Basura Gregory (Orcid ID: 0000-0002-5574-7385)

fNIRS Probes Adapted to the Ear Canal

Tinnitus and Auditory Cortex; Using Adapted Functional Near-Infrared-Spec
Imaging in Humans

Tianqu Zhai, BS[1], Angela Ash-Rafzadeh, BS[2,3], Xiaosu Hu, PhD[2,3], Jessica Kim[2]
Charles Filipiak, BS[1], Kaiwen Guo, PhD[1], Mohammed N. Islam, PhD[1], Ioulia K
J. Basura, MD,PhD[3,4]

[1]Department of Electric Engineering. The University of Michigan; 1100 W M
Arbor, MI 48109
[2]Department of Psychology. The University of Michigan; 500 Church Street;
[3]Center for Human Growth and Development; The University of Michigan; 3
Arbor, MI 48109
[4]Department of Otolaryngology/Head and Neck Surgery; Kresge Hearing Re
Michigan; 1100 W Medical Center Drive; Ann Arbor, MI 48109

Corresponding Author:
Gregory J. Basura, M.D., Ph.D.
Associate Professor
Otolaryngology/Head and Neck Surgery
Division of Otology/Neurotology and Skull Base Surgery
1500 E. Medical Center Dr.
The University of Michigan
Ann Arbor, MI 48109
Office Phone: (734) 232-6303
Fax: (734) 764-0014
Email: gbasura@umich.edu

Running Title: fNIRS Probes Adapted to the Ear Canal

Meeting: Presented that the Association for Research in Otolaryngology; Sa

Financial Disclosure: The authors have no financial relationships to disclose

fNIRS Probes Adapted to the Ear Canal

**Abstract**

**Objectives:** Phantom sound perception (tinnitus) may arise from altered br
cortex. Auditory cortex neurons in tinnitus animal models show increased s
may be a core characteristic of tinnitus. Functional Near Infrared Spectrosc
findings in human auditory cortex. Current fNIRS approaches with cap reco
depth of signal penetration due to the skull thickness. To address this limita
innovative fNIRS approach via probes adapted to the external auditory cana
placed deeper and closer to temporal lobe of the brain to bypass confining
neural recordings.

**Methods:** Twenty adults with tinnitus and 20 non-tinnitus controls listened
broadband noise during standard cap and adapted ear canal fNIRS neuroim
not blinded, but the protocol and post-processing for the two groups were

**Results:** Standard fNIRS measurements in participants with tinnitus revealed
activity during silence that was suppressed during auditory stimulation with

applications to future studies to investigate brain changes not only in tinnit

states that may involve the temporal lobe and surrounding brain regions.

**Key Words:** Auditory Cortex; Functional Near Infrared Spectroscopy; Hemo

**Level of Evidence:** NA

fNIRS Probes Adapted to the Ear Canal

**Introduction**

Tinnitus is phantom sound perception in the absence of a sound stimulus. T
tinnitus is not clear yet is typically associated with peripheral ear disease (i.
brain activity or "neural gain" within central auditory pathways may underli
tinnitus. Animal models of tinnitus have consistently reported central neura
spontaneous neural firing rates and neural synchrony) within auditory corte
changes in animals touted as "tinnitus neural/physiologic correlates" are no
AC in tinnitus. Limited objective findings in human tinnitus is due, in part, to
technology to characterize neural changes in real time.

Functional Near-Infrared Spectroscopy (fNIRS) has emerged as a non-invasi
capable of measuring human AC and non-AC activity through hemodynamic
functional connectivity (RSFC)[4,5]. fNIRS uses near-infrared (NIR) light to mea
concentration in brain regions of interest (ROI; AC in this study)[4]. As with fu
measures changes in localized oxygenated hemoglobin (HbO) and deoxygen
an effective direct metabolic marker or index/correlate of neural activity[6].

approaches restrict NIR penetration (3cm) to outer cerebral cortex. Howeve
likely extend to deeper AC, out of measurable reach with current fNIRS con
necessary to investigate ways to improve NIR light penetration and detectio
measure putative tinnitus correlates (HA and RSFC).

One strategy to expand temporal lobe brain surveillance is to modify NIR-pr
NIR-limiting skull bone and scalp by placing the probe in the external audito
source or detector could then sit flush with superior aspect of the EAC to di
(detector) NIR light from deep temporal lobe. The goal is to physically place
closer to brain structures of interest. Here we describe the first-ever docum
fNIRS technology to NIR probes that transit the EAC to potentially measure
temporal lobe. The key innovation and goal of this *proof of concept study* w
and validate adapted fNIRS probes for lateral skull base placements for mea
recordings through the native EAC. The primary purpose was not to identify
tinnitus, but rather to use our previously published changes in human HA as
*platform to validate* the adapted EAC probes for functional efficacy and app
second goal was to validate and extend our previous observation of basal h

**Materials and methods**

*Participants*

Twenty normal/near-normal hearing adults (10 females; 10 males; average
subjective bilateral tinnitus and 20 non-tinnitus controls (10 females; 10 ma
participated. Exclusion criteria of normal/near normal hearing tinnitus and
prior otologic surgery, unilateral tinnitus, conductive hearing loss or sensori
than 30dB HL at any frequency. All research was conducted in accordance w
Michigan Institutional Review Board who approved the study. Informed con
extensive explanation of the protocol. All tinnitus participants suffered from
subjective auditory percepts in the "head" or in both ears equally. Speech r
and word discrimination scores (WDS) were within the normal range for all
questionnaires were utilized for these participants in this proof of concept s

*fNIRS Imaging/Cap Configuration*

We used a continuous wave fNIRS system (CW6, Techen Inc., USA) with
830nm). For traditional cap fNIRS recordings, a customized configurat
hemisphere; source/detector; Fig.1) inserted into a silicone band was wr

fNIRS Probes Adapted to the Ear Canal

*Adapted fNIRS EAC probes*

Adapted EAC probes were modeled after those previously used by our t
detector fiber was connected to the continuous wave fNIRS system th
connector. The detector fiber is a borosilicate fiber bundle with a large diam
contain two identical multimode fibers (400µm diameter). Catheter distal e
a resin ferrule to hold the fiber, two grooves to accommodate both a NIR-s
and two right angle prisms for each fiber (Fig. 2A). Resin ferrule (outer d
grooves (widths of ~2.3mm and ~0.5mm) to fit the detector and source fibe
angle prism (Tower Optical Corporation, FL) rotated light $90^0$ toward th
temporal lobe (distal end length is >20 mm).

To house and stabilize the adapted probes within each EAC we obtained cus
each participant. EAC impressions are imaged with a CT scanner and 3D pr
composite housing is custom fit to each participants' EAC anatomy and mod
out to accommodate and hold the adapted probe fiber and prism inserted th
2C).

was achieved by isolating only those channels in control participants wit
stimuli and subsequent declines during silence[5,7].

*Stimuli Protocol*

A passive listening block-paradigm design protocol was used that consist
chosen 18-second blocks of broadband noise (BBN) separated by intervenin
(inter-stimulus rest; ISR) between each auditory stimulus. Two, 5-minute p
after the paradigm was used (Fig. 3). Audacity (GNU General-Public Licens
and normalized with Praat 4.2[14] as published[5,7] (Fig. 3). Auditory stimuli
(Psychology Software Tools Inc., Pittsburgh, PA, USA) and played at a
loudspeakers approximately 2 feet from the participant in a sound-field
pressure level (SPL; Creative Inspire T12). This achieved a consistent SPL tha
20dB and comparable pure tone averages (PTAs). Thus, the SPL level was wit
detection range. Participants were positioned at arm's length from a desk
with a projected "plus sign" image to maintain stable head position (with
platform). Participants were presented with the entire block-paradigm desig
stimulation using BBN was selected to evaluate HRs during complete AC tone

interested in whether there are significant changes of HbO in response to
Thus, we focused on the trend of the waveform rather than the absolute valu
signal-to-noise ratio (SNR) for each block was calculated and blocks with
standard deviations from mean) SNR were removed. HbO data were down-s
filtered (0.3Hz) to eliminate physiological fluctuations and high-pass
instrumental noise.

Channel 4 from the cap configuration on the right hemisphere is used as th
adapted probe. Due to the assumed variability of the bony skull (i.e., ana
thickness and pneumatization) between the superior EAC and temporal lob
might have HRs that vary from person to person. We therefore selected the
with the highest Pearson's correlation coefficient (R-value) to channel 4 in
for analysis.

Since the HR following auditory stimulation takes approximately 4-6 secs to
data were averaged across all artifact-free blocks for both BBN and ISR withi
along the entire time course. Each block baseline for BBN or ISR is remove

fNIRS Probes Adapted to the Ear Canal

The effectiveness of adapted EAC probes was further evaluated with P
($p<0.05$) of HbO waveforms between the selected adapted EAC probe chan
probe. The analysis was conducted on the averaged HbO waveform of all 9 it
for each participant, (i.e., 36sec waveform where the first 18 secs reside in
reside in ISR). Correlation coefficient r-value of 1 indicates maximal positi
correlation; -1 indicates a negative correlation. These were converte
transformation); a stabilizing function to correct for variance of Pearson's co
change depending on proximity to 0[17]. Averaging and an independent t-test w
correlation coefficients. The r-values were transformed back using inverse F

**Results**

*Behavioral Data Analyses*

For controls, the average SRT was 15dB HL with an average WDS of 100%, w
average SRT of 16.5dB HL and 98.3% WDS. Independent t-tests indicated
either hearing thresholds or average age between tinnitus and control parti

*BBN Increases Hemodynamic Activity (HA) in Control AC*

fNIRS Probes Adapted to the Ear Canal

Using the adapted EAC probe, BBN (0.51, SE=0.39) led to a significant incr
channels associated with ROI as compared to ISR (-0.38, SE=0.19; p<0.05; F
from EAC probes replicated HbO responses in ROI observed with cap probes.
correlation calculation was performed, HbO responses from the cap (chann
showed a strong correlation with each other within the time course. The av
coefficient after Fisher's Z transformation is 0.44, and independent t-test pe
difference from 0 (p<0.05; Fig 5A), with a t-value of 4.59. These data sugge
two separate probes (cap and EAC) are likely derived from the same H
correlated waveforms between the cap and EAC probe that both showed ex
in controls not only replicated our previous cap data[7], but also valida
technology.

*HA in ROI is elevated in tinnitus during ISR*

In tinnitus participants, cap probe measurements of ROI displayed as expec
ISR. The mean HbO concentration during ISR (0.91, SE=0.43) was significant
baseline (p<0.05; Fig 4B), replicating our reported findings using cap probes
conclusion that ROI in tinnitus has elevated metabolic activity at baseline/r

we see expected changes in the tinnitus ROI during ISR and BBN. During ISR
significant difference from baseline at approximately 9 secs into the block p
value for ISR (0.29, SE=0.19) is higher than BBN (0.05, SE=0.16). This, like th
suppression of HA with BBN that may also reflect a forward masking in ROI
adapted probe-generated waveforms exhibited strong correlations to each
Pearson's correlation coefficient after Fisher's Z transformation is 0.50, and
performed showed a significant difference from 0 ($p<0.05$; Fig 5B), with a t-
waveforms and temporal profile responses to ISR and BBN in tinnitus ROI b
adapted probes during respective durations of the blocks helps validate the
suitable probe for recording for the current experiments and those going fo
signal amplitude generated between the two probes implies that the optica
may not completely overlap.

**Discussion**

We have successfully fabricated and implemented the use of a highly innov
conventional fNIRS cap probes to the human EAC to expand brain recording
the first of its kind and based on our promising results, will likely expand br

Our cap and adapted EAC probe findings showing increased HA during silen
in tinnitus highlights plasticity within AC that may underlie phantom sound
during ISR may directly reflect increases in spontaneous neural discharge ra
models AC[1,2] and brainstem[18,19]. These physiologic correlates of tinnitus ma
objectified findings in humans with fNIRS cap and adapted technology. In a
studies[5,7], only one other report[8], demonstrated the effects of tinnitus in hu
phantom sound perception may be the result of increased neural (cortical,
findings are consistent with PET and fMRI studies that also demonstrated e
activity across multiple central auditory centers as a potential correlate of t

While tone-evoked neural firing rates are increased following sound stimuli
models[1,2,3], our cap and adapted EAC probe data demonstrated decreased H
decreases, as expected based on our previous observations[7], were seen in F
suppression likely represents forward masking/residual inhibition; external
perception[21,22,23]. BBN likely disrupts abnormal synchronous activity in tinni
networks[24]. This concept has been seen in non-fNIRS studies in tinnitus. Mi

adapted EAC probes have the capacity to pass and receive NIR-light through extrapolate neural activity. However, the impact of multiple media (amount of anatomic variability in the skull base will need to be more closely examin addition, future studies will also match audiograms closer between tinnitus out any effects of hearing loss on NIRS outcome.

**Conclusions**

The present *proof-of-concept study* successfully implements fNIRS probes a a new technology. We have successfully fabricated and validated these prob HR in tinnitus and non-tinnitus AC. These probes have shown the capacity t discern subtle and dynamic changes in AC HA under conditions of silence an both normal and aberrant neural circuits. This novel and highly innovative a broadened and non-invasive means to image the brain utilizing fNIRS techn

**Author Contributions**

Conception or Design of Study: TZ, CF, KG, MI, IK, GJB

Acquisition, Analysis, or Interpretation of Data: TZ, AAR, JK, XSU, GJB

**References**


1. Noreña A and Eggermont J. Changes in spontaneous neural activity
acoustic trauma: Implications for neural correlates of tinnitus. *Hear*
153.
2. Basura G, Koehler S and Shore S. Bimodal stimulus timing-depende
auditory cortex is altered after noise exposure with and without tin
2015; 114:3064-3075.
3. Takacs J, Forrest T and Basura GJ. Noise Exposure Alters Long-Term
Synchrony in Primary Auditory and Rostral Belt Cortices Following E
*Research*. 2017;356:1-15.
4. Ferrari M and Quaresima V. A brief review on the history of human
spectroscopy (fNIRS) development and fields of application. *Neuroi*
5. San Juan J, Xiao-su H, Issa M, Bisconti S, Kovelman I, Kileny P and Ba
Resting State Functional Connectivity (RSFC) in Human Auditory and
as Measured by Functional Near-Infrared Spectroscopy (fNIRS). *PLO*
6. Huppert T, Hoge R, Diamond S, Franceschini M and Boas D. A tempo
ASL, and NIRS hemodynamic responses to motor stimuli in adult hu

9. Langguth B, Kreuzer PM, Kleinjung T, De Ridder D. Tinnitus: causes a management. *Lancet Neurol*. 2013;12:920-930.

10. Ayaz H, Onaral B, Izzetoglu K, Shewokisa P, McKendrick R and Paras monitoring of brain dynamics with functional near infrared spectros neuroergonomic research: empirical examples and a technological *Hum Neuroscience*. 2013; 7:871.

11. Klem GH, Lüders HO, Jasper HH, and Elger C. The ten-twenty electro International Federation. The International Federation of Clinical N *Electroencephalography and Clinical Neurophysiology Supplement*.

12. Bisconti S, Shulkin M, Hu X, Basura G, Kileny P and Kovelman I. Funct Spectroscopy Brain Imaging Investigation of Phonological Awarenes Comprehension Abilities in Adult Recipients of Cochlear Implants. *J and Hearing Research*. 2016; 59: 239-253.

13. Alexander V, Shi Z, Iftekher F, Welsh M, Gurm H, Rising G, Yanovich M. 2014. Renal denervation using focused infrared fiber lasers: a po hypertension. *Lasers in Surgery and Med.* 2014;46:689-702.

14. Boersma P and Weenink D. 2004. Praat: doing phonetics by

17. Fisher RA. Frequency distribution of the values of the correlation co
indefinitelylarge population. *Biometrika*. 1915;10:507-21.

18. Dehmel S, Cui YL and Shore SE. Cross-modal interactions of auditor
brainstem and midbrain and their imbalance in tinnitus and deafne
*Audiology*. 2008;17:S193-S209.

19. Kaltenbach JA, Zacharek MA, Zhang J, and Frederick S. Activity in th
hamsters previously tested for tinnitus following intense tone expo
2004;355:121-125.

20. Lanting CP, de Kleine E and Van Dijk P. Neural activity underlying ti
from PET and fMRI. *Hearing Research*. 2009;255:1-13.

21. Tyler RS, Conrad Armes D and Smith PA. Postmasking effects of sensorineu
investigation. *Journal of Speech and Hearing Research*. 1984;27:466-474.

22. Tyler RS, Babin RW and Niebuhr DP. Some observations on the masking ar
tinnitus. *Journal of Laryngology and Otology*. 1984 (Suppl. 9):150-156.

23. Tyler RS. The psychophysical measurement of tinnitus. In: J-M. Aran & R.
Proceedings of the Fourth International Tinnitus Seminar. 1992 (17-26). A

24. Roberts LW, Moffat G, Baumann M, Ward LM, and Bosnyak DJ. Res

fNIRS Probes Adapted to the Ear Canal

**Figure 1**

**Title:** Brain fNIRS optode configuration.

**Caption/Legend:**

Configuration of channels (numbers), detectors (blue circles) and sources (r
hemispheres for “cap” configuration. Channel 4 5 & 6 for adapted probes a
lines, the detector/source modes are operated in different configuration.

**Figure 2**

**Title:** fNIRS adapted EAC probe configuration.

**Caption/Legend:**

**2A.** The adapted probe-design. Photograph shows the current adapted prob source or IR-detector that are activated separately during fNIRS recordings. impression that is then converted into a 3D printed/replicated composite h holds the adapted probe within the external ear canal (EAC) for the duratio and **e** show the adapted probe inserted into the custom-made 3D housing p fNIRS recordings. **Fig. 2B.** Photograph of the adapted probe and housing ins participant (the principal investigator on the project in this case to avoid pa issue) with the concurrent cap probes in place during a typical recording ses source that is on and detected in the right EAC. **Fig. 2C.** Banana shape optic probe optodes and cap probe optodes relative to the ear-brain coronal ana signal can reach a lower part of the auditory cortex which cap probe lack th reach.

**Figure 3**

**Title:** fNIRS recording paradigm.

**Caption/Legend:**

Schematic of block auditory testing paradigm. Control and tinnitus participa
broadband noise (BBN) for 18sec each, immediately followed or preceded b
period consisting of silence/absence of auditory stimulation for 18 sec for a
17 minutes. Each paradigm was repeated 9 times. Prior to and after the rec
protocol, each participant listened to 5 minutes of silence to calculate the r
connectivity (RSFC; data not shown in this manuscript).

**Figure 4**

**Title: f**NIRS probes adapted to the EAC replicate expected findings in contr
probes

**Caption/Legend:**

**A**. Averaged waveform of HbO signal within control participants during bloc
(regular probe on the left) and the adapted probe (IR-detector mode on the
auditory stimulation with BBN, significant increases in HbO concentration a
silence (ISR) in both cap and adapted fNIRS probe configurations (*=p<0.05
standard error). **B.** In tinnitus participants, the absence of sound stimulus (I
significant increases in HbO concentration in both cap and adapted probes;
suppressed by auditory stimulation with BBN (adapted probe IR-source mo
indicate standard error).

**Figure 5**

**Title:** fNIRS probes adapted to the EAC show strong waveform correlations
cap fNIRS probes in both control and tinnitus.

**Caption/Legend:**

Histogram of the Pearson's correlation coefficient of temporal HbO signal b
probe and the adapted probe across all participants in both (**A)** control and
mean coefficient is 0.44 in controls and 0.50 in tinnitus. The y-axis indicates
each bin; total of 20 participants for each group (Note: values less than 0 in
correlation between the two probes. Note 3 control participants with corre

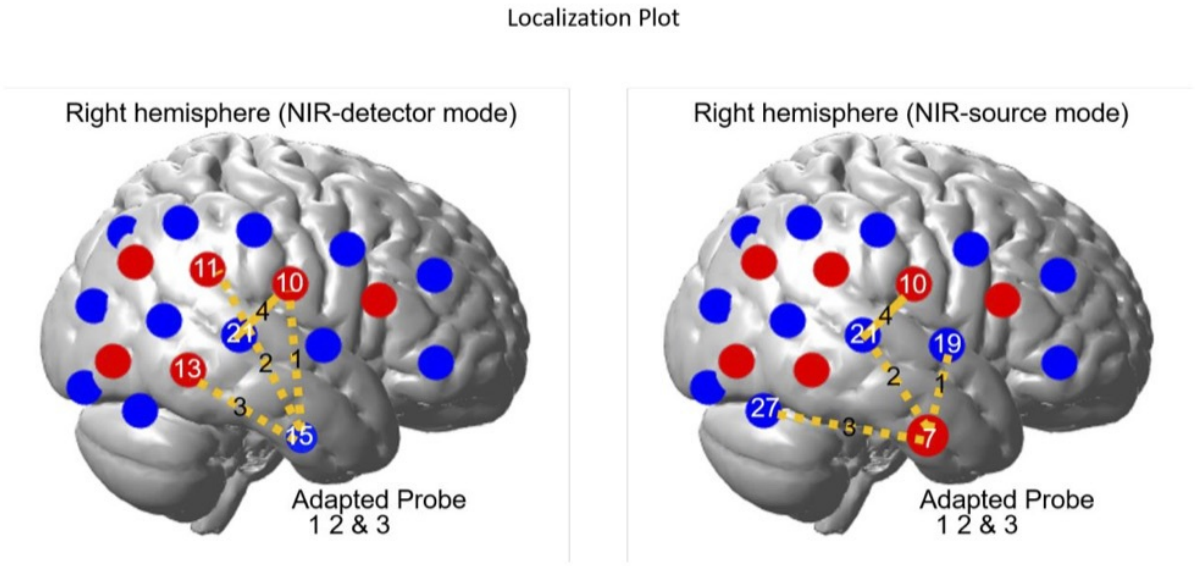


Figure 1.jpg

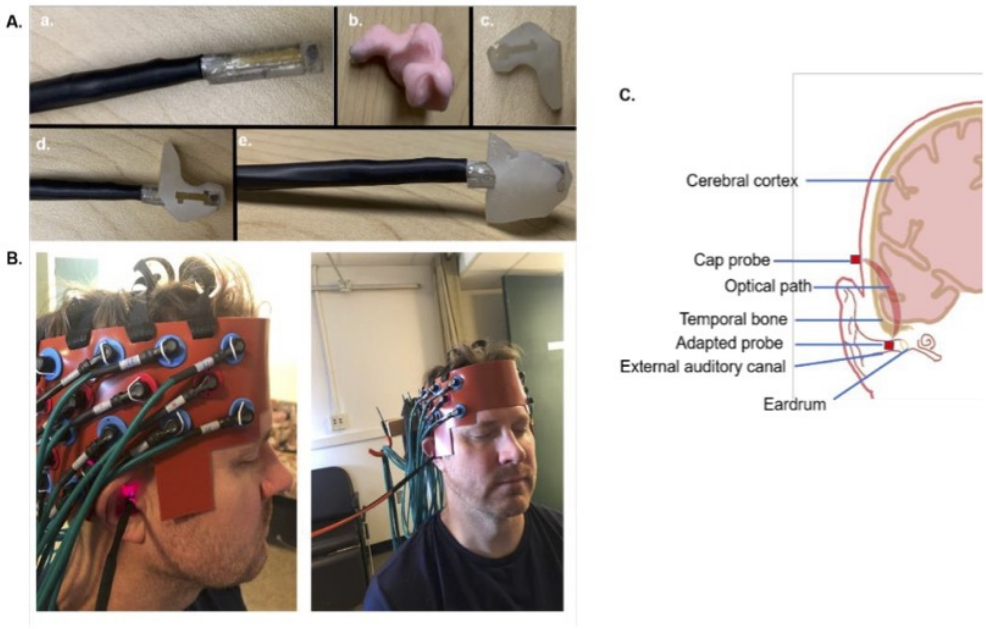


Figure 2.jpg

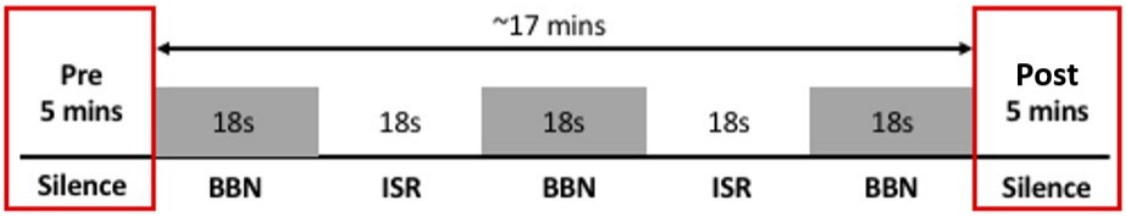


Figure 3.jpg

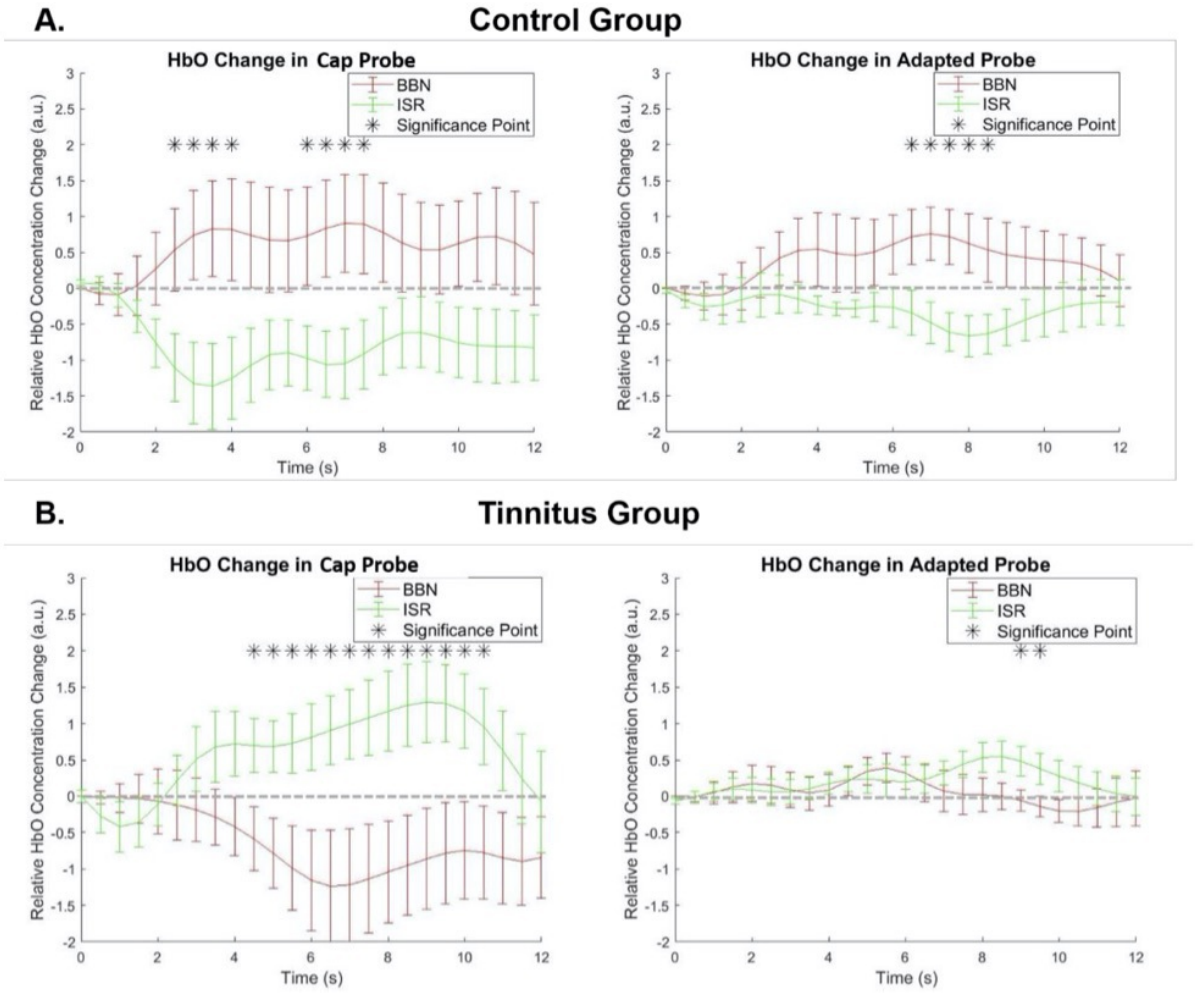


Figure 4 .jpg

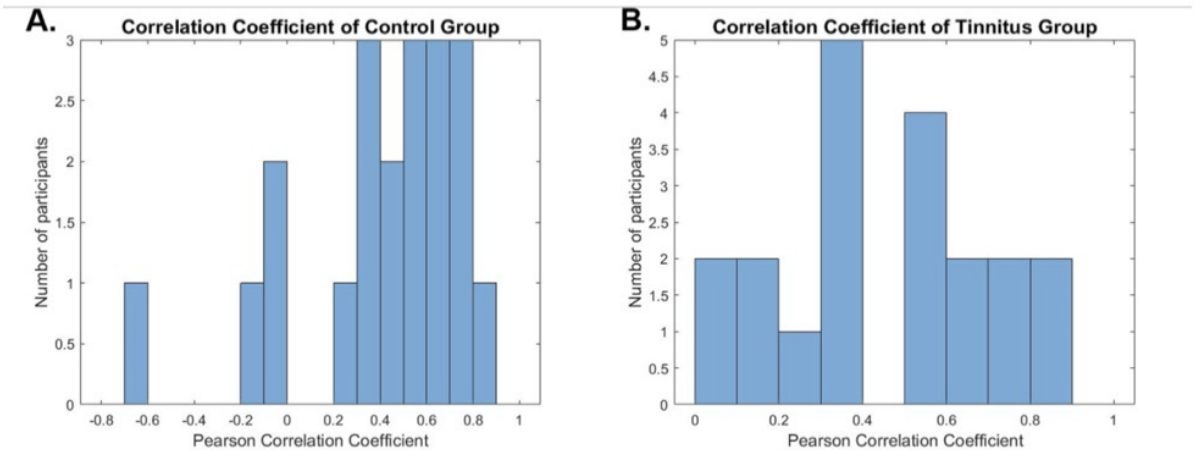


Figure 5.jpg