 2.37, *p* = .02).

taVNS Improves Performance on Memory Questions

We next evaluated whether taVNS improved reading accuracy or reading rate, as prior work suggested repetitive transcranial magnetic stimulation (TMS) can improve performance on these reading metrics (Costanzo et al., 2013) and may also have benefitted from our stimulation protocol. 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 9A). In terms of average reading rate (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 9B). These results suggest that unlike other forms of non-invasive stimulation, taVNS does not influence the mechanics of reading within the session.

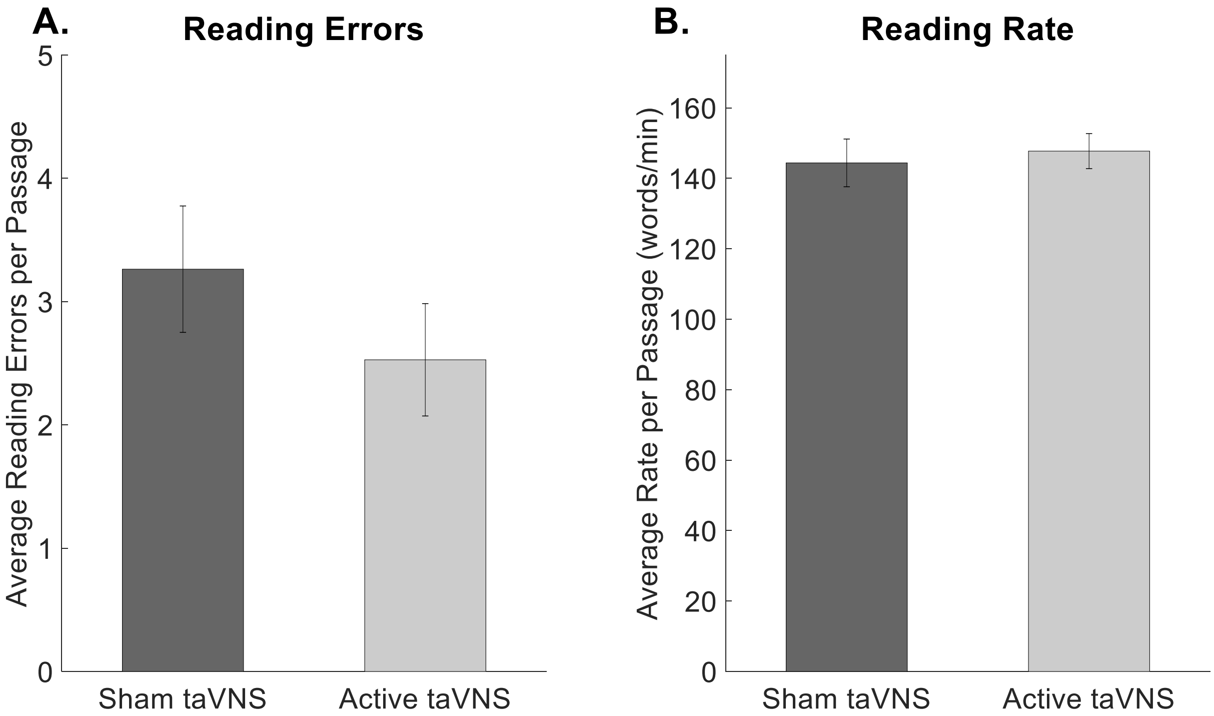


Figure 9. No benefit of taVNS on reading mechanics. During reading, average errors made per passage and average reading rate per passage (words/min) were each quantified. There was no group difference between active taVNS and sham taVNS on average errors during reading (**A**) or reading rate (**B**).

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 10A) such that active taVNS improved performance compared to sham taVNS. To determine whether this effect was driven by performance on a specific question type, we evaluated whether taVNS improved performance on the subsets of memory and comprehension questions separately. There was a significant group difference on memory questions (*t* (22) = 3.00, *p* = .007, *d* = 1.23) such that the active taVNS group (49.63 ± 3.47%) significantly outperformed the sham taVNS group (37.04 ± 3.47%; Figure 10B). 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 10C).

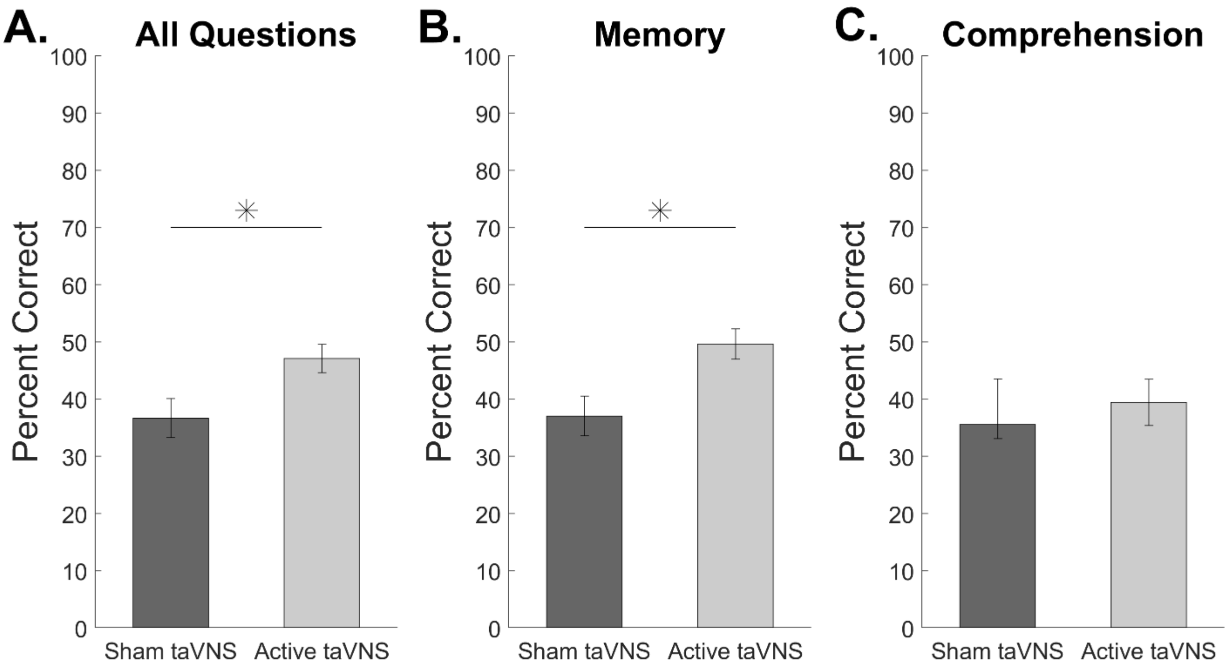


Figure 10. Performance on reading comprehension questions. (**A**) There was a significant benefit of active taVNS compared to sham taVNS on all test questions. This effect was driven by a significant benefit active taVNS for memory comprehension questions (**B**), but not for comprehension questions (**C**).

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. In the entire sample (*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 used the Parasym device (*n* = 10). There was again no significant relationship between current intensity and percent correct (*r* = .33, *p* = .35; Figure 11), demonstrating that current intensity did not influence taVNS efficacy in this sample.

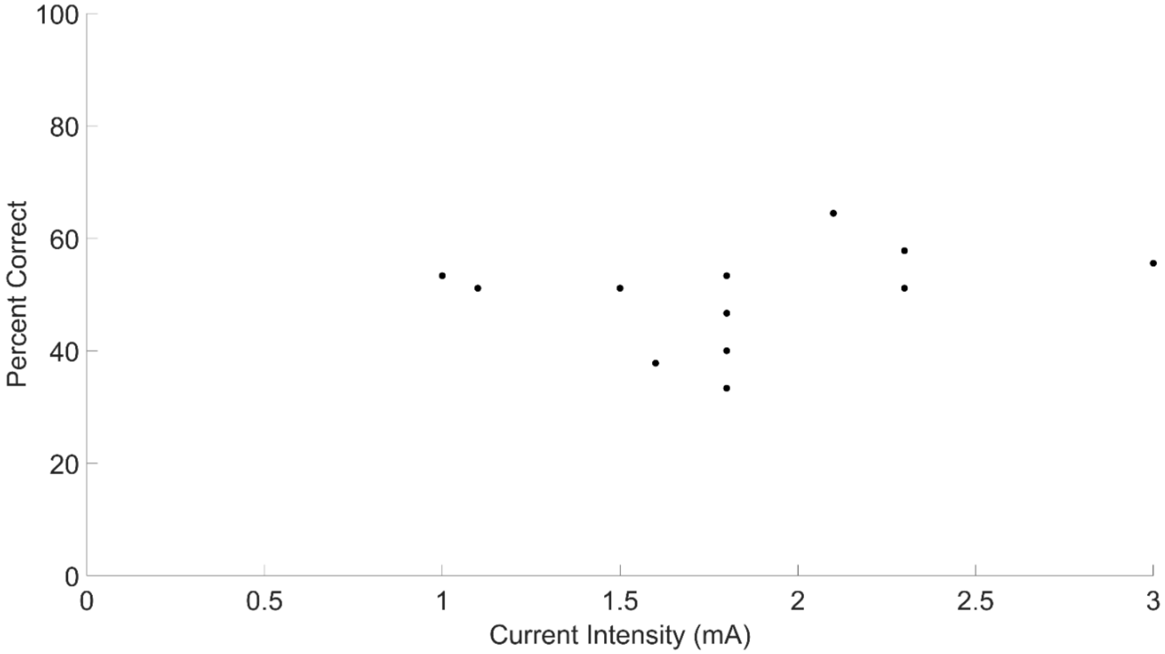


Figure 11. Relationship between current intensity and performance on memory questions in participants receiving active taVNS. There was no significant relationship between taVNS current intensity and percent correct on memory-based comprehension questions.

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 the analyses in the participants that received stimulation from the Parasym device and replicated the pattern of results observed in the full sample. 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 trending benefit of active taVNS across all test questions (*t* (18) = 1.91, *p* = .07), which was driven by a significant benefit on memory questions (*t* (18) = 2.33, *p* = .03). There was no group difference on comprehension questions (*t* (18) = .19, *p* = .86). This consistent pattern suggests that stimulation device differences did not impact the efficacy of posterior tragus stimulation of the auricular vagus nerve on our dependent measures.

Relationships between Verbal Working Memory and Comprehension

Based on prior evidence that comprehension abilities require working memory skills (Cain, Oakhill, & Bryant, 2004), we next utilized Pearson's r to evaluate the relationships between verbal working memory and performance on memory questions. In the sham taVNS group, performance on the Verbal Learning Core (WRAML-2; Sheslow & Adams, 2009) was not correlated to performance on memory questions ($r = .05$, $p = .88$), but it was significantly and positively correlated within the active taVNS group, even after correction ($r = .65$, $p = .023$). In the sham taVNS group, performance on the Verbal Learning Recall (WRAML-2; Sheslow & Adams, 2009) was not correlated to performance on memory questions ($r = -.39$, $p = .24$), but there was a significant, positive relationship in the active taVNS group, even after correction ($r = .65$, $p = .021$).

Discussion

The goal of Aim 2 was to evaluate the effect of taVNS on a cognitive skill such as reading comprehension in a sample of typical young adult readers. Our results demonstrate, for the first time, that taVNS paired with reading improves performance on reading comprehension questions and that this benefit appears to be selective to memory-based recall. We observed no effect of taVNS on comprehension questions or the mechanics of oral reading (e.g., reading accuracy and reading rate). These findings support prior work demonstrating that taVNS is capable of improving reading skills (Thakkar et al., 2020). However, our findings also suggest that the efficacy of taVNS may be limited to tasks relying on sensory plasticity and memory.

Vagus Nerve Stimulation Improves Memory

There is a well-documented literature of both cVNS and taVNS demonstrating significant learning in both the animal and human models (Engineer et al., 2011; De Ridder et al., 2013; Jacobs et al., 2015; Redgrave et al., 2018). When taVNS was investigated in the sensory and motor domains, data suggest significant behavioral benefits (e.g., learning of motor movements), suggesting that it can provide the same benefits as cVNS. For example, taVNS paired with sound therapy for ten sessions led to decreased tinnitus symptoms in a small sample of patients, unique for those specific sounds exposed during training (Lehtimaki et al., 2013). Further, patients receiving taVNS paired with physical rehabilitation over 18 sessions also showed significant improvements in learning of trained movements (Redgrave et al., 2018). These findings provide additional evidence that VNS can boost sensory memory, taking advantage of precisely timed neurotransmitter release.

However, benefits observed as a result of taVNS are unique to the trained tones or trained movements. Ultimately, the goal of therapy and rehabilitation should be for the intervention to generalize into untrained stimuli to enhance recovery. For example, cVNS and taVNS paired with training have increased post-stroke motor function recovery (Redgrave et al., 2018), but those benefits are specific to the movements taught in training. A key limitation of many previous cVNS and taVNS studies is that they did not measure whether benefits generalized to movements not rehearsed during training. However, in overall post-stroke recovery, it is important for a patient to recover all possible motor functions, not just ones explicitly taught during training. Similarly, reading comprehension requires more than verbal recall. Readers must extract meaning from text beyond information that is explicitly stated (i.e., comprehension or inference). Since our data suggest no benefit of taVNS on comprehension questions, future research should examine other parameters or paradigms to investigate if taVNS is capable of improving inferential skills. For example, previous taVNS research (Jacobs et al., 2015) employed stimulation during encoding (training) and a brief consolidation period. In the context of Aim 2, it is possible that adding stimulation during a brief consolidation period after reading would yield benefits on comprehension questions. Given the importance of comprehension during reading, future work is needed to explore whether changes to the stimulation protocol can elicit a taVNS effect.

Comparison to Behavioral-Based Interventions

In Aim 2, we observed robust effects of taVNS on memory questions in a single session of stimulation. Previous interventions, such as *Let's Know!* (LARRC, 2015; LARRC & Chiu, 2018; LARRC, Pratt, & Logan, 2014) and randomized controlled trials (Clarke et al., 2009; LARRC; 2015) require multiple sessions per week for several weeks to produce significant improvement in reading comprehension, broadly, without specifying direct benefits to memory or inference learning. Similar to previous interventions, reading comprehension was measured through standardized English assessments (e.g., the Neale Analysis of Reading Ability II Form B, used in Clarke et al., 2009). However, there were crucial differences between previous interventions and the taVNS intervention used in Aim 2. First, previous interventions focused weeks- or months- long intervention on lower-level skills needed to improve reading comprehension, such as vocabulary learning (Clarke et al., 2009). In the current study, we attempted to bypass this long training time by pairing taVNS with a single session of real-time reading. While we observed significant benefits of taVNS in a single session, it is unknown whether these effects are short-lived or long-lived, as we did not evaluate the effect of taVNS on long-term reading comprehension skills in the days and weeks after the stimulation session. It is likely that extended benefits could be observed, since long-term sensory plasticity has been reported in both the rodent model up to three weeks after auditory therapy (Engineer et al., 2011) and in humans between three- and six-months after movement therapy (De Ridder et al., 2013). Additionally, data from Aim 1 suggest that taVNS was beneficial after a seven-day delay, rather than immediately after training was completed. Future research would benefit from understanding the long-term time-course of taVNS driven plasticity, since students often must comprehend and store information for assessments (i.e., exams) that take place days or weeks after the material is taught in the classroom. While exams measure the amount of learning, students must remember the material read and infer meaning for application or more complex comprehension questions seen on exams.

Second, while other classroom programs or interventions require multiple hours of training each week for many weeks (Clarke et al., 2009; Martins & Cárnio, 2019), we were able to enhance performance on memory questions during a single session. Together, these differences suggest that stimulating the brain during reading can improve reading skills faster than using other strategies over many sessions. This difference is important because interventions that demand longer periods of time can also be taxing for students, and it is possible that some students may be unable to complete a full intervention schedule. The addition of an approach like taVNS, which may shorten the time needed for intervention, could increase the likelihood that children are able to complete and benefit from the full program.

Third, previous interventions (e.g., Martins & Cárnio, 2020) were applied in struggling readers and found that children benefitted from intervention and experienced increased motivation. Aim 2 was conducted on typically developing young adults, 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, phonological awareness (Zuk et al., 2018), and automaticity (Pennington & Bishop, 2009; Wolf & Obregón, 1992). These deficits often lead to individuals focusing their cognitive resources on the mechanics of reading rather than on absorbing the content of a passage. In Aim 2, all the participants were typically developing readers and thus exhibited average or above average low-level reading skills. It is therefore possible that a taVNS intervention for dyslexia would require a focus on the mechanics of reading rather than on comprehension. Our prior work demonstrated a benefit of taVNS on letter-sound learning and subsequent improvement in automaticity and decoding (Thakkar et al., 2020). It is unknown whether this approach is also effective in dyslexia and our ongoing work is designed to investigate potential effects in individuals with dyslexia.

Baseline Verbal Memory Skills Influence Reading Comprehension

With regard to baseline memory skills, a significant, positive correlation between verbal learning and recall and performance on memory questions emerged in the active taVNS group, but not the sham taVNS group. These significant correlations remained significant after correcting for multiple comparisons, supporting similar correlations observed in Aim 1, which did not survive correction. Executive functions, such as updating and shifting, each have been shown to contribute to reading comprehension (see Butterfuss & Kendeou, 2018, for a review). Working memory is essential for retaining and integrating information from text, which is a marker of understanding. Data from both children and adults have suggested that oral language and decoding skills mediate the relationship between working memory and reading comprehension (Spencer et al., 2020). Additional findings have corroborated these relationships between memory skills and reading comprehension with other verbal memory tasks (e.g., sentence span; Daneman & Carpenter, 1980) and in individuals with inadequate reading skills (see Peng et al., 2018, for a meta-analysis). Prior studies have further elucidated the role of memory skills in reading comprehension. 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 various variables, such as age or type of assessment used (Follmer, 2018). Collectively, these data suggest that regardless of age, memory consistently plays a significant role in comprehension ability. As such, it is possible that pairing stimulation with reading takes advantage of certain baseline skills to boost memory of what is being read. Since taVNS operates through precise timing of neurotransmitter release, we speculate that taVNS strengthens pre-existing neural circuitry to drive behavioral benefits. Additionally, since previous data have suggested that memory is still essential for comprehension in struggling readers, it is reasonable to speculate that our significant correlation can be replicated. Future research, however, is still needed to investigate the potential effect of taVNS and verbal memory interactions in individuals with dyslexia.

No Effect of Current Intensity on taVNS Efficacy

Previous work investigating the impact of current intensity on cVNS efficacy in the rat model reported that moderate stimulation intensities were more effective than higher stimulation intensities (Borland et al., 2016). 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 (Clark et al., 1999). 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. In support of this hypothesis, prior research has revealed benefits of taVNS at a variety of intensities. One study reported that taVNS delivered at intensities below sensory threshold can selectively enhance speech sound categorizations (Llanos et al., 2020). Other studies conducted above sensory threshold reported a benefit of taVNS in cognitive tasks, such as face-name association (Jacobs et al., 2015) and novel letter-sound learning (Thakkar et al., 2020). However, it is important to note that these prior studies did not manipulate current intensity or systematically investigate potential relationships between current intensity and learning and retention. Future research is needed to systematically investigate the influence of current intensity on outcome measures. Such studies are needed to determine ideal parameters to enhance performance and drive neural plasticity across a range of tasks.

Limitations

There are three limitations in the current study. First, most of the passages used for testing included a high number of 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. 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, which is generally made up of individuals from high SES backgrounds. In turn, this stunts our ability to generalize these findings. Previous research suggests that home environment and SES play a role in future reading ability (Bowey, 1995; Bradley & Corwyn, 2002; Cheng & Wu, 2017; Kieffer, 2010). Specifically, children from a low SES background have more phonological deficits than those from a higher SES, and phonological skills are necessary for successful reading (Bowey, 1995). Future research should replicate the current methodology in a sample that comes from a wider range of SES to determine whether the biological impact of a lower SES upbringing impact the efficacy of taVNS. Additionally, the sample should include a group of participants with dyslexia, as struggling readers have been shown to have impaired reading comprehension performance compared to their typically reading peers (Simmons & Singleton, 2000).

Third, our sample size is small due to the forced discontinuation of in-person research during the COVID-19 pandemic. While significant effects were found, the current sample did not meet the initial *a priori* power analysis (Faul et al., 2007). Despite not meeting recruitment goals, a post-hoc analysis ($d = 1.23$, $\alpha = .05$, $n_{\text{sham}} = 12$, $n_{\text{active}} = 12$) yielded a power of .82, suggesting we did meet adequate power. Future research is needed to replicate these findings in a larger sample size that meets an *a priori* target sample size.

Aim 3: Becoming Automatically Fluent in Reading Research: Delineating between Two Key Reading Skills

In Aim 2, we found that taVNS paired with training can improve some aspects of reading comprehension performance, but it did not seem to improve reading mechanics such as accuracy or reading speed, which are often defined in the field as automaticity and fluency, respectively. In the process of interpreting our body of work on taVNS and reading, we discovered that terms like “automaticity” and “fluency” are often used interchangeably, as each can be measured using accuracy and/or speed, thus muddying the clarity of any findings related to these reading skills and adding difficulty to those studying early reading acquisition. Given the importance of these low-level reading skills, future research should explore the efficacy of taVNS on these metrics. However, prior to conducting any additional taVNS studies, it is important to review the ways in which these terms are used in the literature and clarify their metrics to encourage a standardized approach to reading research in the future. Thus, the goals of the Aim 3 were to: (1) examine the literature on automaticity and fluency in the context of language and reading abilities, (2) compare and contrast operational definitions of these terms in empirical studies to identify a discrepancy in reading research, (3) evaluate neural correlates of automaticity and fluency through neural imaging studies, and (4) propose operational definitions and assessments of evaluating these skills.

Importance of Reading

Reading is an integral skill to daily life, with variations in reading ability impacting multiple facets of academic (Olofsson, Taube, & Ahl, 2015) and vocational (Culliver & Sigler, 1991) success. This skill is integral given the ubiquity of print in the developed world, including print on road signs, information in textbooks, directions for cooking, increased usage of text messaging and emailing as a means of communication, and procedures to conduct experiments. Although print reading is ubiquitous in daily life, the printed word is a human invention. Thus, the brain has not yet developed a hard-wired reading network at birth (Cohen et al., 2002; Dehaene & Cohen, 2007; Dehaene & Cohen, 2011; but see Saygin et al., 2016) and reading acquisition requires significant training and years of practice to master. Importantly, reading acquisition and eventual mastery relies on many subskills, including, but not limited to, grapheme-phoneme mapping (i.e., mapping a visual example of a letter and the sound it makes), letter identification, automaticity, decoding, fluency, and comprehension (Kim et al., 2014; Mesmer & Rose-McCully, 2017; Schwanenflugel et al., 2004). All of these skills are needed to smoothly decipher printed words as well as to understand and infer meaning in text.

Research in pre-reading children as young as four years old suggests that lower-level skills, especially rapid automatized naming, are predictive of later reading success (Lervag & Hulme, 2009; Norton & Wolf, 2012). However, not all individuals acquire adequate reading skills even after many years of reading instruction and approximately 15% of the population acquire a dyslexia diagnosis (Pennington & Bishop, 2009; Shaywitz et al., 1992). While some of these individuals improve their reading skills as a result of intervention, poor reading will persist into adulthood in approximately 4% of the dyslexia population (Soriano-Ferrer & Martínez, 2017). Subsequently, individuals with dyslexia often experience lower self-esteem (Riddick et al., 1999), increased rates of anxiety (Carroll & Iles, 2006), and increased rates of delinquency (Eissa, 2010). As such, it is increasingly important to define and measure key reading skills in a consistent manner to facilitate early diagnosis and intervention of reading deficits. Further, by remediating key deficits at the individual level early in life, struggling readers will regain confidence and experience higher self-esteem or decreased levels of anxiety.

Automaticity and fluency are well-documented predictors of future reading ability and are therefore frequently utilized metrics in research and in diagnosis (Norton & Wolf, 2012; Shahreef, Ostberg, & Hedenius, 2019). For example, a growing number of studies utilize automaticity in pre-readers as an early screening measure for future reading outcomes (Kim, 2015), while fluency is used as a marker of expertise in reading (Wolf & Katzir-Cohen, 2001). While automaticity and fluency are both important metrics of reading, these terms are often used interchangeably in the field, which can cause theoretical and practical confusion when researchers attempt to summarize their findings in the context of prior research or when clinicians attempt to bring in new research to their practice. Due to the unique role of each of these skills, it is integral for the field to define, measure, and apply them in a consistent manner. Clinicians often use measurements of both skills to identify core deficits at the child level.

Reading Frameworks

Given the large number of subskills critical for successful reading acquisition (including phonological awareness, rapid naming, and decoding), a number of theories have been developed to explain how these skills contribute to reading development. These behavioral and neural theories explain how reading acquisition develops, and they provide insight into how and why some individuals do not acquire adequate reading skills. The prevailing theory of dyslexia, the double-deficit hypothesis (Wolf & Bowers, 1999), proposes that individuals with dyslexia have deficits in rapid naming skills, deficits in phonemic decoding skills, or deficits in both of those skills. The double-deficit hypothesis separates those with these deficits into subgroups, supporting the idea that there is heterogeneity within the dyslexia population. This suggests that those individuals with deficits in both rapid naming and phonological awareness may also have impairments in many subsequent reading skills, while those with one core deficit may only have selective impairments. In fact, when evaluated in a sample of adolescents and young adults, those with a RAN deficit (i.e., lower composite scores on Rapid Digit Naming and Rapid Letter Naming) exhibited significantly worse reading fluency, as measured by number of sentences read in one minute, than did those with a phonological awareness deficit. Neither group was different from a group of participants with both deficits (Nelson, 2015).

As another example, the Simple View of Reading (SVR; Gough & Tunmer, 1986; Hoover & Gough, 1990) has been well-supported and proposes that reading ability is the product of lower-level reading skills, such as decoding, and higher-level skills, such as comprehension. The SVR framework defines decoding as fluid word recognition and comprehension as the ability to interpret words and sentences. The SVR definition of decoding actually overlaps with some definitions of automaticity (i.e., reading quickly) and fluency (i.e., a skill that emerges in skilled readers) in the literature, showing potential issues that can arise since the SVR has been studied immensely. Since the SVR lacks a clear definition of fluency, researchers have also suggested that the SVR should be updated to focus on fluency rather than just word reading accuracy (Adolf, Catts, & Little, 2006). Due to this potential lack of clarity between automaticity and fluency, it highlights the need for a well-understood definition of these skills, both theoretically and empirically. The SVR framework has been well-supported over the last 30 years and has served as the foundation for a number of intervention programs (Clark et al., 2009; LARRC, 2015). In context of the SVR, researchers have also evaluated the influence of fluency by analyzing performance in 248 fourth-grade children. Using structural equation modeling, they suggested that the connection between a lower-level skill (decoding) and higher-level skill (comprehension) is mediated by oral reading fluency (mean number of words read per minute across two passages; Silverman et al., 2013). Despite being very well-studied, a more recent, updated version of SVR, the Complete View of Reading (CVRi), was proposed to bridge certain limitations of the SVR (Francis, Kulesz, & Benoit, 2018) such as failing to account for individual variability in developmental milestones. Thus, the CVRi extends the SVR by accounting for additional heterogeneity within the population to better understand reading development and translations to reading interventions. For example, while fluency, the number of words read per minute, systematically improved with grade level, there were some more inconsistent effects of fluency being impacted by difficulty of the passage, suggesting that fluency skills can vary more at the level of an individual reader (Francis, Kulesz, & Benoit, 2018).

In addition to the abundance of support for the Double-Deficit Hypothesis and the Simple View of Reading, many studies have further investigated the nature of heterogeneity within individuals with dyslexia (e.g., Centanni et al., 2018; Lachmann et al., 2005; Lachmann & Van Leeuwen, 2008; Manis et al., 1996; Manis et al., 1999; Murphy & Pollatsek, 1994; Neef et al., 2017; Zoubrinetzky, Bielle, & Valodis, 2014). This emphasis on investigating deficits in reading skills highlights the need for a common definition and set of metrics for use in the field and in research. Previous research has measured both skills using overlapping metrics, with a specific focus on the amount of time a participant requires to complete a reading task (e.g., words per minute, time to read a passage, rapid naming time). This reliance on speed has created an unintentional overlap in the literature, with some studies using measures such as words read per minute as a reflection of automaticity (Roembke et al., 2019) and other studies using this same measure to reflect fluency (Cho et al., 2018). Thus, prior to making any recommendations about use of these terms, we must first evaluate the status of the field with respect to the definition and measurement of automaticity and fluency.

Automaticity

The effortless ability to quickly and correctly identify a letter is essential for reading acquisition. A reader must be able to map a letter to a correct sound to read a word or decode a new word, which, in turn, enables accurate passage reading. In movement research, automaticity is defined as an action that can be completed with little to no conscious control or effort (LaBerge & Samuels, 1974; Nicolson, Fawcett, & Dean, 2001; Samuels, 2006). In the context of reading, automaticity is often measured by tasks in which participants identify stimuli such as letters, objects, digits, and colors, quickly and accurately, indicating minimal conscious effort (Georgiou & Parrila, 2020; Georgiou, Parrila, Cui, & Papadopoulos, 2013; and see Kirby, Georgiou, Martinussen, & Parrila, 2010 for a review).

In the 1970s, seminal research found that children with dyslexia exhibited slower naming speeds but intact accuracy on a naming task (Denckla & Rudel, 1974; Denckla & Rudel, 1976), which led to the development of the rapid automatized naming measure. This original naming task required a participant to read a series of printed items as quickly and accurately as possible. The printed items used included colored squares (red, green, black, blue, yellow), numbers (2, 4, 6, 7, 9), objects (comb, key, watch, scissors, umbrella), and letters (a, d, o, p, s). To administer this measure, a short practice set of five items was given, followed by the test series of fifty stimuli arranged in a 5 x 10 grid in randomized order. Updated versions of the task are now part of two standardized batteries: as the Rapid Automatized Naming task (RAN; Wolf & Denckla, 2005) as well as the Rapid Naming (Digits or Letters) subtests of the Comprehensive Test of Phonological Processing (CTOPP-2; Wagner, Torgesen, & Rashotte, 2013). Regardless of which battery is used, this measure is commonly referred to as rapid automatized naming (RAN).

Rapid automatized naming ability, when administered in young children and pre-readers, is the most accurate predictor of future reading ability (see Norton & Wolf, 2012, for a review). In a large study of 233 first grade children tracked for 37 months, alphanumeric RAN robustly predicted text reading fluency up to 2.5 years after enrollment in the study (Lervag & Hulme, 2009). Additional evidence also supports the RAN-reading relationship such that word reading accuracy improved in children with dyslexia over the course of a RAN-focused intervention on object naming speed, but their typically developing peers had more growth in word reading speed (Stappen, Dricot, & Reybroeck, 2020). Results from this study suggest that interventions may benefit readers with and without dyslexia differently, and speed may be harder to improve in readers with dyslexia. Since alphanumeric RAN was not employed in the study, it is possible that certain results are attributed to differences in the stimuli used.

While much of the prior research has been conducted in English, RAN remains a stable predictor in a variety of orthographies (Landerl et al., 2013; Shany & Share, 2011). In one study of native Dutch speakers, children with and without dyslexia learned novel Hebrew graphemes via a computerized video game. After one training session, children were assessed for their ability to read as many high-frequency Hebrew words as possible in a span of three minutes (Aravena et al., 2018). In spite of improvements following training, participants with dyslexia continued to perform significantly worse than participants without dyslexia. Most importantly for the purpose of this review, RAN scores in the dyslexia group were predictive of individual reading ability in the newly learned orthography, as analyzed through logistic regression (Aravena et al., 2018). Further, in a study investigating second grade children and college undergraduates, variations of the RAN letters completion times were evaluated for their ability to predict reading fluency (Georgiou & Parilla, 2020). In this case, reading fluency was measured by participants' ability to silently read sentences and report if the sentence made sense or not under a time constraint. The researchers altered the RAN task in two ways. While the original RAN letters task included ten repetitions of each of five letters, one variation used in this study had 25 repetitions of only two letters (*a* and *d*). A second variation used included two repetitions of 25 letters of the alphabet (all except *w*). Their results showed that, regardless of which RAN task was used, participants consistently revealed significant, moderate correlations with both oral reading fluency and silent reading fluency between age groups (Georgiou & Parilla, 2020).

While RAN skills are predictive of future reading when measured in young children, automaticity does continue to develop with practice and instruction. One such study investigated the development of RAN in typically developing children by testing them at six time points between the ages of four and ten (Avall, Wolff, & Gustafsson, 2019). The greatest increase in scores occurred in automaticity for objects within the 4–6-year-old development window, while automaticity for digits and letters exhibited similar growth later in development. This important finding highlights the importance of non-alphanumeric RAN earlier in reading development, but the later alphanumeric RAN is integral in the acquisition of expertise in reading print-like stimuli (e.g., numbers and letters). Another key finding from this work was that children who struggled with RAN at the beginning of the study continued to do so, when compared to their typically developing peers, and they reached a mastery of RAN later in development (Avall, Wolff, & Gustafsson, 2019).

Since automaticity is an integral skill for reading, effective methods for improving these skills through intervention are vital (de Jong & Vrielink, 2004). In spite of the value of such an intervention, a number of prior intervention options for improving automaticity have failed. For example, first grade children completed short training sessions each day for ten days in groups (de Jong & Vrielink, 2004). The letter training group practiced naming of graphemes through naming graphemes, searching for graphemes, and practicing serial naming over ten days. The math training control group received training focused on simple addition math problems rather than reading training. Unfortunately, the authors did not find a significant effect of the grapheme intervention on rapid naming speed (de Jong & Vrielink, 2004). Their lack of improvement could be attributed to the fact that their training program was not always directly training speed, making detecting a RAN improvement more difficult at the testing sessions. In another automaticity intervention attempt, 44 children with slower rapid naming scores, as measured by taking the mean of two trials of digit naming and having completion times longer than 41.5 s (Levy et al., 1999), underwent one of three training programs and completed subsequent outcome measures. Participants received control arithmetic training or two experimental trainings (letter training and orthographic pattern), with order received counterbalanced across participants. The letter training portion prompted children to read each matrix, as done in the RAN task, as quickly and accurately as they could from a computer screen for five trials daily for six days. The orthographic pattern training portion taught children to recognize patterns of letters in a word and manipulated whether the pattern occurred at the beginning (e.g., *gra*pe) or end (e.g., qu*it*) of the word. Their results suggested that children benefitted from training and their improvement generalized to the RAN task (Conrad & Levy, 2011). Another investigation of RAN training in first-grade students from low socioeconomic (SES) backgrounds found that an experimental training group benefitted from RAN intervention compared to controls. Over the course of twelve 15-minute training sessions, letters were presented and taught repeatedly for many trials to increase learning, but benefits did not persist at a post-intervention follow-up session (Fugate, 1997).

It is possible that novel interventions that are biologically based instead of strictly behavioral can provide new avenues to increase RAN skills. A previous experiment in our lab employed transcutaneous auricular vagus nerve stimulation (taVNS) with training where young adults learned novel grapheme-phoneme pairings in Hebrew. Participants were tested after five days of training, and results suggested that received active taVNS had faster automaticity scores than did individuals in the control groups (Thakkar et al., 2020). However, this study was conducted in a between-groups design, preventing us from claiming that taVNS intervention can improve automaticity performance within individuals. To further elucidate this claim, a pre-training/post-training design would be needed to establish actual improvement, and future research should also test for performance after a period without training to test for effects in the long-term. This still opens an avenue for biologically based interventions to be tested over time, within children, and hopefully within struggling readers.

While RAN is the most common approach for measuring automaticity, it is certainly not the only metric in use. Other methods for quantifying automaticity include the number of words read per second (Aravena et al., 2018), words read per minute (Pedersen et al., 2016) word reading completion time (Davis et al., 2016), and performance on a Stroop task (Megherbi et al., 2018). These additional measures for automaticity are problematic as they are also commonly used to measure a higher-level reading skill, fluency. Researchers and clinicians agree that automaticity is crucial in reading development and reliably predicts future reading ability. However, since automaticity is a low-level reading skill, researchers also often evaluate higher-level reading measures, such as fluency. Fluency is comprised of previous reading skills that develop earlier (e.g., automaticity and decoding) and is therefore a more advanced measure of reading expertise. Thus, it is likely that fluency measures are capable of identifying different deficit profiles compared to measures that target those earlier reading skills.

Fluency

While automaticity develops early in childhood and is a prerequisite for reading acquisition, fluency is a higher-order reading skill that emerges in later stages of reading development. Fluency is often defined as one's ability to read text smoothly and accurately, with intact decoding (Wolf & Katzir-Cohen, 2001). The ability to read fluently implies that lower-level reading skills are present and well-developed, which allows the reader to focus on the meaning of text. For a reader to exhibit fluency, the individual must have a solid foundation of grapheme-phoneme pairings, automaticity, and decoding skills, which together facilitate ease in reading passages (Oppenheimer, 2008). A prior review on fluency interventions suggested that automaticity contributes to fluency because a successful reader needs to automatically process text in order to focus on fluid reading and extracting meaning from text (see Kuhn & Stahl, 2003, for a review). In previous studies, the skill of fluency has been operationally defined as words read correctly within 45 seconds (as measured by the Test of Word Reading Efficiency; Georgiou & Parilla, 2020), words read per minute (Cho et al., 2018), ability to read accurately and at a rate that enables comprehension (Cho et al., 2018), total correct responses on category fluency task (Davis et al., 2016), silent reading of sentences during fMRI (Christodoulou et al., 2014), and the sum of reading accuracy and reading time, as calculated by the standardized GORT-4 assessment (Moore et al., 2014). This array of measures highlights the inconsistency with which fluency is defined in the field. As mentioned in the prior section, many studies use these definitions to operationalize automaticity. Further, several studies utilizing these measures have not differentiated between word reading fluency and text reading fluency. While word reading and text/passage reading are related, it is possible for participants to perform differently across these two measures (Kim et al., 2014). Thus, it is likely that word and text/passage reading fluency reflect different skills or at least different dimensions of fluency.

Given the relationship between early success in developing automaticity and later fluency skills over a range of measures, it is perhaps not surprising that these two metrics are often measured and discussed in the same studies. For example, a study conducted in 104 children reported significant, positive correlations between the digit, letter, color, and object RAN measures and oral reading fluency, as measured by reading rate and errors (Pham et al., 2011). Importantly, the relationship between automaticity and fluency was stronger than other variables explored in the study as potential predictors of fluency, such as working memory. It is important to note, however, that while automaticity is a commonly described predictor of fluency, it is not the only significant predictor. One study reported that both phonological and morphological awareness were significant predictors of word reading fluency in third-grade Hebrew-speaking children (Shechter, Lipka, & Katzir, 2018). Another study suggested that listening comprehension, vocabulary, and orthographic knowledge were all predictive of reading fluency. Monolingual kindergarten and first-grade children in Korea completed various reading assessments, including reading fluency. In this study, text reading fluency was measured as the number of syllables read correctly in 40 seconds, and the authors reported significant, positive correlations between word reading fluency, or the number of accurately words in 40 seconds, and text reading fluency, as measured by the number of correctly read syllables (Kim, Park, & Wagner, 2014). The variety of skills that reliably predict fluency may be due to the orthographic depth used in the study. Orthographic depth refers to the degree of consistency in letter-sound relationships within a system of print (Ellis et al., 2004; Katz & Feldman, 1983). For example, children learning to read in shallow or transparent orthographies (e.g., Hebrew, Hiragana) often require less instruction because the relationships between each letter and its corresponding sound are consistent. However, more instruction is required in deep or opaque orthographies (e.g., English) because the sound associated with a given letter often varies depending on the context within a word and in some cases, the context of a sentence.

Fluency has also been well-studied in individuals with inadequate skills. For example, fifth grade students in an intervention program completed training for 30 minutes per day over 16 weeks during which they read and summarized written passages. In this case, fluency was defined as number of words read correctly per minute, and struggling readers responded well by reading approximately 3.5 more words per month of intervention (Cho et al., 2018). In another study, 77 adolescents with dyslexia were tested on various executive functions (e.g., nonverbal IQ, untimed real and pseudoword reading, receptive language) and reading fluency (reading rate and accuracy; GORT-3). Verbal working memory emerged as the strongest correlate of reading fluency, above and beyond the other functions measured (Rose & Rouhani, 2012). Participants read a Danish narrative and then answered some questions about the passage. Importantly, typically developing college students exhibited faster reading rate than did the individuals with dyslexia (Pedersen et al., 2016). Researchers in that study broadly defined fluency as “automaticity and decoding” and operationalized it as words read per minute. This definition, which includes automaticity in its definition of fluency, exemplifies the existing overlap in constructs and definitions used for automaticity and fluency and highlights the need for consistency.

As seen with automaticity, fluency has also been improved in various samples of children and adults (Rakhlin et al., 2019; Tobia & Marzocchi, 2014). A large sample of typically developing Italian children participated in a study that sought to investigate fluency throughout elementary school. The data from first and second grade children revealed that phonological awareness and RAN predicted fluency. In this case, participants read a passage for four minutes, and fluency was measured as correct syllables read per second. The model with older elementary school children also included additional significant predictors, such as vocabulary and short-term memory (Tobia & Marzocchi, 2014). In a study of Russian, a transparent orthography, typical and struggling readers completed a task of orthographic processing skills (choose the homophone out of a list with two real words and one homophone), and performance on that task was moderately correlated with reading fluency, as measured by words read per minute, converted to standardized norms, in both skilled and struggling readers (Rakhlin et al., 2019). Additionally, word unitization (i.e., number of words read as whole units) was the strongest correlate to oral reading fluency in both skilled and struggling readers (Rakhlin et al., 2019). A longitudinal study of Dutch students that were struggling readers operationalized fluency as the number of real words read in one minute and the number of pseudowords read in two minutes (van Setten et al., 2018). Their results suggested that fluency in third grade significantly predicted fluency in the sixth grade in the sample, suggesting that fluency can improve over time.

In addition to training and improving fluency in transparent and opaque orthographies, fluency has also been successfully taught in artificial orthographies. Twelve typically developing, monolingual young adults participated in approximately 20 hours of training over ten sessions where they learned a novel orthography called HouseFont (Martin et al., 2019). During the training program, participants went through various stages of reading development including grapheme-phoneme associations (where graphemes are houses), word-level decoding, and passage reading. At the end of the ten sessions, participants were tested on their reading acquisition through reading passages from the GORT-4 that were translated into their novel orthography. Their results suggested that reading fluency, number of words correctly read per minute, steadily increased during each session and was equivalent to a beginning English reader (Martin et al., 2019). These findings also agree with a previous study that used a novel FaceFont which tested 24 typically developing young adults in a ten-session training with testing to follow (Moore et al., 2014). Though these studies were able to train fluency in readers, they did not evaluate whether fluency was sustained after a period without training.

In the prior sections, we have highlighted the wide array of definitions used in operationalizing fluency and automaticity and importantly, the degree of overlap with which metrics are used to measure each of these skills (Table 6). These overlaps highlight the need for a more unified approach in the field. Importantly, several measures used to quantify fluency have separately been used to quantify automaticity (e.g., words read within a time limit), which makes it difficult for researchers and clinicians to draw meaningful conclusions from these data for use in diagnosis and intervention. Since these behavioral measures are often utilized in neural imaging studies of reading, it is likely that the discrepancies observed in behavioral studies leads to overlapping results from neural imaging studies.

Table 6

Summary of Operational Definitions Used in Investigating Automaticity and Fluency

Behavioral Measure	Study and Construct
words read per minute	Cho et al. (2018), fluency Martin et al. (2019), fluency Pedersen et al. (2016), automaticity
words read per second	Aravena et al. (2018), automaticity Kim et al. (2014), fluency
completion time to name stimuli	Georgiou & Parrila (2020), automaticity Georgiou et al (2013), automaticity
sum of accuracy and rate	Pham et al. (2011), fluency Rose & Rouhani (2012), fluency

Neural Correlates of Automaticity and Fluency Skills

While the previous sections have emphasized behavioral studies on automaticity and fluency, there is a well-established literature on the neural bases of reading. Behavioral definitions have enabled clinicians to facilitate diagnosis as early as possible but combining behavioral and neural bases may help understand why an individual may not be responding to intervention. In turn, this can lead to more effective intervention options. This is especially important given that children are not born with a dedicated neural circuit for reading (Dehaene & Cohen, 2007). Since print reading is a cultural invention, the human brain must develop the reading network from scratch in every individual.

The neuronal recycling hypothesis proposes that in order to develop a reading network, the brain takes advantage of pre-existing brain areas allocated for vision, speech, hearing, and comprehension and re-allocates them for the purpose of supporting reading (Cohen et al., 2002; Dehaene & Cohen, 2007; Dehaene & Cohen, 2011). In addition to the reallocation of regions in support of this skill, existing brain structures also develop connections to the new network, as reading requires both specific (e.g., decoding) and cognitive (e.g., verbal memory) skills. For example, one specific region within this reading network, the visual word form area (VWFA), a part of the fusiform (Devlin et al., 2006; Shaywitz et al., 2002) develops selectivity for print or print-like stimuli, such as letters, with its activation being a potential neural marker of expertise (McCandliss, Cohen, & Dehaene, 2003). The VWFA, located on the fusiform gyrus, shows a protracted course of development, with the process of optimization lasting into early adulthood (Centanni et al., 2017) and requiring connections to other brain regions, including the dorsal stream, to develop this specificity (Younger, Tucker-Drob, & Booth, 2017). This long trajectory of neural plasticity in the reading network explains the behavioral observation that reading acquisition takes many years of practice and instruction. Of note, the development of the reading network is markedly different in those with dyslexia (Waldie et al., 2017). For example, well-replicated research has suggested that individuals with dyslexia have hypoactivated VWFA (Brem et al., 2020; Kronbichler et al., 2006; Maurer et al., 2011; Meyler et al., 2007; Paz-Alonso et al., 2018; Schulz et al., 2008), and some individuals exhibit right-hemisphere activation as compensation after intervention (e.g., Olulade et al., 2015). However, the extent to which these neural abnormalities contribute to specific reading deficit profiles in dyslexia is largely unknown. In addition to the VWFA, another hallmark region that has been implicated in the reading network is the cerebellum (Alvarez & Fiez, 2018; D’Mello et al., 2020; Stoodley & Stein, 2013). Of particular importance to the current review, the cerebellum has been implicated in automaticity skills. In the context of the cerebellum, automaticity has been defined as the level of proficiency at which skills become so fluent that conscious control is no longer needed (Nicolson, Fawcett, & Dean, 2001). With respect to reading, the cerebellar deficit hypothesis (Nicolson, Fawcett, & Dean, 2001), suggests that cerebellar abnormalities are linked to poor automaticity skills in both children and adults. The cerebellar deficit hypothesis speculates that individuals with dyslexia struggle with automaticity, and that this deficit may also impact other sensory domains, leading to deficits such as motor learning delays and poor visual attention. In support of this idea, empirical research has shown that the cerebellum was hypoactivated in reading tasks in children and adolescents with dyslexia (Siok et al., 2008; Hu et al., 2010). Together, these studies establish that the cerebellum is indeed implicated as a region of interest in the reading network, and hypoactivation in the cerebellum can be related to poorer reading skills than those with normal activation patterns. Given the increasing research linking the cerebellum to reading skills, it is important to ensure that researchers have a unified account how automaticity is studied and evaluated. To improve our understanding of dyslexia as well as to operationalize the key measures for automaticity and fluency, it is critical that we identify the neural correlates of these individual reading skills.

A number of studies to date have investigated the neural bases of automaticity (Cummine et al., 2015; Lam et al., 2017; Misra et al., 2004; Rollans et al., 2017) and fluency (Christodoulou et al., 2014) in both typical readers and individuals with dyslexia (Waldie et al., 2017; Xia et al., 2018). In one study of the neural basis of automaticity, typically developing young adults completed an in-scanner task in which they silently completed a RAN task. Automaticity for objects and letters share a number of neural correlates, both eliciting activation in the inferior frontal and temporo-parietal regions (Misra, Katzir, Wolf, & Poldrack, 2004). Similarly, in another study with typically developing young adults, participants completed the digits and letters subtests of the RAN and reading of real words and pseudowords. In their work, they structured the word and pseudoword reading tasks to mimic the original RAN task such that the words and pseudowords were presented in a grid with a time limit for the participant. Key ROIs that emerged during RAN and word and pseudoword reading included the left inferior temporal gyrus, left superior temporal gyrus, left inferior frontal gyrus, left cerebellum, left dorsal precentral gyrus, and left supplementary motor area (Cummine et al., 2015). A third study in typically developing young adults tested the relationship between rapid naming and rapid word reading measures using diffusion tensor imaging (DTI). Their results from brain-behavior correlations suggested that the left inferior fronto-occipital fasciculus was correlated with rapid naming of objects, but not rapid naming of letters and digits (Rollans et al., 2017). All of these studies were conducted in typically developing individuals, thus establishing neural bases of automaticity in the reading network. Given some behavioral evidence that fluency also engages verbal memory skills, we speculate that the neural bases of fluency will also incorporate brain regions implicated in memory.

Broadly, neural imaging studies in typically developing readers have supported that the neural correlates of fluency extend into memory networks (Xia et al., 2018), while studies of automaticity have not replicated the involvement of memory. In one study, young adults with and without dyslexia completed cognitive assessments as well as an in-scanner task where they read sense and nonsense sentences at slow, medium, and fast speeds. Regardless of whether or not a reader had dyslexia, increased activation occurred in the reading network during faster speeds compared to slower speeds (Christodoulou et al., 2014). When comparing young adults with dyslexia to those without dyslexia, the readers with dyslexia exhibited hypoactivity in a number of reading network regions, including the inferior frontal gyrus, precentral gyrus, and supramarginal gyrus. In a study comparing children with and without dyslexia, participants completed an in-scanner reading fluency task, where they read short, four-word sentences presented at a normal reading rate and an accelerated reading rate (35% faster). During reading, both groups of children displayed reliable activation in the reading network, but a key difference occurred between groups at fast speeds. Specifically, the fusiform gyrus was implicated such that typically developing children exhibited more activation in the fusiform gyrus during faster speeds while this region was hypoactive in children with dyslexia (Langer et al., 2015). This supports that the fusiform gyrus plays an integral role in the neural reading network, and its activation mediates key reading skills. Since individuals with dyslexia consistently have hypoactivation to this area, future research is needed to investigate potential consistent compensatory mechanisms that occur as a result of training and intervention.

Many studies have investigated neural correlates of reading and its associated subskills, such as automaticity and fluency (Cummine et al., 2015; Misra et al., 2004; Rollans et al., 2017; Xia et al., 2018). In these studies, tasks during imaging are often the same as those used in behavioral studies. As a result, it is possible that some of the neural findings are confounded, given the discrepancy of these skills observed in behavioral studies. For example, some key regions have been implicated in both automaticity and in fluency (e.g., supramarginal gyrus; Table 7). If researchers used a more standardized approach in operationalizing these terms, it is likely that future studies could clarify the regions of interest in the brain that support automaticity and those that support fluency. Since fluency takes longer to develop compared to automaticity, longitudinal work would be the most informative to see changes in regions of activation across children that are typical and struggling readers. Findings from such a study may show the shift of ROIs as fluency develops in reading development.

Table 7

Summary of Neuroimaging Studies Investigating Automaticity and Fluency

Region of Interest (ROI)	Study and Construct
Cerebellum	Cummine et al. (2015), automaticity
Middle Temporal Gyrus	Cummine et al. (2015), automaticity
Supramarginal Gyrus	Cummine et al. (2015), automaticity Xia et al. (2018), fluency
Superior Temporal Region	Christodoulou et al. (2014), fluency Xia et al. (2018), fluency
Inferior Frontal Cortex	Misra et al. (2004), automaticity Waldie et al. (2017), fluency
Fusiform Gyrus	Rollans et al. (2017), automaticity Waldie et al. (2017), fluency

Disentangling these Similar, yet Distinct Constructs

Taken together, we propose unified operational definitions for each of these related, yet distinct constructs in reading research. Such an approach is necessary, since previous studies have used the terms automaticity and fluency interchangeably or defined them in overlapping ways. For example, words read per minute has been used as an operational definition for both skills in prior studies (Cho et al., 2018; Kim et al., 2014). Since these skills are predictive of overall reading ability, are implicated in dyslexia diagnoses, and have unique implications for intervention approaches, it is essential to have a comprehensive and integrated approach in measuring them.

We propose that automaticity should be defined as the completion time for a rapid naming task of objects, colors, numbers, or letters, measured in seconds. In line with the established literature, standardized measures such as the RAN/RAS (Wolf & Denckla, 2005) and CTOPP-2 (Wagner, Torgesen, & Rashotte, 2013) are acceptable ways to measure performance on automaticity. Further, we propose that fluency be further divided into word reading fluency and text reading fluency. In line with established literature, standardized measures such as the TOWRE-2 (Torgesen, Wagner, & Rashotte, 2012) are appropriate for word reading fluency, where scores are determined by the correct number of real words (Sight Word Efficiency subtest) or pseudowords (Phonemic Decoding Efficiency subtest) read in 45 seconds. Since words read per minute has been used as an operational definition for both automaticity and fluency, it is also important for researchers to treat word reading fluency as its own construct, apart from automaticity and passage reading fluency. This is primarily because reading of words, especially nonwords, requires a level of conscious effort above the minimal effort needed in automaticity. Further, standardized measures such as the GORT-4 (Weiderholt & Bryant, 2001) and the WRMT-3 Oral Fluency subtest (Woodcock, 2011) provide excellent ways to measure fluency skills at the passage level. Additionally, should standardized testing be unavailable, it is also possible for researchers to create new passages and still measure fluency as words read correctly per minute.

These suggestions are not a dramatic departure from the approaches currently in use in research and in the clinic. Rather, we argue that researchers should apply consistent, clear operational definitions in both behavioral and neural studies of automaticity and fluency. Both automaticity and fluency are currently measured by assessments that utilize time and accuracy as key scoring criterion. However, in this review we have provided examples of studies that use the same assessment (e.g., words read per minute) as a measure of both automaticity and fluency, which can have critical implications in both clinical practice and in clinically relevant research. Further, certain ROIs (e.g., supramarginal gyrus) have been highlighted in studies investigated both automaticity and fluency. Thus, our recommendation is that the field continues research of both automaticity and fluency using our updated operational definitions accurately. By unifying the definitions and measures of these terms, the field can better understand deficits, as well as potential effects driven by taVNS research.

General Discussion

Taken together, the research presented in this dissertation highlights the potential utility of taVNS as a biologically-based intervention for language and reading. In both Aim 1 and Aim 2, we report benefits of taVNS after single-session training protocols. These findings extend the application of neuromodulation technology into language and reading domains. It is well known that taVNS takes advantage of precisely timed neurotransmitter release to aid in learning and memory (Borland et al., 2016; Engineer et al., 2011; Khodaparast et al., 2013; Porter et al., 2012). In Aims 1 and 2, we applied this paradigm using a novel non-invasive approach in human participants paired with cognitive tasks, demonstrating, for the first time, benefits in language learning and performance on memory questions from previously read passsages. Importantly, our data highlight the applicability of paired-plasticity in cognitive tasks, the importance of optimizing key parameters, such as stimulation frequency, and potential interactions with baseline abilities in participants. Since our empirical studies were conducted using typically developing young adults, there are many avenues for future research including: expanding into individuals with language and reading delays, evaluating taVNS parameters, and importance of evaluating the amount of practice (i.e., total taVNS pairings per stimulus) during a training session.

Importantly, our work also suggests, for the first time, specific baseline skills that may facilitate taVNS efficacy in these domains. Previous work implicated verbal memory as a necessary baseline skill to support both vocabulary learning (Gupta & MacWhinney, 1997; Jarrold, Thorn, & Stephens, 2009) and reading comprehension (Peng et al., 2018). Our taVNS studies to date have revealed that certain baseline skills may facilitate the efficacy of taVNS when learning reading skills. For example, our previous study in typically developing young adults found significant correlations between baseline pseudoword reading ability and several outcome measures in participants who received stimulation but not in participants in control groups (Thakkar et al., 2020). Similarly, we found that higher scores on the Verbal Learning Recall measure was significantly correlated with a higher percent correct on a cued-recall vocabulary task seven days after training (Aim 1) and performance on memory questions from previously read passages (Aim 2). Interestingly, these correlations emerged only in the active taVNS groups that exhibited significant improvement on outcome measures. These findings suggest that active taVNS may enhance the utility of existing and efficient neural networks that support these higher baseline skills.

Given the replication of this pattern across both Aim 1 and Aim 2, it is likely that taVNS itself influences the relationship between baseline skills and outcome measures, such that those with higher baseline scores receive a larger benefit of taVNS intervention. However, the mechanism by which baseline verbal memory interacts with taVNS is unknown. We hypothesize that those with higher baseline verbal memory scores have a stronger neural circuit for verbal memory, allowing taVNS to take advantage of this circuitry to improve performance. taVNS is thought to operate through a mechanism of precisely timed neurotransmitter release. As such, taVNS likely enables the brain to strengthen connections. This has been seen in previous studies that demonstrated the importance of timing stimulation with the target stimulus (Borland et al., 2016; Porter et al., 2012). Other neuromodulation techniques, such as tDCS, operate through different mechanisms. Since anodal tDCS increases membrane potential and increases likelihood of neurons firing, it is possible that baseline verbal memory would not be predictive of tDCS efficacy. This could be attributed to new connections being formed, rather than pre-existing circuits being strengthened. In other words, the mechanism of tDCS may focus on baseline skills equally, as compared to taVNS which may be highlighting baseline memory skills above and beyond other skills (e.g., IQ, reading, attention). Since tDCS has been more promising in struggling readers than typical readers, it is possible that tDCS helps form new circuits to benefit those with more room for growth on outcome measures, as compared to those who may already be performing very well on outcome measures. Future research is needed to determine whether these regions of interest exhibit increased activation after our taVNS interventions to evaluate the claim that these neural circuits support both baseline verbal memory and our outcome measures.

Another potential explanation for this relationship is the similarity between the baseline Verbal Learning Recall measure and our seven-day cued-recall outcome measure in Aim 1. In Verbal Learning Recall, participants hear a list of words for four trials and repeat them after a fifteen-minute delay. In our Aim 1 training program, participants learned to associate novel words with their translations, then recall them after a significant delay, ranging from approximately 20 to 45 minutes, depending on the block in which the novel word is initially taught. Here, it is also important to note that both vocabulary and reading require other skills besides memory. Thus, it is possible that nonsignificant correlations emerged in the sham taVNS group because the brain is utilizing various circuits equally, such that verbal memory does not appear above and beyond other skills, such as attention.

Further, it is important to note that participants in Aim 1 and Aim 2 were typically developing young adults, and most participants performed well on this task. To extend this finding further, future research is needed in a well-powered sample in individuals with lower memory scores or individuals with language and reading delays to investigate the generalizability of this result.

If our hypothesis is correct, that taVNS works by strengthening existing circuits in the brain, future work is needed to probe the comparison between our neuromodulation approach and other techniques, such as transcranial direct current stimulation (tDCS; Medeiros et al., 2012). While taVNS is thought to operate through precise release of neurotransmitters, tDCS is thought to operate through a mechanism of priming underlying neurons for learning. Specifically, anodal stimulation increases the likelihood of firing, and cathodal stimulation decreases the likelihood of firing. Comparison of non-invasive neuromodulation techniques is essential, since unpublished pilot data from our lab suggest that taVNS paired with letter-sound training does not lead to group differences in individuals with dyslexia. However, prior work has suggested that tDCS can be effective for individuals with dyslexia in enhancing reading skills (Costanzo et al., 2013).

Another important area for future research involves parameter optimization for this relatively new technique. Our data from letter-sound learning (Thakkar et al., 2020) and reading comprehension (Aim 2) suggest that 5 Hz stimulation is effective, but the 5 Hz stimulation group was not effective in vocabulary learning immediately after training or after a seven-day delay (Aim 1). These findings support the need for future research to evaluate the role of stimulation frequency and other parameters (e.g., location of stimulation) in taVNS protocols (Groves & Brown, 2005). This is especially important since previous work has found that low frequency stimulation (8 Hz) can be effective in a memory task (e.g., face-name association learning; Jacobs et al., 2012) and high frequency stimulation (25 Hz or 30 Hz) can be effective in sensory and motor tasks. Currently, cVNS is FDA approved for clinical use in the 20-30 Hz frequency range (Sackeim et al., 2001; DeGiorgio et al., 2000; Morris et al., 1999) in human participants. Researchers have established this as a potential ideal frequency range based on previous evidence in the rodent model (Borland et al., 2016; Engineer et al., 2011; Husley et al., 2016). While some previous work observed significant benefits at lower frequencies (Aim 2; Jacobs et al., 2015; Thakkar et al., 2020), they did not enroll participants in a higher frequency group. Thus, it is possible that higher frequencies are more beneficial, but previous study designs did not allow for those systematic comparisons. Additionally, some previous taVNS studies only tested behavioral outcome measures, so future research is needed to investigate if low-frequency or high-frequency stimulation alter the extent of neural plasticity.

As discussed in Aim 3, the reading network involves a number of regions of interest, and no study has systematically evaluated the effects of taVNS on these regions together. Since findings from the current studies suggest behavioral benefits of taVNS, it is likely that neural plasticity will be observed. Findings from such a study would also inform on how taVNS effects networks in typically developing individuals and those with dyslexia or other learning disabilities. Collectively, we believe that taVNS may be an effective intervention for typical readers. Future research in other groups, such as those with dyslexia, is needed to evaluate if taVNS can truly be a novel intervention.

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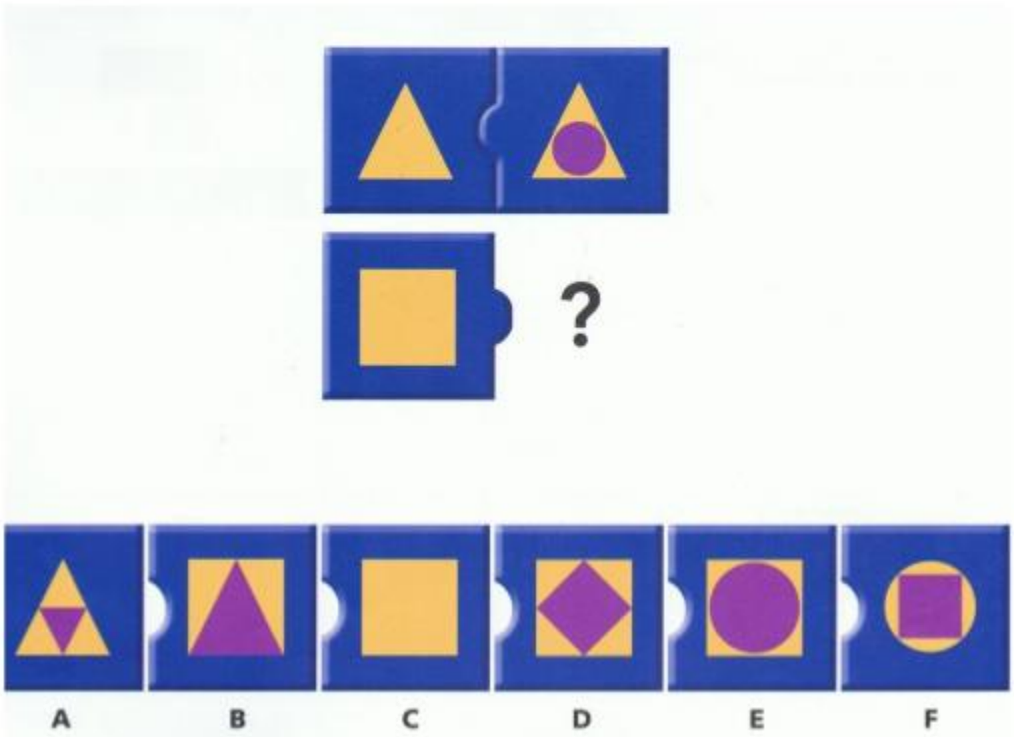
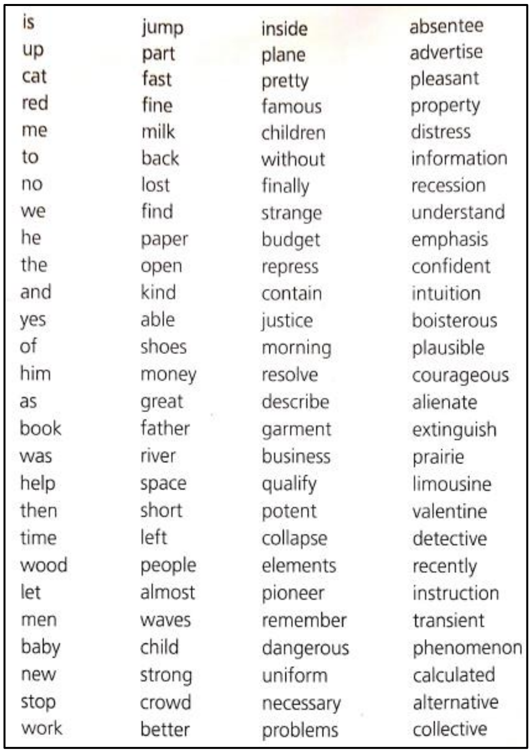
Appendix A: Descriptions of Standard English Assessments

The Kaufman Brief Intelligence Test, Second Edition (KBIT-2; Kaufman & Kaufman, 2004) is a brief measure of nonverbal IQ. In the current work, we utilized the Matrices subtest, which measures one's ability to solve new problems and complete visual puzzles. In each item, participants view incomplete pictures and choose an item that best completes the pattern or picture from six possible choices. Participants began at an entry point and continued until the assessment ended or ceiling was reached (i.e., four consecutive incorrect answers). Raw scores ranged from 0 to 46. Participants must have achieved a standard score of 85 or higher to qualify for the study. An example item from the assessment is shown below.



The Test of Word Reading Efficiency, Second Edition (TOWRE-2; Torgesen, Wagner, & Rashotte, 2012) included two subtests: Sight Word Efficiency (shown below on the left) and Phonemic Decoding Efficiency (shown below on the right). In this task, participants practiced on a short sample list of eight real words. Then, participants were given a card of 4 by 27 grid of real words and read through as quickly and accurately as possible in 45 seconds. Next, participants were given an example list of eight pseudowords before seeing a test card which included a 3 by 22 grid of pseudowords to complete in 45 seconds. Raw scores ranged from 0 to 108 on the Sight Word Efficiency and 0 to 68 for Phonemic Decoding Efficiency. Raw scores were then converted to age-normed standard scores, and a standard score of 90 or higher was required on each subtest to qualify for the study as typically developing.



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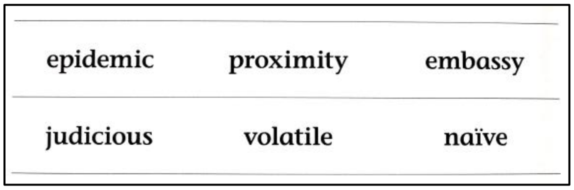
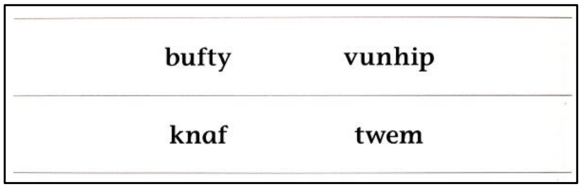
clirt
sline
dreff
prain
zint
bloot
trisk
kelm
strone
lunaf
cratty
trober
depate
glant
sploosh
dreker
ritlun
hedfert
bremick
nifpate
brinbert
clabom
drepnort
shrattec
plofent
smucrit
pelnador
fornalask
fermabalt
crenidmoke
emulbatate
strotalanted
prilingdorfent
chunfendilt

The Woodcock Reading Mastery Test, Third Edition (WRMT-3; Woodcock, 2011) includes many subtests: Phonological Awareness, Listening Comprehension, Rapid Automatic Naming, Oral Reading Fluency, Letter Identification, Word Identification, Word Attack, Word Comprehension, and Passage Comprehension. Of these subtests, we administered the Word Identification and Word Attack as part of inclusion criteria. The Word Identification (shown below on the left) and Word Attack (shown below on the right) subtests were of untimed real word and untimed pseudoword reading, respectively. Each participant began at an entry point and continued until ceiling (i.e., four consecutive wrong answers) or the end of the assessment was reached. Raw scores ranged from 0 to 46 for Word Identification and 0 to 26 for Word Attack. Raw scores were converted to age-normed standard scores. On each subtest, participants needed to achieve a standard score of 90 or higher.



epidemic **proximity** **embassy**

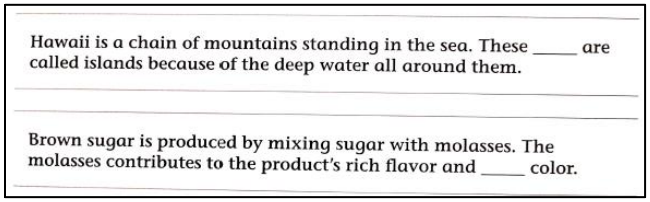
judicious **volatile** **naïve**



bufty **vunhip**

knaf **twem**

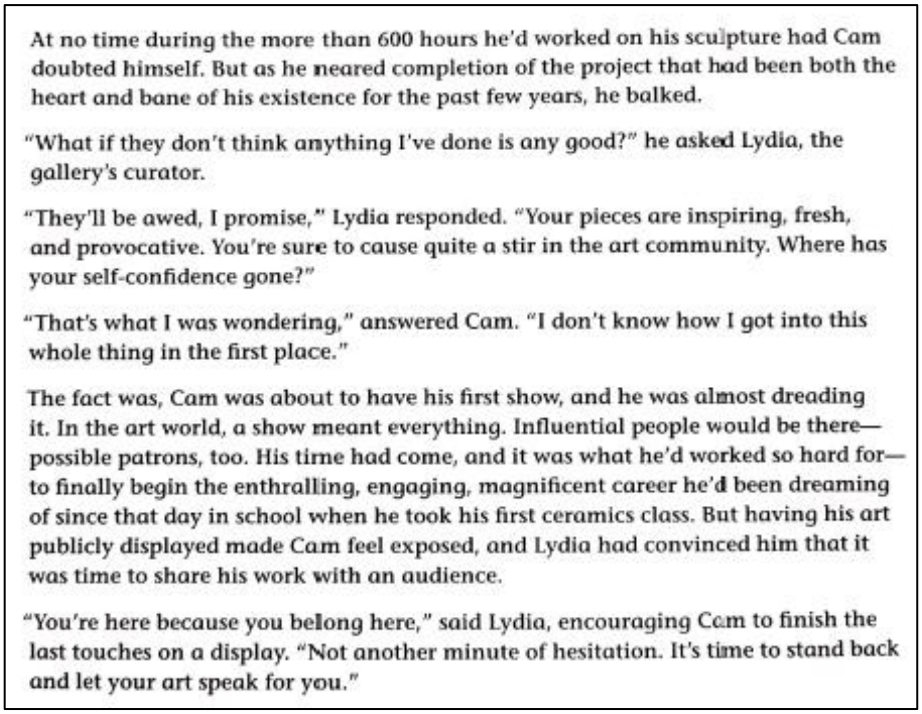
The WRMT-3 (Woodcock, 2011) also has a subtest on Passage Comprehension. This measure has a series of passages with a blank. Participants were instructed to read the item silently to themselves and provide a single word answer out loud to best complete the passage. As with other assessments, participants began at an entry point and continued until they met ceiling (i.e., four consecutive incorrect answers) or finished all items. Two sample items are shown below. Raw scores ranged from 0 to 38, and raw scores were converted to age-normed standard scores. Standard scores for Passage Comprehension were not included in inclusion criteria.



Hawaii is a chain of mountains standing in the sea. These _____ are called islands because of the deep water all around them.

Brown sugar is produced by mixing sugar with molasses. The molasses contributes to the product's rich flavor and _____ color.

Another subtest from the WRMT-3 (Woodcock, 2011) that was administered in the current work was the Oral Fluency subtest. In this measure, participants read Passages J (244 words) and K (235 words) out loud in their normal tone and normal pace. A researcher tracked time to complete reading the passage, as well as errors made in reading. Passage J is shown below. A passage score was calculated by taking the difference between words in the passage and errors made in reading, dividing by time taken to read, multiplying by ten, and rounding to the nearest whole number. Raw scores were calculated by adding both passage scores together and converting to a gross scale value (GSV). GSV scores were converted to age-normed standard scores. The standard score from this measure was not part of the inclusion criteria.



At no time during the more than 600 hours he'd worked on his sculpture had Cam doubted himself. But as he neared completion of the project that had been both the heart and bane of his existence for the past few years, he balked.

"What if they don't think anything I've done is any good?" he asked Lydia, the gallery's curator.

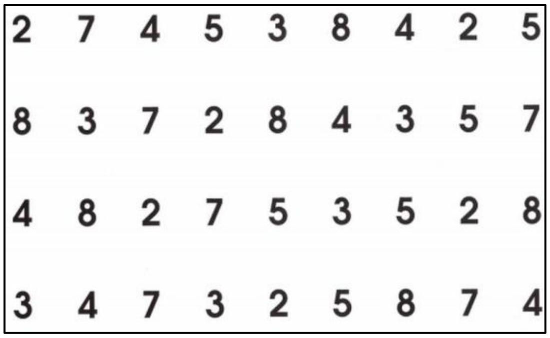
"They'll be awed, I promise," Lydia responded. "Your pieces are inspiring, fresh, and provocative. You're sure to cause quite a stir in the art community. Where has your self-confidence gone?"

"That's what I was wondering," answered Cam. "I don't know how I got into this whole thing in the first place."

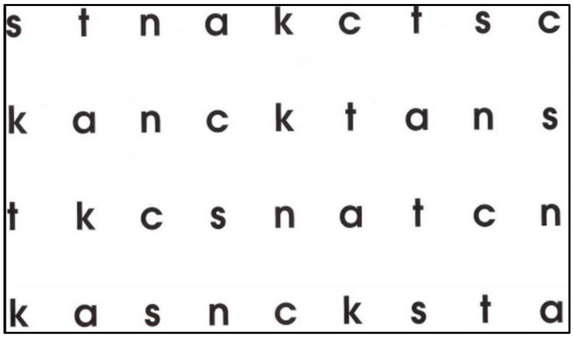
The fact was, Cam was about to have his first show, and he was almost dreading it. In the art world, a show meant everything. Influential people would be there—possible patrons, too. His time had come, and it was what he'd worked so hard for—to finally begin the enthralling, engaging, magnificent career he'd been dreaming of since that day in school when he took his first ceramics class. But having his art publicly displayed made Cam feel exposed, and Lydia had convinced him that it was time to share his work with an audience.

"You're here because you belong here," said Lydia, encouraging Cam to finish the last touches on a display. "Not another minute of hesitation. It's time to stand back and let your art speak for you."

The Comprehensive Test of Phonological Processing, Second Edition (CTOPP-2; Wagner, Torgesen, & Rashotte, 2013) includes subtests that test for rapid automatized naming (RAN). In the current studies, participants completed the Rapid Digit Naming (shown below on the left) and the Rapid Letter Naming (shown below on the right) subtests. In each of these measures, participants were given one row of six items as practice before completing a nine-by-four test grid. On the test card, participants read as quickly and accurately as they could until they finished the entire card. Time to read and errors were measured by a researcher. The raw score was the time taken to read the card, rounded to the nearest second, and then raw scores were converted to age-normed standard scores.

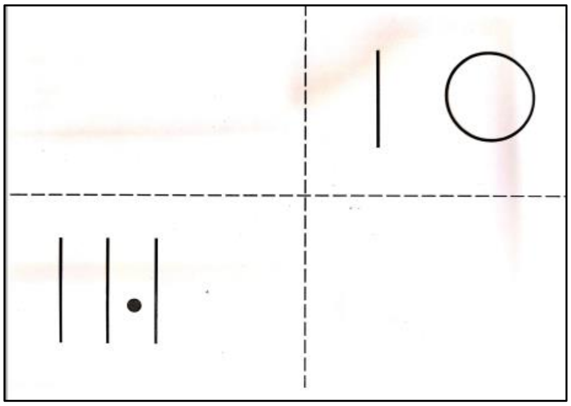


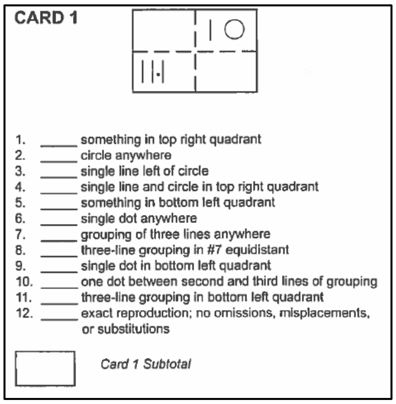
2	7	4	5	3	8	4	2	5
8	3	7	2	8	4	3	5	7
4	8	2	7	5	3	5	2	8
3	4	7	3	2	5	8	7	4



s	t	n	a	k	c	t	s	c
k	a	n	c	k	t	a	n	s
t	k	c	s	n	a	t	c	n
k	a	s	n	c	k	s	t	a

The Wide Range Assessment of Memory and Learning, Second Edition (WRAML-2; Sheslow & Adams, 2009) provides various tests examining working memory and attention. In the current work, a researcher first administered the Design Memory Core. Participants saw a card with some shapes on them for five seconds, then had a ten second delay, and then redrew what they remembered from memory in a booklet. This procedure was then repeated four more times, for a total of five cards shown to participants. The first card administered is shown below on the left as an example. Each card was scored on features correctly drawn (i.e., 1 point if a needed feature was correctly drawn, 0 points if a needed feature was incorrectly drawn or missing). Each card was worth 12 points, as shown below on the right, so the total raw scores ranged from 0 to 60 points. Raw scores were then converted to age-normed standard scores, and this measure was not part of inclusion criteria.





CARD 1

1. _____ something in top right quadrant
2. _____ circle anywhere
3. _____ single line left of circle
4. _____ single line and circle in top right quadrant
5. _____ something in bottom left quadrant
6. _____ single dot anywhere
7. _____ grouping of three lines anywhere
8. _____ three-line grouping in #7 equidistant
9. _____ single dot in bottom left quadrant
10. _____ one dot between second and third lines of grouping
11. _____ three-line grouping in bottom left quadrant
12. _____ exact reproduction; no omissions, misplacements, or substitutions

☐ *Card 1 Subtotal*

The next subtest of the WRAML-2 (Sheslow & Adams, 2009) is the Verbal Learning Core. This subtest involves a researcher reading a list of 16 words to a participant, in a steady pace, for four trials. At the end of each trial, participants repeated all words from the list they can remember, in any order. One point was awarded for each word correctly recalled, so each trial was worth up to 16 points. Raw scores ranged from 0 to 64. The words read to the participants were sand, game, hat, tree, ear, comb, flag, wood, map, door, ice, nail, boat, page, ant, and lake, in the same serial order for each trial.

The Number-Letter subtest of the WRAML-2 (Sheslow & Adams, 2009) is a measure of attention. A researcher read lists of numbers and letters to a participant, and the participant then repeated the trial back to a researcher in the same order as it was said. Items start simple and get progressively more difficult. All participants began at the first item, and the assessment ended after ceiling was met (i.e., three consecutive incorrect answers) or the participant completed all items. Raw scores ranged from 0-25, and those were converted to age-normed standard scores. This measure was not included in inclusion criteria.

The Design Memory Recognition subtest of the WRAML-2 (Sheslow & Adams, 2009) included 46 items. For each item, participants decided if they had (i.e., a “yes” response) or had not (i.e., a “no” response) seen the item previously during the Design Memory Core measure. One point was awarded for each correct response, so raw scores ranged from 0 to 46. Raw scores were converted to age-normed standard scores, and this measure was not part of inclusion criteria.

The Verbal Learning Recall subtest of the WRAML-2 (Sheslow & Adams, 2009) was the final measure given. Participants simply recalled all words from the Verbal Learning Core that were read earlier, in any order. Raw scores ranged from 0 to 16, and those scores were converted to age-normed standard scores, which were not included in inclusion criteria.

Appendix B: List of All Reading Comprehension Test Questions

Table 8

Classification of Test Questions by Passage

Passage	Question	Classification
A11	What does the story state as to why jazz is difficult to define?	Memory
	Why are jazz musicians probably less organized than other musicians?	Comprehension
	According to the last sentence of this story, what two elements do jazz musicians value more than tradition?	Memory
	In the story, what one word described a dominant feature of jazz?	Memory
	According to this story, what group has never accepted jazz?	Memory
A12	What is the emphasis on in this story?	Comprehension
	What was the queen’s councilor’s name?	Memory
	What one word would you use to describe the queen’s actions in this story?	Comprehension
	What did the councilor probably tell the queen upon his death?	Comprehension
	What does the story say about how the queen dealt with opposition to her wishes?	Memory
A13	What did Mr. Weston do to cause Harriet to react as she did?	Memory
	How did Harriet regard Mr. Weston’s motives?	Comprehension
	How do you think the writer in this passage regards Mr. Weston?	Comprehension
	What one word in this story was used to describe Mr. Weston’s chivalry?	Memory
	According to this story, why did Mr. Weston propose to Harriet?	Memory
A14	What is the tone of this story?	Comprehension
	Where do the people work in this story?	Memory
	Which of the people’s needs has been provided for in this story?	Memory
	What one word was used in the second sentence of the story to describe the housing developments?	Memory
	The homes in this story are described as replicas of what?	Memory
A15	What two states were arguing over the terrain of Wyoming?	Memory
	Which state won its argument in court?	Memory
	In the last sentence, to what are states compared?	Memory
	What rule of law was cited as obliging the states to submit the matter to the courts?	Memory
	What do you think was the writer’s attitude toward Connecticut at the end of the story?	Comprehension

A16	What is the story mainly about?	Memory
	In what county and state were the walnuts first found?	Memory
	Where did the sprout first grow?	Memory
	On average, how many nuts are there per pound?	Memory
	What is the name of the person in the story who discovered the walnuts?	Memory
B11	According to this story, how does someone add credibility to legends?	Memory
	How does the story distinguish legends from other genres of folk narrative?	Memory
	How are tall tales described in this story?	Memory
	How does the story say that legends become implausible?	Memory
	How are legends contrasted with myths in the story?	Memory
B12	How do most people feel about Hamilton?	Memory
	This passage emphasizes what about Hamilton?	Memory
	Why do you think Hamilton could be considered a dangerous person?	Comprehension
	What one word in the story was used to describe Hamilton’s temper?	Memory
	Who did Hamilton interrogate in this story?	Memory
B13	What is the main idea of this story?	Comprehension
	What does the author want theorists to do in this story?	Memory
	Which genre was described as being “stylized” in this story?	Memory
	What does the writer imply about the terms *film* and *cinema*?	Memory
	According to this story, how are the terms *film*, *movie*, and *cinema* usually described?	Memory
B14	What is the main idea of this story?	Comprehension
	What causal connection is made in this story?	Memory
	How is media portrayed in this story?	Comprehension
	According to the story, how does the media respond to public concerns?	Memory
	What does the story say occurs as a result of moral pressure?	Memory
B15	In what country is the law already applied?	Memory
	In what country was this story probably written?	Comprehension
	What does the law probably deal with?	Memory
	What is probably occurring to warrant consideration of a bill?	Comprehension
	How long does the writer recommend people be allowed to fish?	Memory

B16	In the first sentence, to what does the author compare the current situation?	Memory
	Name two states mentioned in this story.	Memory
	In what century was the story likely written?	Comprehension
	The author would like the reader to awake from the deceitful … what?	Memory
	What has caused what the author calls “the inconveniences felt everywhere?”	Memory

VITA

Vishal Jayesh Thakkar was born on April 15, 1994 to Jayesh and Hetal Thakkar. He grew up with his family in Mount Prospect and Elgin, IL. After graduating from Central High School in Burlington, IL, he went on to pursue his Bachelor of Science degree in Neuroscience at Saint Louis University (SLU), where he also completed minors in both health care ethics and medical humanities. During his time at SLU, he began his research career while working in the labs of Dr. Tony Buchanan, investigating the neuroscience of stress and aging, and Dr. Brenda Kirchhoff, studying the neural correlates of learning and memory in young and old adults. After graduation, he moved to the Dallas-Fort Worth area to complete his Master of Science degree in Experimental Psychology, emphasizing in cognition, at Texas Christian University in Fort Worth, TX. For his thesis work, he worked in the lab of Dr. Tim Barth, studying moral cognition and ethical decision making.

Currently, Vishal is working towards his Doctor of Philosophy degree in experimental psychology, specializing in neuroscience, while working as a teaching assistant in the Department of Psychology. He has been working on projects in the Genetics of Auditory Perception and Plasticity (GAPP) Lab with Dr. Tracy Centanni using vagus nerve stimulation in the context of language and reading. He has also helped in teaching courses on memory and cognition, introductory psychology, research methods, and sensation and perception.

Outside the lab and classroom, Vishal enjoys spending time with his family and friends, learning about culture, reading and writing for fun, biking, or exploring newfound hobbies, like painting canvases and playing board games. Upon completion of his doctoral degree, Vishal hopes to advance his career in higher education through teaching and research, while settling down with his family again.

ABSTRACT

NON-INVASIVE VAGUS NERVE STIMULATION IMPROVES LANGUAGE AND COMPREHENSION: EMPIRICAL EVIDENCE AND A REVIEW OF READING SKILLS

By: Vishal Jayesh Thakkar, M.S., 2019
Department of Psychology
Texas Christian University

Dissertation Advisor: Dr. Tracy M. Centanni, Assistant Professor of Behavioral Neuroscience

Adequate language and reading skills are essential to our daily life. However, these are difficult to acquire, especially in adulthood. There are classroom-focused and computer-based training programs that aim to improve vocabulary learning and reading comprehension, but previous research has suggested that computer programs may take many weeks of intervention with poor memory. Thus, there is a need for a novel intervention that can accelerate learning and improve retention. One method that has driven long-lasting neural plasticity is cervical vagus nerve stimulation (cVNS), which, when paired with an external stimulus (e.g., tone or movement) decreased tinnitus symptoms and increased motor function recovery in post-stroke patients. While cVNS has shown promising results, it requires an expensive, invasive procedure, making it impractical for language and reading interventions. Neural imaging data have suggested that transcutaneous auricular vagus nerve stimulation (taVNS) to the posterior tragus of the left ear activates similar deep brain structures as cVNS, making it a viable, non-invasive alternative. taVNS paired with an external stimulus has led to enhanced motor function recovery, associative memory, and learning of novel letter-sound correspondences. To extend taVNS research, the objective for the current dissertation was to evaluate taVNS in language and reading skills. In Aim 1, we evaluated the effect of taVNS on the learning and retention of novel vocabulary words and found that higher frequency taVNS led to superior memory of trained words after a seven-day delay. In Aim 2, we evaluated the effect of taVNS on overall reading comprehension

performance and found that taVNS led to improved performance on memory questions. However, taVNS did not aid in oral reading mechanics or performance on comprehension questions. In Aim 3, we presented a brief literature review of two reading skills, automaticity and fluency, since these are often interchangeably used in the literature. This causes theoretical confusion, especially since these skills are often used in dyslexia diagnoses and interventions. Importantly, further clarity on metrics of these skills is needed in order to effectively design future studies using taVNS. Collectively, the current dissertation expands on taVNS and reading literatures with implications for clinical applications.