In vivo muscle conduction study of the tongue using a multi-electrode tongue depressor

Xuesong Luo, MSc[1]**, Hilda Victoria Gutierrez Pulido, MD**[2]**, Seward Brian Rutkove, MD**[2]**, and Benjamin Sanchez, PhD**[1]

[1]Sanchez Research Lab, Department of Electrical and Computer Engineering, University of Utah, Salt Lake City, UT 84112, USA.

[2]Department of Neurology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA 02215, USA.

ABSTRACT

OBJECTIVE: To test a novel technology for assessment of the volume conduction properties (VCPs) of the tongue. These properties are electrophysiological data that might reflect alterations in patients with tongue involvement.

METHODS: Seven healthy individuals were self-measured. The depressor was placed on the surface of the anterior tongue. Directional differences of VCPs were determined with standard descriptive statistics.

RESULTS: Conductivity in longitudinal direction was larger than in transverse direction at 16 ($p<0.05$), 32 ($p<0.05$), 64 ($p<0.01$), and 128 kHz ($p<0.01$). No differences were found in relative permittivity. The intraclass correlation was 0.778 and 0.771, respectively.

CONCLUSIONS: Our technology provides, for the first time, VCPs of the healthy human tongue.

SIGNIFICANCE: Tongue VCPs are standard electrophysiological, quantitative and objective data reflecting ionic content and membrane integrity which could find value for diagnostic purposes and treatment monitoring.

Address correspondence to: Dr. Benjamin Sanchez, Sorenson Molecular Biotechnology Building, Office 3721, 36 South Wasatch Drive, University of Utah, Salt Lake City, UT 84112, USA, phone: (801) 585-9535, email: benjamin.sanchez@utah.edu.

Keywords: tongue, muscle conduction study, volume conduction properties, anisotropy, near-field potentials

Highlights:

- Tongue volume conduction properties are measured using a novel multi-electrode depressor.
- The technology can assess non-invasively the volume conduction properties of the bulk of the tongue.
- Participating subjects performed the measurements on themselves with minimal training.

Introduction

With successful therapies for neuromuscular disorders now beginning to arrive at a steady pace, their specific applications will require better and more focused assessment tools. Ideally, such tools would be deeply tied to the pathogenesis of the disease while at the same time being able to reflect clinical effect and physical status of the patient. One commonly affected muscle in many neuromuscular disorders is the tongue (Yamanaka et al., 2001; Engel-Hoek et al., 2013). Notwithstanding the importance of tongue function decline on speech and swallowing which directly impacts overall quality of life and life expectancy, current tools for tracking tongue impairment and response to therapy have important limitations (Yunusova et al., 2019).

For example, tongue force/pressure using the Iowa Oral Performance Instrument (IOPI Medical LLC, Redmond, WA) or the TPM-01 device (JMS Co., Ltd., Hiroshima, Japan) are helpful at evaluating tongue strength; however, data is highly dependent on subject motivation, number of trials, feedback, and tongue and jaw position (Clark et al., 2003; Solomon, 2004). Ultrasound and magnetic resonance imaging can visualize alterations in tongue muscle tissue, but ultrasound images are difficult to quantify in a consistent fashion since alterations in probe pressure and angle can greatly distort image quality, whereas magnetic resonance imaging is very expensive to perform and the test is typically slow (Hensiek et al., 2020). Finally, videofluoroscopic swallowing studies can also provide information on tongue movement during drinking and eating (Wright and Jordan, 1997), but suffer from a number of substantial limitations, including radiation exposure and lack of portability. While there are methods for quantifying real-time moving images, these are typically done in research settings and involve considerable cost and technical expertise.

Electrical impedance myography (EIM) is another test for tongue evaluation (Sanchez and Rutkove, 2017a,b; Rutkove and Sanchez, 2018). Previous studies used a basic 4-electrode plastic tongue depressor and measured tongue EIM in only one direction (Shellikeri et al., 2015; McIlduff et al., 2016; Mcilduff et al., 2017). The electrodes were made of conductive metal film cut and then placed at a 0.5 centimeters distance from one another. The connection between EIM electrodes and interfacing cables were made using a metallic conductive epoxy and then covered with dental adhesive to provide mechanical strength. This basic setup was used to collect lingual resistance and reactance values of patients with amyotrophic lateral sclerosis (ALS). Data at 50 kiloHertz (kHz) were found to be significantly lower than those of healthy volunteers and correlated with standard measure of tongue endurance (Shellikeri et al., 2015). While valuable, resistance and reactance values obtained during an EIM test are intrinsically limited since they cannot be universally standardized as a measure of disease status or the effect of therapy (Sanchez et al., 2016). Moreover, they cannot provide a deeper understanding on the electrophysiological alterations that occur in neuromuscular disorders.

With more sophisticated impedance theoretical analyses and increased number of electrodes (Kwon et al., 2019c,a), it is possible a more focused interrogation of muscle itself and uncover the underlying volume conduction properties (VCPs) of the tongue. Simply put, lingual resistance and reactance data directly recorded with an EIM procedure are generated by the underlying VCPs of the tongue as well as other experimental parameters including the distance between electrodes and their placement. However, unlike their surrogate resistance and reactance measures, the VCPs are true physical properties of muscle (Duck, 1990). As such, they are standard in nature and provide quantifiable and objective data on the ability of muscle (or any material) to conduct electrical current. Importantly, the VCPs of muscle are closely tied to ionic concentration and myofiber membrane integrity, two physiological features known to be altered with disease (Nagy et al., 2019). Here, we describe a novel

16-electrode tongue depressor for direct in vivo assessment of healthy human tongue VCPs including their spatial dependence (Figure 1).

Methods

Subjects

Healthy volunteers $N = 7$ (6 male, 1 female) with mean age of 44.6 years, range 26-71 years were recruited from the electrodiagnostic lab without regard to their background under Institutional Review Board (IRB) approval at Beth Israel Deaconess Medical Center, Boston, MA (Clinicaltrials.gov Identifier: NCT02118805).

Multi-electrode tongue depressor

The tongue depressor has standard dimensions length 100 and width 17.5 millimeters (mm) with 16 surface electrodes arranged in two concentric circles of radii 4 and 7 mm, respectively; and measuring directions determined by the angles 0, 45, 90 and 150 degrees (see the directions in Figure 2 A). The depressor connects directly to the impedance measuring instrument without cables through the expansion connector located at the tongue's opposite side. The single-use tongue depressors were sterilized via autoclave prior to use described below.

Tongue volume conduction properties measuring device

We built a battery-powered device for measuring the tongue VCPs (Figure 2 B). The instrument received IRB approval for human testing as an investigational device. Instrument control was performed with an Android app developed for this purpose. Wireless communication between the device and the app was done via Bluetooth. De-identified tongue VCP data were downloaded from the app via email for statistical analysis. The device's accuracy is $<0.5\%$ from 8 to 64 kHz and $<1\%$ from 128 to 256 kHz supplying a sinusoidal current 100 microamperes.

Tongue measurements

Tongue VCPs measurements were made by the participants themselves while comfortably seated. Each person performed measurements after being taught how to do so by the senior author (BS) while being observed. The depressor was plugged into the measuring device and then placed on the top surface of the anterior tongue applying pressure so as to ensure that all electrodes made electrical contact with surface of the tongue. The patients were instructed to maintain constant pressure to ensure good electrode contact while maintaining the tongue stationary in as much as possible during each measurement. Repeated measurements were performed after a pause of 10 seconds between measurements, a complete frequency scan took $\sim$20 seconds. For each tongue VCPs measurement, 24 tongue conductivity and relative permittivity (also known as dielectric constant) values in the longitudinal and transverse directions –i.e., along and perpendicular to the tongue's major axis, respectively- were collected at 8, 16, 32, 64, 128 and 256 kHz. Longitudinal and transverse tongue VCPs were automatically plotted in the smartphone app at the completion of each experiment for real-time data verification by the senior author (BS).

Data analysis

Multi-frequency conductivity and relative permittivity curves were downloaded from the Android app and pre-processed in MATLAB (The Mathworks, Natick, MA). The senior author (BS) filtered the data to remove measurement artifacts due to poor electrode contact resulting in erroneous conductivity and relative permittivity values or values that were out of physiological range in the frequency range measured. In the conductivity analysis, the lower and upper cut off margins were 0 (caused by the lack of electrical contact indicating the tongue would be a perfect insulator) and 2 Siemens per meter (S m^{-1}) –a conductivity value greater than saline solution at frequencies measured–, respectively (Nagy et al., 2019). For the relative permittivity, only the lower cut off margin was set to 0 (dimensionless) –the minimum value possible representing a tongue without any viable myofiber membrane– to discard 0 and negative values due to contact artifacts. In total, for the conductivity analysis, the entire conductivity dataset from one subject was removed (12 data points) along with 14 additional discrete frequency values from the other participants (6 values in longitudinal and 8 values in transverse direction), leaving 58 points analyzed. For the relative permittivity analysis, 10 frequency values were removed (4 values in longitudinal and 6 values in transverse direction), leaving 74 points analyzed. Conductivity and relative permittivity differences in longitudinal and transverse direction were analyzed in Prism (GraphPad Software, San Diego, CA) at each frequency using a mixed effect model with Bonferroni correction, statistical significance was $p<0.05$.

Results

The procedure was well tolerated by all participants and there were no adverse events. Tongue VCP values are shown in Figure 3. The frequency dependences of the conductivity and relative permittivity properties are consistent with membrane polarization mechanism occurring in biological tissues (Duck, 1990). As expected, conductivity values in longitudinal direction were significantly larger than transverse direction at frequencies 16, 32, 64 and 128 kHz (Figure 3 A), as it is easier for the electrical current to flow in the direction along the fibers than perpendicular to the fibers. No directional differences were found in the relative permittivity (Figure 3 B). The only tongue VCPs available in the literature from measuring a single subject without directional distinction is shown for comparison (Gabriel, 1996). Preliminary reproducibility study shows the slope of the fitted line for the conductivity is closer to 1 than for the relative permittivity (Figure 4), a slope of 1 representing perfect reproducibility. The intraclass correlation coefficient was 0.778 and 0.771 for conductivity and relative permittivity, respectively.

Discussion

Here, we show that by using a 16-electrode tongue depressor, it is possible to measure in vivo the VCPs of the tongue without the need to biopsy the muscle, i.e. the gold standard for measuring ex vivo the VCPs of tissues (Nagy et al., 2019). We applied a high frequency, weak electrical current, and assessed it propagation through the tongue tissue in 4 directions (0, 45, 90 and 150 degrees) using different set of electrodes. The relationship between applied current and measured voltage signals determines the ability of electrical conduction of the bulk of the muscle. The technology developed was conveniently tested at the clinic by the participants themselves without requiring expensive instrumentation such as an ultrasound system or magnetic resonance imaging scanner. The electronic tongue depressor is built with standard printed circuit board manufacturing processes and it is non-invasive, non-toxic, disposable and can be sterilized by autoclave. Basic repeatability data shows promise of the technique for tongue assessment.

There are several clinically important aspects to this work. First, knowledge of tongue VCPs can provide a deeper understanding of clinically relevant findings in standard tongue needle electromyography practice, where the recording electrodes are placed in relatively close proximity to myofibers producing electrical signals (Tankisi et al., 2013). Specifically, as a result of the propagation of spontaneous discharges (e.g., fasciculation and fibrillation potentials) and motor unit potentials through the tongue conductor volume, the morphological features (amplitude, duration, phases) will be frequency-filtered by the VCPs (Kwon et al., 2019b). For example, if VCPs showed decreased conductivity due to interstitial fat deposition, then theoretical models predict that the propagated electromyography waveforms would show increased amplitude compared to a tongue with a normal conductivity. Second, VCPs have the potential serve as biomarkers of tongue health in and of themselves. Indeed, our previous work has shown contrast in muscle electrical properties from healthy and diseased murine models of neuromuscular disorders (Nagy et al., 2019). Tongue VCPs values reflect tissue ionic content and membrane integrity, two indicators of muscle structure and composition. Thus, fibrofatty changes with age and gender or the presence of atrophied myofibers, connective tissue or fat deposition in the bulk of the tongue accompanying neuromuscular conditions affecting the tongue are expected to change tongue VCPs.

Due to the invasiveness of standard biopsy procedures for collecting ex vivo VCP data, in vivo assessment of human tongue VCPs has been only pursued once before in a single healthy individual. In that study, the authors did not attempt to identify differences in their spatial dependence (Gabriel, 1996), even though the myoarchitecture of the striated muscle is highly anisotropic, consisting of bundles of fibers aligned in longitudinal and transverse directions (Gaige et al., 2007). Here, we provide for the first time the VCPs of healthy human tongue tissues including their electrical anisotropy (Kwon et al., 2017, 2019a). The conductivity values previously reported are well within the range of filtered values reported here in longitudinal and transverse directions (Figure 3 A). In contrast, for the relative permittivity (Figure 3 B), there is a tenfold difference between values. In the absence of other in vivo studies, if we compare our data against ex vivo VCPs from healthy murine gastrocnemius muscle (Nagy et al., 2019), those values are actually closer to the values reported here and it is possible those earlier values are in error.

This study has important limitations. These include only a small number of healthy subjects evaluated and, despite being a novel device, inter-session variability were not assessed. In addition, we did not study any diseased individuals since our goal here was to establish the technology before assessing individuals with abnormal values and confirm its basic reproducibility. In the future, we plan integrate a pressure sensor to account for this variable affecting the quality of the measurements. Despite these limitations, the preliminary data provided warrant future work expanding our findings in a larger number of healthy individuals to establish normative tongue values studying age and gender differences. Employing our technology in diseased populations will also be pursued to assess its sensitivity and specificity compared to other accepted clinical outcomes.

In summary, electrophysiological assessment of tongue VCPs using the non-invasive technology presented provides standardized, quantitative and objective data reflecting tongue tissue ionic content and membrane integrity. Future work will evaluate the clinical value of VCPs as new biomarkers of tongue health in patients with neurological disorders that involve the tongue and further explore their value in the interpretation of standard electrophysiological data.

Conflict of interest statement

Dr. Sanchez has equity and serves a consultant and scientific advisor to, Haystack$^{\mathrm{Dx}}$ Inc., Ioniq Sciences Inc., and B-Secur Ltd. Haystack$^{\mathrm{Dx}}$ has an option to license patented impedance technology of which Dr. Sanchez is named as an inventor. He also serves as a consultant to Myolex Inc., Impedimed Inc., Texas Instruments Inc., and Gideon Health Inc., companies that develop impedance related technology for consumer, research and clinical use. Dr. Rutkove has equity in, and serves a consultant and scientific advisor to, Myolex Inc. and Haystack^{Dx} Inc. This study did not employ any relevant company technology.

Acknowledgments

This work was funded by the China Scholarship Council grant 201906020024 (XL) and National Institutes of Health grant R41 NS112029-01A1 (BS).

Author Contributions

Conceived and designed the experiments: B.S. Performed the experiments: X.L., H.V.G and B.S. Analyzed the data: B.S. Wrote the paper: S.R and B.S contributed equally. All authors revised and approved the manuscript.

References

Clark, H. M., Henson, P. A., Barber, W. D., Stierwalt, J. A. G., and Sherrill, M. Relationships Among Subjective and Objective Measures of Tongue Strength and Oral Phase Swallowing Impairments. *Am. J. Speech-Language Pathol.*, 2003, 12(1):40–50.

Duck, F. A. Electrical Properties of Tissue. In *Phys. Prop. Tissues*, pages 167–223. Elsevier, 1990. ISBN 9780122228001.

Engel-Hoek, L., Erasmus, C. E., Hendriks, J. C. M., Geurts, A. C. H., Klein, W. M., Pillen, S., Sie, L. T., Swart, B. J. M., and Groot, I. J. M. Oral muscles are progressively affected in Duchenne muscular dystrophy: implications for dysphagia treatment. *J. Neurol.*, 2013, 260(5):1295–1303.

Gabriel, C. Compilation of the dielectric properties of body tissues at RF and microwave frequencies. Technical report, 1996.

Gaige, T. A., Benner, T., Wang, R., Wedeen, V. J., and Gilbert, R. J. Three dimensional myoarchitecture of the human tongue determined in vivo by diffusion tensor imaging with tractography. *J. Magn. Reson. Imaging*, 2007, 26(3):654–661.

Hensiek, N., Schreiber, F., Wimmer, T., Kaufmann, J., Machts, J., Fahlbusch, L., Garz, C., Vogt, S., Prudlo, J., Dengler, R., Petri, S., Nestor, P. J., Vielhaber, S., and Schreiber, S. Sonographic and 3T-MRI-based evaluation of the tongue in ALS. *NeuroImage Clin.*, 2020, 26:102233.

Kwon, H., Guasch, M., Nagy, J. A., Rutkove, S. B., and Sanchez, B. New electrical impedance methods for the in situ measurement of the complex permittivity of anisotropic skeletal muscle using multipolar needles. *Sci. Rep.*, 2019a, 9(1): 3145.

Kwon, H., Nagy, J. A., Taylor, R., Rutkove, S. B., and Sanchez, B. New electrical impedance methods for the in situ measurement of the complex permittivity of anisotropic biological tissues. *Phys. Med. Biol.*, 2017, 62(22):8616–8633.

Kwon, H., de Morentin, M. M., Nagy, J. A., Rutkove, S. B., and Sanchez, B. Approximate complex electrical potential distribution in the monodomain model with unequal conductivity and relative permittivity anisotropy ratios. *Physiol. Meas.*, 2019b, 40(8):085008.

Kwon, H., Malik, W. Q., Rutkove, S. B., and Sanchez, B. Separation of subcutaneous fat from muscle in surface electrical impedance myography measurements using model component analysis. *IEEE Trans. Biomed. Eng.*, 2019c, 66(2):354–364.

McIlduff, C., Yim, S., Pacheck, A., Geisbush, T., Mijailovic, A., and Rutkove, S. B. An improved electrical impedance myography (EIM) tongue array for use in clinical trials. *Clin. Neurophysiol.*, 2016, 127(1):932–935.

Mcilduff, C. E., Yim, S. J., Pacheck, A. K., and Rutkove, S. B. Optimizing electrical impedance myography of the tongue in amyotrophic lateral sclerosis. *Muscle Nerve*, 2017, 55(4):539–543.

Nagy, J. A., DiDonato, C. J., Rutkove, S. B., and Sanchez, B. Permittivity of ex vivo healthy and diseased murine skeletal muscle from 10 kHz to 1 MHz. *Sci. Data*, 2019, 6(1):37.

Rutkove, S. B. and Sanchez, B. Electrical Impedance Methods in Neuromuscular Assessment: An Overview. *Cold Spring Harb. Perspect. Med.*, 2018, page a034405.

Sanchez, B. and Rutkove, S. B. Electrical Impedance Myography and Its Applications in Neuromuscular Disorders. *Neurotherapeutics*, 2017a, 14(1):107–118.

Sanchez, B. and Rutkove, S. B. Present Uses, Future Applications, and Technical Underpinnings of Electrical Impedance Myography. *Curr. Neurol. Neurosci. Rep.*, 2017b, 17(11):86.

Sanchez, B., Pacheck, A., and Rutkove, S. B. Guidelines to electrode positioning for human and animal electrical impedance myography research. *Sci. Rep.*, 2016, 6(1):32615.

Shellikeri, S., Yunusova, Y., Green, J. R., Pattee, G. L., Berry, J. D., Rutkove, S. B., and Zinman, L. Electrical impedance myography in the evaluation of the tongue musculature in amyotrophic lateral sclerosis. *Muscle Nerve*, 2015, 52(4):584–91.

Solomon, N. P. Assessment of tongue weakness and fatigue. *Int. J. Orofac. Myol.*, 2004, 30:8–19.

Tankisi, H., Otto, M., Pugdahl, K., and Fuglsang-Frederiksen, A. Spontaneous electromyographic activity of the tongue in amyotrophic lateral sclerosis. *Muscle Nerve*, 2013, 48(2):296–298.

Wright, R. and Jordan, C. Videofluoroscopic evaluation of dysphagia in motor neurone disease with modified barium swallow. *Palliat. Med.*, 1997, 11(1):44–48.

Yamanaka, G., Goto, K., Matsumura, T., Funakoshi, M., Komori, T., Hayashi, Y. K., and Arahata, K. Tongue atrophy in facioscapulohumeral muscular dystrophy. *Neurology*, 2001, 57(4):733–735.

Yunusova, Y., Plowman, E. K., Green, J. R., Barnett, C., and Bede, P. Clinical Measures of Bulbar Dysfunction in ALS. *Front. Neurol.*, 2019, 10:106.

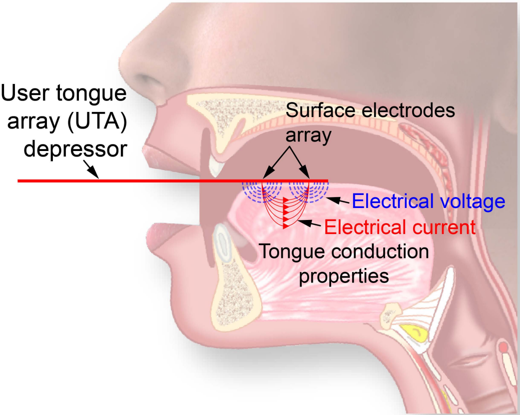
Figure captions

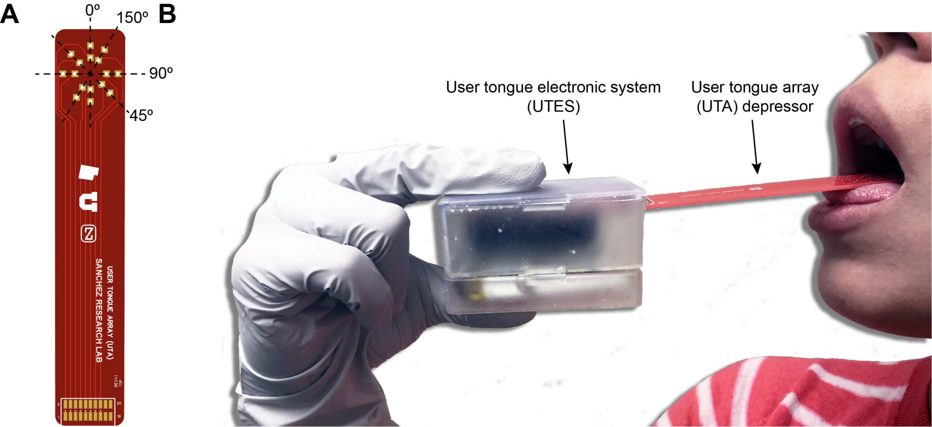
Figure 1. Illustration of the technology developed called user tongue array (UTA) depressor for in vivo assessment of tongue volume conduction properties.

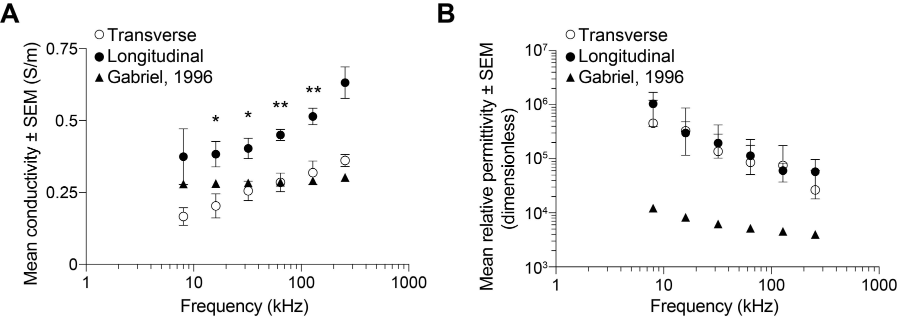
Figure 2. (A) Detail of the tongue depressor and dimensions. (B) Example of measurement of the tongue electrical conduction study with the depressor connected to the recording device called user tongue electronic system (UTES).

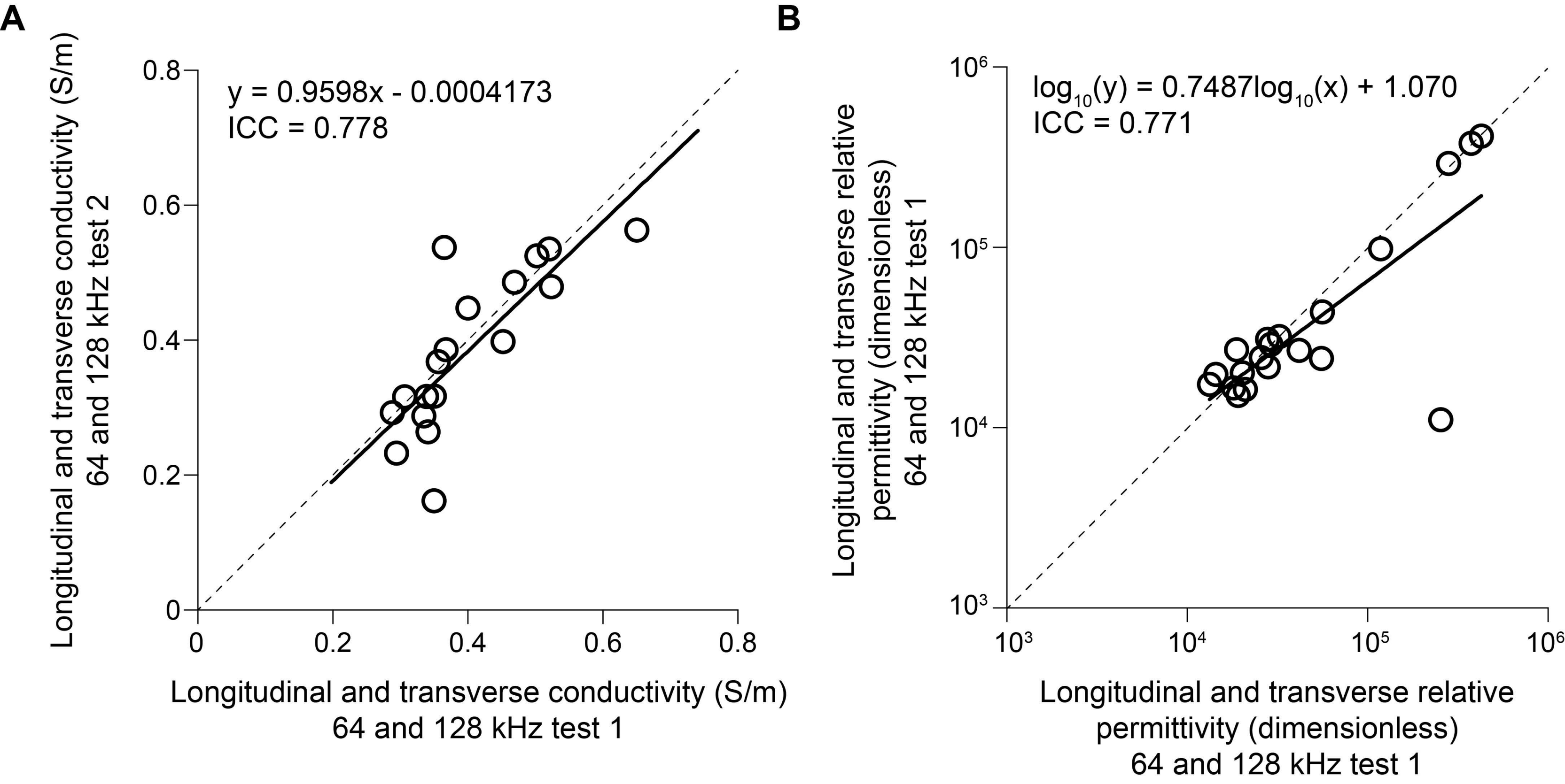
Figure 3. In vivo volume conduction properties of healthy human tongue: conductivity (A) and relative permittivity (B) in longitudinal and transverse directions. Mean ± standard error of the mean (SEM). Significance: *, $p<0.05$; **, $p<0.01$.

Figure 4. Test versus retest reproducibility of conductivity (A) and relative permittivity (B) at selected frequencies. ICC, intraclass correlation.


User tongue array (UTA) depressor
Surface electrodes array
Electrical voltage
Electrical current
Tongue conduction properties


A
0º
150º
90º
45º
USER TONGUE ARRAY (UTA)
SANCHEZ RESEARCH LAB
REV1.1
TOP
2
20
1
19
B
User tongue electronic system
(UTES)
User tongue array
(UTA) depressor


A
○ Transverse
● Longitudinal
▲ Gabriel, 1996
Mean conductivity ± SEM (S/m)
0.75
0.5
0.25
0
*
*
**
**
1
10
100
1000
Frequency (kHz)
B
○ Transverse
● Longitudinal
▲ Gabriel, 1996
Mean relative permittivity ± SEM (dimensionless)
10^7
10^6
10^5
10^4
10^3
1
10
100
1000
Frequency (kHz)


A
Longitudinal and transverse conductivity (S/m)
64 and 128 kHz test 2
y = 0.9598x - 0.0004173
ICC = 0.778
0.8
0.6
0.4
0.2
0
0
0.2
0.4
0.6
0.8
Longitudinal and transverse conductivity (S/m)
64 and 128 kHz test 1
B
Longitudinal and transverse relative permittivity (dimensionless)
64 and 128 kHz test 1
$\log_{10}(y) = 0.7487\log_{10}(x) + 1.070$
ICC = 0.771
10^6
10^5
10^4
10^3
10^3
10^4
10^5
10^6
Longitudinal and transverse relative permittivity (dimensionless)
64 and 128 kHz test 1