

Exploratory Analysis of Brainstem fMRI Data During Sustained Phonation

Carey Smith¹, Hu Cheng¹, Pertti Palo², Daniel Aalto², Steven M. Lulich¹

¹Indiana University

²University of Alberta

cjs3@iu.edu, hucheng@u.edu, pertti.palo@taurlin.org, aalto@ualberta.ca, slulich@iu.edu

Abstract

Very little work has been done on functional imaging of the cranial nerve nuclei in the brainstem in the context of motor control. This study is a preliminary step in understanding the functional organization and involvement of the brainstem during speech motor control. We aim to identify the impact of using contrastive sustained phonation tasks in isolating activation patterns. We provide preliminary observations of activation patterns in the cranial nerve nuclei. In the study 4 participants performed sustained phonation of [a] and [i] for 15 seconds, repeated over 12 trials. Phonation of [a] resulted in greater activation in the upper pons, in the vicinity of the trigeminal nucleus, compared to [i]. Phonation of [i] elicited activation more anterior and inferior, consistent with expected locations of the facial nucleus. Both phonemes resulted in activation in the medulla, consistent with the expected location of the hypoglossal nucleus.

Index Terms: neuroimaging, brainstem, speech motor control, sustained phonation, vowel production, fMRI, cranial nerve nuclei

1. Introduction

The brainstem forms a bridge between the cerebral hemispheres, the cerebellum, and the spinal cord. It is home to nuclei of the somatosensory and motor nerve tracts that ultimately control the body, and it is crucial for maintaining vital functions of the human body, including respiration and swallowing, as well as being essential in speech motor control [1-5].

Magnetic Resonance Imaging (MRI) has provided insight into structural analysis of the brainstem and cranial nerves. This methodology has allowed for high resolution imaging of soft tissues with greater contrast between cerebrospinal fluid and solid structures [5-9]. Landmarks have been established for many cranial nerve nuclei relevant to speech production, including the trigeminal nerve (CN V), the facial nerve (CN VII), and the hypoglossal nerve (CN XII) [2, 6, 8, 11, 12]. The trigeminal nerve, which innervates the jaw and floor of mouth muscles, originates from the dorsolateral pontine tegmentum; and the facial nerve, which innervates muscles in the face, pharynx, and lips, originates from the ventrolateral pontine tegmentum [6], [5, 13-18]. The nucleus of the hypoglossal nerve, responsible for motor control of the tongue, is located in the posterior portion of the medulla in a structure called the hypoglossal trigone [5, 13, 19-21]. These landmarks are visualized in Figure 1.

Sustained phonation requires careful coordination of laryngeal and respiratory subsystems and serves as a model for speech production. Studies using full brain fMRI detail cortical and subcortical networks underlying motor control during

phonation [24-30]. In particular, periaqueductal grey (PAG) in the brainstem shows concurrent activity with ventral laryngeal motor area in the cortex [27]. However, fMRI studies using sustained phonation tasks have not reported activity patterns within the medulla [24]. Structures in the brainstem are small and tightly packed, making it difficult to distinguish them [28], [29]. The brainstem is also subject to greater physiological noise interference due to the large arteries that lie in parallel to it [28]. However, recent connectivity analysis of brainstem shows that resting state fMRI with 3T scanners is sufficient to reveal functional units [30]. Due to the challenges, only a few studies have attempted to image brainstem activity during oral-motor activity, with a focus on isolating cranial nerve nuclei. In one study, activation was observed on the dorsal surface of the medulla during isometric tongue elevation exercises, consistent with the location of the hypoglossal nucleus [31].

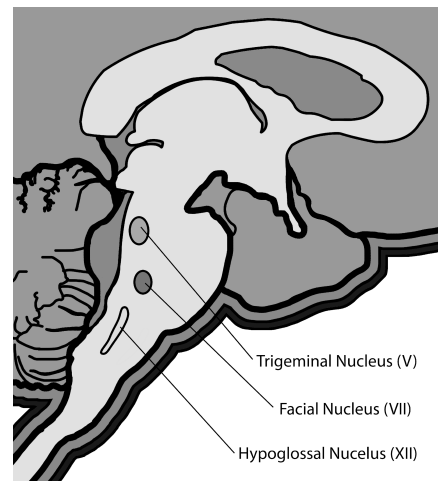


Figure 1: Location of trigeminal nucleus, facial nucleus, and hypoglossal nucleus, adapted from Sharma [22] and Marieb and Hoehn [23].

In 2002, Komisaruk and colleagues studied 7 healthy adults performing a variety of sensory and motor tasks to functionally map facial and oral innervation. The motor tasks relevant to speech production included smiling and puckering lips, tongue elevation against the hard palate, and swallowing. They found activation in the facial motor nucleus (CN VII) during smiling and puckering, the hypoglossal nucleus (CN XII) during tongue elevation against the hard palate, and the nucleus ambiguus (CN IX and CN X) during swallowing [29].

Given the limited research that has been done previously in functional brainstem anatomy related to speech motor control,

there are many unknowns. Komisaruk and colleagues report significant variability in activation; across participants, an average of 48% tasks elicited no observable activation in the expected brain region [29]. Furthermore, while nuclei can be visualized in functional activity, no previous work has attempted to contrast activation within the nucleus based on task. Moreover, as the only study that has focused on identifying cranial nerve nuclei across multiple oropharyngeal motor tasks, Komisaruk and colleagues faced a number of methodological challenges, the resolution of which may provide new avenues for research. This previous study utilized a 1.5T magnet, with a 4 millimeter voxel resolution. And the significance of their findings may be less certain, as they did not use smoothing or cluster thresholds to minimize the effect of artifacts [29].

Therefore, this study aims to address the following questions:

- 1) to identify the effectiveness of using contrastive sustained phonation tasks to elicit brainstem activation
- 2) to provide a preliminary observation of the activation patterns in the cranial nerve nuclei during vowel phonation.

We expect that utilizing sustained phonation tasks during high resolution imaging will result in more consistent activation compared to prior work, and that this will provide insight into the differential activation of nuclei based on which muscles are needed in order to approximate the target vowel.

To our knowledge, this study is the first to capture brainstem activation during sustained phonation, and therefore this study aims to further understanding of neuromotor control of speech. Additionally, this study aims to contribute to functional neuroimaging methodology in speech science by advancing mechanisms for acquiring and analyzing data in the brainstem.

2. Methods

2.1. Data Collection

Four participants are included in this study ($F = 3$, $M = 1$). Data was collected as part of a larger study on brainstem activation in simple speech gestures. Participants were included in the study if they were between the ages of 18 and 25 years old, right handed, and native speakers of English. Participants were screened by a staff member of the Indiana University Imaging Research Facility for safety prior to beginning the study. The protocol was approved by the Indiana University Institutional Review Board and all participants provided written informed consent upon enrollment.

A block design protocol was used. Participants produced sustained phonation of vowels [a] and [i] for 15 seconds, alternating with 15 seconds of rest, during which participants held their tongue lightly against the hard palate, with their teeth and lips closed. Phonation conditions were counterbalanced, using ABBA counterbalancing, where participants were presented with trials in the order of [a], [i], [i], [a] for the first block, and [i], [a], [a], [i] in the subsequent block. Each block lasted 2 minutes, and participants completed a total of 6 blocks. Tasks were alternated with other lingual motor tasks, which were excluded from this analysis.

Participants were instructed to keep articulators in place if they needed to stop and breathe during phonation. Participants were given an opportunity to practice all tasks prior to beginning the

study and were observed by an investigator to make certain they performed the tasks correctly. A brief T1 scan at the beginning of the study was also used to confirm that all participants were performing tasks accurately and consistently in the scanner.

Scanning was conducted on a 3T Prisma scanner using a 64-channel head/neck coil. A high resolution (0.8 mm isotropic resolution) T1-weighted anatomical image was acquired using the MP2RAGE pulse sequence ($TR/TE = 5000/2.98$ ms, $TI1 = 700$ ms, $TI2 = 2500$ ms). The fMRI scan utilized a fast imaging technique of simultaneous multi-slice echo-planar imaging (EPI) with acceleration factor of 6 ($TR/TE = 470/30$ ms, and flip angle = 46, 2 mm isotropic resolution) to minimize aliasing of physiological noise from cardiac pulsation and respiration. Additionally, a pair of spin-echo EPI images with opposite phase-encoding directions was acquired to calculate the field map for distortion correction of the EPI images.

2.2. Data Analysis

Data was analysed using Blood Oxygen Level Dependent (BOLD) response during [a] and [i] phonation. The functional images were distortion-corrected using TOPUP and APPLYTOPUP in FSL [32-34], and then preprocessed using SPM12 [35], including coregistration to the T1w image, and Gaussian smoothing with a 4 mm kernel. A general linear model (GLM) was applied in SPM12 to obtain participant-level contrasts of activation during phonation of [a] compared to [i] (i.e. [a] activation greater than [i] activation) and activation during phonation of [i] compared to [a] (i.e. [i] activation greater than [a] activation). The estimated motion parameters, including three translational (x, y, z) and three rotational (pitch, roll, yaw) parameters, were used in the GLM to account for residual motion-related variance. The first-level statistics were carried out by setting the α -value to 0.05, with family-wise error (FWE) correction. Clusters of fewer than 10 voxels were removed from analysis. A threshold of 10 was deemed appropriate given the size of the brainstem.

3. Results

3.1. Activation of the brainstem during phonation ([a]>[i])

Phonation of [a] resulted in significantly greater activation along the dorsal and medial portions of the pons compared to [i] in Participants 1 and 2, and activation along the dorsal portion of the medulla in all 4 participants.

Images representing activation patterns for phonation of [a] compared to [i] can be seen in Figures 2-5. Dashed yellow lines in the sagittal plane identify location of axial slices. Statistics for clusters at each level are included in the caption.

3.2. Activation of the brainstem during phonation ([i]>[a])

Participants 1 and 3 demonstrated increased BOLD response in the medial pons in [i] compared to [a]. All participants exhibited increased activation in the medulla in [i] compared to [a].

Images representing activation patterns for phonation of [i] compared to [a] can be seen in Figures 6-9. The slices have been cropped to focus on areas of activation. Dashed yellow

lines in the sagittal plane identify location of axial slices. Statistics for clusters at each level are included in the caption.

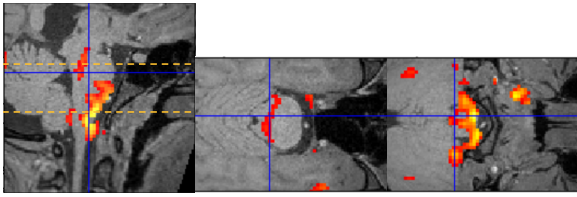


Figure 2: Areas of increased activation during phonation of [a] compared to [i] in Participant 1. ($k_1 = 16$, $T = 9.86$); ($k_2 = 14$, $T = 9.95$).

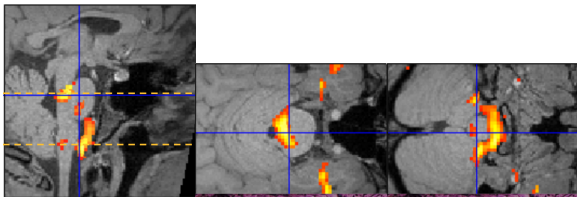


Figure 3: Areas of increased activation during phonation of [a] compared to [i] in Participant 2. ($k_1 = 28$, $T = 14.8$); ($k_2 = 17$, $T = 8.01$).

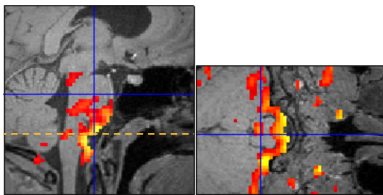


Figure 4: Areas of increased activation during phonation of [a] compared to [i] in Participant 3. ($k = 22$, $T = 16.71$).

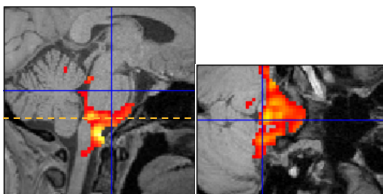


Figure 5: Areas of increased activation during phonation of [a] compared to [i] in Participant 4. ($k = 17$, $T = 16.14$).

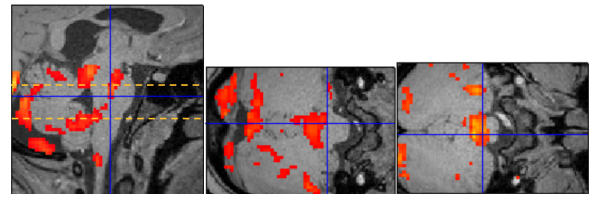


Figure 6: Areas of increased activation during phonation of [i] compared to [a] in Participant 1. ($k_1 = 26$, $T = 11.65$); ($k_2 = 20$, $T = 8.80$).

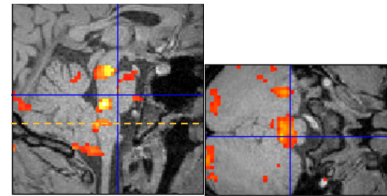


Figure 7: Areas of increased activation during phonation of [i] compared to [a] in Participant 2. ($k = 26$, $T = 11.31$).

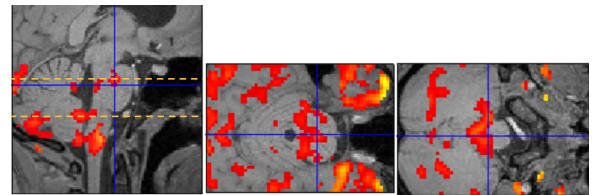


Figure 8: Areas of increased activation during phonation of [i] compared to [a] in Participant 3. ($k_1 = 21$, $T = 12.13$); ($k_2 = 17$, $T = 11.08$).

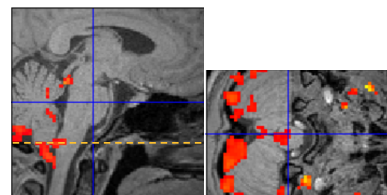


Figure 9: Areas of increased activation during phonation of [i] compared to [a] in Participant 4. ($k = 23$, $T = 8.6$).

4. Discussion

Similar to the findings by Komisaruk and colleagues [29], brainstem activations vary between the four participants in this study.

A number of analyses revealed significant activation in the anterior portion of the medulla. Before correcting for family-wise error, these clusters extend dorsally and may represent activation in the nucleus ambiguus or the hypoglossal nucleus. Alternatively, the pattern could result from an imaging artifact due to the proximity of the vertebral arteries. As functional MRI data is interpreted based on regional blood flow, the presence of a large artery may appear as significant clusters of activation [36]. Therefore, we are not considering these clusters as confidently representing brainstem activation at this time.

Although participants did complete a rest condition, these conditions were not included in analysis. We expected no significant activation during these conditions in comparison to phonation tasks, but found that the BOLD response was stronger and more variable than expected. This may be the result of confounds related to oxygenation during sustained phonation [37]. Another possibility is that 15-second sustain of phonation may be demanding, and additional time may be required to return to baseline and be at true rest.

When comparing the BOLD response that was greater for [a] phonation to the expected cranial nerve nuclei locations illustrated in Figure 1, the activation pattern observed in the pons for Participants 1 and 2 may be consistent with the location of the trigeminal nerve nucleus. The lowering of the jaw to produce the low, back vowel [a] may account for this possible activation in the trigeminal nucleus. The trigeminal nerve nucleus may also be activated for the vowel [i], but our findings suggest greater activation in [a] than [i].

Similarly, greater activation during [i] production is present in a region that may be consistent with the facial nerve nucleus for Participants 1 and 3. Komisaruk and colleagues observed activation in this nucleus during smiling and puckering, and the articulation of [i] requires lip retraction similar to smiling [29]. The facial nerve nucleus may also be activated for the vowel [a], but our findings suggest greater activation in [i] than [a].

All participants demonstrated activation in the medulla during phonation of both [a] and [i]. When compared to the regions in Figure 1, this activation of the medulla may be consistent with the location of the hypoglossal nerve. The hypoglossal nerve is involved in motor control of the tongue, which suggests it should be active across phonation tasks. In Participants 1-3, activation was generally more amplified and more consistent during [i] phonation than during [a] phonation. Komisaruk and colleagues found hypoglossal activity during lingual elevation, so this may suggest that a high, front vowel would be characterized by greater hypoglossal involvement [29], even if [a] also involves the hypoglossal nerve nucleus.

The first aim of this study was to identify how effective contrastive phonation tasks may be for functional brainstem imaging. In comparison to Komisaruk and colleagues findings, which successfully elicited an observable response in about 48% of runs, 100% of contrastive sustained phonation produced significant outcomes. Given the challenges of brainstem imaging and the small sample size, we took measures to reduce the risk of Type I errors by including only clusters greater than 10 voxels. Despite these restrictions on interpretation, this protocol has elicited several interpretable patterns of activation. In addition to improved sensitivity in eliciting brainstem

activation compared to prior work, these data are resilient to smoothing, error correction, and thresholding, further supporting the use of contrastive phonation tasks in future work.

The second aim of this study was to provide a preliminary observation of activation patterns in the cranial nerve nuclei. We can describe activation during [a] phonation in the pons in the vicinity of the trigeminal nerve nucleus, and activation during [i] phonation in the vicinity of the facial nerve nucleus. Activation during both [a] and [i] was also observed in the posterior medulla, consistent with the expected location of the hypoglossal nerve nucleus. These findings are consistent with prior functional data of lingual, labial, and mandibular motor control, but they allow new insight into the differential patterns of motor control of similar tasks [29].

This study has several limitations. The sample is very small, and we did not conduct any group-level analyses to observe for patterns of activation across participants. The results are characterized by high individual variability, and the brainstem is notoriously susceptible to artifactual interference. Furthermore, these analyses are limited to contrastive patterns of activation and do not fully explain all of the activity in the brainstem during each task.

This is part of an ongoing larger study of brainstem activity in speech. Future work will include larger sample sizes, including group-level analysis, and will incorporate additional tasks to both mitigate any task effects and further explore nuclear control of oral gestures.

5. Conclusions

The brainstem is an important structure for speech motor control, as well as maintaining life-support. However, due to challenges in measuring functional activity in the brainstem, most fMRI studies have not focused on the brainstem. This study aimed to advance understanding of the cranial nerve nuclei in speech motor control, as well as methods in studying these nuclei. We find BOLD response in the brainstem similar to those found in tongue and lip activity done in prior work, and we find contrastive differences in phonation of [a] versus [i]. The result of this preliminary analysis suggests that with high resolution imaging and distortion correction, robust clusters of functional activation in the brainstem can be measured and interpreted.

6. References

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