THE EFFECT OF TRANSCUTANEOUS AURICULAR VAGUS NERVE STIMULATION ON NOVEL LANGUAGE LEARNING

by

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ABSTRACT

While learning a novel language is possible with intense instruction and practice, it becomes increasingly difficult with age. A large body of evidence suggests that there is a critical period for learning a second language that ends around ages 8 or 9, and the ability to learn a second language declines after this critical period closes (Johnson & Newport 1989). Others argue that the period of learning may decline from birth (Guion et al., 2000; Hernandez et al., 2005) or that the ability to learn remains constant, but deteriorates from other causes such as higher disinterest from adults (Hakuta et al., 2003; Hernandez et al., 2005). While the age where this critical period closes or begins is still being debated, the relative ease with which children learn a second language compared to adults is well-documented (Hartshorne et al., 2018). The goal of the current study is to evaluate a novel intervention approach that improves novel language learning in adults.

Introduction

Learning a new language is becoming increasingly important in the modern world. In 2017, the U.S Census Bureau's American Community Survey (ACS) reported that close to 67 million U.S citizens spoke a foreign language, which was a 7-million-person increase compared to the 2010 ACS results. In an increasingly global market and economy, it is important for job applicants and educators to be able to learn a novel language and achieve fluency. While learning a novel language is possible with intense instruction and practice, it becomes increasingly difficult with age. A large body of evidence suggests that there is a critical period for learning a second language that ends around ages 8 or 9, and the ability to learn a second language declines after this critical period closes (Johnson & Newport 1989). Others argue that the period of learning may decline from birth (Guion et al., 2000; Hernandez et al., 2005) or that the ability to learn remains constant, but deteriorates from other causes such as higher disinterest from adults (Hakuta et al., 2003; Hernandez et al., 2005). While the age where this critical period closes or begins is still being debated, the relative ease with which children learn a second language compared to adults is well-documented (Hartshorne et al., 2018). The goal of the current study is to evaluate a novel intervention approach that improves novel language learning in adults.

Cervical Vagus Nerve Stimulation

The vagus nerve, which is cranial nerve X, originates from four nuclei in the medulla oblongata (Dorsal Nucleus, Nucleus Ambiguus, Nucleus of Tractus Solartarius and the Spinal Nucleus of the Trigeminal) and is the longest of the cranial nerves (Ogbonnaya and Kaliaperumal 2013). Early studies demonstrated the utility of electrical stimulation of the vagus nerve for reducing seizures in dogs (Zabara et, al. 1985). This finding spawned a new area of research, focused on the utility of vagus nerve stimulation for clinical use in humans. The most

prevalent approach currently for stimulating the vagus nerve is cervical Vagus Nerve Stimulation (cVNS). This is an invasive approach that requires surgical implantation of a cuff electrode on the midcervical portion of the left vagus nerve and a subdural pulse generator to control the stimulation (DeGiorgio, et al. 2000). Given demonstrations that cVNS is a safe and effective long-term treatment for epilepsy (DeGiorgio et, al. 2000), this approach is FDA approved as a treatment for this condition in humans (Ogbonnaya and Kaliaperumal 2013). cVNS is also effective as a treatment for pharmaceutically-resistant depression (Bottomley, et al. 2020; Rush et al., 2000). To date, epilepsy and depression are the only conditions for which cVNS is FDA-approved.

In addition to the benefits described above, cVNS improves cognitive function in patients (Sjogren et, al. 2002). Sjogren et, al (2002) found cognitive improvements in Alzheimer's patients 3 and 6 months after device implantation. Cognitive functions were measured by the median improvement of scores in the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) and the Mini-Mental State Examination (MMSE). Patients implanted with cVNS for the treatment of depression also significantly improved in several neurocognitive tasks including verbal fluency, working memory, and logical reasoning when receiving stimulation (Sackeim et, al. 2001). Further evidence of cognitive improvement was demonstrated when participants with refractory epilepsy made fewer errors on working memory subtasks after receiving cVNS (Sun et al., 2017).

Although the efficacy of cVNS has been demonstrated for multiple clinical uses and evidence supports its efficacy for cognitive improvement, cVNS is expensive and invasive (Yu, Zhao, Guo, Rong 2016). Thus, cVNS is not a practical alternative for second language learning.

We therefore chose to investigate a noninvasive and less expensive method: transcutaneous auricular vagus nerve stimulation (taVNS).

Transcutaneous Auricular Vagus Nerve Stimulation

Transcutaneous auricular Vagus Nerve Stimulation (taVNS) is a relatively new intervention that is both safe (Kreuzer et al., 2012) and as effective at driving plasticity as cVNS (Redgrave et al., 2018; Stefan et al., 2012). Researchers are able to stimulate noninvasively using taVNS because the auricular branch of the vagus nerve (ABVN) has a high density of projections in the cymba conchae and tragus of the ear (Badran et al., 2018; Peuker ET, Filler TJ 2002). Using functional magnetic resonance imaging (fMRI) Kraus et al., (2007) established that taVNS is able to increase activation of the insula, precentral gyrus and the thalamus, and decrease signals in the limbic area including the amygdala, hippocampus, parahippocampal gyrus, middle and superior temporal gyrus. Kraus et al., (2007) was able to use this information to make a strong comparison between the similar outcomes of cVNS and taVNS. Badran et al., (2018) reiterated this point with their study by finding that taVNS is a promising alternative to cVNS because of its ability to stimulate the vagal pathway. Since establishing the efficacy of taVNS, research has found significant improvements using taVNS as a treatment for epilepsy, depression, tinnitus, insomnia, schizophrenia and cognitive dysfunction (Yu et al., 2016). Hein et al., (2012) reported a significant decrease in Beck Depression Inventory Score in patients with major depressive disorder using taVNS compared to sham stimulation. Stefan et al., (2012) found that taVNS was safe to use in patients with epilepsy, and could be tolerated comfortably for long periods of time, while also decreasing seizure activity in the majority of participants.

taVNS has been shown to improve cognitive function in older patients by improving scores in associative memory tasks (Jacobs et al., 2015). There may also be a link to increased

creativity levels by increased divergent thinking measured by Alternate Uses Tasks (Colzato et al., 2018). Borges et al., (2020) found increased cognitive flexibility with taVNS in set shifting paradigms, but did not find any significant changes in any other paradigms used or changes in cognitive inhibition tasks. Our lab has contributed to this field of research by providing evidence that taVNS drives improvement in novel sound-letter learning (Thakkar et al., in review).

Current Study

The goal of the current study was to evaluate whether taVNS improves novel language learning in participants. We hypothesized that participants who receive taVNS compared to sham stimulation will recognize words more quickly and do better at retaining novel language words they had learned during their training session.

Method

Participants and Study Design

A total of 22 students (17 females) were screened for this study. The median age for participants was 19.62± 1.24. Undergraduate students were recruited from an online participation pool (i.e. SONA Systems) in exchange for course credit. Participants were asked to come into the lab for an initial assessment session that lasted approximately 60 minutes. During this initial screening session, participants completed a brief survey to gather demographic information such as age, ethnicity, race and gender as well as information about their reading and language background. Exclusion criteria for this study included previous participation in other taVNS studies, history of medical disorders and/or diagnosis, or medical implants.

Participants then completed several assessments designed to measure nonverbal IQ, reading, and memory. These measures are described in detail below.

KBIT-2. The Kaufman Brief Intelligence Test II (KBIT-2; Kaufman & Kaufman, 2004) was administered during the first assessment to measure verbal and nonverbal intelligence. The Matrices subtests of the KBIT-2 were administered, which asks participants to match incomplete images to one of the five complete images provided. Raw scores for each participant were converted by the testing guidelines into standard scores.

TOWRE-2. The Test of Word Reading Efficiency, Second Edition (TOWRE-2; Torgersen, Wagner, & Rashotte, 2012) was administered during the first assessment and used two of the subtests: Sight Word Efficiency (SWE) and Phonemic Decoding Efficiency (PDE). SWE measures participants' ability to pronounce printed words, and PDE measures participants' ability to pronounce phonemically regular nonwords. Both subtests measure accuracy and fluency. Raw scores for each subtest from each participant were converted to standard scores using the test guidelines.

WRMT-3. The Woodcock Reading Mastery Tests, Third Edition (WRMT-3; Woodcock, 2011) was administered during the first assessment. This study utilized two subtests, Word Attack and Word ID, which measure participants' ability to pronounce words out loud. Word ID includes real words in the English while the Word Attack subtest includes nonwords. Raw scores for each subtest were converted to standard scores using the test guidelines for each participant.

WRAML-2. The Wide Range Assessment of Memory and Learning, Second Edition (WRAML-2; Sheslow & Adams, 2003) was administered during the first assessment to measure memory function and learning. This study used five subtests within WRAML-2: Design Memory, Verbal Memory, Number Letter, Design Recognition and Verbal Recall (WRAML-2;

Sheslow & Adams, 2003). In the Design Memory subtest, participants view a presented picture for 5 seconds and then draw what they remembered from the image after a 10 second delay. In the Verbal Memory subtest, participants listen to a list of 16 words and are asked to recall as many words as possible. This process is then repeated four additional times. In the Number Letter Subtest, participants listen to a series of number and letter combinations and are asked to repeat back each string, with each string increasing in difficulty. In the Design Recognition subtest, participants are presented with a booklet with similar figures from the previous Design Memory subtest, and circle "yes" or "no" to indicate if they had seen the image previously. In the Verbal Recall subtest, participants are asked to recall as many of the 16 words from the previous Verbal Memory subtest as possible. Raw scores for each subtest were converted to standard scores using the test guidelines for each participant.

CTOPP-2. The Comprehensive Test of Phonological Processing, Second Edition (CTOPP-2; Rashotte, Torgesen, & Wagner, 1999) was administered during the first session of this study and assessed participants' reading related phonological processing skills. This study used two subtests within the CTOPP-2: Rapid Digit Naming and Rapid Letter Naming (CTOPP-2; Rashotte, Torgesen, & Wagner, 1999). In the Rapid Digit Naming subtest, participants read a list of numbers as quickly and accurately as possible. In the Rapid Letter Naming subtest, participants read a list of letters as quickly and accurately as possible. Raw scores for each subtest were converted to standard scores using the test guidelines for each participant.

Inclusion criteria for this study included a standard score of 85 or above on the KBIT-2 (KBIT-2; Kaufman & Kaufman, 2004) and a standard score of 90 or above on the TOWRE-2 (TOWRE-2; Torgersen, Wagner, & Rashotte, 2012) and the WRMT-3 (WRMT-3; Woodcock, 2011). Finally, participants completed a Palau assessment during the first session as a pretest to

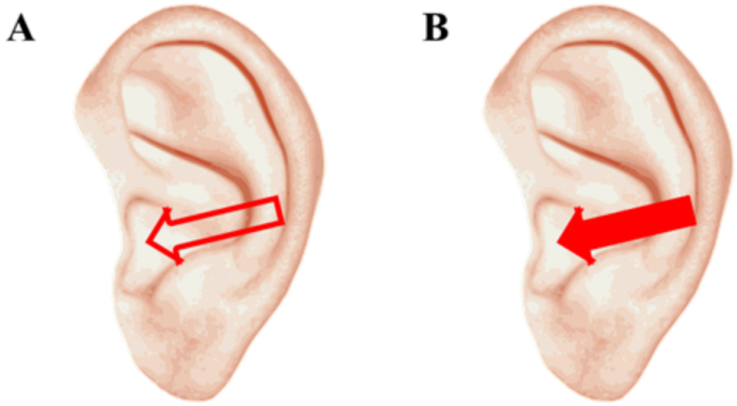
determine their background knowledge of the language. The pretest consisted of 30 Palau words where participants were asked to fill in the blank with the English definition of the word provided. If they did not know they were asked to make their best guess or report not knowing.

Of the participants who were screened, 20 participants were excluded for low reading scores, 17 were excluded for conflicting medications or medical diagnoses, 2 were excluded for IQ scores and 4 withdrew or had scheduling conflicts. The final sample included 22 participants (n=17 females). Participants who were eligible were invited back to the lab to complete two additional sessions. The testing session (session two) lasted approximately 60 minutes and the retention session (session three) a week later lasted approximately 10 minutes.

taVNS Device. The stimulation parameters for the taVNS device were 5Hz frequency, 200 microsecond pulse width with square biphasic pulses. A trained researcher fitted the taVNS device on the posterior side of the left tragus of the participant (see Figure 1). Four measures were then taken by the researcher to determine optimal stimulation intensity for each participant. Stimulation intensity was increased until the participant indicated they could feel a sensation and this number was recorded. The second measure was taken when the stimulation was increased and the participant said the stimulation was uncomfortable, but not painful. The stimulation was then decreased until the participant said they were unable to feel any stimulation and the number was recorded. The final measure occurred when the researcher increased the stimulation until the participant said it was uncomfortable, but not painful. The researcher then averaged the four measurements, and used this intensity value as the safe thresholding level for the individual participant. Participants that were randomized into the sham control group completed the device thresholding but did not receive stimulation during training. The sham control group experienced the same interaction from the researcher, including the illusion of stimulation ramping on and

off, to mimic the active group as best as possible, but the device was turned off without participant knowledge. For both the sham group and active group, the device was hidden behind a barrier.

Figure 1. Posterior side of the left tragus where the taVNS device was placed by a trained researcher.



*A= device sham control, B= 5 Hz taVNS

Palau Training and Assessment. During the second session participants completed the Palau training session while receiving active or sham stimulation. Participants were shown slides consisting of a single Palau word, a representative visual image of the word, and its English translation. Each word was visible for four seconds. Words were presented in blocks containing five different words and participants saw each word five times for four seconds each in the block while receiving active or sham stimulation. After each exposure block, stimulation was ramped off and the participant completed a knowledge check. Stimulation of the device was turned off during knowledge checks so that stimulation was only given to the left posterior tragus when correct pairings of Palau and English translations were provided. Knowledge checks consisted of participants seeing a Palau word and selecting the correct English translation out of four possible choices. Once participants completed knowledge checks for the five words they had just learned,

this process (exposure block with stimulation and associated knowledge check) was repeated five additional times, with each block set containing a new group of 5 words. Participants were exposed to 6 blocks of 5 words repeated five times each for four seconds lasting a total of ten minutes (600 seconds) with 150 total knowledge checks after exposure to 5 word pairings. The participant was then offered a short break before repeating the process one more time. In total, each participant was exposed to all 30 words 10 times each. Once participants had finished their training session, they completed the same Palau assessment they received at pre-test. The assessment consisted of the 30 trained Palau words and participants were instructed to fill in the English definition for each, guessing or filling in "I don't know" if they were unsure, making sure to not leave any spots blank. At the retention session a week later, participants completed this same assessment.

Data Analysis Plan

To ensure active and sham groups were matched on age, nonverbal IQ, and reading, we used a repeated measures ANOVA to test for an effect of group on each measure. To determine the effect of stimulation on word learning, we used unpaired one-tailed to compare sham vs. active stimulation at the post-test and at retention.

Results

English Assessment. Participants' average English assessment scores between stimulation groups are reported in Table 1. There was a significant difference for Word ID task scores between participants' in the sham and active taVNS groups. Participants in the sham group did significantly better than participants in the active taVNS group for Word ID task

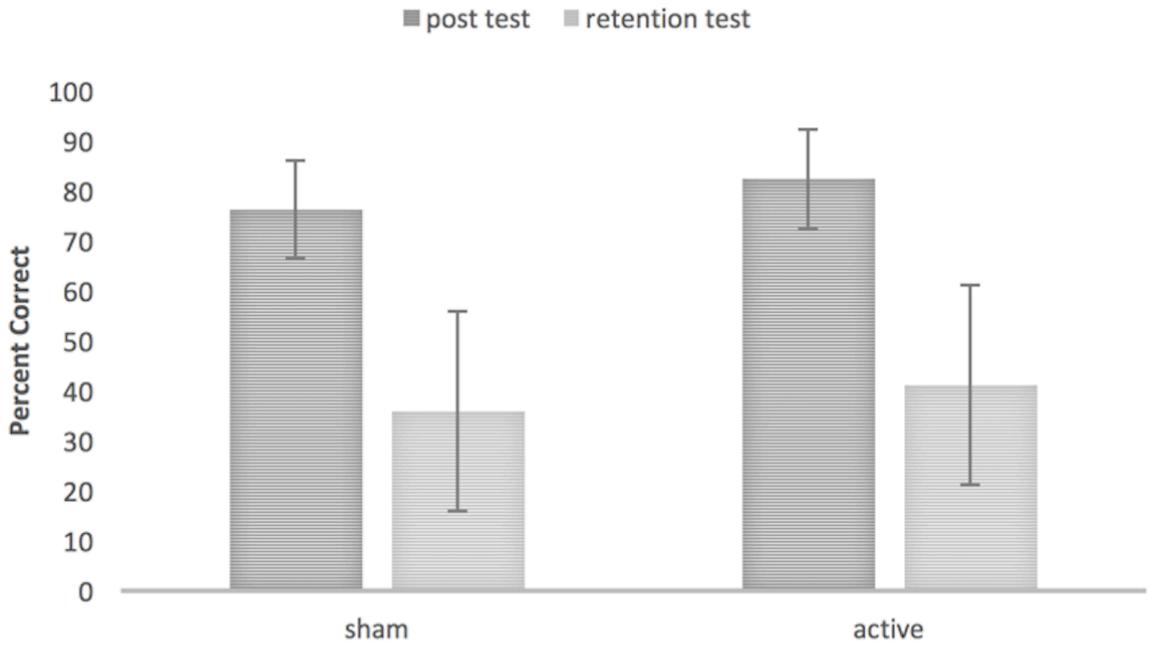
scores. This difference may have occurred by chance. There were no other significant differences between groups or assessment scores. In order to compare scores across groups we used a one tailed independent sample t-test. The nonsignificant results for English assessment scores indicate that participants were all around the same in English language capabilities and one group did not have a preexisting advantage before this study took place.

Assessment and Retention Session. There was no main effect of group (sham vs taVNS, $F(1,15)=.37$, $p=.55$), but there was a significant main effect of time (post-test vs retention, $F(1,15)=71.76$, $p<.001$). There was no interaction between group and time ($F(1,15)= .01$, $p=.9$)(Figure 2). Participants scored significantly lower across both groups at their retention session compared to at their assessment session. To determine the effect of taVNS on language learning we utilized a 2-way mixed design ANOVA of the groups (stim vs active, between groups) and tests (post and retention, within groups) on percent correct shown in Figure 2.

Table 1. English assessment scores of sham and active taVNS participant groups.

Assessment	Sham	Active	T-Statistic
Sample (F)	8 (2)	8 (3)	
Age	19.75±1.40	19.46±1.07	
K-BIT	107.25	100.6	1.17
SWE	108.5	112.5	0.84
PDE	112	109.8	0.78
WID	111.67	105.2	2.62
WA	105.67	110.1	1.27
RDN	11.17	12.1	1.57
RLN	10.67	11.2	0.72
DMC	9.08	8.3	0.87
VLC	11.17	11.2	0.03
NL	12.42	12.6	0.23
DMR	9.83	9.8	0.04
VLR	11.17	10.3	0.88

Figure 2. Percent correct of participants' posttest and retention test scores between the active and sham stimulation groups.



Discussion

The aim of the current study was to look at the effect of taVNS on novel language learning after one training session and at a one-week retention. We hypothesized that participants receiving active taVNS would recall significantly more Palau words as compared to the sham stimulation group. This hypothesis was based on previous literature that showed significant improvement driven by taVNS on cognitive function (Borges et al., 2020; Colzato et al., 2018; Jacobs et al., 2015), and specifically, in letter-sound learning in a novel orthography (Thakkar et al., under review). In contrast, our results suggest that there is no benefit of 5 Hz taVNS on novel language learning.

In spite of the null interaction, we did observe a main effect of time on performance. Participants scored significantly lower during their retention session a week later compared to

their post training test. This result is not surprising because short term memory loss is likely to increase over time (Baddeley & Scott, 1971; Barrouillet et al., 2004). Longer retention intervals are associated with poorer recall (Baddeley & Scott, 1971), so future studies should look at the effect of having a shorter retention interval between taVNS sessions to see if this can produce a significantly higher retention score for participants. Another significant result was found in the English assessment all participants took at the beginning of the study. Participants in the sham stimulation group did significantly better in the Word ID task compared to the taVNS group. This measure quantifies participants' ability to pronounce real words in the English language. This result may have occurred by chance. It also may have occurred because participants in the sham group had a higher exposure to the English vocabulary before this experiment and were better able to use the words given because of prior experience. To test for this exposure level, future studies should provide a more in depth questionnaire about participants' familiarity with the English language and their previous education.

There are at least two limitations of this current study. One potential limitation was using a small sample size because our data set only included 16 participants, 8 per stimulation group. It is possible that a better-powered study would reveal a significant effect of stimulation, thus future studies should look at the implications of increasing the number of participants. A second limitation of this study was including only two participant groups for stimulation, 5 Hz and sham. This limitation hindered the study because we were not able to rule out low stimulation levels as a cause for insignificant results. Future studies should look at different taVNS levels and the implications this may have on participants' ability to recall a higher number of words. Previous taVNS studies have shown improvement using 25 Hz for stimulation level and reported significant results (Badran et al., 2018; Borges et al., 2020; Stefan et al., 2012). An fMRI study

looking at optimal parameters for taVNS in human participants found placing the taVNS device on the cymba conchae produced the strongest activation on the vagal pathway, and used 25 Hz as their stimulation level (Yakunina et al., 2017). Borgers et al., (2020) investigated improvements in cognitive flexibility paired with taVNS and found significant results with set shifting paradigms using 25 Hz. Pilot data from our lab has found significant improvement in participants in novel language learning using taVNS at 25 Hz compared to 5 Hz and sham. Future studies should investigate this limitation by adding additional parameters.

Another possible direction for future studies is to include different word types during training. The current study used concrete nouns that had straight forward definitions for participants, such as banana and bow tie. Research should investigate whether other word types, such as abstract nouns that are not easily visualized, would have a significant relationship with taVNS pairings. It may be possible that concrete nouns were too memorable to participants that already had significant prior experience to help with recall. Thus, it is possible that abstract nouns would be more easily recalled in follow-up tests because of their novelty.

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