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Ashwini Joshi

University of Kentucky, 22.ashwini@gmail.com

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ABSTRACT OF DISSERTATION

ASHWINI JOSHI

THE GRADUATE SCHOOL
UNIVERSITY OF KENTUCKY

2011

CENTRAL NEURAL AND BEHAVIORAL CORRELATES OF VOICE SECONDARY
TO INDUCED UNILATERAL VOCAL FOLD PARALYSIS

ABSTRACT OF DISSERTATION

A dissertation submitted in partial fulfillment of the
requirements for the degree of Doctor of Philosophy in the
College of Health Sciences
at the University of Kentucky

By
Ashwini Joshi

Lexington, Kentucky

Co-Directors: Dr. Joseph C. Stemple, Professor of Communication Sciences and
Disorders

and Dr. Patrick Kitzman, Associate Professor of Physical Therapy
Lexington, Kentucky

2011

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ABSTRACT OF DISSERTATION

CENTRAL NEURAL AND BEHAVIORAL CORRELATES OF VOICE SECONDARY TO INDUCED UNILATERAL VOCAL FOLD PARALYSIS

Understanding the involvement of the central nervous system (CNS) in voice production is essential to incorporating principles of neuroplasticity into therapeutic practice for voice disorders. Early steps to attaining this goal require the identification of specific neural biomarkers of the changes occurring in the CNS from a voice disorder and its subsequent treatment. In the absence of an adequate animal vocalization model, the larynx has not been acutely and reversibly perturbed to concurrently examine the effect on both peripheral and central processing of the altered input/output.

Using a unique, reversible perturbation approach, it was the purpose of this study to perturb the larynx to mimic a voice disorder and study short-term neuroplastic response. Functional magnetic resonance imaging (fMRI) was the neuroimaging tool of choice for this study due to its superior spatial and temporal resolution. The voice was perturbed by anesthetizing the right recurrent laryngeal nerve, with a solution of lidocaine hydrochloride and epinephrine to induce a temporary right vocal fold paralysis. The paralysis lasted for approximately 90 minutes and had an overt presentation similar to that of a true vocal fold paralysis. Behavioral and fMRI data were obtained at three time points- baseline, during the vocal fold paralysis and one hour after recovery.

Patterns of activity on fMRI during the three time points were found to be distinct on both subjective examination and statistical analysis. The regions of interest examined had distinct trends in activity as a function of the paralysis. Interestingly, males and females responded differently to the paralysis and its subsequent recovery. Strong correlation was not observed between the behavioral measures and fMRI activity reflecting a disparity between the overt presentation and recovery of vocal fold paralysis and cortical activity as seen on fMRI.

The fictive paralysis model employed in this study provided a perturbation model for phonation that allowed us to examine behavioral and central neural correlates for disordered phonation in a controlled environment. Although this data is representative of acute changes from a transient paralysis, it provides an insight into the response of the cortex to sudden perturbation at the peripheral phonatory mechanism.

Key words: Voice production, Vocal fold paralysis, FMRI, Perturbation model, Neuroplasticity

Ashwini Joshi

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By

Ashwini Joshi

Joseph C. Stemple
Director of Dissertation

Patrick H. Kitzman
Director of Graduate Studies

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CHAPTER 1 : INTRODUCTION

Voice production and voice disorders were described as early as 700 BC in ancient Hindu writings. The earliest descriptions of laryngeal anatomy followed much later during the Renaissance through exquisite carvings and drawings of laryngeal structures by the great anatomists/artists of the period.¹ Over the past many centuries significant advancement has been made in the understanding of the vocal tract mechanism as well as in evaluation methods and treatments of disorders pertaining to this mechanism. The working of the peripheral systems involved in voice production, respiratory, phonatory, and resonance systems, have been well studied providing us with an in-depth knowledge about their interactions in the production of normal voice quality.²⁻⁸

The unique nature of human voice production used for communication and artistic endeavors has drawn interest and attention from diverse specialties. Laryngologists, speech language pathologists, singing teachers, voice coaches, and communication specialists have all studied voice from their various perspectives. Study by those in the health sciences has led to an understanding of the pathophysiology of various voice disorders at the peripheral level. This understanding has led to a variety of well-established treatment options for voice disorders including, medical,^{9, 10} surgical,¹¹⁻¹⁴ and behavioral treatment^{1, 15, 16} approaches. These approaches have yielded a large body of data related to the peripheral presentation of voice disorders as indicated on various measures including auditory and visual perceptual measures, acoustic and aerodynamic assessments, and patient self-assessment tools.

Lacking in the knowledge of voice production is an understanding of the role of the central nervous system (CNS) in voice production. The absence of an appropriate animal model that is truly representative of human vocalization is largely responsible for the latency in research of this central laryngeal representation. With the advent of neuroimaging techniques and improved methodology, studies that provide insight into the functioning of the brain's cortical and subcortical systems during voice production have started to emerge.

Understanding the involvement of the CNS in voice production is essential to incorporating principles of neuroplasticity into therapeutic practice for the treatment of voice disorders. This line of research in individuals with limb paralysis lead to the development of constraint-induced therapy for patients with hemiparesis after a cerebrovascular accident based on principles of neuroplasticity has brought about significant benefits to this population. Motor cortex plasticity was observed first in the non-human primate and then in the human by constraining the healthy limb and performing intensive treatment for the paretic limb.¹⁷⁻²³

Transcranial magnetic stimulation and direct current stimulation have been used therapeutically using neuroplastic principles in patients with stroke and traumatic brain injury for optimal rehabilitation by physical therapists.²⁴ Similarly, a synthesis of the knowledge of the peripheral laryngeal mechanism with principles of neuroplasticity will solidify therapeutic benefits allowing for longer term maintenance of the newly learned voice production skills secondary to an injury or disease. Early steps to attaining this goal require the identification of specific neural indicators or biomarkers of the changes occurring in the CNS from a voice disorder and its subsequent treatment. These

biomarkers then have to be examined across various voice disorders pre and post treatment. Neuroplastic changes will have to be compared longitudinally across different treatment modalities and as a combination of different treatment modalities to develop a cause-effect relationship between voice disorders, subsequent treatment and neuroplastic changes. This will aid in developing new treatment strategies and modifying current methods for long term maintenance of clinical gains.

Preliminary information available about Parkinson's disease,^{25, 26} spasmodic dysphonia,²⁷⁻²⁹ and unilateral vocal fold paralysis³⁰ demonstrates the potential of the human brain to change its functional topography secondary to a peripheral perturbation such as a voice disorder, and as a function of treatment for these disorders. These early data, however are yet to provide us with an understanding of a broad spectrum of commonly occurring voice disorders. One barrier to understanding the contribution of the CNS to voice production is a lack of mechanistic details of the CNS for voice disorders and consequent treatment. These details are critical to 1) the understanding of these disorders, 2) the system-wide effects of medical, surgical and behavioral treatment on these disorders and 3) to aid in further development of treatment methods. The lack of homogeneity in population demographics, etiology, symptomatology, treatment options and outcomes for voice disorders has been another barrier in the study of central laryngeal representations in voice production.

The human anatomy makes it difficult to externally perturb the larynx in a controlled manner without causing permanent damage to the mechanism. Perturbation models have been used extensively in studies of speech production to investigate the compensatory processes, feed-forward and feedback mechanisms that occur as a result of

the unexpected disruption of function.³¹⁻³⁵ In the absence of an adequate animal vocalization model, the larynx has not been acutely and reversibly perturbed to examine the effect on both peripheral and central processing of the altered input/output. Based on previous animal and human studies on the effects of sensorimotor perturbation to the limbs and the preliminary data on voice disorders, we know that the modulation in sensorimotor input brings about significant central neuroplastic changes. Using a unique, reversible perturbation approach, it was the purpose of this study to similarly perturb the larynx to mimic a voice disorder and study short-term neuroplastic responses. Functional magnetic resonance imaging (fMRI) was the neuroimaging tool of choice for this study due to its superior spatial and temporal resolution in the absence of radiation exposure, allowing repeated multiple measurements.

The voice was perturbed by anesthetizing the right recurrent laryngeal nerve (RLN), with a solution of lidocaine hydrochloride and epinephrine to induce a temporary right vocal fold paralysis. The paralysis lasted for approximately 90 minutes and had an overt presentation similar to that of a true vocal fold paralysis. Behavioral and fMRI data were obtained at three time points- prior to the paralysis (baseline), during the induced unilateral vocal fold paralysis (iUVFP) and one hour after recovery from the paralysis, indicated by visualization of the vocal folds, perceptually normal voice quality and participant self-report.

The behavioral data collected included auditory-perceptual ratings using the Consensus Auditory Perceptual Evaluation of Voice (CAPE-V);³⁶ acoustic measures for noise to harmonic ratio; aerodynamic measures for subglottal pressure and laryngeal airway resistance and; visualization using videostroboscopy to assess laryngeal structure

and function as well as glottal gap size at the three time points. FMRI data was analyzed using the Analysis of Functional Neuroimaging (AFNI)³⁷ to examine task dependent change in overall cortical activity and percentage change in blood oxygen level in sensorimotor regions of interest.

The results of this study will direct understanding of the neuroplastic events that occur surrounding the onset and resolution of dysphonia as a consequence of controlled perturbation to the laryngeal sensorimotor environment on a compressed time scale. A future comparison of this data to that from a population with true UVFP will provide more detailed information about the time scale required for neuroplasticity as well as the window of time available to maximize recovery with treatment.

This chapter was intended to provide the reader with an overview of the significance and methods used in this study. The next chapter provides a more detailed review of literature pertinent to this study in the areas of neuroimaging and voice disorders as well as neuroplasticity as a consequence of peripheral sensorimotor perturbation.

CHAPTER 2 : REVIEW OF LITERATURE

INTRODUCTION

This chapter will review pertinent literature in the domains of vocal fold paralysis and neuroplasticity secondary to sensorimotor perturbation, followed by the purpose and hypotheses for this study. First, a brief overview will be provided to inform the reader on laryngeal anatomy as it relates to vocal fold paralysis; assessment and treatment of vocal fold paralysis, and a review of studies that have induced vocal fold paralysis for research purposes. The second section will review literature pertinent to sensorimotor neuroplasticity and will include studies that have identified central representations of the larynx and the disordered voice, as well as a review of neuroplastic events that occur as a consequence of peripheral perturbation in animal models and humans. The chapter concludes with a discussion on the implications of the current study.

UNILATERAL VOCAL FOLD PARALYSIS

Vocal fold paralysis is one of the most common pathologies associated with voice disorders in treatment seeking populations.³⁸ It has been defined as the acquired immobility in one or both vocal folds resulting from damage to the peripheral nervous system.¹⁵ The focus of this review and study is on unilateral vocal fold paralysis (UVFP).

Voice quality resulting from UVFP can be severely disturbed causing various degrees of hoarseness and a significant increase in effort to produce voice. Causes and treatments for adductor UVFP vary among individuals based on multiple factors such as degree of hoarseness, presence of dysphagia and the effect of the UVFP on the individual's quality of life.³⁹ This section provides a review of the laryngeal anatomy and

physiology involved in UVFP, etiology, presentation, assessment, and treatment of this common disorder.

Relevant anatomy and physiology of the larynx

A basic understanding of the laryngeal muscle anatomy and innervation is necessary to appreciate the effect of vocal fold paralysis on the voice. The larynx is encapsulated by nine cartilages, one bone and includes ligaments, membranes and, extrinsic and intrinsic laryngeal muscles. The thirteen intrinsic muscles have their origin and insertion on the cricoid, thyroid and arytenoid cartilages. They act in harmony during phonation, respiration and airway protection.⁴⁰

Vocal folds are a pair of five layered folds with the bulk formed by the thyroarytenoid muscle (TA) with attachments to the thyroid cartilage anteriorly and the vocal processes of the arytenoid cartilages posteriorly. The posterior cricoarytenoid (PCA), paired muscles situated on the posterior larynx, are the sole abductors of the vocal folds. When the PCA contracts, the vocal processes of the arytenoid cartilages swing laterally, abducting the vocal folds thus, opening the glottis.⁴⁰ The TA, lateral cricoarytenoid (LCA) and interarytenoid (IA) muscles function as adductors of the vocal folds and together work to close the glottis during phonation and airway protection. The TA is the intrinsic relaxer of the vocal folds and is an antagonist, co-contracting with the cricothyroid (CT) to change vocal pitch. The CT rocks the thyroid cartilage closer to the cricoid ring causing the vocal folds to stretch and tense resulting in an increase in vocal pitch.⁴⁰

Sensory innervation to the larynx is supplied by the internal branch of the superior laryngeal nerve (iSLN). The PCA, TA, LCA and IA all receive motor innervation by the recurrent laryngeal nerve (RLN), while the CT is innervated by the external branch of the SLN (eSLN).⁴⁰ A unilateral or bilateral lesion to one or both of these nerve branches may lead to paralysis of one or more muscles innervated by them. This causes vocal fold paralysis with varying severity based on the site and extent of the lesion.

Etiology

Vocal fold paralysis can be caused by factors ranging from concomitant disease processes, vagus nerve, RLN, SLN lesions, trauma, neuritis and idiopathic causes.⁴¹ Iatrogenic injuries during thyroidectomy, cardiac surgery, tonsillectomy, carotid endarterectomy, anterior approach to cervical fusion and difficult intubation during surgeries can cause UVFP as well. Thyroidectomy is one of the most common surgeries causing UVFP.⁴¹ In their study, Havas et al. found iatrogenic injury to be the leading cause of UVFP followed by neoplasms with a large number of patients presenting with idiopathic UVFP.⁴²

Signs and symptoms of UVFP

With a UVFP secondary to RLN damage, the paralyzed vocal fold is often unable to approximate to the midline causing a glottal gap upon phonation. The resultant change in the vocal fold due to paralysis of the RLN leads to flaccidity and improper vertical positioning of this vocal fold which in turn causes asymmetric vocal fold vibration. The glottal gap during phonation is responsible for the paralytic voice characterized by breathiness, hoarseness, roughness, diplophonia and reduced pitch and loudness

dynamics.⁴³ Symptoms may vary from mild to severe depending on the distance of the paralyzed vocal fold from midline. The increased loss of air during phonation can cause vocal fatigue and substantially increased effort during speech.¹⁵ The increased glottal gap reduces the protection provided by the adduction of the vocal folds for swallowing causing aspiration and dysphagia in some cases.

Unilateral paralysis of the SLN leads to unequal rocking of the CT joints causing an overlap of the folds or an oblique positioning.⁴³ This positioning limits glottic closure during vocal fold vibration and decreases the ability to build subglottic air pressure necessary to drive the vocal folds when producing voice. Symptoms in unilateral SLN paralysis involve mainly reduction in the control of pitch, vocal fatigue and the inability to sing.⁴³ For the purposes of this study, we will focus on UVFP caused by RLN paralysis as the paralysis will be pharmacologically induced in the right RLN.

Assessment

Voice assessment methods have traditionally been classified into five domains: auditory- perceptual measures, acoustic and aerodynamic analysis of the voice, visualization of the vocal folds and patient self-assessment. A patient with vocal fold paralysis typically undergoes assessment in each of these five areas. *Auditory perceptual assessment* involves the clinician's perception of the patient's voice. The clinician may use a rating scale in the form of an equal appearing interval (EAI), visual analog scale (VAS) or direct magnitude estimation (DME).⁴⁴⁻⁴⁹ The pitch, loudness and quality of the patient's voice are rated using one of these scales. A patient with unilateral adductor vocal fold paralysis may show signs of reduced phonational range, reduced intensity and

intensity range, increased breathiness,⁵⁰ hoarseness, roughness and intermittent diplophonia.^{43, 50} The Consensus Auditory Perceptual Evaluation of Voice (CAPE-V) will be used in this study.^{36, 51} This visual analog scale validated by the American Speech-Language-Hearing Association provides information on the overall severity, roughness, breathiness, strain, pitch and loudness.⁵¹

Acoustic analysis of voice is achieved by measuring the voice signal using a microphone to electronically transduce voice into an acoustic signal, that is analyzed using specialized instruments or computer software.^{52, 53} Multiple measures related to frequency (fundamental frequency, frequency range, jitter), intensity (average speaking intensity, shimmer) and signal- to- noise ratios (noise-to-harmonic ratios) are calculated. The definitions of these measures are as follows:

Fundamental frequency (F_0): Acoustic correlate of pitch and represents the number of vibrations of the vocal folds per second. It is measured in Hertz (Hz).⁴⁴ Adult males have an average F_0 of 106 Hz (range from 77 Hz to 482 Hz) and adult females have an average F_0 of 193 Hz (range of 137 Hz to 634 Hz).⁵⁴

Frequency range: Difference between the highest and lowest frequency a person can produce. It is measured in Hz or semitones.⁴⁴ Both adult males and females have been found to have a range of 24 to 36 semitones.⁴⁴

Jitter: Measure of pitch perturbation and is the cycle-to-cycle variation in frequency. It may be measured in percentage (%) of mean cycle-to-cycle perturbation in frequency to the mean overall frequency of the voice signal.^{44, 55} A jitter of < 1% is considered normal.^{56, 57}

Average speaking intensity: Acoustic correlate of loudness and is measured in dB SPL.¹ Adult males have an average speaking intensity of 70 dB (range from < 60 - 110 dB) and females have an average intensity of 68 dB (range <60 - 106 dB).⁵⁴

Shimmer: Measure of amplitude perturbation and reflects the cycle-to-cycle variation in amplitude. It is measured in dB.⁵⁵ An average shimmer value of <0.7 dB was described in a study by Heiberger and Horii⁵⁸ for adult males and females.⁵⁹

Noise-to-harmonic ratio (NHR): Ratio of the acoustic noise in a person's voice relative to the signal in their voice and is measured in dB.^{1,55} An average NHR of 0.112 is considered normal for adults.⁶⁰

In general, patients with UVFP may have reduced fundamental frequency, frequency range, average speaking intensity, elevated jitter and shimmer⁵³ and elevated noise-to-harmonic ratios as compared to persons with a normal voice quality.⁶¹

Aerodynamic analysis informs vocal function by measuring airflow, air pressure and lung volumes. Commonly used aerodynamic measures include mean air flow rate, maximum phonation time, subglottal pressure and laryngeal airway resistance.⁵⁵ They are defined as follows:

Mean airflow rate: Total volume of air used during phonation for the duration of the phonation. It is defined in liters/second (L/s).² An average rate of 0.119 L/s in males and 0.115 L/s in females has been reported for a normal voice quality.⁵⁴

Maximum phonation time (MPT): Maximum duration that a vowel may be sustained while using maximum airflow volume.¹ A range 15 - 30 seconds has been observed in adult males and females with normal voice quality.^{44, 62}

Subglottal pressure (P_s): Measure of air pressure beneath the vocal folds necessary to overcome the resistance of the approximated folds to initiate and maintain phonation.¹ P_s is estimated by measuring intraoral pressure during production of a voiceless plosive. Average intraoral pressure for males and females was found to be 5.91 cmH₂O and 6.09 cmH₂O respectively.⁶³

Laryngeal airway resistance (LAR): LAR is a ratio of subglottal pressure to mean flow rate and is a valuable measure of glottal efficiency.² Holmberg, Hillman and Perkel obtained an average LAR of 32.6 cm H₂O/L/sec in males and 30.8 cm H₂O/L/sec in females.⁶³

Generally, UVFP results in significant deviations from normative measures due to incomplete glottic closure. The affected measures may cause increased mean airflow rate, reduced mean air flow volume, reduced maximum phonation time, reduced subglottal pressure and reduced LAR.

Visual perceptual assessment of the vocal folds may be accomplished in a variety of ways including indirect assessment using a laryngeal mirror, flexible or rigid endoscopy for identifying pathology, videostroboscopy and high speed video imaging for assessing vocal fold vibration patterns. With the latter procedures, the symmetry of vocal fold movement, periodicity of movement, closure pattern, amplitude, mucosal wave and non- vibratory segments may be studied.⁶⁴⁻⁶⁶ Finally, *measures of self-assessment* ask

patients to provide a description of their perception of the voice problem including social, functional and physical domains. The Voice Handicap Index (VHI),⁶⁷ Voice- Related Quality of Life (V-RQOL),⁶⁸ Voice Activity and Participation Profile (VAPP)⁶⁹ and Voice Symptom Scale (VoiSS)⁷⁰ are examples of such self-assessment scales. We will not be using self-assessment measures during this study as the changes in voice occur over a short time span and would not allow the individuals to adequately experience the effect of the UVFP in the domains measured by these scales.

Treatment

Treatment for unilateral adductor vocal fold paralysis may be categorized into surgical, behavioral, or a combination of both treatments. The treatment of choice for a particular patient is dependent upon the degree of dysphonia, presence of dysphagia, patient motivation, general health status of the patient, probability of recurrent laryngeal nerve recovery and glottal configuration post paralysis.³⁹

Surgical treatment methods are aimed at restoring the tonicity, shape and position of the affected vocal fold, to reduce the glottal gap during phonation and bring about an immediate change in voice quality.⁷¹ *Behavioral treatment* or voice therapy is used to reduce the glottic gap by helping the unaffected vocal fold to cross over the midline and approximate the paralyzed vocal fold.¹⁶ The concept of behavioral treatment in UVFP is controversial due to the limited literature on this aspect of treatment. No studies have demonstrated that the normal fold actually crosses the midline of the glottis to improve glottic closure. Researchers are unsure if the changes seen in the voice are due to behavioral therapy or spontaneous recovery.⁷² However, conservative behavioral

treatment may be of benefit before surgical treatment is undertaken.⁷³ When successful, voice therapy may preclude an unnecessary surgical procedure thus, limiting the patient's exposure to surgical complications. Voice therapy may also be implemented to address hyperfunctional compensatory behaviors leading to muscle tension and vocal fatigue⁷³ secondary to the paralysis pre- or post-surgical treatment.

Although active intervention was not implemented in this study, the UVFP inducement procedure and subsequent recovery may simulate effects seen as a function of surgical treatment. The immediate improvement in voice quality seen with vocal fold augmentation and medialization is similar to that seen when the effects of anesthesia dissipates and the UVFP resolves to give normal vocal fold function. The following section reviews studies that have used this inducement procedure to paralyze the vocal fold and assess the effects of this paralysis.

Inducement of Unilateral Vocal Fold Paralysis

Injecting the RLN with a solution of lidocaine hydrochloride induces an acute UVFP (iUVFP). Lidocaine inhibits the ionic fluxes required for the initiation and conduction of impulses and thus stabilizes neuronal membranes thereby bringing about a local anesthetic effect. A solution of lidocaine hydrochloride with epinephrine is often used as epinephrine acts on the sympathetic nervous system and is an antihistamine.⁷⁴ Epinephrine acts as a vasoconstrictor, prolonging the action of the anesthetic agent by delaying the absorption of the anesthetic into the bloodstream.⁷⁵

Temporary inducement of UVFP was routinely used clinically in patients with adductor spasmodic dysphonia (ADSD), to evaluate candidacy for nerve sectioning as a

treatment for this disorder⁷⁶⁻⁸⁰ and was first described by Dedo in 1976.⁷⁶ Dedo performed the block to examine the patient's response to a UVFP, approximating the effect of the surgical technique he would consider performing. More recently, this procedure was used to experimentally induce vocal fold paralysis to study muscle tension dysphonia and the results of SLN paralysis.^{79, 81} Similar in design to the current study, ten vocally healthy volunteers received a lidocaine injection to induce paralysis of the external branch of the SLN. Behavioral measures were obtained at baseline and during paralysis for these volunteers. No complications from the lidocaine nerve block were reported in any of these studies. However, along with the RLN, the SLN and in effect, the CT muscle may also be paralyzed due to the proximity of the two nerves resulting in a globus or "lump in the throat" sensation.⁷⁶

The above section provided an overview of the anatomy and physiology relevant to UVFP, signs and symptoms, assessment, treatment and the procedure for inducement of temporary UVFP. The next section is a brief overview of neuroimaging techniques with a focus on functional MRI, the tool of choice for this study.

NEUROIMAGING TOOLS

Several methods have been developed which help observe brain activities in healthy, awake subjects.⁸²⁻⁸⁶ These methods, referred to as neuroimaging techniques, have led to considerable advancement in cognitive and behavioral neuroscience and have provided a reliable way of mapping human brain activities and in determining areas that are activated during various tasks.⁸⁷ Neuroimaging techniques are of two basic types- structural and functional.⁸⁸

Structural Neuroimaging Techniques

Structural neuroimaging techniques are used to study the anatomy of the brain⁸⁹, examine for any abnormalities and investigating connectivity patterns of the neural circuitry but is not a direct indicator of brain function.⁹⁰ These techniques include Computed Tomography (CT), Magnetic Resonance Imaging (MRI), and Diffusion Tensor Imaging (DTI).

A CT scan is a more elaborate X-ray technique that obtains cross-sectional images of the body.⁸³ CT scans reveal both bone and soft tissues, which include organs, muscles, and tumors.⁹¹ Structural MRI on the other hand shows differences between different types of tissues- white and gray, based on the proportion of water in them⁸⁹ and is one of the most common techniques used to examine brain structure.⁹⁰ This technique uses nuclear magnetic resonance technology, where magnetic fields are used to align the atomic nuclei in the body, absorb energy from tuned radiofrequency pulses, and emit radiofrequency signals as the excitation induced in the atomic nuclei decays.⁹² DTI is a form of diffusion MRI and is based on the principle of nuclear magnetic resonance and the Brownian motion of water.⁹³ Observations about the diffusion of water molecules in the body provide information about the structure and geometric organization of the tissues.⁸⁵

Functional Neuroimaging Techniques

Functional neuroimaging techniques include those techniques that are used to image the CNS during a particular task to identify the areas of the brain that are activated during this task. These techniques include Magnetic Resonance Spectroscopy (MRS),

Magnetoencephalography (MEG), Electroencephalography (EEG), Transcranial Magnetic Stimulation (TMS), Positron Emission Tomography (PET), and functional Magnetic Resonance Imaging (fMRI).

MRS is a non invasive technique for tissue characterization. The MRS uses the signal from hydrogen protons to determine the concentration of metabolites such as N-acetyl aspartate (NAA), choline (Cho), creatinine (Cr) and lactate in the tissue. MEG is a noninvasive technique that investigates neuronal activity of the brain. Weak magnetic fields created by current loops flowing in neurons are measured using multichannel gradiometers. The detected magnetic field distribution can indicate the sites in the cerebral cortex that are activated by an external stimulus.⁹⁴ In an EEG, surface electrodes are placed on the scalp at multiple areas of the brain to detect and record patterns of electrical activity and to check for abnormalities.⁸⁴ TMS is now a commonly used clinical tool in neurophysiology, rehabilitation and intraoperative monitoring.^{95,96} A high pulse current in a magnetic coil produces a magnetic field that stimulates the brain to either excite or inhibit specific regions of the brain.⁹⁵ The varying versions of the TMS allow the motor output to be precisely mapped for a given region of the body. TMS is also a good therapeutic tool as the effect of the stimulation can exceed the time the brain is stimulated.⁹⁵

PET was the first neuroimaging technique that measured local blood flow in the brain when performing an experimental task.⁹⁰ A radioactive substance is administered to the patient during the scan and tiny particles called positrons are emitted from this radioactive substance. Physiologic images are acquired based on the radiations emitted from these positrons with different colors or level of brightness in these images indicative

of the different levels of tissue or organ function.⁹⁷ Radioactive tracers aid in imaging metabolic processes with different tracers highlighting different aspects of metabolic functioning. The ability of the PET technique to measure regional cerebral blood flow during functional tasks made it a commonly used technique for studies of speech and language.^{90, 98}

To overcome the disadvantages of the PET with regard to the use of a radioactive tracer and improved spatial resolution, Ogawa et al. first described the paramagnetic properties of venous blood that can be used as a contrast agent during MRI⁹⁹ and the procedure came to be known as functional MRI (fMRI). This agent, called the blood oxygenation level dependent (BOLD) contrast, is thus dependent on the hemodynamic response to the task at hand. FMRI can map brain activity in humans and hence makes it possible to study brain activity for a range of functions from finger tapping to thoughts and emotions.⁹³

fMRI has better spatial (the smallest detail between two points in an image that can be detected as separate details¹⁰⁰), temporal resolution (the shortest time interval between two events that can be measured¹⁰¹) and a higher signal- to- noise ratio (used to describe the relative contributions to the detected signal of the true signal and background noise¹⁰²) than PET, thereby offering higher quality images than the PET scan. Further, fMRI can also localize activations in individual participants as opposed to PET, which requires signal averaging over a larger sample size. This property benefits the researcher when performing case studies or with a small sample size. While EEG and MEG have temporal resolutions features which are superior to the fMRI, these methods are directly linked to the electrical activity of neurons and do not offer true three dimensional

imaging modalities¹⁰³. The high spatial and temporal resolution, ability to obtain valid data in single participants and lack of radiation exposure make fMRI the tool of choice for our study.

The fMRI has its share of limitations with regard to its temporal resolution, spatial normalization to a template, movement artifacts and scanner noise.⁹⁰ Modifications in study designs have helped in minimizing the effects of limitations such as movement artifacts and scanner noise.¹⁰⁴ However, it continues to provide valuable information while better techniques are being developed.

Neuroimaging tools for speech production

Animal models were and continue to be used to examine the neural pathway involved in vocalization.¹⁰⁵⁻¹¹² Although the knowledge gained from these animal models is significant and vital, the results are limited in their application to the human speech production mechanism. Initial human studies used the WADA technique to examine cerebral dominance for speech by injecting sodium amobarbital into the internal carotid artery to temporarily prevent the activity in one cerebral hemisphere for memory or language and assess the function of the other hemisphere.¹¹³ Since this procedure fifty years ago, the investigation of cortical functioning for speech production has significantly improved. With the advent of neuroimaging techniques, early examination of human speech production was undertaken in the late 1980s and 1990s with one of the first studies using overt speech in 1988 by Petersen, Fox, Posner et al.⁹⁸

Using PET as a tool for assessing cortical representation for speech production, Petersen et al found a change in regional cerebral blood flow for primary motor and

sensory areas along with superior temporal gyrus (STG) and supplementary motor area (SMA) for tasks involving single word processing.⁹⁸ A number of studies used PET to continue to assess cortical regions involved in speech production^{114, 115} and the effect of aphasia^{116, 117}, dysarthria^{25, 118}, fluency disorders¹¹⁹⁻¹²¹ and voice disorders^{122, 123} on this activation. With the shift towards the use of fMRI as the tool of choice for functional neuroimaging, speech production came to be assessed under a different scanner. The advantages of the fMRI currently outweigh those of the PET for the purpose of speech production. However, with constantly improving techniques, the unique parameters of the PET as a direct measure of cortical activity and the ability to study neurotransmitters as a function of speech disorders will be an added asset to the available neuroimaging techniques.

At the outset, only covert speech production was used as stimuli during fMRI studies as the motion caused by articulatory and respiratory movements as well as the change in air cavities in the vocal tract during overt speech production caused significant artifacts during imaging. A block design was used to assess speech production^{124, 125} but the overlap of the hemodynamic response across trials and movement artifacts decreased the validity of these results. The artifacts can mask or mimic BOLD signal changes associated with neuronal activity.¹²⁶ The later developed event-related, sparse sampling design, aimed to avoid scanning during the act of speech production,¹⁰⁴ has allowed the use of more representative speech through overt speech stimuli to study speech production and the CNS. In this design the temporal properties are modified and the scanner is turned on and off to match the time of task production. The hemodynamic response for speech and that for the motion of articulators associated with speech

production vary and this sampling design utilizes this difference to capture BOLD activity for speech alone. BOLD for speech occurs approximately six seconds after the initiation of the task while motion-induced BOLD activity occurs during the task itself.¹²⁶ Thus, the scanner time can be coordinated with the required BOLD activity to minimize movement artifacts. An added advantage of utilizing this method for speech production tasks is the elimination of the need for speaking over the loud scanner noise when performing a task. This allows the participant to produce the task with a more comfortable manner of speaking.

An event-related paradigm is now a commonly used method for studies examining speech and language production for the reasons mentioned. The following section provides an overview of some of these studies with an emphasis on neuroplasticity as it relates to voice and also secondary to perturbation of the system similar to that seen with induced UVFP.

NEURAL CONTROL OF PHONATION

The human brain has been shown to have tremendous potential to change its functional topography secondary to a disruption in normal sensory input¹²⁷ due to environmental and/or experiential perturbation. This feature, neural plasticity, has been examined extensively in animal and human studies for various voluntary control activities of the upper and lower extremity.¹²⁸⁻¹³⁹ An understanding of cortical plasticity from perturbed phonation, a combined voluntary and reflexive action, is still in its nascent stages. The literature for cortical changes secondary to disordered voice production is limited to a handful of studies in persons with spasmodic dysphonia^{27, 29, 122}, two studies in persons with Parkinson's disease^{25, 26} and a case study in a person with

UVFP and subsequent surgical treatment.³⁰ The recent emergence of neuroimaging techniques for speech and language now allow for better isolation of phonatory activity from speech. This section will highlight cortical activity as understood for normal and disordered phonation in humans.

Cortical and subcortical regions for phonation

The human primary motor cortex was first mapped and described by Penfield and Rasmussen in 1950.¹⁴⁰ This map, known as the homunculus, represents the density of innervation to various body parts and hence is disproportionate to the actual extent of various body parts. The homunculus as originally conceived did not have a clear representation for the larynx although we now know that the larynx, especially the posterior glottis, is richly innervated by low-threshold mechanoreceptors.¹⁴¹ The lips, jaw, tongue and pharynx have a sequential dorsoventral organization but Penfield and Rasmussen were unable to localize the region for vocalization.¹⁴² Over the next many years, speech production was examined but laryngeal function could still not be isolated.

In 1997, Murphy, Corfield, Guz et al¹¹⁵ were the first to isolate cortical laryngeal function using PET. They used phrases as stimuli in four different conditions: comfortable phonation, silent mouthing, without articulation and thought silently. Using this protocol, they were able to identify bilateral activation in the primary sensorimotor areas, thalamus, cerebellum, supplementary motor area (SMA) and superior temporal gyrus (STG) specific to phonation. Their findings were indicative of the interplay between primary and secondary sensorimotor areas for phonation. A few years later, in 2002, Huang, Carr and Cao¹⁴³ performed an fMRI study comparing silent and overt

speech at the syllable and word level. They identified a region posterior to Broca's area within the primary motor cortex (M1) that was activated stronger during the overt condition and was separate from the region in the motor cortex responsible for the mouth, lips and tongue. They termed this region as the "inferior vocalization region" of the primary motor cortex and in all probability reflecting the laryngeal motor cortical zone.

A TMS study performed in 2004 by Rodel et al.¹⁴⁴ examined the human motor cortical representation of the larynx. They found bilateral representation of the intrinsic laryngeal muscles in M1 with separate representation of the muscles that receive innervation from the RLN (TA) and SLN (CT). The CT had a more medial representation in M1 as compared to the TA.

In a PET study that identified the activation of the limbic system, periaqueductal gray (PAG) and sensory systems during vocalization, Schulz et al.¹²³ found that in addition to primary and secondary sensorimotor regions, visceromotor mechanisms (PAG, middle frontal gyrus and the anterior cingulate cortex) play a critical role in concert with neocortical mechanisms (medial prefrontal cortex and SMG). Using voiced and whispered narration as stimuli, the authors hypothesized that activation in the medial temporal gyrus (MTG), STG and superior temporal sulcus (STS) was the result of self-monitoring for the online correction of laryngeal and oral articulatory movements. The authors found the strongest paramedian cortical activity in the medial prefrontal cortex (MPFC), more than that seen in the anterior cingulate cortex (ACC). Animal studies have shown that the PAG receives projections from both the MPFC and the ACC.¹⁴⁵ The activity of the PAG in the Schulz et al study might be a reflection of increased sensory feedback in addition to emotional/ involuntary vocalization seen in both human and non-

human primates. The activity in the PAG forms a distinguishing characteristic between non-human primate vocalization and the more developed control for human vocalization. In addition, increased activity was seen in the cerebellar vermis during voicing suggesting an integration of auditory and motor systems to form a circuit between the cortical auditory and cerebellar motor areas for improved timing. The basal ganglia was also found to be active and is thought to regulate the activity of the SMA.¹²³

The results of an fMRI study by Ozdemir et al¹⁴⁶ in 2006 comparing neural activity during singing and speech were in agreement with the previous studies. They found activation of M1, primary sensory cortex (S1), STG, STS and, inferior frontal gyrus (IFG). The IFG activity reflects the need for motor planning during phonation. Right-lateralized activity was seen for the IFG, STG and inferior frontal operculum during singing as compared to speech demonstrating increased motor planning along with the need for auditory feedback. The main difference in the neural correlates for phonation and exhalation are related to auditory feedback as well.

In a study by Loucks et al.¹⁴⁷ in 2007, similar neural correlates for phonation and exhalation were identified. A difference between the Loucks et al. and Ozdemir et al. study were that in the Loucks et al. study increased activity in the auditory cortex was seen for auditory monitoring. The results of the overall neural correlates for phonation and exhalation were similar to those in previous studies. Studies that have followed have all confirmed the activation of M1, S1, SMA, STG, anterior and posterior cingulate gyrus, SMG, frontal operculum, thalamus, cerebellum, basal ganglia and the PAG during phonation.¹⁴⁸⁻¹⁵⁰ A functional connectivity analysis and diffusion tensor imaging (DTI) study by Simonyan et al¹⁵¹ showed a common structural network of the laryngeal motor

cortex for the laryngeal motor cortex. However, what varied with the laryngeal task demands were the functional networks overlaid on this structural network. For example, bilateral organization was observed during controlled breathing versus left-lateralization during simple, learned voice production tasks such as production of a glottal stop syllable /iʔi/.

A region more dorsal in position to the inferior vocalization region identified by Huang et al.¹⁴³ in the primary motor cortex was identified to be the laryngeal motor cortex in an fMRI study by Brown et. al (2008).¹⁴² In this study, researchers isolated the laryngeal area using vowel production and glottal stops. This region, identified to be controlling the human intrinsic laryngeal muscles, was found to be significantly different in location from that identified in an anatomical study of the non-human primate.¹⁴²

Peck et al¹⁵⁰ (2009) examined the central neural phonatory representation involved in pitch variation. They used production of a vowel at low, comfortable and high pitches to delineate the cortical mechanism involved in pitch variation. Bilateral activations were shown in the cerebellum, STG, insula, S1, M1, inferior parietal lobe, and post-cingulate gyrus. In the left hemisphere, activations in the medial and middle frontal gyri were also observed. Regions active during high pitch production, compared to the comfortable pitch condition, were evident in the cerebellum bilaterally, left IFG, left cingulate gyrus, and left posterior cingulate. During low pitch generation, activations were present in the left hemisphere for IFG, insula, putamen, and cingulate gyrus. The right IFG produced greater activity than the left IFG during high and low pitch generation and seems to play a critical role in pitch modulation.¹⁵⁰

The studies until date have identified the primary sensorimotor cortices, STG, SMA, prefrontal cortex, insula, putamen, cingulate gyrus, supramarginal gyrus, thalamus, cerebellum, basal ganglia and PAG as key regions involved in non-disordered phonation. Identification of these regions will aid in comparing the cortical and subcortical activity seen as a result of a disordered voice detailed below. There continues to be a need to examine cortical and subcortical activity for a normal voice quality for a more complete understanding of the system.

Cortical and subcortical regions in the disordered voice

Understanding normal voice production is important not only from a need to gain mechanistic knowledge of the system but also to ultimately compare the neural representation to that in the disordered state and find similarities. Targeting these differences during treatment with compensatory and/or adaptive strategies will ultimately provide improved treatment outcomes and clinical care. Being a new area of research in the field of speech pathology, a complete understanding of neural activity for normal phonation is yet to be gained due to a paucity of data on the central neural representation in the disordered voice population. However, there have been a few treatment studies largely in persons with spasmodic dysphonia, one in persons with Parkinson's disease and a case study in a person with unilateral vocal fold paralysis^{25, 27, 29, 30, 122}, demonstrating treatment-related central neural adaptation.

A pre-post treatment study was performed in persons with idiopathic Parkinson's disease using overt speech as stimuli for PET imaging.²⁵ Persons were tested before and after Lee Silverman's Voice Treatment protocol, a commonly used voice treatment

approach in this population.¹⁵²⁻¹⁵⁶ Brain activity for these two time points were compared to that in healthy volunteers as well as a group with Parkinson's disease yet not receiving any form of voice treatment. Based on regional cerebral blood flow changes detected by PET, a reduction in premotor and motor activation was observed post treatment approaching the activation level seen in the healthy volunteer group. There was also an increase in basal ganglia, anterior insula and dorsolateral prefrontal cortex (DLPFC) activity. The authors postulated that this change indicated a shift to a more automated production of speech with a reduction in effort. The change in central activity was also reflected at the periphery with an improvement in behavioral measures for vocal loudness, the variable of choice for this study. The results of this study further validated the use of this treatment method in this population, beyond the improvement seen at the periphery.

Haslinger et al.²⁷, Ali et al.¹²² and Simonyan et al.^{28,29} have all performed neuroimaging studies in persons with spasmodic dysphonia (SD) using fMRI, PET or DTI respectively as their functional neuroimaging tool of choice. The fMRI study by Haslinger et al. and the PET study by Ali et al. both examined persons with SD before and after treatment with Botulinum toxin (Botox) injections and compared the results to those of healthy volunteers.^{27,122} Both studies found reduced activation in the primary sensorimotor cortices and the basal ganglia prior to Botox. Ali et al.¹²² saw hyperactivity in motor areas such as the cerebellum and SMA possibly as a result of increased effort in these patients. Post treatment however, the two studies have conflicting results. While, Haslinger et al.²⁷ did not find an increase in the activation of the motor areas in their fMRI study post Botox, Ali et al.¹²² saw an increase in activity in these regions after the

Botox injection was administered. The cause for this difference is unclear. However, both studies saw a significant difference in cortical activation for primary sensorimotor areas as compared to healthy volunteers. The recent fMRI study by Simonyan and Ludlow²⁸ characterized cortical activity in adductor and abductor SD using multiple tasks and showed abnormal activation of the primary somatosensory region in the parameters of activation extent, intensity, correlation with other regions and symptom severity. Thus, there is growing circumstantial evidence of the primary sensorimotor region being involved in the pathophysiology of spasmodic dysphonia.

The DTI study by Simonyan et al²⁹ examined white matter integrity in patients with SD either naïve to Botox treatment or well past their last Botox injection. These investigators found an increase in overall diffusivity bilaterally in the corticobulbar/corticospinal tract. There was also an increase in the middle cerebellar peduncle and deep cerebellar white and gray matter with no difference in diffusivity in the ACC region between healthy controls and the SD population. Since the ACC is responsible for voluntary control during emotional states and has reciprocal connections with the motor cortex, this DTI study demonstrated why the SD population typically has an improved voice during highly emotional states such as laughing or crying, with phonatory breaks at other times.²⁹

Finally, a recent study assessing cortical representation in the disordered voice population was by Galgano et al³⁰. fMRI analysis was performed on a patient with UVFP pre- and post-surgical treatment with Type I Thyroplasty. The small sample size and other co-existing health conditions weaken the study but continue to provide a glimpse into the changes associated with this form of treatment in the UVFP population. A

significant difference in activation patterns was observed pre and post therapy with different patterns for the varying pitches that were tested. The primary and secondary sensory areas, S1 and superior parietal lobe, in particular showed an increase in activity post surgery. The hypoactivity or hyperactivity of cortical regions varied with comfortable, low and high pitches, with increased activity post surgery for the comfortable and low pitch productions versus increased activity pre surgery during the high pitch production. The increased activity for high pitch production post surgery may be reflective of an increased effort when producing higher pitches. The authors found neural activity changes correlating with the changes in behavioral measures. The study demonstrates the feasibility of using neuroimaging techniques in assessing pre and post treatment changes despite the extraneous variables clouding the significance of the results.

A pilot case-study was performed with the currently proposed protocol, described in more detail in the next section.¹⁵⁷ The previously reviewed studies in addition to our pilot case-study lead us to hypothesize that we would observe differential activity in the primary motor and sensory areas, cerebellum, ACC, DLPFC (including the inferior and middle frontal gyri), temporoparietal region, superior frontal gyrus, thalamus, and parahippocampal gyrus. These regions have also shown a change in level of activity in treatment studies for SD, Parkinson's disease and vocal fold paralysis^{25, 27-30, 122} and demonstrate that these disorders are amenable to cortical changes as a function of treatment. Based on these outcomes the ACC, precentral gyrus, postcentral gyrus, DLPFC and the cerebellum serve as regions of interest (ROI) for this study.

NEURAL REORGANIZATION WITH PERIPHERAL DENERVATION: NON-HUMAN AND HUMAN STUDIES

Peripheral injuries causing a change in sensorimotor functioning have been shown to trigger alterations in the cortical and subcortical neural substrate. This activity-dependent functional reorganization affects neural networks involved directly or indirectly in the processing of the impaired function.¹⁵⁸ Early studies on the reorganization of the somatosensory cortex in non-human primates were performed by sectioning the median nerve, a sensory nerve, to the thumb of the glabrous hand.¹⁵⁹ On examining the deprived somatosensory cortex, neurons representing the dorsal part of the hand innervated by an intact radial nerve responded to the inputs, indicating a shift in cortical receptive fields. These findings have been replicated and confirmed in other non-human primate studies.¹⁶⁰⁻¹⁶² Reorganization of the primary motor cortex in non-human primates involved in forelimb injury requiring amputation demonstrated a similar alteration in organization where stimulation of the deprived cortex caused a response of the stump of the limb of the shoulder.^{163, 164} Studies in humans with unilateral amputations also demonstrated reorganization of the motor cortex effectively activating muscles ipsilateral and proximal to the stump of the amputated limb by stimulating the motor cortex representing the amputated limb.¹⁶⁵

Chronic deafferentation has been shown to cause a dramatic reorganization of the somatosensory cortex. To examine short-term plasticity, peripheral neural damage in animal models¹³³ and in human¹⁶⁶ digits has been examined previously using local anesthesia to assess input-related changes in cortical mappings. These studies have shown areal increases post-anesthesia inducement within the representation of the intact digits

and within the cortical representation zone of the anesthetized body segment. These changes were seen within a few minutes after anesthesia inducement.^{130, 167} Cortical representation returned to their original mapping when the effect of the nerve block had worn off, taking from a few minutes to a few hours to completely return to baseline.^{133, 166} This input-dependent shift in representation after peripheral nerve blockade and its subsequent recovery are indicative of a latent anatomical network of overlapping thalamocortical projections to the sensory cortex and a shift in the balance of excitatory and inhibitory activity in the representational zone.

Overlapping arbors of thalamocortical projections that cross a representational boundary can be modulated dynamically by shifting the balance of excitatory and inhibitory activity in a use-dependent manner.^{168, 169} The expansion of the cortical receptive fields of the denervated digits examined has been attributed to unmasking of previously suppressed inputs to the cortical neurons. This may represent a limit to the use-dependent plasticity that can occur in these receptive fields.¹³³ New fields may arise from a change in the inhibitory-excitatory balance secondary to a denervation from the unmasking of previously suppressed synapses. This new balance represents the new dynamic system reflective of modified neural circuits.¹⁷⁰ Restoration of this balance will result in further reorganization to obtain the original receptive field.¹⁷¹

A large number of studies have focused on the primary sensorimotor cortex to examine the effects of deafferentation. However, these changes are seen at multiple levels of the sensorimotor system.^{172, 173} In a study characterizing responses to the activation of new receptive fields induced by local anesthesia or amputation of a digit in twelve rats¹⁷³, the authors obtained single-unit recordings from the ventral posterior lateral thalamus of

rats. Five of these rats underwent temporary deafferentation with the anesthetic and on complete recovery also underwent a digit amputation. With the anesthetic, new receptive fields were formed on the adjacent digit but on recovery, a reversible change was seen with a return of the original receptive fields. In the rats that received the digit amputation, new receptive fields were also present on the adjacent digits, irreversible in nature. The rats that received both anesthesia and amputation demonstrated new receptive fields in the same location. Thus the nature of the deafferentation- temporary or permanent, did not affect the location of the new receptive fields but only the reversible nature.

This study has strong implications for research conducted with perturbation models simulating pathology. If the receptive fields for acute and chronic injury of the same form are truly common, studying acute injury using a fictive model in a controlled environment will allow for stronger results and in-depth examination of neural reorganization, without confounding variables and co-existing morbidities often seen in the patient population. Given the methodological constraints in studying central laryngeal representation in voice disorders, an acute perturbation model is a first step in assessing chronic pathology. The proposed study will examine cortical activity in acute UVFP before inducement i.e., baseline with normal voice quality; during UVFP and on recovering from the UVFP. The UVFP will be induced using a lidocaine/epinephrine solution as a local anesthetic.

This fictive paralysis model will give us a controlled model in the form of the iUVFP to examine the mechanism of UVFP and various diagnostic and treatment paradigms for the patient population in the absence of an appropriate animal model. A comparison between the acute and chronic UVFP results will provide information

regarding the time required for neuroplastic changes to occur and stabilize. It is understood that the mechanism for synaptic changes during acute deafferentation may not be representative of chronic deafferentation¹⁷⁴ and that similarities and differences between these two models will have to be cautiously examined. The iUVFP perturbation model is a means to studying the dysphonic voice. Given the sudden nature of onset of UVFP and the quick improvement in voice quality after surgical treatment, it allows for isolated study of factors affecting the voice without the added layers of environmental and psychosocial factors. The fictive paralysis model simulates the sudden nature of onset of symptoms and quick return of a normal voice quality after the effect of the anesthetic dissipates. The iUVFP model is thus a good representation of characteristics seen in the UVFP patient population.

In a pilot case-study using the iUVFP protocol, significant deviations in cortical activity were observed between baseline, iUVFP and recovery.¹⁷⁵ One hour after recovery from the iUVFP indicated by normal vocal fold mobility on visualization and a perceptually normal voice, cortical activity was significantly elevated from that seen at baseline and with iUVFP. In the previously mentioned digit deafferentation studies on human and non-human primates, the original neural map reappeared with a few minutes to a few hours of recovery suggestive of a system of reciprocal connectivity between the various cortical regions.¹⁵⁷ The results of this study are limited in its application by its case-study design. A larger sample size is required to make more concrete interpretations of the findings of the pilot study. These results will also be correlated to behavioral measurements assessing the peripheral manifestation of UVFP. This correlation helps in determining if neuroplastic changes compare to peripheral changes in terms of time of

onset and time required to change post treatment. A significant difference in the peripheral and central manifestation of changes secondary to the iUVFP may warrant a reexamination of current treatment methods to maximize benefits gained from therapy.

The current knowledge base on UVFP and neuroplasticity in voice disorders as well as from injury to the limb structures has guided us in narrowing and defining the purpose and hypotheses for this study and are detailed in the next section of this chapter.

PURPOSE

The current vocal fold paralysis model is unique in that it will allow us to obtain pre and post paralysis data in each of the individuals. It is rarely possible to obtain pre-morbid data in individuals with UVFP as the disorder has a sudden nature of onset. Hence, this study will allow us to compare cortical activation patterns during the iUVFP and post recovery, to the baseline within the same person and across individuals, strengthening the results and inferences from the study. This study is the first step in understanding the brain's capacity to reorganize in the event of a voice disorder and its consequent treatment. Information obtained from this data will allow us to ultimately develop better treatment programs and offer patients a more informed plan of treatment.

HYPOTHESES

The overall hypothesis of this study is that a difference in cortical activity exists as a function of acute, induced vocal fold paralysis as measured by the BOLD contrast during fMRI. Further, correlations between behavioral (auditory-perceptual, acoustic and aerodynamic) and central measures (BOLD activation) will be seen at three time points

(baseline, iUVFP, and recovery). The specific null and alternative hypotheses for the study are as follows:

Null hypothesis 1: Percent BOLD signal levels and hemispheric laterality for regions of interest (anterior cingulate cortex, pre and postcentral gyrus, dorsolateral prefrontal cortex, and cerebellum) will not be significantly different at the three time points (baseline, iUVFP and recovery).

Alternative hypothesis: Percent BOLD signal levels and hemispheric laterality for regions of interest (anterior cingulate cortex, pre and postcentral gyrus, dorsolateral prefrontal cortex, and cerebellum) will be significantly different at the three time points (baseline, iUVFP and recovery).

Null hypothesis 2: A positive or negative correlation will not be seen between behavioral (auditory-perceptual, acoustic, aerodynamic and visualization) and central measures (BOLD activation) at the three time points (baseline, iUVFP, and recovery).

Alternative hypothesis: A positive or negative correlation will be seen between behavioral (auditory-perceptual, acoustic, aerodynamic and visualization) and central measures (BOLD activation) at the three time points (baseline, iUVFP and recovery).

CHAPTER 3 - METHODOLOGY

In Chapter 3, the methodologies for the study will be discussed with details on the study population, study design and data analyses. The main purpose of this study was to compare cortical activation before, during and after an induced, acute unilateral vocal fold paralysis. Cortical activation at these three stages was also correlated to clinical behavioral data to gain an understanding of the similarities and differences in peripheral and central manifestation of iUVFP.

STUDY POPULATION

Sample size calculations were performed apriori based on data from a pilot study done previously using nQuery®¹⁷⁶ giving us a sample size of ten participants to obtain 80% power with a medium effect size (0.5) after accounting for a 20% attrition rate. Ten participants (four males, six females) in the age range of 23-31 years were recruited. FMRI and behavioral data from one participant was excluded, as the effect of the injection did not last through the following scanning session increasing the effect size of the study with 80% power. Participants were included if they were: between 21-40 years of age, with normal voice quality, without a history of a voice disorder or neurological disorders, non-smokers, native English speakers, right handed, non-professional users of voice and, compatible for MRI scanning. The Institutional Review Board at the University of Kentucky approved the protocol and written informed consent was obtained from all participants.

STUDY DESIGN

A prospective, repeated measures cohort study design was implemented in this protocol with baseline, iUVFP and recovery as the three time points. At all three stages, the participants underwent behavioral assessment of their voice followed by an fMRI. Figure 1 provides a schematic of the timeline used in this study.

Behavioral assessment

Behavioral assessment included auditory-perceptual, acoustic, aerodynamic and visualization methods. The measures in each of these domains are detailed in Table 1. Considering the limited time course of the induced paralysis (90 – 120 minutes), only carefully selected behavioral measures were obtained. These measures were selected for their perceived high informational content to further understand the behavioral impact of the paralysis. For acoustic assessment, the Computerized Speech Lab Model 4500 by KayPentax was used with a hand-held microphone (mouth-to-microphone distance = 3 inches) [System Requirements: Analog Inputs: 4 channels: two XLR and two phono-type, 5mV to 10.5V peak-to-peak, adjustable gain range >38dB, 24-bit A/D, Sampling Rates: 8,000-200,000Hz, THD+N: <-90dB F.S. Frequency Response (AC coupled): 20-22kHz +.05dB at 44.1kHz. Digital Interface: AES/EBU or S/P DIF format, transformer-coupled. Software Interface: ASIO and MME. Computer Interface: PCI (version 2.2-compliant), PCI card; 5.0" H x 7.4" W x 0.75" D (half-sized PCI card). Analog Output: 4 channels, line and speaker, headphone output, channels 1 & 2 provide line & speaker outputs. Physical: 4" W x 8.25" H x 12.5" D, 4 lbs. 12 oz., 45 watts, speaker, and microphone (Shure SM-48 or equivalent, XLR-type)].¹⁷⁷

The Phonatory Aerodynamic system Model 6600 by KayPentax was used for the aerodynamic measurements (300 ml pneumotachograph. System requirements same as CSL model 4500).¹⁷⁸ Laryngeal videostroboscopy was performed to visualize the vocal folds using Kay Elemetrics Rhino-Laryngeal Stroboscope – (Model RLS 9100 B, Halogen lamp: 150 watts, Xenon lamp: 120 watts, frequency range: 60 Hz – 1500 Hz, laryngeal microphone), a Kay Elemetrics 70 degree rigid scope (Model 9106, total length: 252 mm) and a C-mount camera (Panasonic GP-US522HA).

Inducement of vocal fold paralysis

All injections were conducted in the ENT clinic, Kentucky Clinic, by a licensed and board certified otolaryngologist with more than 20 years experience with this specific procedure. Participants were positioned sitting in an elevated examination chair. The otolaryngologist palpated the neck to identify the space between the carotid artery and trachea on the right side. The right RLN was chosen due to its shorter course of travel as compared to the left RLN and was the preferred side for the otolaryngologist. The neck was prepped with alcohol prior to the injection. With the head extended up and to the left, stretching the neck in the desired region, 5 cc of 2% lidocaine HCL with epinephrine diluted at 1:100,000 was injected parenterally below the thyroid gland where the RLN courses to the larynx. The adequacy of the injectate was verified by asking the participant to phonate and through videostroboscopic examination. A hoarse voice quality due to inadequate glottal closure from an immobile right vocal fold would be indicative of UVFP. Infiltration of this space was expected to provide an effective peripheral nerve block for an average of 90 minutes.

Functional magnetic resonance imaging

Participants were instructed in a sentence reading task that required the production of multiple trials of six phonetically balanced sentences from the Consensus Auditory-Perceptual Evaluation of Voice (CAPE-V).^{36, 51} Three sentence runs comprising of 30 sentence trials (ten trials each for whisper, voiced and imagined conditions) and 60 rest trials were used during each functional scan. These performance conditions differed in their demand on the laryngeal system, allowing for examination of task-related cortical activity as a function of the production complexity of the sound source. For example, the “imagine” condition had minimal laryngeal movement, no involvement of the vocal folds and no articulatory activity. The “whisper” condition had minimal movement of the vocal folds but retained involvement of the supralaryngeal articulatory system. Finally, the “voiced” condition had a completely engaged larynx that was normally integrated with supralaryngeal articulatory behavior. The varying laryngeal and articulatory demands in each performance condition with common cognitive and language demands allowed us to isolate cortical activity as a consequence of laryngeal function primarily. The participants were familiarized with the task prior to entering the scanner by presenting the sentences using a PowerPoint™ slideshow to mimic the presentation of tasks in the scanner.

The instructions and stimuli were displayed onto a small screen attached to the head coil of the MRI system. Commercially available software (E-Prime, Psychology Software Tools Inc., Pittsburgh, PA) and an MRI compatible projection system (Silent Vision SV-6011 LCD, Avotec Inc.) were used to project the task instructions and stimuli. An event-related sparse sampling design was used to obtain fMRI data in this study. A screen providing the instruction for the task to follow was presented for 3 seconds. The

next screen provided the target stimulus and the participants were instructed to produce the sentence displayed (e.g. “Peter will keep at the peak”) at a steady pace and at a comfortable loudness as per their training. The task time was varied (jittered) from 3.5 to 4.5 seconds to ensure capture of the hemodynamic response peak (**Figure 2**). The delayed latency of the hemodynamic response during the task allowed for an efficient use of an event-related design. The sentences within each run were pseudo-randomized.

Structural and functional MRI data were acquired on a Siemens Magnetom TRIO 3 Tesla MRI scanner located in the MRISC at the University of Kentucky. Two steps were taken to decrease the influence of movement artifact during signal acquisition: 1) participants’ heads were stabilized using foam padding between the head and the head coil; and 2) an event-related, sparse sampling approach was used, wherein the scanner gradients were turned on during the first 3 seconds of instructions to obtain a whole brain volumetric scan of the BOLD activity during the previous task performance. The scanner was turned off during the next 3.5 to 4.5 seconds during speech production, thus minimizing motion and acoustic contamination during data acquisition.¹⁷⁹ The functional images were T-2* weighted echo-planar images. A single echo-planar imaging volume (EPI) was acquired with TR= 7.0 seconds. A high-resolution, 3D anatomic image was acquired using a sagittal T-1 weighted (MPRAGE) sequence (TR = 2100 ms, TE = 2.93 ms, TI = 1100 ms, flip angle = 12°, FOV= 192mm x 224 mm x 256 mm, with 1mm (isotropic voxels). The following parameters were applied: TR=2.5s; TP=156; TE = 30 ms; flip angle = 81°; 39 axial slices; 224mm x 224mm FOV (field of view); slice thickness = 3.5 mm; 64 x 64 matrix (yielding 3.5 mm x 3.5 mm x 3.5 mm voxel size); bandwidth = 2056 Hz/Px.

DATA ANALYSES

Linear Mixed Models were used to investigate the main effects of time (three levels-baseline, iUVFP, recovery), gender (two levels-male and female), and the interaction of time and gender on the behavioral value of interest. In order to further investigate the effects of time, gender, and the interaction of time and gender on the behavioral values of interest, post-hoc tests were used. When the data suggested potential interactions between time and gender ($p \leq 0.2$), comparisons were made investigating the effect of time on gender.

The individual measures of CAPE-V, noise to harmonic ratio, subglottal pressure and laryngeal airway resistance formed the dependent variables for the behavioral data. The levels for these dependent variables included time point (baseline/iUVFP/recovery) and gender (male/female). For the BOLD data, each ROI served as the dependent variable with levels for time point (baseline/iUVFP/recovery), gender (male/female), side/ hemispheric laterality (right/left) and condition (whisper/voice/imagine).

Image processing and analyses were conducted using the Analysis of Functional Neuroimages (AFNI) software package.³⁷ After preprocessing, the structural 3D data were transformed into Talairach space using AFNI.³⁷ The first and last three functional volumes were eliminated due to T-1 saturation effects and differences in timing between slices due to acquisition order and sync interpolation. The fMRI data were motion corrected to the image obtained nearest in time to the structural image and smoothed (4 mm FWHM). The general linear model on event-related fMRI was used to estimate the

evoked hemodynamic delay for each trial type with no assumptions about the shape of the BOLD responses.

The regions of interest (ROI) were defined anatomically using AFNI software. We calculated the averaged EPI activations in the brain for voice production, imagined or whisper. The brain regions showing significant signal enhancement or reduction were defined as voxels (three dimensional unit of volume) with $p < 0.05$ for the overall experimental effect. All of the voxels were averaged within the ROI for each time point creating a single, spatially averaged time course for each trial type. The percent BOLD signal level for each condition was calculated in the ROIs for further analysis using AFNI and functioned as the dependent variable. The Talairach and Tournoux (TT) Atlas Daemon¹⁸⁰ was used to create automated masks for the ACC, precentral and postcentral gyrus. ROI masks were manually drawn for the DLPFC and cerebellum. A mask of Brodmann's areas 9 and 46 was drawn as the DLPFC and separate masks were drawn for the spinocerebellum and lateral hemispheres of the cerebellum using the Talairach Daemon structural database as a guide.³⁷ The spinocerebellum includes the vermis and intermediate hemispheres receiving somatosensory input from the spinal cord. The lateral cerebellar lobes are phylogenetically more recent and receive input from the cerebrum and is involved in complex motor and cognitive functions.¹⁸¹

A second level analysis inclusive of percentage BOLD signal changes (from the resting state) from each participant, as a random factor, was conducted using SAS v9.2.¹⁸² Linear Mixed Models were used to investigate the main effects of time (three levels), gender (two levels), hemisphere (two levels-left and right except for the cerebellum-three levels of left, right and midline), condition (three levels-whisper, voice,

imagine) and their interactions for percentage BOLD signal change in the ACC, precentral and postcentral gyri, the spinocerebellum and lateral hemispheres of the cerebellum; and the DLPFC for the sentence production conditions of “whisper”, “voice” and “imagine” during the three time points of baseline, iUVFP and recovery. The mixed model analyses allowed us to examine between subject factors as well as repeated measures between subjects.¹⁸³ In order to further investigate the effects of time, gender, side, condition and the interaction, post-hoc tests (least square means estimate/ multiple pair wise comparison) were used. When the data suggested potential interactions ($p \leq 0.2$), comparisons were made investigating the effect of time on gender, side and condition. A significance value of $p \leq 0.2$ was chosen to minimize the chances of a Type II statistical error given the small sample size. A p-value less than 0.05 was considered statistically significant for the post-hoc results.

A Pearson’s correlation was performed to assess whether percent BOLD signal level could be predicted from behavioral measures obtained as a consequence of iUVFP and its recovery. A p-value less than 0.05 was considered statistically significant.

The null hypothesis for both BOLD percentage values and behavioral data states that the population mean for each dependent variable during each of these three stages are equal and can be represented as follows:

$$H_0: \mu_{\text{baseline}} = \mu_{\text{iUVFP}} = \mu_{\text{recovery}}$$

This chapter has provided a description of the methods used for this study. Chapter 4 provides details of the results obtained in this study with the described methods.

Table 3.1. Domains and Measures used in behavioral assessment	
Assessment domain	Measures
Auditory perceptual	Consensus Auditory Perceptual Evaluation of Voice (CAPE-V) ^{36, 51}
Acoustic	Noise to harmonic ratio (NHR) (dB)
Aerodynamic	Subglottic pressure (Ps) (cmH ₂ O) Laryngeal airway resistance (LAR) (cmH ₂ O/L/s)
Visualization	Presence or absence of paralysis

Figure 3.1. Timeline for testing and protocol at each of three sessions

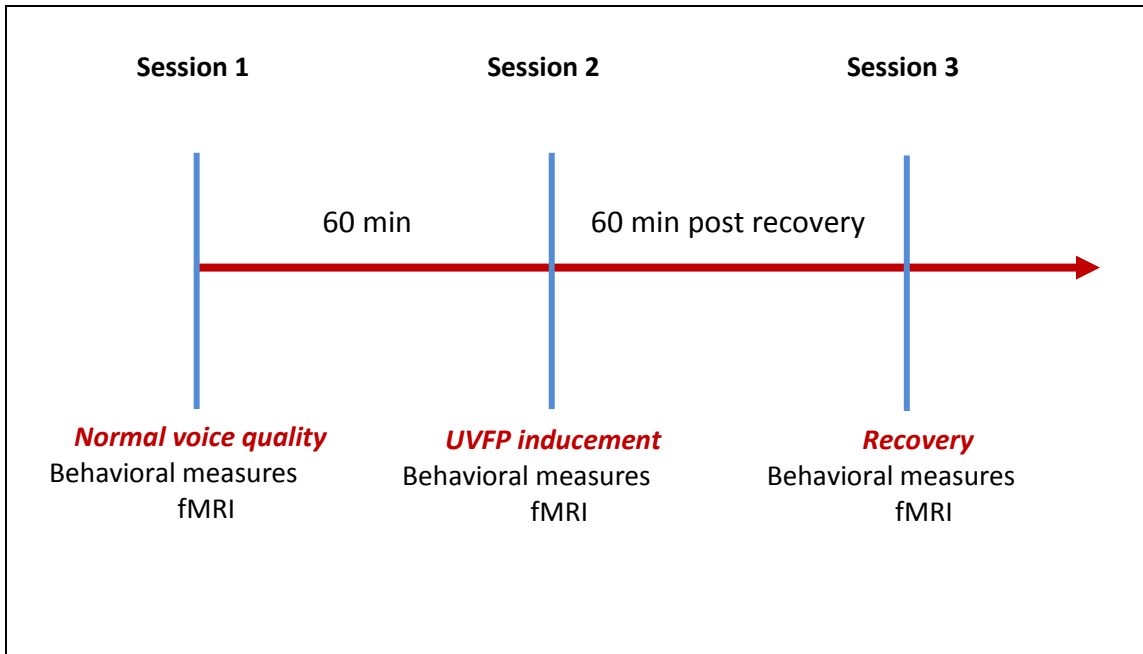
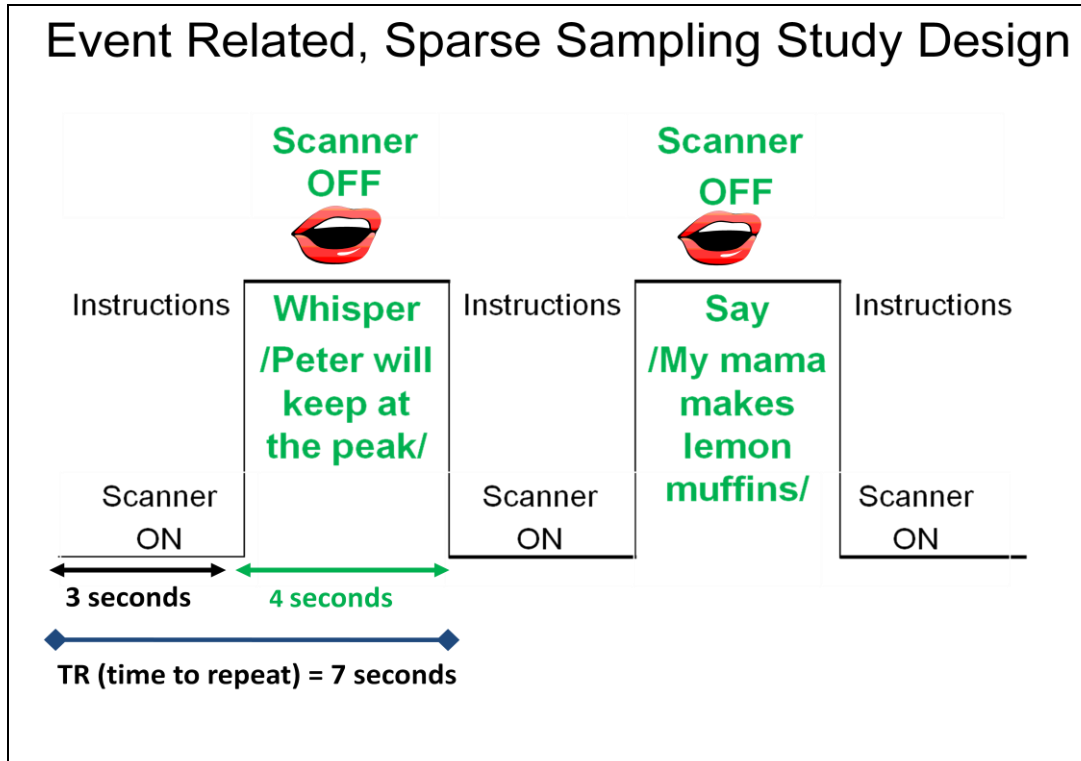


Figure 3.2. Schematic of the sparse sampling testing paradigm used for fMRI



CHAPTER 4 : RESULTS

This chapter will present the readers with the results for the behavioral data, fMRI data and the correlation between these two forms of data collected and analyzed using the methods described in Chapter 3.

PARTICIPANT DEMOGRAPHICS

Data from four males (mean age: 26.8 years, range 23-28 years) and five females (mean age: 26 years, range 25-31 years) was included in this study. The participants received an average of 5.27cc of lidocaine/epinephrine solution as the injectate with the iUVFP lasting an average of 95 minutes. Participants had a mean of 48 minutes after recovering from the iUVFP prior to the final fMRI scan. A range of 30-70 minutes was seen for this period for logistical reasons that were difficult to control such as availability of the scanner, availability of the otolaryngologist and variance in time between the injection and onset of iUVFP. Table 4. 1 gives the readers a breakdown of this data on each participant.

BEHAVIORAL DATA

Auditory-perceptual ratings (CAPE-V), acoustic (NHR), aerodynamic (Ps, LAR) and visualization measures (laryngeal videostroboscopy) were taken by a licensed speech language pathologist for all participants. Statistical analyses were performed for the CAPE-V, NHR, Ps and LAR results. Videostroboscopy was used only to assess the presence of normal laryngeal structure and function at baseline and on recovery; and a presence of right vocal fold immobility during the iUVFP.

Participant profile plots for each of the behavioral variables are provided. These plots demonstrate the trends present in the data. In these plots, time “0” represents baseline values, “1” represents iUVFP values and “2” represents recovery values. See Table 4.2 for means and standard errors for each of the behavioral variables and Table 4.3 for F-values, degrees of freedom and significance levels.

Consensus of Auditory-Perceptual Evaluation of Voice (CAPE-V)

CAPE-V exhibited a significant main effect due to time ($p < 0.0001$). In addition, there was sufficient evidence ($p \leq 0.2$) to suggest that an interaction of time and gender was present and further post-hoc tests were performed. The suggested interaction between gender and time means that men and women’s CAPE-V values changed differently over time. Females had lower means than males during iUVFP (females=36, males= 58) indicating less negative vocal effort from paralysis. Both males and females had a mean of zero at baseline and on recovery. See Figure 4.4 and Table 4.4 for participant profile graphs and statistical data.

Noise to harmonic ratio (NHR)

NHR exhibited a significant main effect due to time ($p = 0.0059$) and gender ($p = 0.0004$). In addition, there was sufficient evidence ($p \leq 0.2$) to suggest that an interaction of time and gender may be present and further post-hoc tests were performed. The suggested interaction between gender and time means that men and women’s NHR values changed differently through time. Females had lower means than males at baseline (females= 0.13dB males= 0.15dB), during iUVFP (females= 0.13dB, males= 0.22dB)

and during recovery (females=0.11dB, males= 0.14dB) indicating less noise in the acoustic vocal signal for females during all voice conditions.

See Figure 4. 5 and Table 4. 5 for participant profile graphs and statistical data.

Subglottal pressure (Ps)

Subglottal pressure exhibited no significant main effects and failed to present sufficient evidence ($p \leq 0.1$) to suggest that an interaction of time and gender may be present. See Figure 4. 6 and Table 4. 6 for participant profile graphs and statistical data.

Laryngeal airway resistance (LAR)

LAR exhibited a significant main effect due gender ($p=0.0448$). There was not sufficient evidence ($p \leq 0.2$) to suggest that an interaction of time and gender may be present. See Figure 4. 7 and Table 4. 7 for participant profile graphs and statistical data.

FUNCTIONAL MAGNETIC RESONANCE IMAGING DATA

Percent BOLD signal activity served as the dependent variable for the overall effect. The regions of interest in this study were ACC, precentral and postcentral gyri, DLPFC and the cerebellum on the basis of previous literature and our pilot data. The extent of BOLD activity presented in Table 4. 8 reflects overall task-related effects within each phase of the experimental procedure at a statistical threshold of $p < 0.05$.

Overall effect

Qualitatively, greater activation was observed during the paralysis phase within several brain regions than at baseline or recovery. Table 4. 8 provides the cortical areas activated at the $p < 0.05$ level and the volume of these areas (indicative of the extent of the activation) for both Talairach-Tournoux (TT) and Montreal Neuroimaging Institute

(MNI) brain area identification systems. As seen from this table, during iUVFP, larger volume of fMRI responses were seen within the precentral gyrus, ACC and medial frontal gyrus among other areas. Seven regions with an arbitrary cut-off of activation greater than one voxel were identified at $p < 0.05$ within the baseline phase as compared to eight regions during iUVFP and one during the recovery phase. At baseline and during iUVFP, left hemisphere dominance was observed except for the right medial frontal gyrus, right precentral gyrus at baseline and right postcentral gyrus during iUVFP. On recovery, large activation was observed in the frontal lobe, specifically the superior frontal gyrus extending bilaterally, greater than that seen in the other phases.

Region of Interest (ROI) Analyses

Main effects of time, gender, side, condition and the interaction of time and gender on each of the ROI were investigated. To further investigate the effects of time, gender, side, condition and the interaction of time and gender on a region, post-hoc tests were used. When the data suggested potential interactions ($p \leq 0.2$), comparisons were made investigating the effect of time and/or gender. The data is presented below for each of the ROI. Figure 4.8 and Figure 4.9 are a graphical representation of the estimated means and standard errors for the overall activity in each of the ROI during the three time points for the group and, for males and females. Table 4. 9 and Table 4. 10 provide information on degrees of freedom, F-values and p-levels for each of the ROI.

ACC

The ACC exhibited a significant main effect due to time ($p=0.0183$) and gender ($p=0.0133$) but no main effects due to side or condition. In addition, there was sufficient

evidence ($p \leq 0.2$) to suggest that an interaction of time and gender may be present and further post-hoc tests were performed. The suggested interaction between gender and time means that men and women's ACC values changed differently through time. Females had higher means than males at baseline (females= 4.81%, males= 3.19%) and during iUVFP (females=4.25%, males= 2.40%), with similar means (females=2.38%, males= 2.43%) during recovery. Overall the left ACC had more activity (3.58%) than the right ACC (2.91%) but this difference was non-significant. See Table 4. 11 for statistical data on estimated means, standard errors, t-values and p-levels.

Precentral Gyrus

The precentral gyrus exhibited a significant main effect due to time ($p < 0.0001$) but no main effects due to gender, side, or condition. In addition, there was sufficient evidence ($p \leq 0.2$) to suggest that an interaction of time and gender may be present and further post-hoc tests were performed. The suggested interaction between gender and time means that men and women's precentral gyrus values changed differently through time. Females had higher means than males at baseline (females=3.91%, males= 2.69%), similar means during iUVFP (females=2.02%, males= 2.23%) and lower means than males (females=1.85%, males= 2.83%) during recovery. See Table 4. 12 for statistical data on estimated means, standard errors, t-values and p-levels.

Postcentral Gyrus

The postcentral gyrus exhibited a significant main effect due to time ($p < 0.0001$) but no main effects due to gender, side, or condition. In addition, there was sufficient evidence ($p \leq 0.2$) to suggest that an interaction of time and gender may be present and

further post-hoc tests were performed. The suggested interaction between gender and time means that men and women's postcentral gyrus values changed differently through time. Females had higher means than males at baseline (females=4.67%, males= 2.71%) lower means during iUVFP (females=1.5%, males= 2.74%) and during recovery (females=1.73%, males= 2.13%). See Table 4. 13 for statistical data on estimated means, standard errors, t-values and p-levels.

DLPFC

The DLPFC exhibited a significant main effect due to time ($p=0.0014$) and gender ($p=0.0182$) but no main effects due to side or condition. In addition, there was sufficient evidence ($p\leq 0.2$) to suggest that an interaction of time and gender may be present and further post-hoc tests were performed. The suggested interaction between gender and time means that men and women's DLPFC values changed differently through time. Females had higher means than males at baseline (females=2.04%, males= 1.81%), similar means during iUVFP (females=2.11%, males= 2.19%) and lower means than males during recovery (females=2.04%, males= 4.10%). See Table 4. 14 for statistical data on estimated means, standard errors, t-values and p-levels.

Cerebellum

The cerebellum exhibited a significant main effect due to condition ($p=0.0022$) and a significant main effect due to side ($p=0.0914$) at $p < 0.01$ but no main effects due to time or gender. In addition, there was sufficient evidence ($p\leq 0.2$) to suggest that an interaction of time and gender may be present and further post-hoc tests were performed. The suggested interaction between gender and time means that men and women's

cerebellum values changed differently through time. Females had higher means than males at baseline (females=2.86%, males= 1.58%), lower means during iUVFP (females=1.58%, males= 2.92%) and recovery (females=1.83%, males= 2.29%). See Table 4. 15 for statistical data on estimated means, standard errors, t-values and p-levels.

Table 4. 16 shows the difference in the estimated means of percent BOLD values between baseline and iUVFP, iUVFP and recovery and, baseline and recovery for the five ROI.

CORRELATION BETWEEN BEHAVIORAL AND FMRI DATA

A Pearson's correlation was performed to assess if percent BOLD signal level activity could be predicted from behavioral measures obtained as a consequence of iUVFP and its recovery (Table 4. 17). The correlation between CAPE-V and the postcentral gyrus ($r^2 = 0.37$) was marginally significant i.e., 37% of the variance in the BOLD activity of the postcentral gyrus could be predicted from the CAPE-V scores, a weak positive relationship. Statistically significant correlation was observed between NHR and the DLPFC ($r^2 = 0.56$). 56% of the variance in the BOLD activity of the DLPFC could be predicted from the NHR score, a strong positive correlation. Significant correlation was also observed between P_s and DLPFC ($r^2 = 0.39$) i.e., 39% of the variance in the BOLD activity of the DLPFC could be predicted from the CAPE-V scores, a weak positive relationship. All other relationships between the four behavioral measures and five ROI were statistically non-significant.

Table 4. 1. Participant demographics, quantity of injectate, duration of iUVFP and time between recovery from iUVFP and final fMRI scan

Participant No.	Gender	Age (years)	Quantity of injectate (cc)	Duration of iUVFP (minutes)	Recovery to final scan period (minutes)
1.	Male	28	5	90	30
2.	Male	27	5	100	30
3.	Male	23	5	120	60
4.	Male	26	8	80	35
Mean for Males		26	5.75	97.50	38.75
5.	Female	25	4.5	90	60
6	Female	26	5	95	60
7	Female	31	5	105	70
8	Female	26	5	90	30
9	Female	26	5	90	60
Mean for Females		26.80	4.9	90	56
Overall Mean		26.40	5.27	95.56	48.33

Table 4.2. Mean and standard error for behavioral data at baseline (0), during iUVFP (1) and recovery (2) for females (F) and males (M).

Time	Gender	CAPE-V		NHR		Ps		LAR	
		Mean	Std. Error	Mean	Std. Error	Mean	Std. Error	Mean	Std. Error
0	F	0.00	5.16	0.12	0.013	6.12	1.32	73.59	23.76
	M	0.00	5.77	0.14	0.015	8.91	1.48	49.08	26.56
1	F	36.00	5.16	0.13	0.013	7.72	1.32	32.15	23.76
	M	58.00	5.77	0.22	0.015	9.84	1.48	20.66	26.56
2	F	0.00	5.16	0.11	0.013	6.54	1.32	138.97	23.76
	M	0.00	5.77	0.14	0.015	7.44	1.48	43.22	26.56

Table 4. 3. Degrees of freedom (DF), F-values and significance levels for behavioral data

Variable	Effect	DF	F Value	Pr > F
CAPE-V	Time	2	49.05	<.0001
	Gender	1	2.69	0.1161
	Time*Gender	2	2.69	0.0914
NHR	Time	2	6.62	0.0059
	Gender	1	17.56	0.0004
	Time*Gender	2	3.51	0.0483
Ps	Time	2	0.85	0.4407
	Gender	1	2.84	0.1065
	Time*Gender	2	0.23	0.7972
LAR	Time	2	3.30	0.0567
	Gender	1	4.56	0.0448
	Time*Gender	2	1.62	0.2217

Table 4. 4. Estimated mean, standard error, t-values and significance levels for main effects of gender (across time) and time (combined gender) and interaction effect of time (baseline = 0, iUVFP = 1, recovery = 2) and gender (female = F, male = M) for Consensus Auditory-Perceptual Evaluation of Voice (CAPE-V)

Effect	Gender	Time	Estimate of Mean	Standard Error	t Value	Pr > t
Gender	F		12.00	2.98	4.02	0.0006
	M		19.33	3.33	5.80	<.0001
Time		0	0.00	3.87	0.00	1.0000
		1	47.00	3.87	12.13	<.0001
		2	0.00	3.87	0.00	1.0000
Time* Gender	F	0	0.00	5.16	0.00	1.0000
	M		0.00	5.77	0.00	1.0000
	F	1	36.00	5.16	6.97	<.0001
	M		58.00	5.77	10.04	<.0001
	F	2	0.00	5.16	0.00	1.0000
	M		0.00	5.77	0.00	1.0000

Table 4. 5. Estimated mean, standard error, t-values and significance levels for main effects of gender (across time) and time (combined gender) and interaction effect of time (baseline = 0, iUVFP = 1, recovery = 2) and gender (female = F, male = M) for noise-to-harmonic Ratio (NHR)

Effect	Gender	Time	Estimate of Mean	Standard Error	t Value	Pr > t
Gender	F		0.12	0.007	16.44	<.0001
	M		0.17	0.008	20.33	<.0001
Time		0	0.13	0.009	13.99	<.0001
		1	0.17	0.009	18.01	<.0001
		2	0.12	0.009	13.22	<.0001
Time* Gender	F	0	0.12	0.013	9.67	<.0001
	M		0.14	0.014	10.13	<.0001
	F	1	0.13	0.013	10.09	<.0001
	M		0.22	0.014	15.15	<.0001
	F	2	0.11	0.013	8.72	<.0001
	M		0.14	0.014	9.94	<.0001

Table 4. 6. Estimated mean, standard error, t-values and significance levels for main effects of gender (across time) and time (combined gender) and interaction effect of time (baseline = 0, iUVFP = 1, recovery = 2) and gender (female = F, male = M) for subglottal pressure (P_s).

Effect	Gender	Time	Estimate	Standard Error	t Value	Pr > t
Gender	F		6.79	0.76	8.87	<.0001
	M		8.72	0.85	10.20	<.0001
Time		0	7.51	0.99	7.56	<.0001
		1	8.77	0.99	8.83	<.0001
		2	6.98	0.99	7.03	<.0001
Time* Gender	F	0	6.12	1.32	4.62	0.0001
	M		8.90	1.48	6.01	<.0001
	F	1	7.71	1.32	5.82	<.0001
	M		9.83	1.48	6.64	<.0001
	F	2	6.53	1.32	4.93	<.0001
	M		7.44	1.48	5.02	<.0001

Table 4. 7. Estimated mean, standard error, t-values and significance levels for main effects of gender (across time) and time (combined gender) and interaction effect of time (baseline = 0, iUVFP = 1, recovery = 2) and gender (female = F, male = M) for laryngeal airway resistance (LAR).

Effect	Gender	Time	Estimate	Standard Error	t Value	Pr > t
Gender	F		81.57	13.71	5.95	<.0001
	M		37.65	15.33	2.46	0.0229
Time		0	61.34	17.82	3.44	0.0024
		1	26.40	17.82	1.48	0.1532
		2	91.09	17.82	5.11	<.0001
Time* Gender	F	0	73.59	23.76	3.10	0.0055
	M		49.08	26.56	1.85	0.0788
	F	1	32.15	23.76	1.35	0.1904
	M		20.66	26.56	0.78	0.4453
	F	2	138.98	23.76	5.85	<.0001
	M		43.22	26.56	1.63	0.1187

Table 4. 8. Talarach-Tournoux (TT) Atlas and Montreal Neuroimaging (MNI) co-ordinates of brain regions ($p < 0.05$) and volume of BOLD-responses for overall effect across the three phases ($n=9$).

Time	Brain Regions	Brodmann Areas	Volume (mm ³)	TT Atlas Co-ordinates			MNI Co-ordinates		
				x	y	z	x	y	z
0	Left superior frontal gyrus	BA 10	333	21	-64	-5	21	-66	2
	Right medial frontal gyrus	BA 10	202	-14	-60	-3	-14	-62	0
	Left cerebellar tonsil		177	44	52	-42	44	51	-43
	Left medial frontal gyrus	BA 10	108	11	-40	-11	11	-42	11
	Left superior temporal gyrus	BA 38	67	26	-21	-35	26	-23	-40
	Right postcentral gyrus	--	58	-16	53	71	-16	58	74
	Left middle frontal gyrus	BA 46	44	43	-42	16	43	42	20
1	Left anterior cingulate cortex, subcallosal gyrus	BA 25	871	5	-23	-10	5	-24	-11
	Right medial frontal gyrus	BA 10	334	-12	-32	-16	-12	-34	-17
	Left superior temporal gyrus	BA 38	152	26	-16	33	26	-18	-38
	Left superior temporal gyrus	BA 38	135	57	-8	-9	58	-9	-10
	Left inferior frontal gyrus	--	120	49	-43	12	49	-44	15
	Left uncus	--	94	25	12	-29	25	11	-35
	Left fusiform gyrus	--	46	45	33	-20	45	33	-26
2	Right and left superior frontal gyrus	BA 6, BA8	483	-8	-34	50	-8	-32	56

Table 4. 9. Degrees of freedom (DF), F-values and significance levels for anterior cingulate cortex (ACC), precentral and postcentral gyri of the fMRI data

Variable	Effect	DF	F Value	Pr > F
ACC	Time	2	4.11	0.018
	Gender	1	6.28	0.013
	Time*Gender	2	1.74	0.179
	Side	1	2.17	0.143
	Condition	2	0.83	0.44
Precentral Gyrus	Time	2	5.34	0.006
	Gender	1	0.00	0.973
	Time*Gender	2	4.30	0.015
	Side	1	0.13	0.719
	Condition	2	2.23	0.112
Postcentral Gyrus	Time	2	11.65	<0.001
	Gender	1	0.11	0.738
	Time*Gender	2	8.62	<0.001
	Side	1	0.13	0.716
	Condition	2	1.81	0.168

Table 4. 10. Degrees of freedom (DF), F-values and significance levels for dorsolateral prefrontal cortex (DLPFC) and cerebellum of fMRI data

Variable	Effect	DF	F Value	Pr > F
DLPFC	Time	2	6.89	0.0014
	Gender	1	5.70	0.0182
	Time*Gender	2	7.25	0.001
	Side	1	0.02	0.894
	Condition	2	1.08	0.342
Cerebellum	Time	2	0.73	0.481
	Gender	1	1.63	0.203
	Time*Gender	2	31.52	<0.001
	Side	2	2.42	0.091
	Gender*Side	2	1.55	0.215
	Condition	2	6.26	0.002

Table 4. 11. Estimated mean, standard error, t-values and significance levels for main effects of gender (female = F, male = M), time (baseline = 0, iUVFP = 1, recovery = 2), side (left = L, right = R) and condition (whisper = W, voice = V, imagine = I); and interaction effect of time and gender for anterior cingulate cortex (ACC).

Effect	Gender	Time	Side	Cond- ition	Estimate	Std Error	t Value	Pr > t
Gender	F				3.82	0.30	12.58	<0.001
	M				2.68	0.34	7.89	<0.001
Time		0			4.005	0.39	10.16	<0.001
		1			3.32	0.39	8.43	<0.001
		2			2.41	0.39	6.12	<0.001
Time* Gender	F	0			4.8	0.53	9.16	<0.001
	M				3.19	0.59	5.43	<0.001
	F	1			4.25	0.53	8.08	<0.001
	M				2.39	0.59	4.08	<0.001
	F	2			3.86	0.53	4.54	<0.001
	M				2.43	0.59	4.15	<0.001
Side			L		3.58	0.32	11.16	--
			R		2.91	0.32	9.08	--
Cond- ition				W	3.66	0.39	9.31	--
				V	3.01	0.39	7.66	--
				I	3.66	0.39	7.83	--

Table 4. 12. Estimated mean, standard error, t-values and significance levels for main effects of gender (female = F, male = M), time (baseline = 0, iUVFP = 1, recovery = 2), side (left = L, right = R) and condition (whisper = W, voice = V, imagine = I); and interaction effect of time and gender for precentral gyrus

Effect	Gender	Time	Side	Cond- ition	Estimate	Std Error	t Value	Pr > t
Gender	F				2.60	0.21	12.50	--
	M				2.59	0.23	11.13	--
Time		0			3.31	0.27	12.23	<0.001
		1			2.13	0.27	7.89	<0.001
		2			2.35	0.27	8.69	<0.001
Time* Gender	F	0			3.92	0.36	10.87	<0.001
	M				2.69	0.40	6.68	<0.001
	F	1			2.02	0.36	5.62	<0.001
	M				2.24	0.40	5.56	<0.001
	F	2			1.86	0.36	5.16	<0.001
	M				2.84	0.40	7.05	<0.001
Side			L		2.54	0.22	11.54	--
			R		2.65	0.22	12.05	--
Condi- tion				W	3.06	0.27	11.36	--
				V	2.36	0.27	8.77	--
				I	2.37	0.27	8.80	--

Table 4. 13. Estimated mean, standard error, t-values and significance levels for main effects of gender (female = F, male = M), time (baseline = 0, iUVFP = 1, recovery = 2), side (left = L, right = R) and condition (whisper = W, voice = V, imagine = I); and interaction effect of time and gender for postcentral gyrus.

Effect	Gender	Time	Side	Condition	Estimate	Std Error	t Value	Pr > t
Gender	F				2.64	0.22	12.12	--
	M				2.53	0.24	10.39	--
Time		0			3.69	0.28	13.06	<0.001
		1			2.12	0.28	7.50	<0.001
		2			1.94	0.28	6.85	<0.001
Time* Gender	F	0			4.67	0.37	12.40	<0.001
	M				2.71	0.42	6.43	<0.001
	F	1			1.50	0.38	3.98	<0.001
	M				2.74	0.42	6.50	<0.001
	F	2			1.74	0.38	4.61	<0.001
	M				2.13	0.42	5.06	<0.001
Side			L		2.53	0.23	10.97	--
			R		2.64	0.23	11.48	--
Condition				W	3.02	0.28	10.71	--
				V	2.32	0.28	8.22	--
				I	2.42	0.28	8.59	--

Table 4. 14. Estimated mean, standard error, t-values and significance levels for main effects of gender (female = F, male = M), time (baseline = 0, iUVFP = 1, recovery = 2), side (left = L, right = R) and condition (whisper = W, voice = V, imagine = I); and interaction effect of time and gender for dorsolateral prefrontal cortex (DLPFC).

Effect	Gender	Time	Side	Condi- tion	Estimate	Std Error	t Value	Pr > t
Gender	F				2.07	0.18	11.66	<0.001
	M				2.70	0.20	13.63	<0.001
Time		0			1.93	0.23	8.37	<0.001
		1			2.15	0.23	9.35	<0.001
		2			3.07	0.23	13.33	<0.001
Time* Gender	F	0			2.04	0.38	6.66	<0.001
	M				1.81	0.34	5.28	<0.001
	F	1			2.11	0.31	6.88	<0.001
	M				2.19	0.34	6.39	<0.001
	F	2			2.04	0.31	6.65	<0.001
	M				4.10	0.34	11.94	<0.001
Side			L		2.40	0.19	12.81	--
			R		2.37	0.19	12.62	--
Condi- tion				W	2.66	0.23	11.59	--
				V	2.26	0.23	9.83	--
				I	2.66	0.23	9.76	--

Table 4. 15 Estimated mean, standard error, t-values and significance levels for main effects of gender (female = F, male = M), time (baseline = 0, iUVFP = 1, recovery = 2), side (left = L, right = R, midline = M) and condition (whisper = W, voice = V, imagine = I); and interaction effect of time and gender for cerebellum.

Effect	Gender	Time	Side	Condition	Estimate	Std. Error	t -Value	Pr > t
Gender	F				2.09	0.09	22.82	--
	M				2.26	0.10	22.30	--
Time		0			2.22	0.12	18.74	--
		1			2.25	0.12	19.02	--
		2			2.06	0.12	17.39	--
Time* Gender	F	0			2.86	0.16	18.10	<0.001
	M				1.58	0.18	8.97	<0.001
	F	1			1.58	0.16	9.89	<0.001
	M				2.92	0.17	16.74	<0.001
	F	2			1.83	0.16	11.58	<0.001
	M				2.29	0.18	12.98	<0.001
Side			L		2.24	0.12	18.87	<0.001
			R		2.32	0.12	19.62	<0.001
			M		1.97	0.12	16.66	<0.001
Gender *Side	F		L		2.31	0.16	14.66	--
			R		2.13	0.16	13.48	--
			M		1.82	0.16	11.41	--
	M		L		2.15	0.18	14.66	--
			R		2.12	0.18	13.48	--
			M		2.52	0.18	11.41	--
Condi- tion				W	2.52	0.12	21.45	<0.001
				V	1.99	0.12	17.00	<0.001
				I	2.02	0.12	16.91	<0.001

Table 4. 16. Differences between estimated means of percent BOLD activity for baseline (0) and iUVFP (1), iUVFP (1) and recovery (2) and; baseline (0) and recovery (2) for the regions of interest (ROI). The differences are calculated for the group (n=9), females (F) (n=5) and males (M) (n=4).

ROI	Mean (0)-Mean (1)			Mean (1)- Mean (2)			Mean (0)- Mean (2)		
	Group	F	M	Group	F	M	Group	F	M
ACC	0.69	0.55	0.80	0.91	0.39	-0.04	1.6	0.94	0.94
Precentral Gyrus	1.18	1.90	0.45	-0.22	0.16	-0.60	0.96	2.06	-0.15
Postcentral Gyrus	1.57	3.17	-0.03	0.18	-0.24	0.61	1.75	2.93	0.58
DLPFC	-0.22	0.07	-0.38	-0.92	0.07	-1.91	-1.14	0.00	-2.29
Cerebellum	-0.02	1.28	-1.34	0.19	-0.25	0.63	0.16	1.03	-0.71

Table 4. 17. Pearson's correlation coefficient (r^2) and p values for behavioral variables and fMRI regions of interest.

Behavioral variables	fMRI Regions of Interest				
	ACC	Precentral Gyrus	Postcentral Gyrus	DLPFC	Cerebellum
CAPE-V	$r^2 = 0.28$ p = 0.151	$r^2 = 0.18$ p = 0.381	$r^2 = 0.37$ p = 0.06*	$r^2 = 0.27$ p = 0.168	$r^2 = -0.08$ p = 0.701
NHR	$r^2 = -0.06$ p = 0.754	$r^2 = -0.11$ p = 0.58	$r^2 = -0.06$ p = 0.7313	$r^2 = 0.56$ p = 0.002*	$r^2 = -0.108$ p = 0.593
Ps	$r^2 = -0.03$ p = 0.871	$r^2 = -0.17$ p = 0.40	$r^2 = 0.05$ p = 0.79	$r^2 = 0.39$ p = 0.047*	$r^2 = 0.18$ p = 0.38
LAR	$r^2 = -0.17$ p = 0.41	$r^2 = -0.10$ p = 0.63	$r^2 = -0.15$ p = 0.46	$r^2 = -0.29$ p = 0.140	$r^2 = 0.04$ p = 0.854

Figure 4. 1. Stroboscopic stills for n=1 at baseline (0), iUVFP (1) and recovery (2). Normal vocal fold positioning seen at baseline and recovery in the abducted position, with a posterior glottal gap in the adducted position. Asymmetric vocal fold positioning seen during iUVFP with the right (R) vocal fold in a paramedian position compared to left (L), and an absence of glottic closure during adduction.

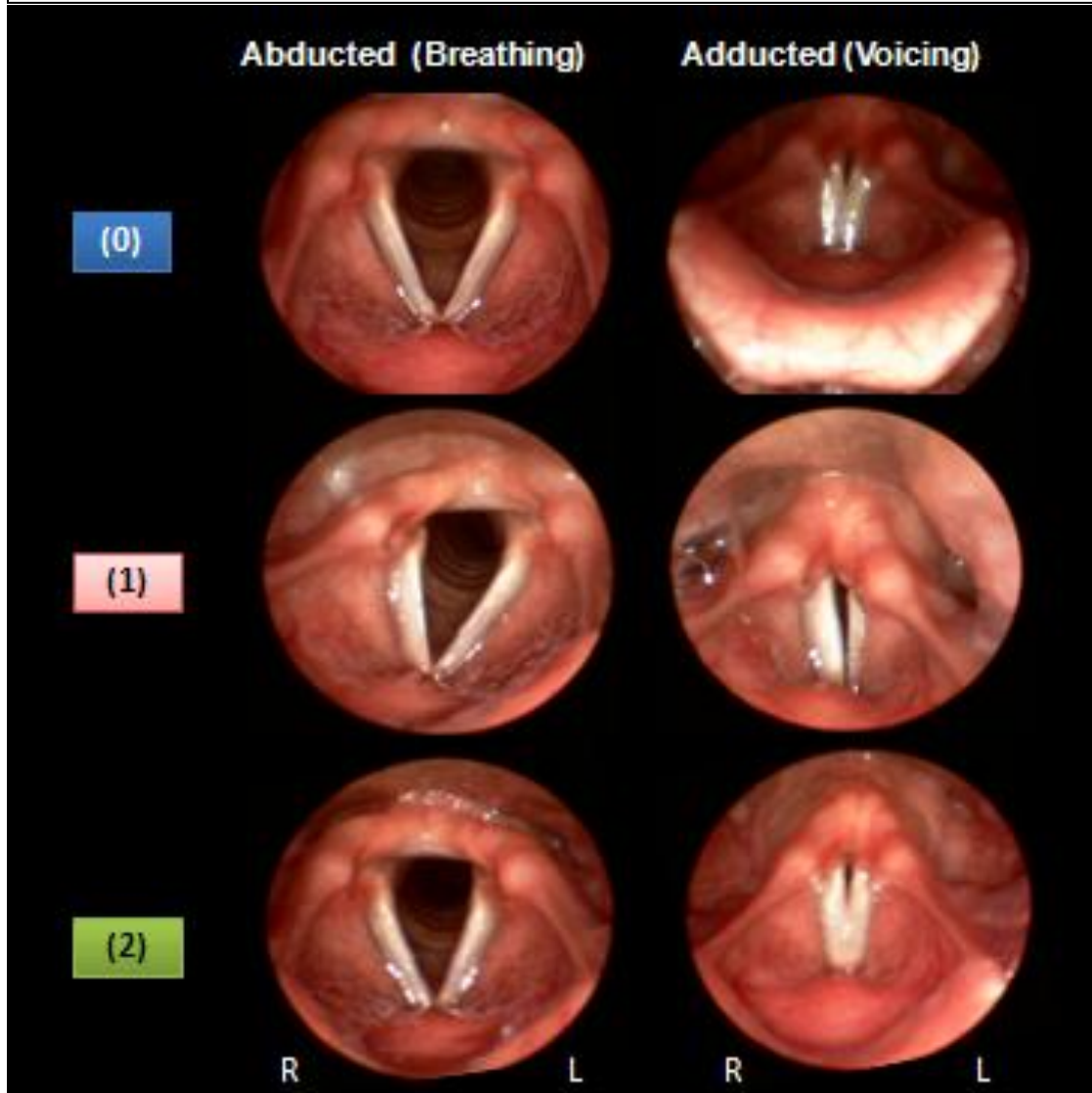


Figure 4. 2. FMRI BOLD-signals (n=9) at baseline (0), during iUVFP (1), and recovery (2) for 3 regions of interest at $p < 0.05$. Activity during the “voice” condition is compared to overall activity. Specific regions of activation are circled.

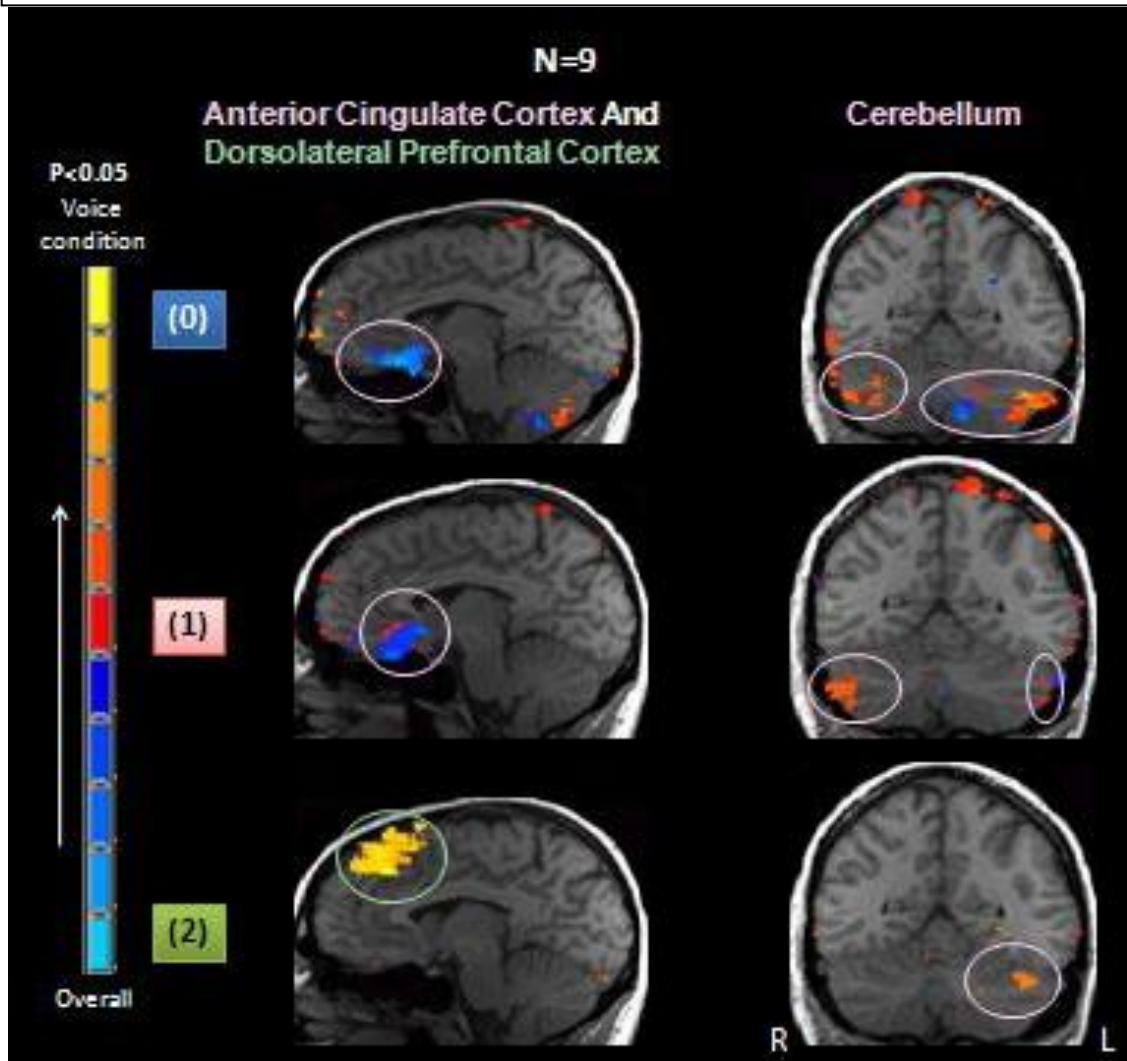


Figure 4. 3. FMRI BOLD-signals (n=1) for a male and female participant at baseline (0), during iUVFP (1), and recovery (2) at $p < 0.0001$. Activity during the “voice” condition is compared to overall activity.

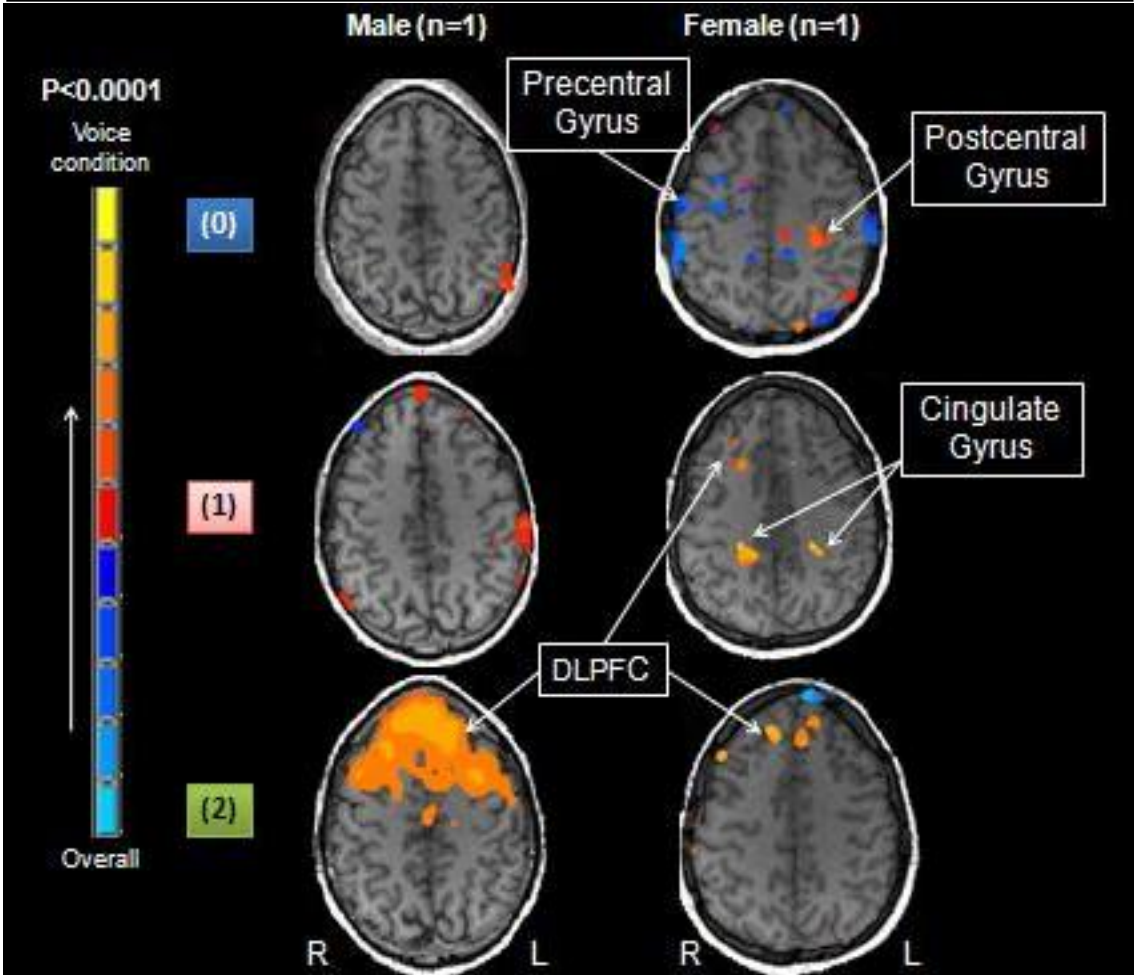


Figure 4.4. Participant profile plots for Consensus Auditory Perceptual Evaluation of Voice (CAPE-V) at baseline (0), iUVFP (1) and recovery (2) for males and females

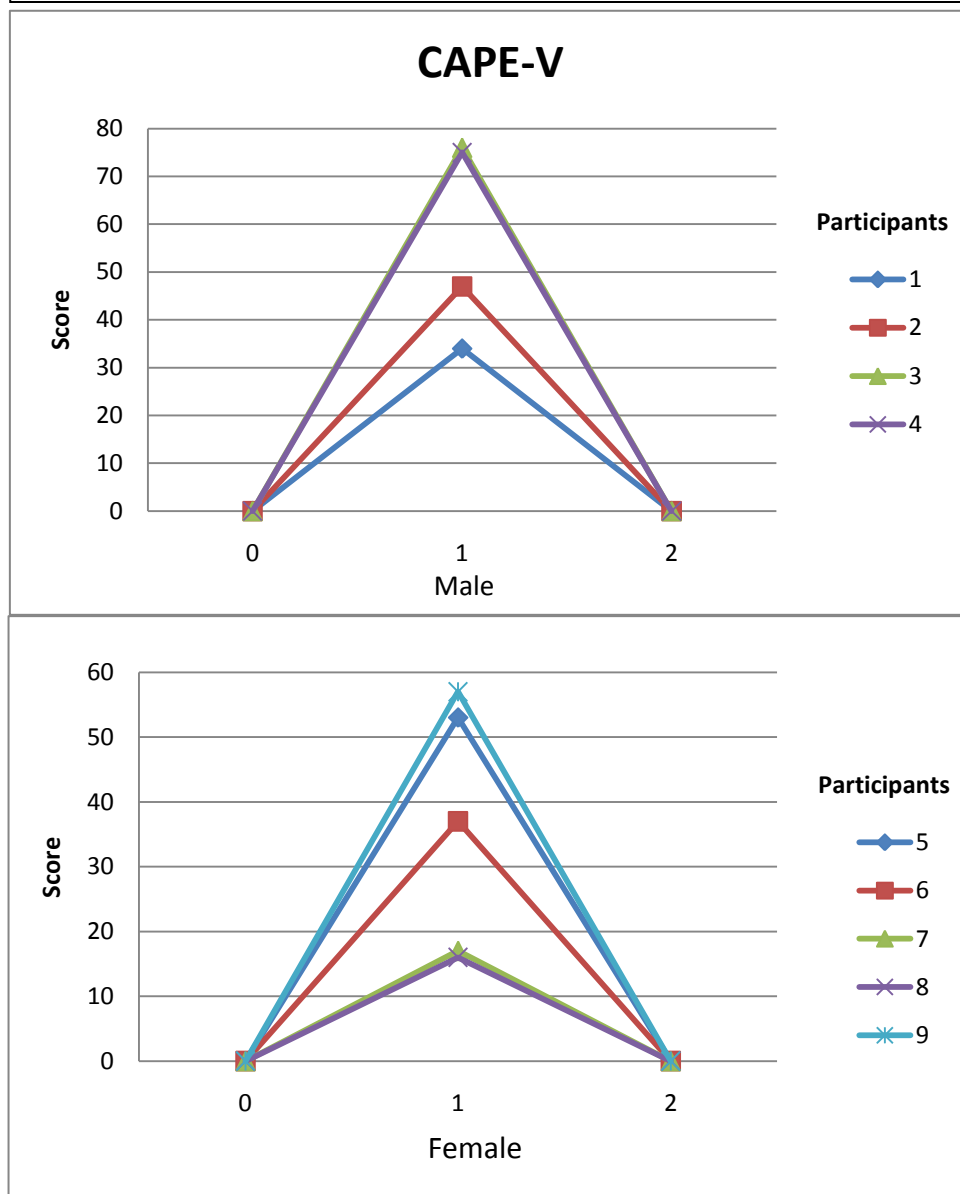
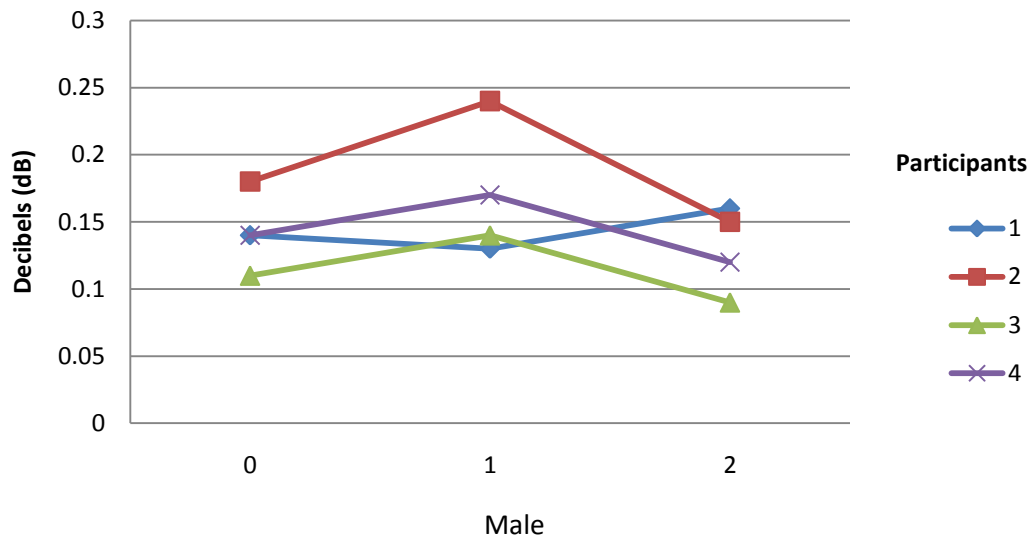


Figure 4. 5. Participant profile plots for noise-to-harmonic ratio (NHR) at baseline (0), iUVFP (1) and recovery (2) for males and females



NHR

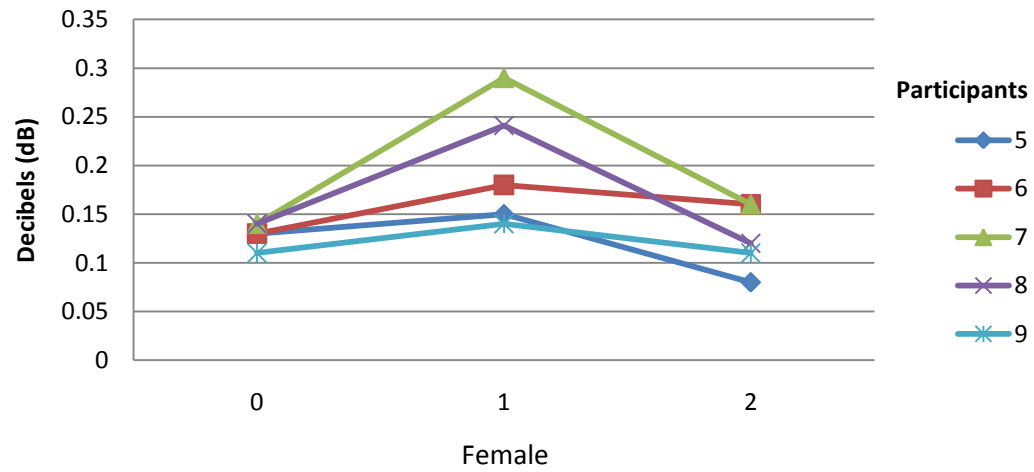


Figure 4. 6. Participant profile plots for subglottal pressure (P_s) at baseline (0), iUVFP (1) and recovery (2) for males and females

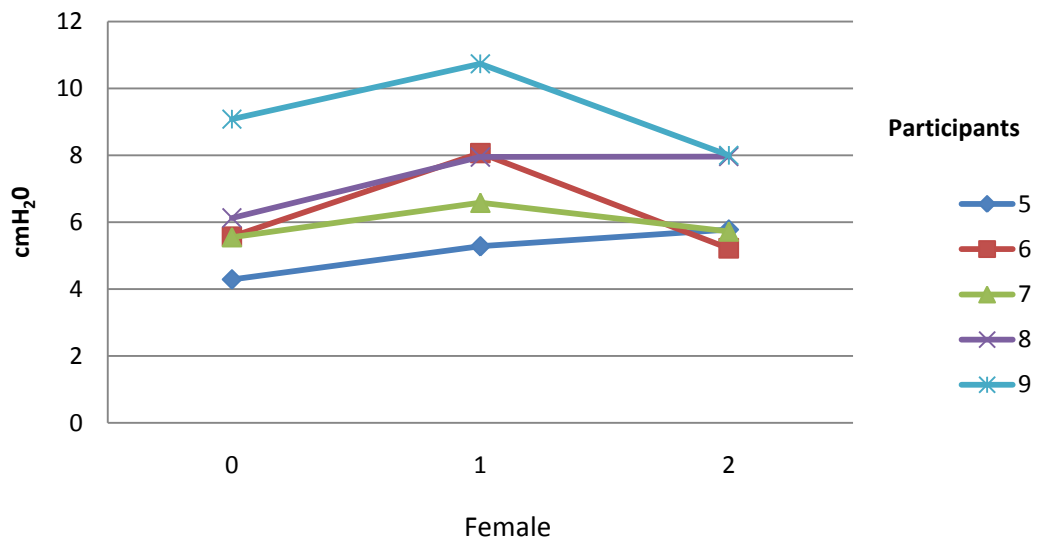
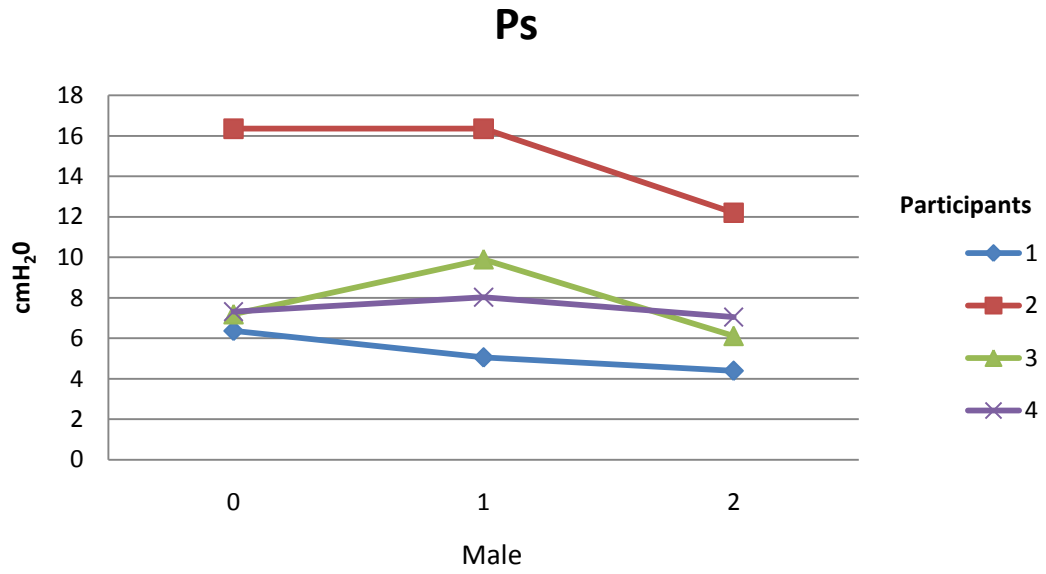


Figure 4. 7. Participant profile plots for laryngeal airway resistance (LAR) at baseline (0), iUVFP (1) and recovery (2) for males and females.

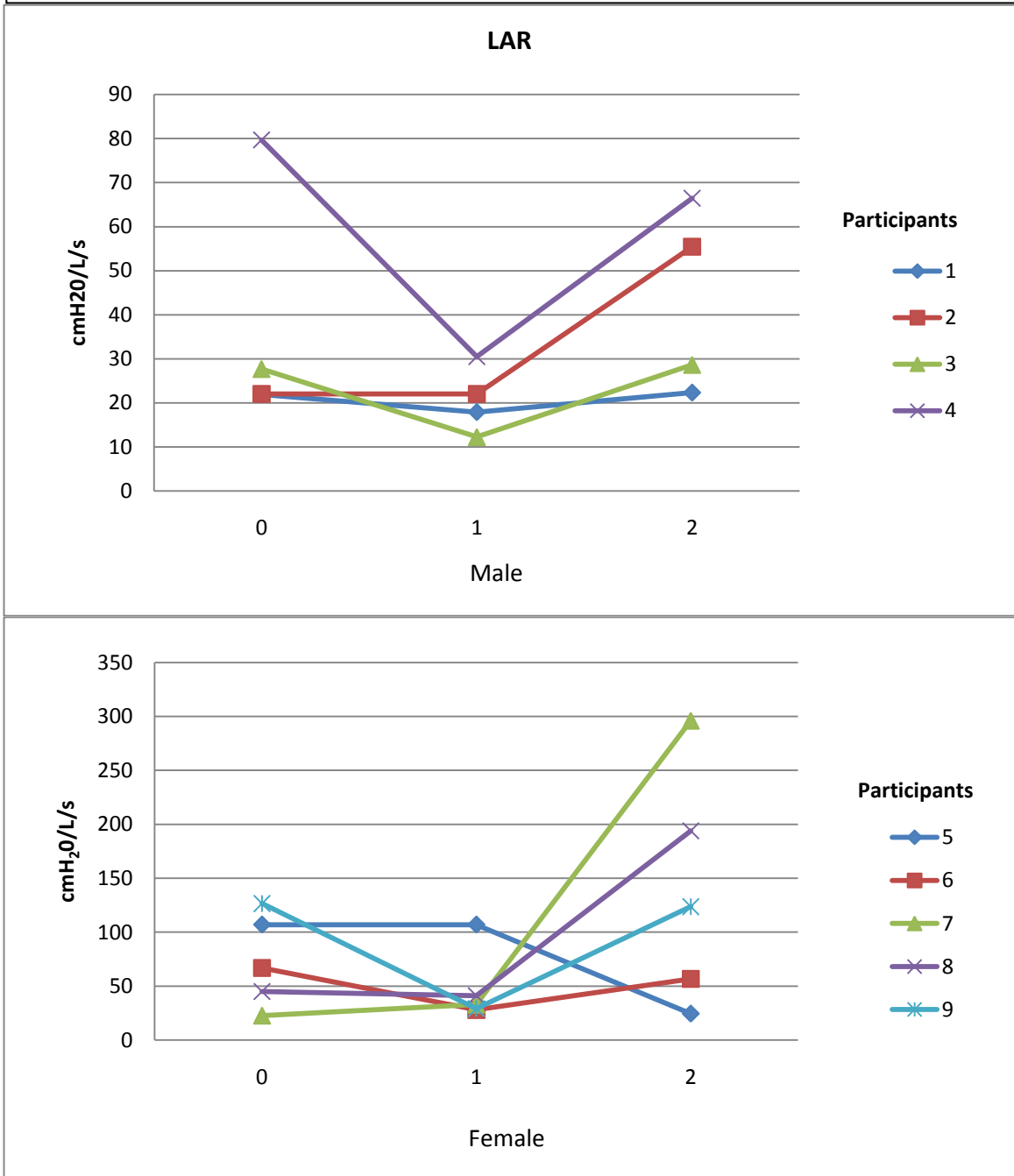


Figure 4. 8 Graph for estimated means of for regions of interest (ROI) for overall activity during baseline, iUVFP and recovery.

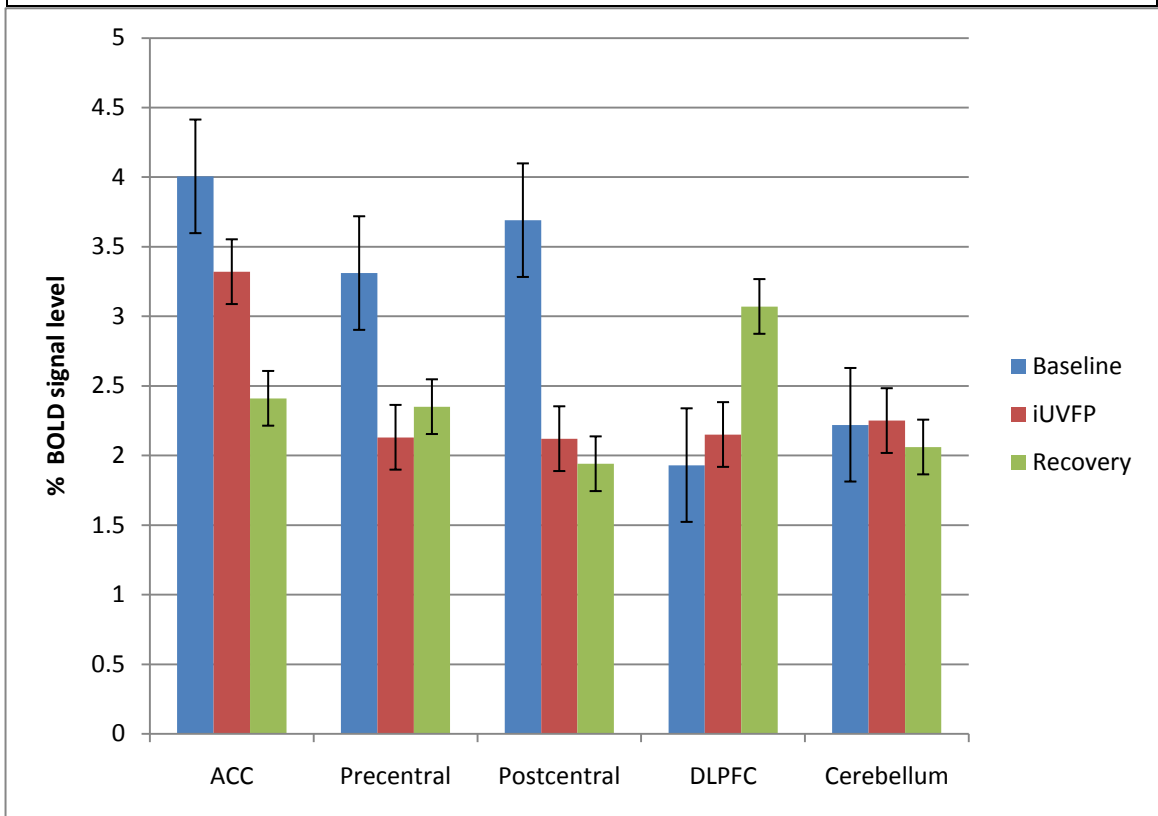


Figure 4.9 Graphs for estimated means for regions of interest (ROI) for overall activity during baseline, iUVFP and recovery for males and females.

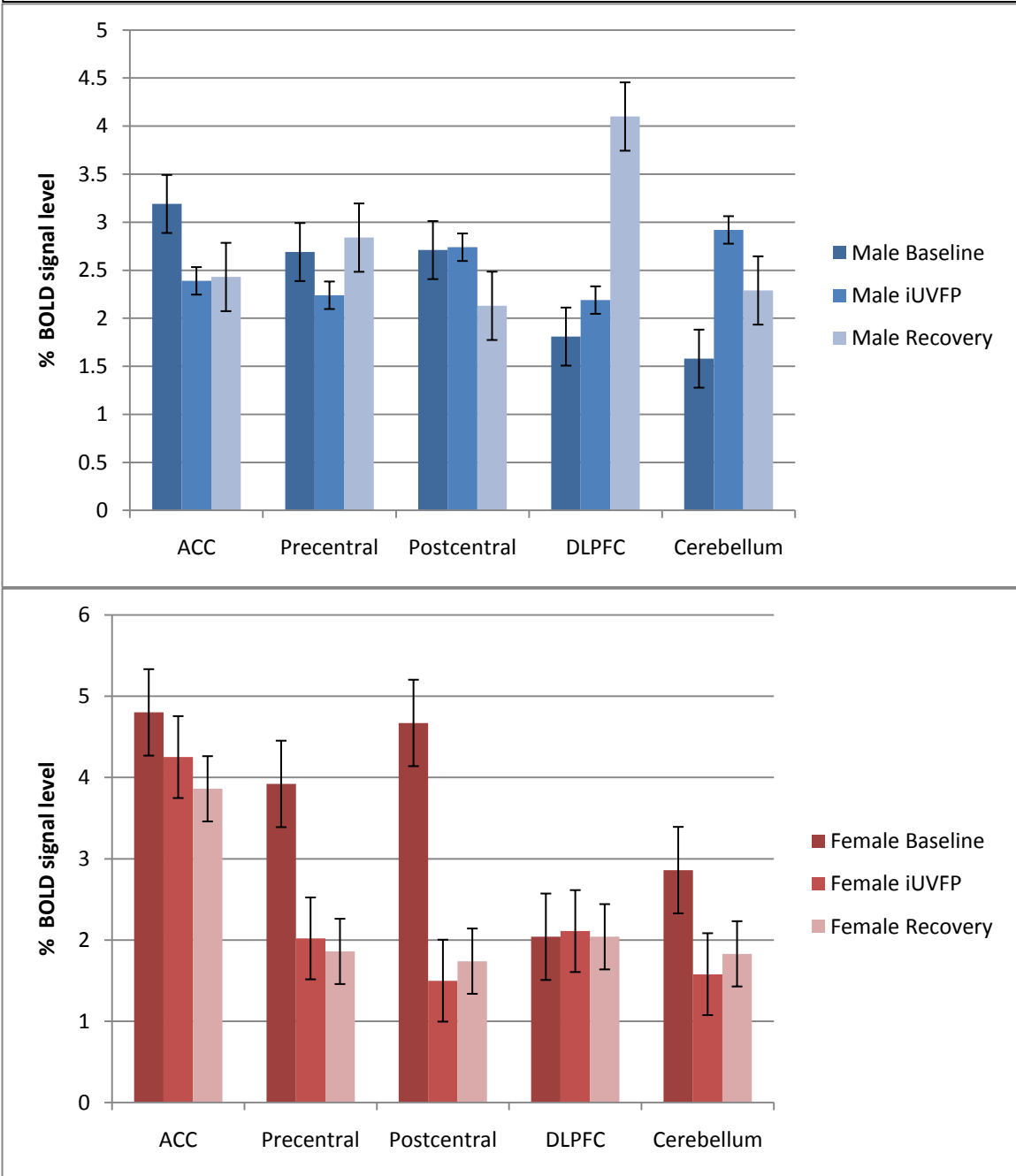


Figure 4. 10 Participant profile graphs for left anterior cingulate cortex (ACC) activity at baseline (0), iUVFP (1) and recovery (2) for males and females for the conditions of whisper, voice and imagine.

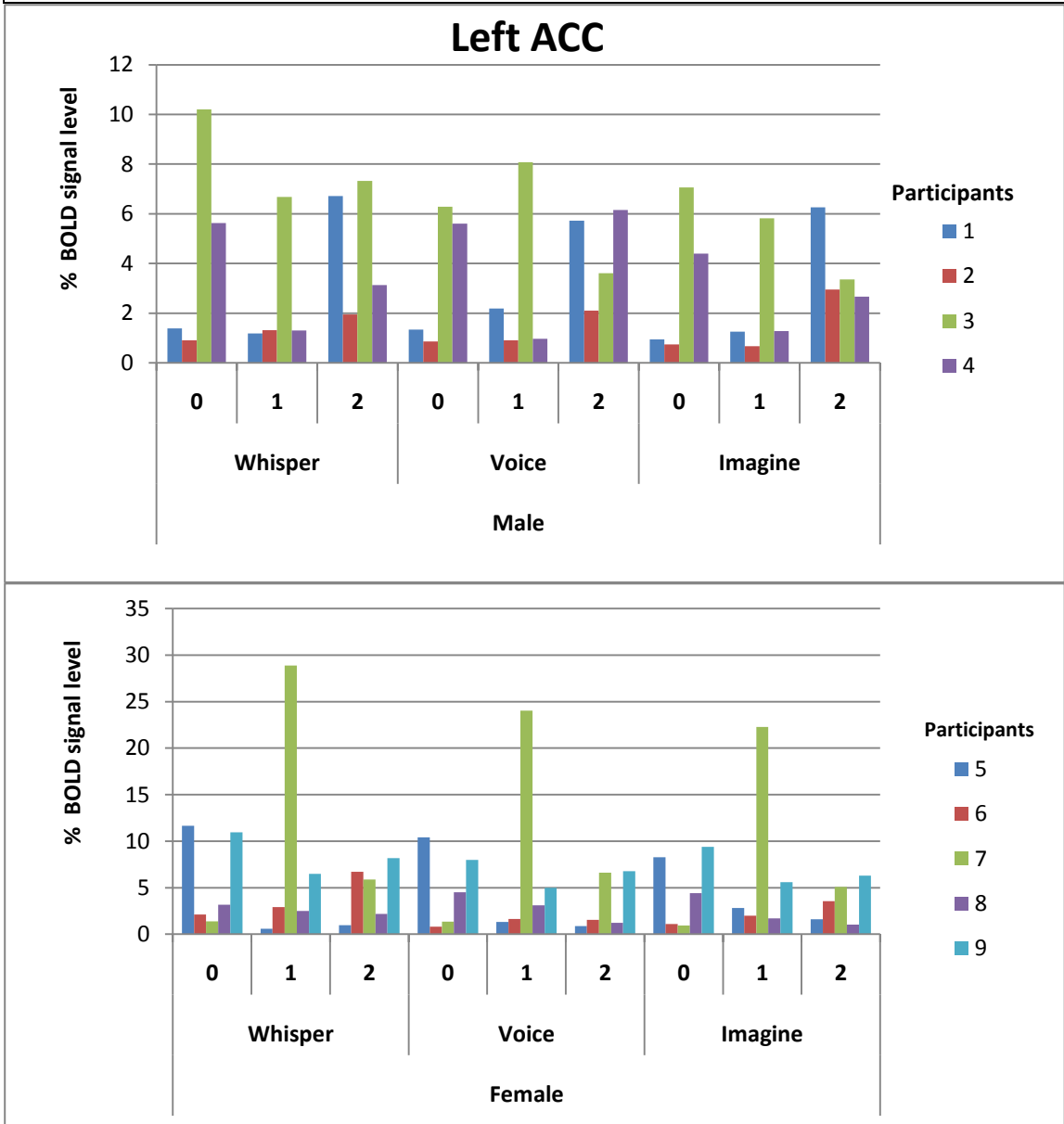


Figure 4. 11 Participant profile plot for right anterior cingulate cortex (ACC) activity at baseline (0), iUVFP (1) and recovery (2) for males and females for the conditions of whisper, voice and imagine.

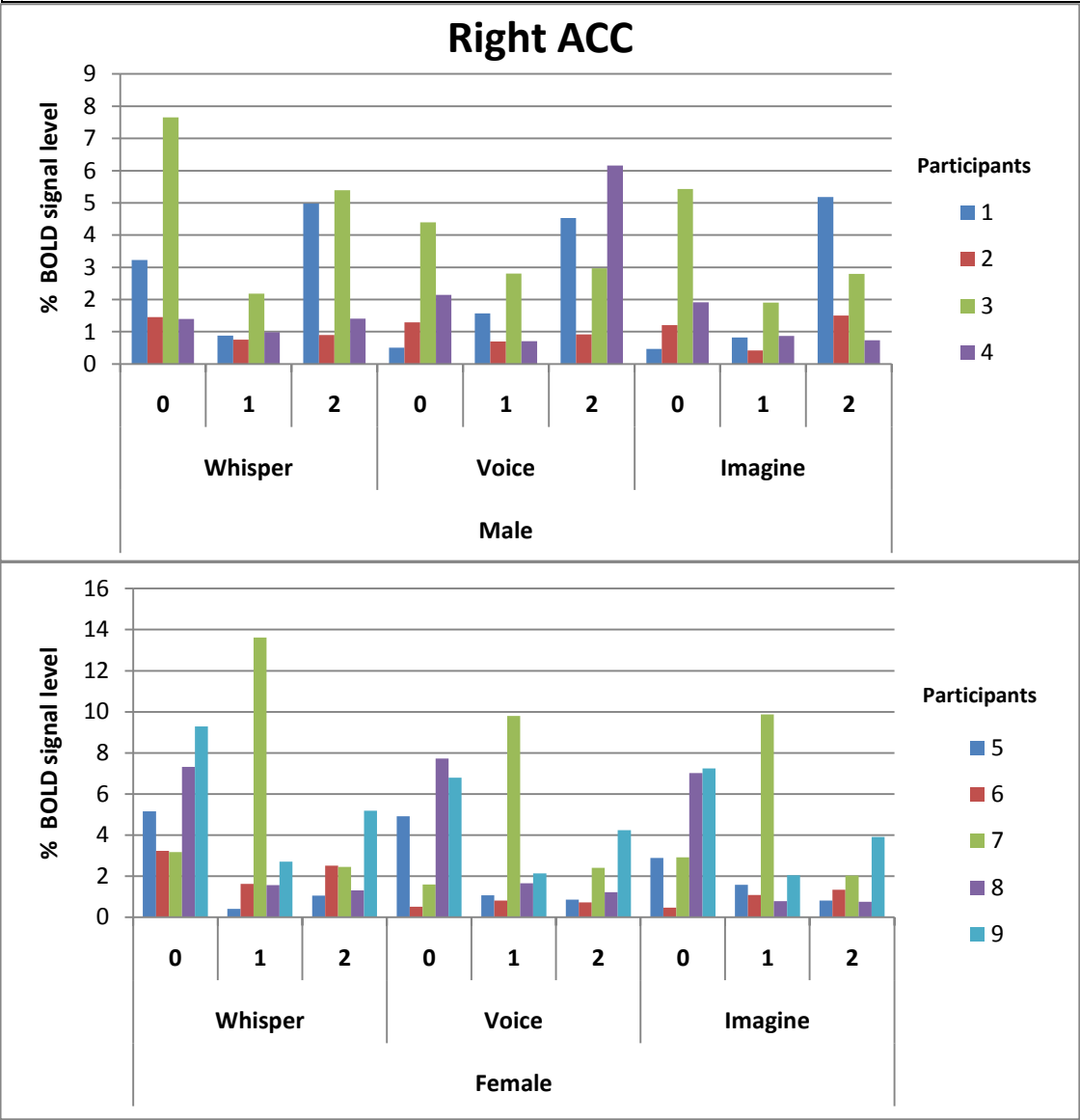


Figure 4. 12. Participant profile plot for left precentral gyrus activity at baseline (0), iUVFP (1) and recovery (2) for males and females for the conditions of whisper, voice and imagine.

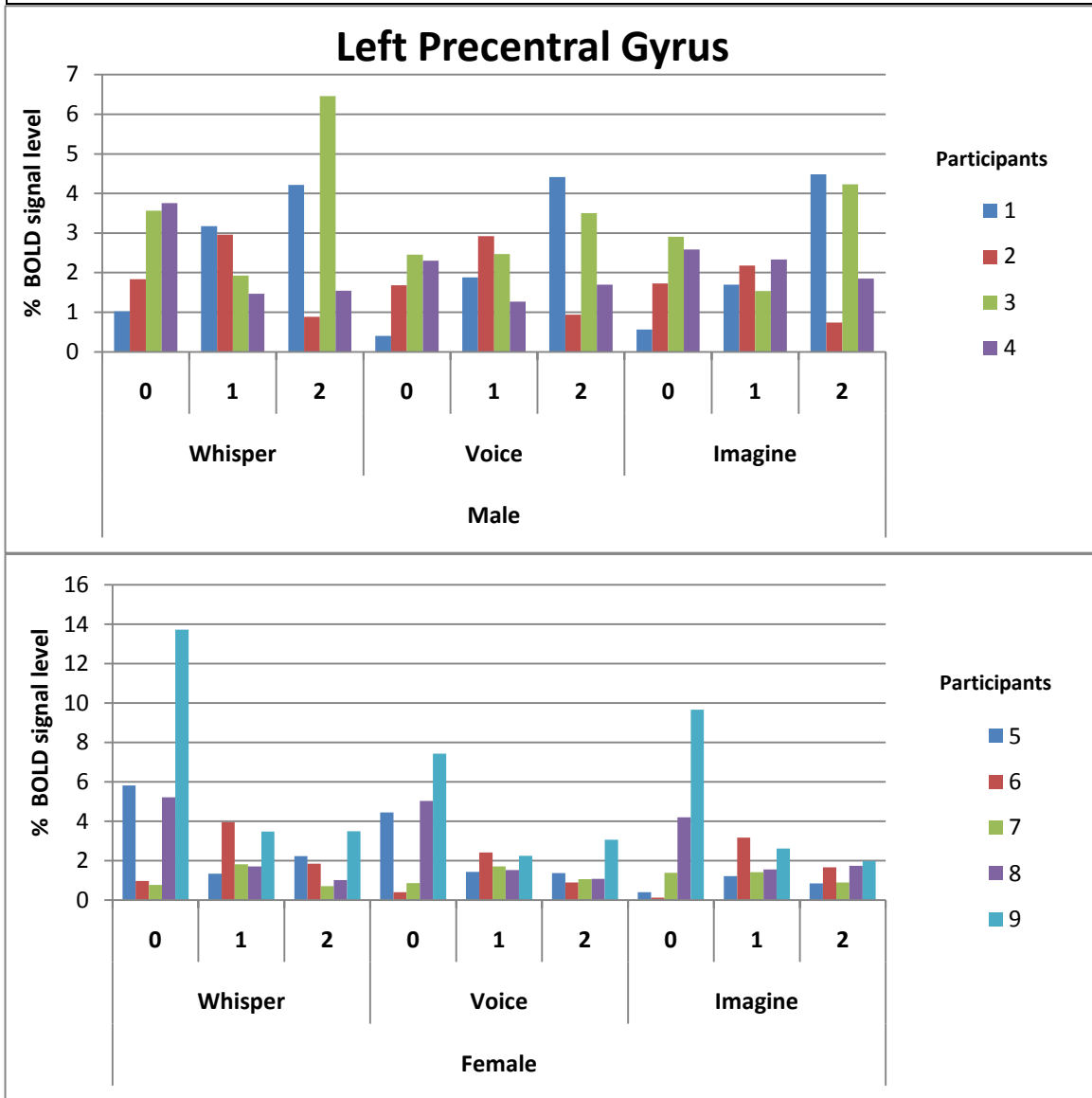


Figure 4. 13. Participant profile plot for right precentral gyrus activity at baseline (0), iUVFP (1) and recovery (2) for males and females for the conditions of whisper, voice and imagine.

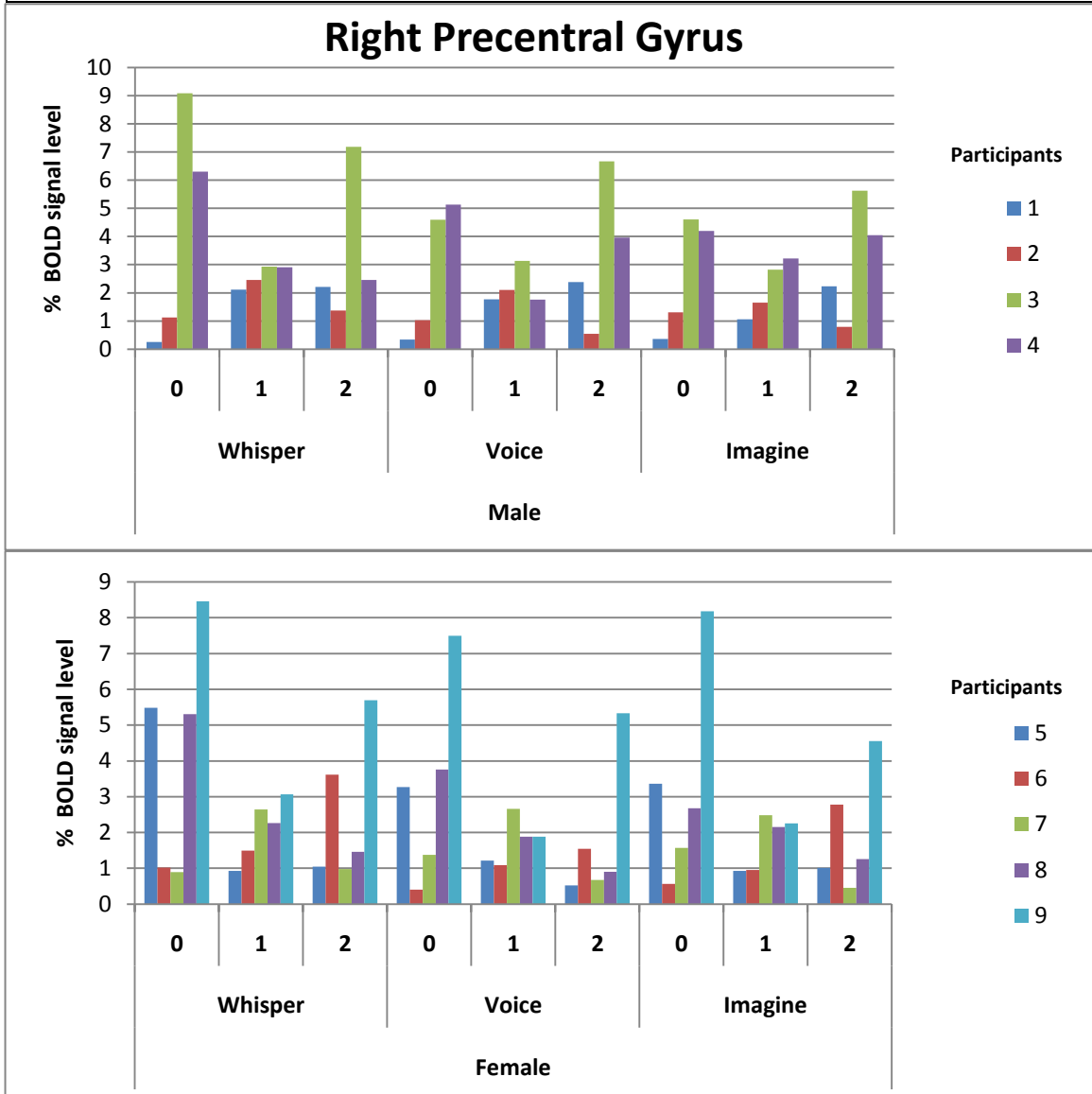


Figure 4. 14. Participant profile plot for left postcentral gyrus activity at baseline (0), iUVFP (1) and recovery (2) for males and females for the conditions of whisper, voice and imagine.

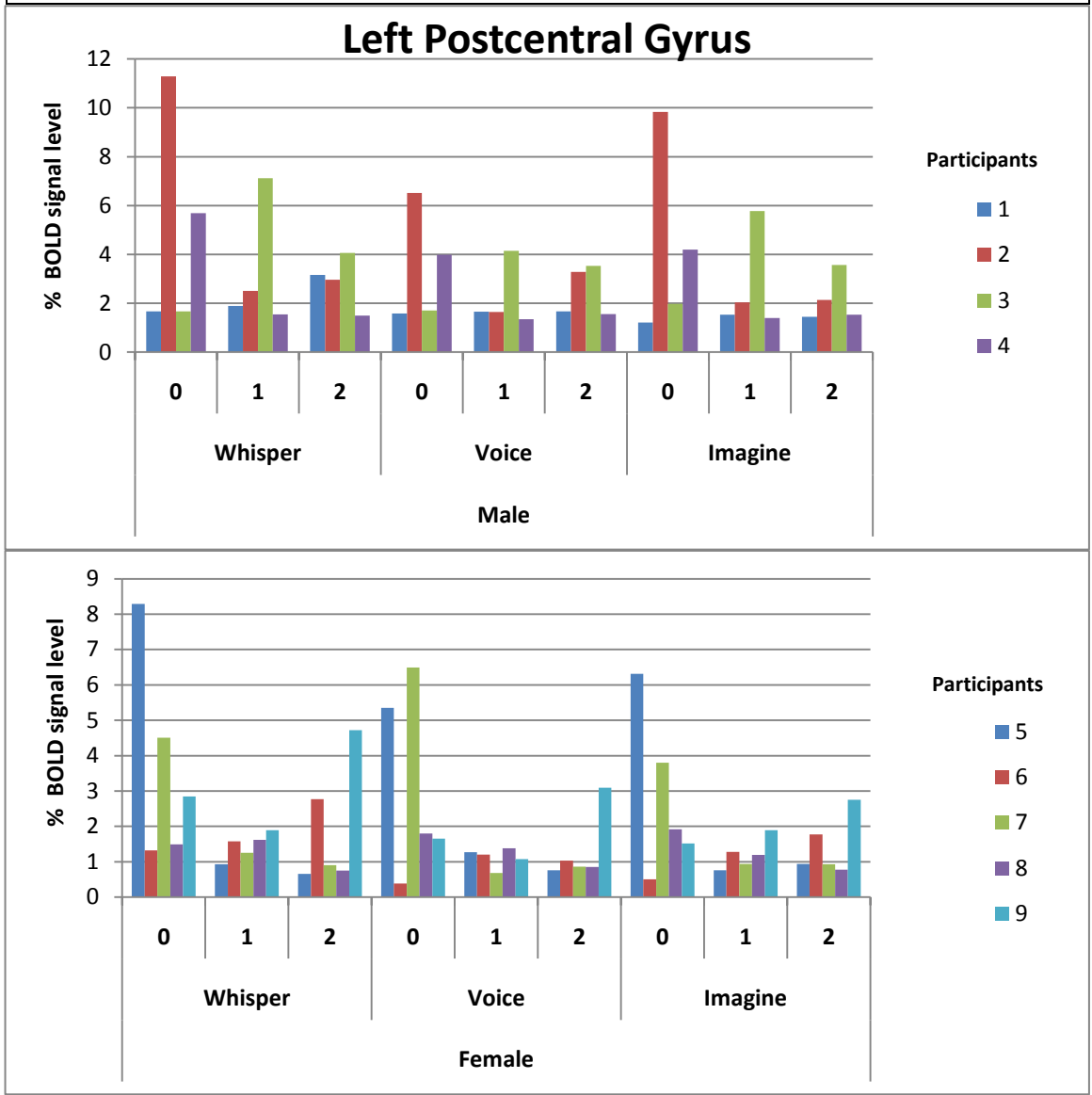


Figure 4. 15. Participant profile plot for right postcentral gyrus activity at baseline (0), iUVFP (1) and recovery (2) for males and females for the conditions of whisper, voice and imagine.

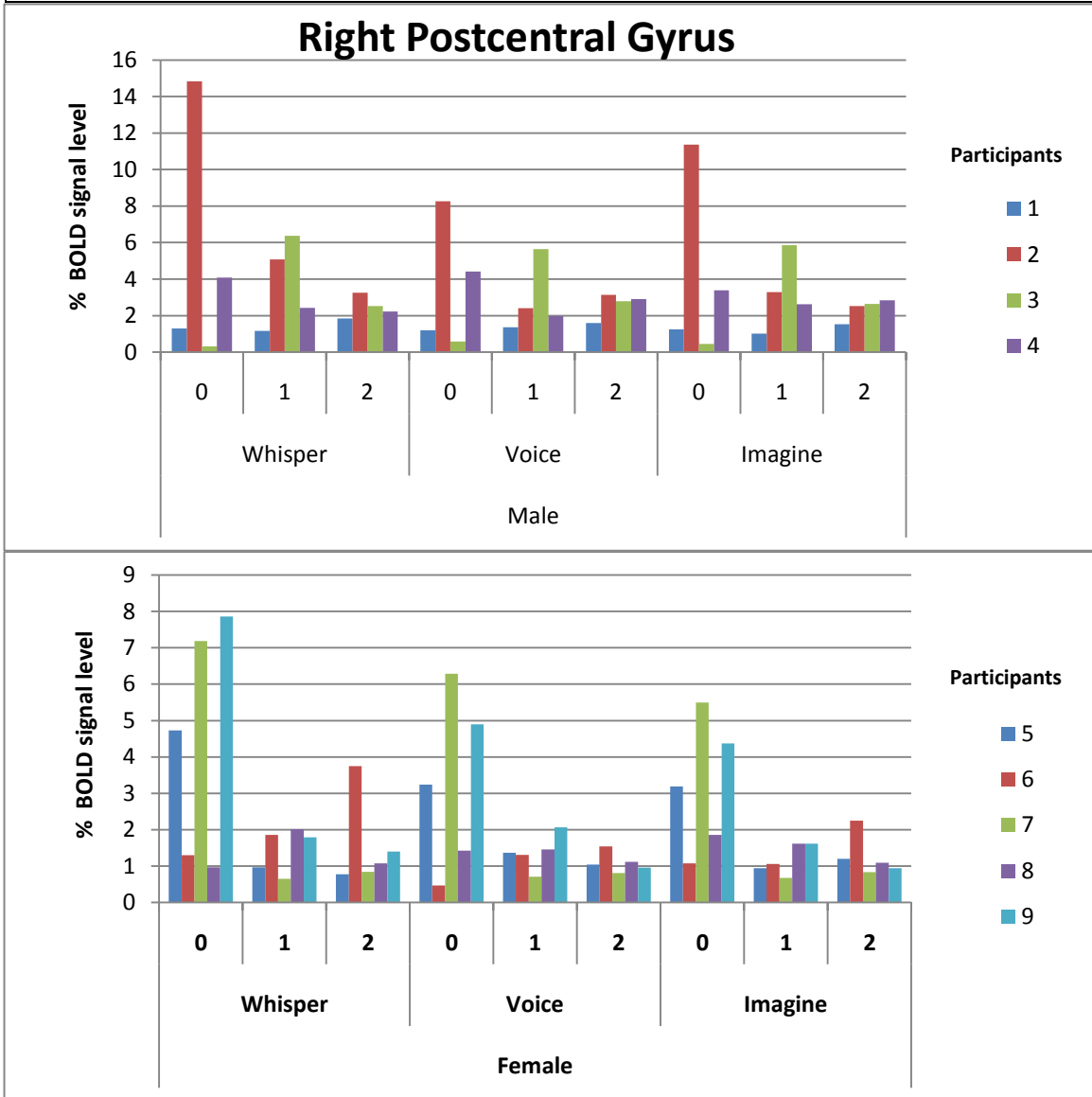


Figure 4. 16. Participant profile plot for left dorsolateral prefrontal cortex (DLPFC) activity at baseline (0), iUVFP (1) and recovery (2) for males and females for the conditions of whisper, voice and imagine.

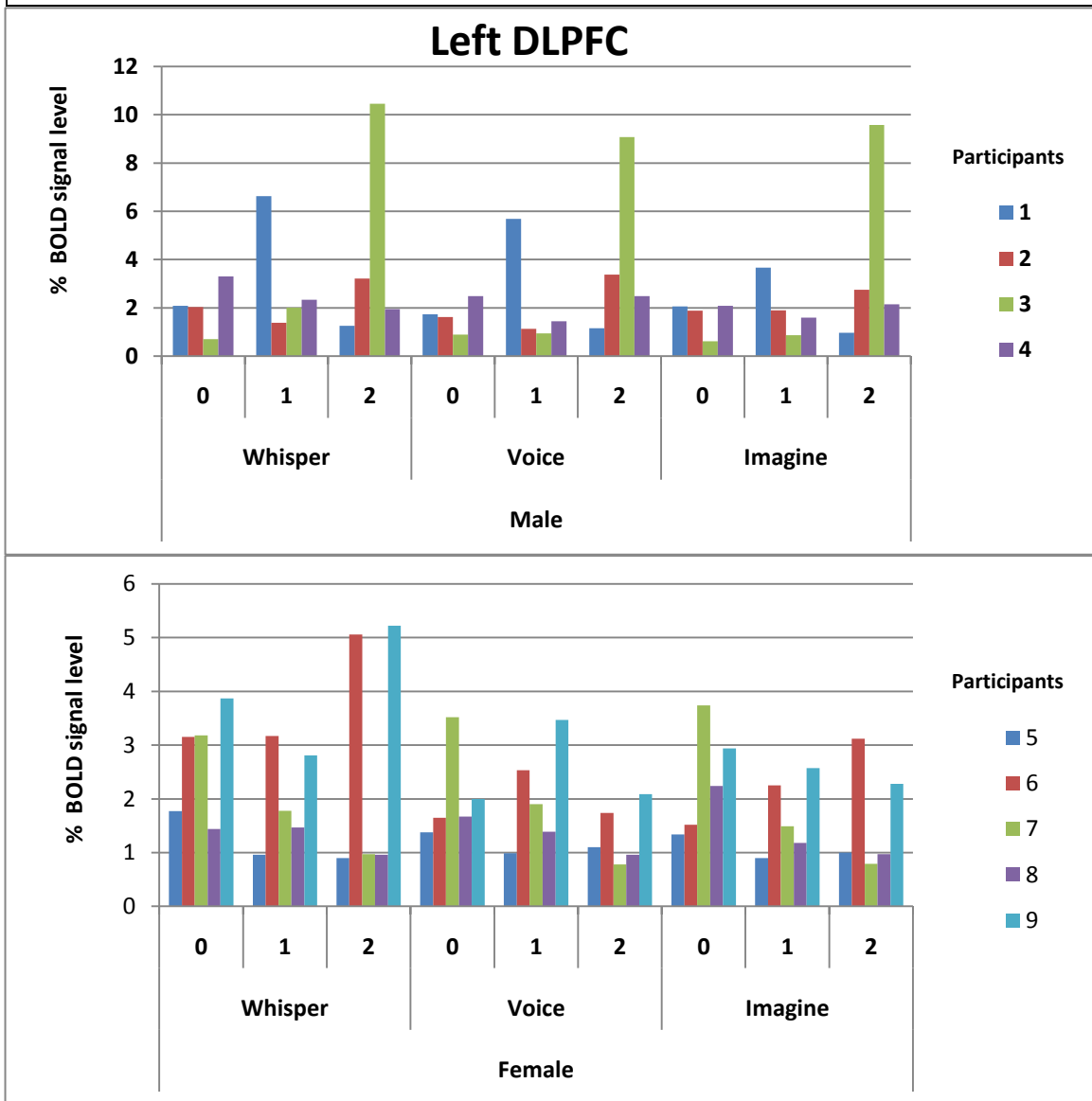


Figure 4. 17. Participant profile plot for right dorsolateral prefrontal cortex (DLPFC) activity at baseline (0), iUVFP (1) and recovery (2) for males and females for the conditions of whisper, voice and imagine.

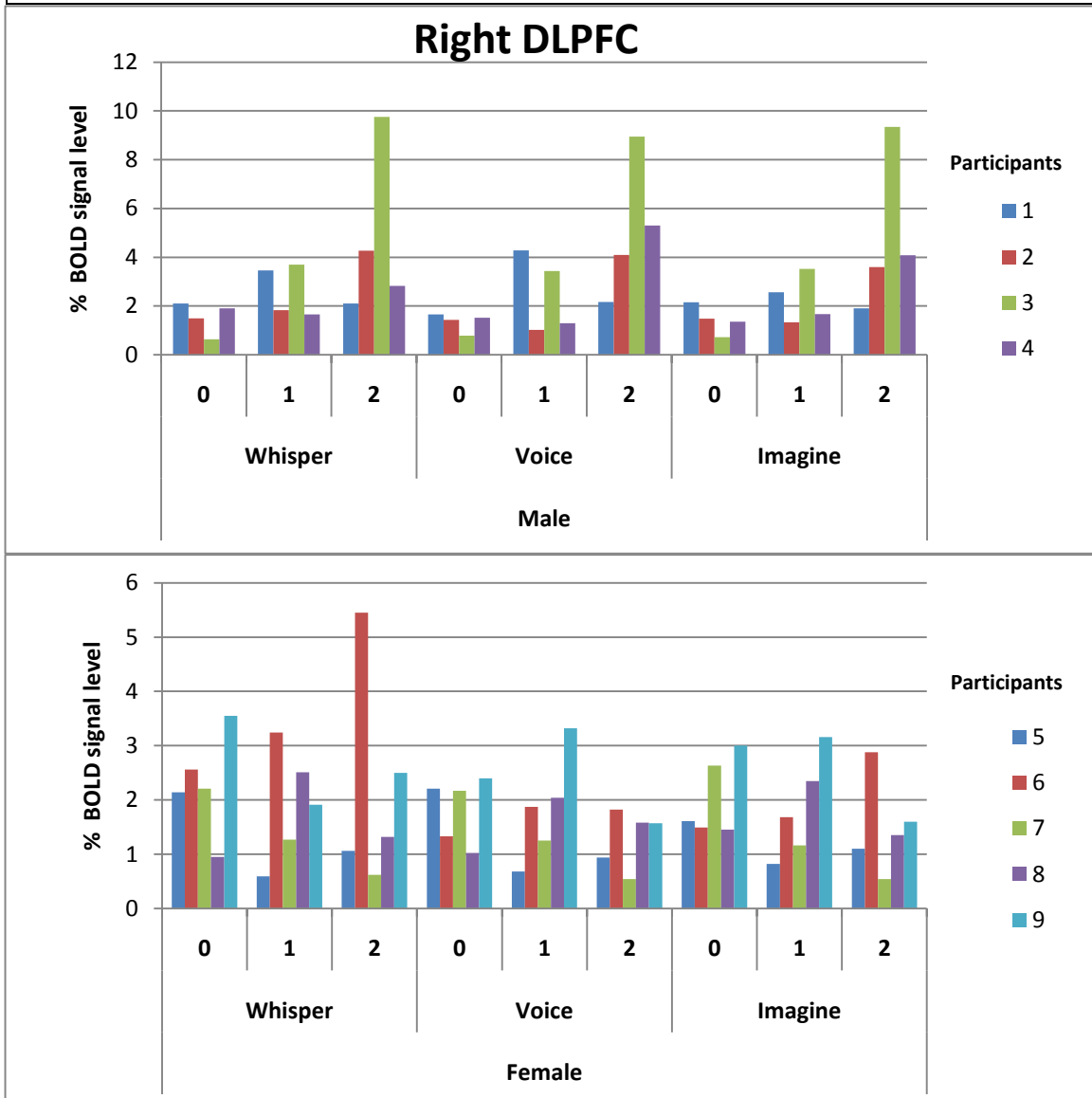


Figure 4. 18. Participant profile plot for left cerebellum activity at baseline (0), iUVFP (1) and recovery (2) for males and females for the conditions of whisper, voice and imagine.

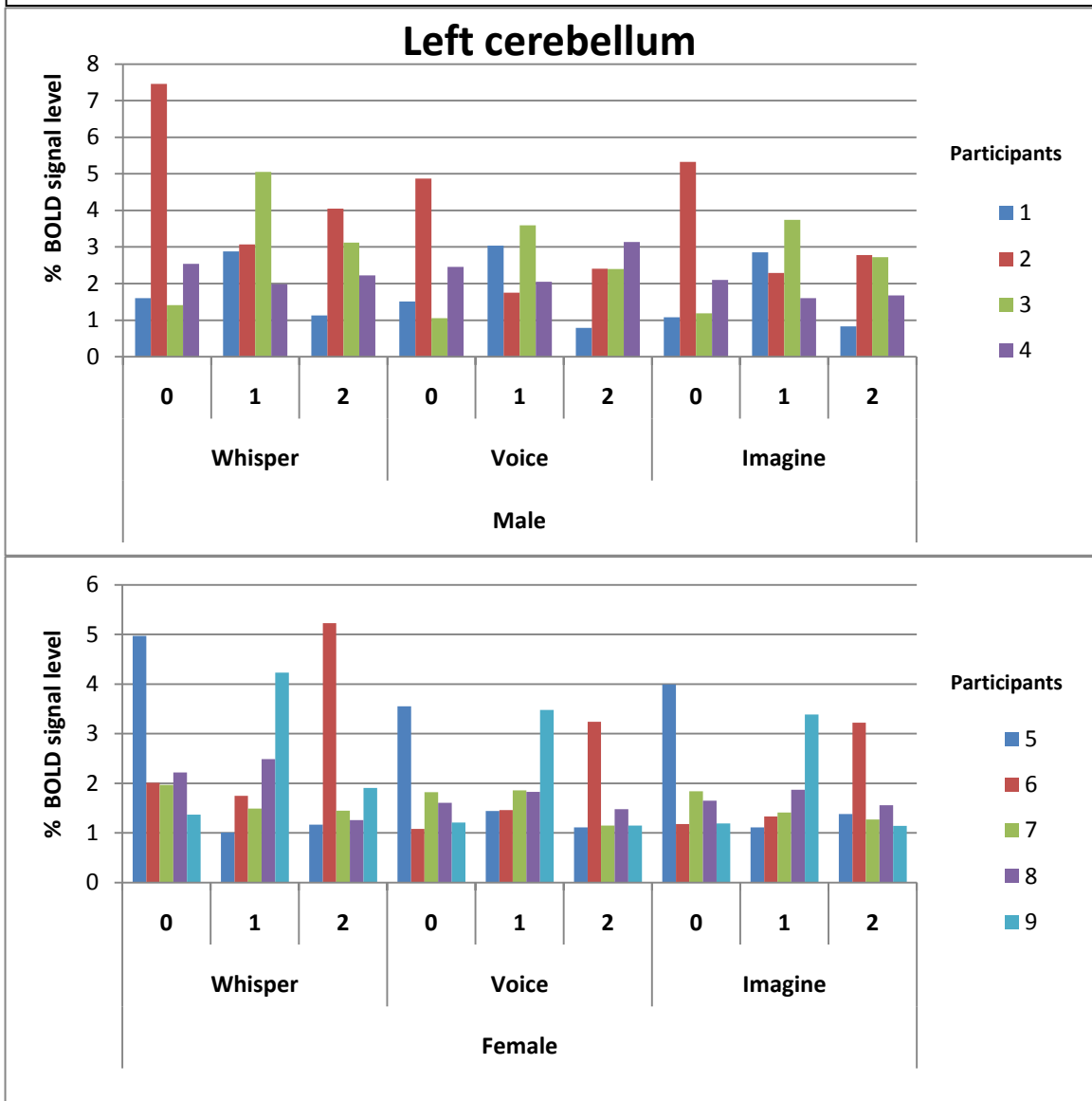


Figure 4. 19. Participant profile plot for right cerebellum activity at baseline (0), iUVFP (1) and recovery (2) for males and females for the conditions of whisper, voice and imagine.

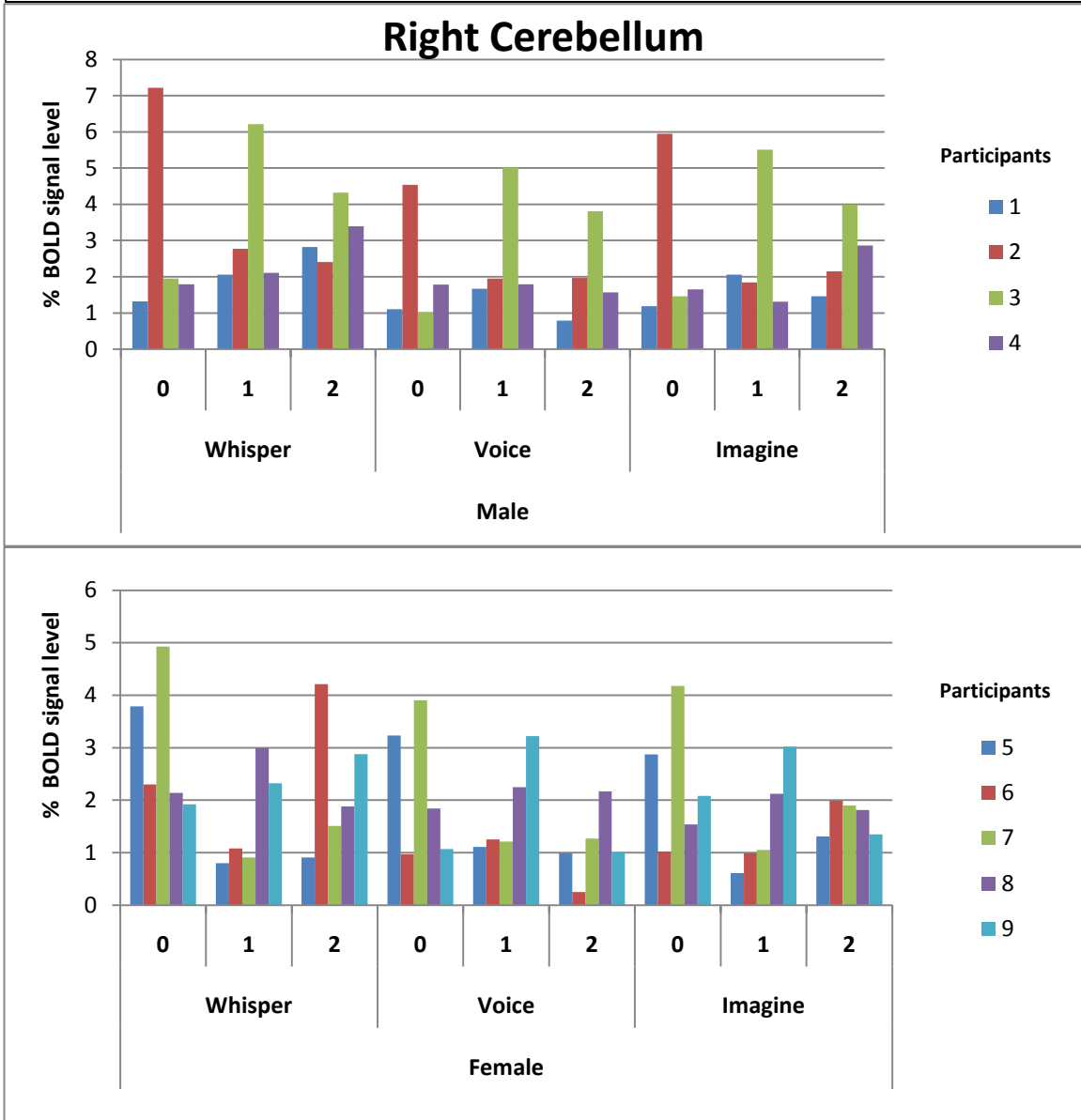
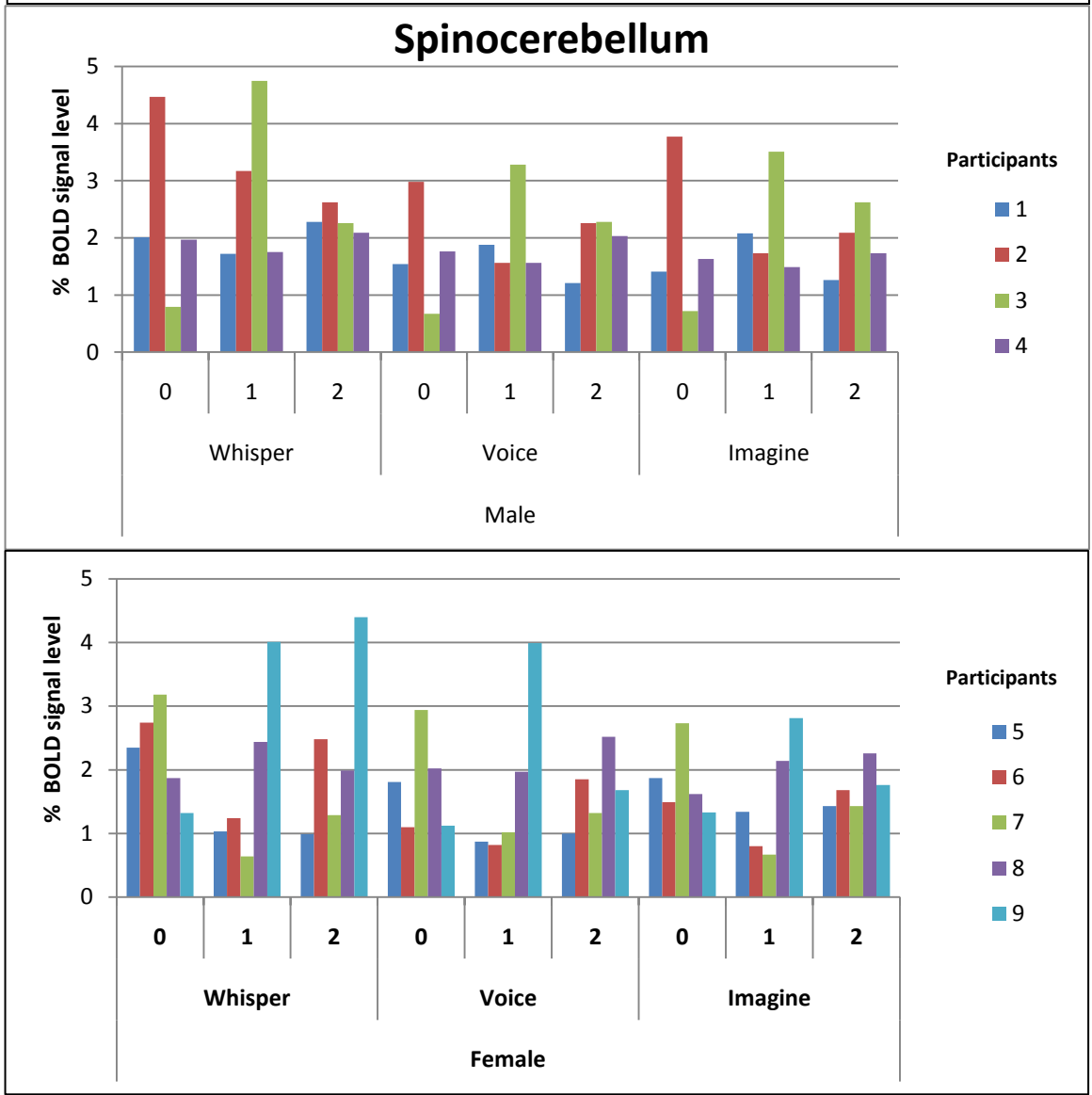


Figure 4. 20. Participant profile plot for spinocerebellum activity at baseline (0), iUVFP (1) and recovery (2) for males and females for the conditions of whisper, voice and imagine.



CHAPTER 5 : DISCUSSION

The results indicate a significant difference in brain activity during iUVFP and following recovery from this iUVFP, as compared to baseline. The behavioral measures and ROI for the fMRI variables were correlated to examine the presence of a relationship between the peripheral and central measures of the laryngeal system. This chapter will discuss the findings related to the overall effect of the paralysis on cortical activity, regions of interest and the correlation of the behavioral results with cortical activity.

BEHAVIORAL DATA

Although the trends seen in the behavioral results alone, are not the focus of our study, it is important to understand the relationship between the behavioral outcome results and the fMRI responses. Significant main effects of time were seen for CAPE-V and NHR and main effects of gender were seen for NHR and LAR for the behavioral data. Significant main effects of time or gender were not seen for Ps. CAPE-V results reflect the normal voice quality in these nine healthy volunteers at baseline and during recovery with dysphonia during the paralysis.^{36, 51} The size of the glottic gap resultant from a UVFP is dependent on the resting position of the paralyzed vocal fold. A more paramedian position will provide a larger glottal gap as compared to a midline positioning of the paralyzed vocal fold. This range in glottal gap size will cause a range in the severity of the hoarseness brought about by the UVFP.¹ As a result, patients vary in the results obtained on behavioral assessment. In addition, the UVFP can be secondarily compensated for by the laryngeal mechanism by *hypofunctioning* the system where compression of the supraglottic structures is reduced, with a disengagement of the

thyroarytenoid muscle.¹ The patients tend to use a falsetto voice¹ with a breathy voice quality due to inadequate glottic closure.

In contrast, the laryngeal mechanism can also *hyperfunction* as a form of compensation with significant medial compression of the ventricular folds and anterior-posterior compression of the glottis.¹ In this case, there may be lower airflow rate in the absence of a glottic closure or a tighter glottic closure during phonation. Elevated subglottal pressure and LAR may be observed in these individuals.² The position of the paralyzed vocal fold cannot be controlled non-surgically in the true patient population or when inducing UVFP and hence the variance in the response to the UVFP cannot be controlled. This may account for the non-significant main effects for subglottal pressure and the individual variability in the behavioral measures in general seen across participants.

FMRI DATA

Patterns of BOLD activity during the three time points were found to be distinct on both subjective examination and statistical analysis. Qualitative examination was performed on overall activity for the group at $p < 0.05$ and activation blobs with volume greater than one voxel (43 mm^3) were included. These data represent cumulative activation for tasks of whisper, voice, imagine and rest and hence may not mimic the activation pattern seen on the ROI analysis. A trend was seen across the regions for an increase in volume of activation with the paralyzed vocal fold specifically in the frontal lobe with the right medial frontal gyrus and in the temporal lobe (left superior temporal gyrus). The increased effort required to phonate with a sudden vocal fold paralysis is perhaps reflected by the increased activity in the frontal lobe. The change in auditory

feedback with a hoarse voice quality and the processing of this variant auditory input may have activated the superior temporal gyrus (STG), a region involved in processing of complex auditory input.^{184, 185} Elevated activity in the STG in the presence of mismatched auditory feedback reflects the involvement of this region in an error detection mechanism when phonation occurs.¹⁸⁶⁻¹⁸⁹ There was increased activity during recovery in the frontal lobe region involving the DLPFC, and superior frontal gyri bilaterally (Figure 4. 2), greater than activity seen at baseline or during paralysis. The adaptation to a return of function in the right vocal fold after an acute paralysis may have triggered the increased activity in the frontal lobe to recalibrate the system to achieve a normal voice quality.

On performing detailed ROI and statistical analysis using a mixed-model approach, four out of the five regions of interest- ACC, precentral gyrus, postcentral gyrus and the DLPFC showed a main effect of time indicating a significant change in BOLD activity as a result of the iUVFP and its eventual recovery. Males and females showed different trends for all of these regions as seen by a significant time by gender interaction, however, the small sample size in each of these groups (5 females, 4 males) makes it difficult to confirm the differing effect and response to the paralysis in males and females. The ACC and DLPFC also had significant gender effects and the cerebellum demonstrated a main effect of condition of task and hemispheric laterality. The discussion is presented here with reference to the hypotheses proposed in Chapter 2.

Null hypothesis 1: Percent BOLD signal levels and hemispheric laterality for regions of interest (ACC, pre and postcentral gyrus, DLPFC and cerebellum) will not be significantly different at the three time points (baseline, iUVFP and recovery).

This null hypothesis was rejected since significantly distinct patterns of activity were observed across time as a consequence of the induced paralysis, as stated previously. Trends of change for the ACC and primary sensory region (postcentral gyrus) had the same direction, with BOLD activity decreasing during paralysis and further dropping on recovery. This is opposite to the trend seen for DLPFC, with an increase in activity during paralysis and a further increase on recovery. The precentral gyrus, the primary motor region was different in direction from the other three regions. There was a decrease in activity with the paralysis and an increase on recovery. BOLD activity for the group at recovery was still lower than that seen at baseline. The cerebellum had a slight increase in activity with the paralysis and a decrease on recovery but this change was non-significant. These trends were seen for overall activity across the three conditions of whisper, voice and imagine for the entire group of nine participants. The role of each of these ROI as it applies to the current study is discussed below.

ACC and DLPFC

The ACC has been shown to be involved in phonation in non-human primates^{110, 111, 190, 191} and humans.^{27, 123, 147} It forms a large region around the rostrum of the corpus callosum with extensive projections into the motor system.¹⁹² In this study, BOLD activity in the ACC (BA 24/25) was seen to vary significantly with the perturbation to the laryngeal mechanism and its recovery. The ACC with its involvement in emotional and cognitive functioning, has been found to play a significant role in error detection.^{193, 194} A drop in BOLD activity over time was observed in this study as tasks became familiar over the three time points in this study and the need for the ACC to monitor errors reduced.

In a study by Raichle, Fiez, Videen et al.,¹⁹⁵ the ACC along with the left prefrontal and posterior temporal cortices, and the right cerebellar hemisphere had a significant practice-related drop in activity. The effect was tested during a naive and practiced performance of a simple verbal response selection task and the ACC was recruited to a significantly lesser extent with increased practice and familiarity of the task. Given the methodology implemented in the present study, it was not possible to randomize the order of the phases. Even though all participants were familiarized with the sentences prior to the first fMRI scan, it is still probable that a practice related effect was seen in the ACC with multiple repetitions of the target sentences.

The ACC plays a complementary role with the DLPFC in cognitive functioning.¹⁹⁶ According to the conflict monitoring hypothesis by Carter et al.,¹⁹³ the ACC does not get activated purely by errors but monitors the competition between processes that conflict during task performance. Similar in concept to the target, error and state maps in the DIVA model for speech acquisition and production described by Guenther and colleagues,^{184, 197, 198} this competition refers to the predisposition of the system to a response that is incorrect and needs to be overcome to elicit a correct response. The ACC recruits the DLPFC to implement control to overcome a conflict in the response¹⁹³ with a perturbation of the system and a need for adaptive processes during the paralysis and its recovery. The DLPFC is formed by BA 9 and 46 and plays a role in retrospective and prospective memory functions (short-term function and attentive set respectively).¹⁹⁹ The DLPFC is seen to represent the broad schema of action in skeletal and speech domains and also in mediating temporal features of these actions.¹⁹⁹

This finding is supplemented by a neural connectivity study performed by Dosenbach and colleagues.²⁰⁰ In their study, the authors suggest two networks involved in cognitive functioning—a fronto-parietal network including the DLPFC and intraparietal sulcus, and a second cingulo-opercular network including the dorsal anterior cingulate/medial superior frontal cortex, anterior insula/frontal operculum, and anterior prefrontal cortex. The fronto-parietal network emphasized start-cue and error-related activity and may initiate and adapt control on an individual trial basis. The cingulo-opercular regions showed activity sustained across the tasks, suggesting its role in controlling goal directed behavior through the maintenance of task sets. Although the activity of the ACC seen in the current study was more ventral in location, the significant increase in activity of the DLPFC can be attributed at least in part to the connections between the ACC and DLPFC.

The treatment study on patients with dysphonia secondary to Parkinson's disease also demonstrated a significant increase in DLPFC post treatment.²⁵ The authors attributed this change to a normalization of a pretreatment abnormality, or the recruitment of an alternative fronto-striatal loop. The findings of the current study are in keeping with the Parkinson's disease study as significantly greater activation was observed in the DLPFC with recovery from the iUVFP. This suggests that the DLPFC plays an important role in the recovery from dysphonia although we still do not have a complete understanding of its exact role. In addition to working with the ACC to monitor errors, it may also be indicative of the effort instilled into the recovery along with adaptive and compensatory behaviors.

The inferior frontal gyrus region (IFG) within the DLPFC is activated during phonation,^{27, 146} provides input to the laryngeal motor cortex for the planning and coordination of speech and voice^{151, 201} and is involved in working memory. In a recent study using fMRI to examine somatosensory feedback after perturbed speech from blocked jaw movement, the IFG along with the supramarginal gyrus, premotor and motor cortices was found to influence the speech motor output³³ providing more evidence of the role of this region in error identification and correction. The activity in these regions involved with error monitoring was right-lateralized, as is also seen in the DIVA model.^{33, 184, 197} In the current study, there was no significant effect of laterality, but while the right hemisphere is more involved with error monitoring, the left hemisphere has been shown to be involved with response selection.²⁰²

The laryngeal motor cortex in the precentral gyrus has been shown to have reciprocal direct connections with the ACC in non-human primates^{111, 203} and is postulated to have these connections in the human as well.^{111, 204} The following section provides more detail on the precentral gyrus housing the laryngeal motor cortex.

Precentral gyrus and Cerebellum

Animal studies have identified the precentral gyrus and the cerebellum along with the supplementary motor area and the STG as primary regions involved in the cortical control of phonation.^{110, 147, 191, 203} Brodmann's area 4p in the human primary motor cortex has been identified to include the laryngeal/phonation area.¹⁴² Bilateral dorsolateral and ventromedial precentral gyri were identified to control the intrinsic muscles of the larynx. The activation changes across time in this region, a decrease with

iUVFP and an increase with recovery, represent the inducement of the paralysis in the RLN, the motor nerve for the intrinsic laryngeal muscles.¹⁹¹ The motor cortex also integrates input from the frontal operculum and somatosensory areas with the cerebellum as part of the feed-forward and feedback system for speech production.¹⁹³ The connectivity between these regions has not been examined in this study but it can be speculated that the varying activity across time in each of these regions may be required to achieve the target production with minimal errors. As seen in the study on patients with spasmodic dysphonia, based on the task at hand and its complexity, the structural network may remain constant but a change is seen in the functional network¹⁵¹ to fulfill task demands.

The larynx area has not been isolated in the current analysis but the findings are in keeping with the results discussed by Brown, Ngan and Liotti.¹⁴² The current study and the studies by Brown et al., Zarate and Zatore²⁰⁵ have identified bilateral activation of the cerebellum during normal phonation while a study by Simonyan and Ludlow²⁰⁶ identified bilateral activation in persons with spasmodic dysphonia and healthy volunteers. Other studies have shown activity lateralized to one cerebellar hemisphere.^{27, 147} Significant differences were observed in this study between the three regions within the cerebellum—the spinocerebellum and the two lateral lobes. Highest overall activity was seen in the spinocerebellum, followed by the right lobe and the left lobe. Midline activation of the cerebellum was observed in our pilot data as well¹⁵⁷ and is consistent with the topographic mapping of the face and vocal tract in the vermis of the spinocerebellum.²⁰⁷⁻²¹⁰ Somatosensory information from peripheral receptors is conducted to the spinocerebellum through direct and indirect neural pathways from where the information

is processed and further conducted to other cerebral regions such as the primary motor cortex via the thalamus. The spinocerebellum also modulates the descending motor systems in the brain stem and cerebral cortex that control the head and neck region.¹⁸¹

The DIVA model has identified the cerebellum to be involved in the feed-forward system for speech production and acquisition.^{184, 197} A marginal difference in the estimated means was observed between the two lateral lobes with both sides having lower means than the spinocerebellum. Laterality of cerebellar activations generally mirrors activity of associated cortical regions due to predominant contralateral cortico-cerebellar activity.⁹⁰ A left hemisphere cortical dominance was observed with the overall experimental effect even though ROI analyses failed to show any significant interhemispheric differences. This may have reflected in the marginal right cerebellar hemispheric dominance. Similar to the ACC and DLPFC, the lateral hemispheres of the cerebellum have perceptual and cognitive functions as seen by studies in patients with lesions in these hemispheres¹⁸¹ and contribute to error correction^{184, 207, 209} which validates the presence of significant BOLD activity in this study.

The cerebellum was also the only one of the five ROI that showed significance in activation based on the condition i.e., whisper, voice and imagine. Although the activations between conditions did not significantly vary over time, the least activation was observed for the voiced condition with maximum activation for the whispered condition. Similar preferential responses in the cerebellum during phonation relative to whispering were found during narrative speech by Schulz et al.¹²³ The whispered production in a majority of persons requires more effort, as witnessed peripherally by supraglottic hyperfunction than either the voiced or imagined condition to maintain the

required laryngeal posture.²¹¹ This explains the maximal activity observed in the cerebellum during this task. In a study on healthy volunteers with a normal voice quality, the primary motor cortex also demonstrated maximal activity for whisper as compared to the other voicing and imagined vocalization, suggestive of a need for increased motor planning and preparation and suppression of practiced patterns of phonation.²¹²

Limb studies have shown that imagery of a task activates the premotor cortex and the cerebellum with similar patterns of activation without performing the task itself.²¹³⁻²¹⁵ Thus when performing a covert vocalization task such as imagining the vocalization of a sentence, it is highly probable that laryngeal posturing occurred without initiation of vocal fold vibration causing activity in the cerebellum. The voicing condition perhaps had the least activation due to its over-practiced nature and ease of production as compared to the whisper and imagine task.

Postcentral gyrus

Previous studies have identified a role of the postcentral gyrus for phonation most commonly in the left hemisphere.¹⁴⁷ Studies in persons with spasmodic dysphonia have demonstrated lower activation in primary somatosensory regions as compared to healthy participants,^{27, 28} similar to that seen in the current study when comparing baseline to the iUVFP phase. The DIVA model also posits the representation of tactile and proprioceptive information from the vocal tract in primary and higher-order somatosensory cortical areas in the postcentral gyrus and supramarginal gyrus.¹⁸⁴ The primary sensory cortex sends inputs to the secondary somatosensory association areas which further propagates the command to the motor cortex.¹⁸⁴

Studies on audition and vision have also shown the ACC to have a top-down control over sensory regions.²¹⁶⁻²¹⁸ Although these studies have been performed for non-laryngeal modalities, modality specific connections were observed between the primary auditory cortex and the ACC as well as the ACC and the visual cortex.²¹⁸ The authors suggest a four stage processing system where the stimulus is first detected by the primary sensory region and transmitted to the ACC exerting bottom-up control. The ACC then exerts top-down control and transmits this signal to the primary sensory region and other neocortical regions including the premotor cortex and temporoparietal cortex where they ultimately respond to the stimulus.²¹⁸

The primary laryngeal sensory cortex has not yet been accurately defined and is postulated to include the postcentral gyrus.²⁰¹ However, if top-down processing does occur for the phonatory system similar to the auditory and visual cortex, a decrease in ACC activity across the three phases may be responsible for a consequent decrease in activity of the postcentral gyrus as evidenced in this study.

Null hypothesis 2: A correlation will not be seen between behavioral (auditory-perceptual, acoustic, aerodynamic and visualization) and central measures (BOLD activation) at the three time points (baseline, iUVFP, and recovery).

A weak positive correlation was observed between the CAPE-V and postcentral gyrus suggesting that an increase/decrease in CAPE-V values brought about a concomitant increase/decrease in the postcentral gyrus. Similarly, a weak positive correlation was also observed between P_s and the DLPFC with a moderately strong positive correlation for NHR and the DLPFC. The relation between the NHR and DLPFC probably reflects the change in these values from baseline to iUVFP. With the onset of

paralysis, there was an increase in the noise-to-signal ratio of the voice as indicated by NHR and a concurrent increase in BOLD activity of the DLPFC. This change was more evident in males than females as evidenced by a time and gender interaction for both NHR and DLPFC. Thus the relation between NHR and DLPFC may be stronger for males than females.

The DLPFC appears to be the strongest predictor amongst the chosen ROI of the behavioral measures obtained. A change in voice quality peripherally does bring about a concurrent change in the activity of the DLPFC, more consistently than that demonstrated by the other regions in this study. The absence of a statistically significant, strong correlation between behavioral and fMRI measures is indicative of a disconnect between the results seen clinically, based on peripheral examination, and those seen at the cortical level.

Correlations between behavioral and fMRI data have not been previously reported in the literature for voice disorders except for the single case-study on UVFP,³⁰ and are critical in demonstrating that a recovery at the periphery in terms of a normal voice quality does not necessarily imply a recovery in the central laryngeal system. This finding has strong implications for voice therapy and treatment protocols. Currently, there is considerable debate on the ideal time frame for treatment of voice disorders and these findings emphasize the importance of a maintenance protocol during treatment. Amongst other causes, a lack of recovery or adaptation at the cortical level may be a major factor causing a recurrence of the voice disorder. The state of flux of the system might cause increased instability and without an adequate maintenance protocol could cause a reversal to maladaptive behaviors. Identifying neural biomarkers and tracking the duration of

treatment and treatment paradigms that can positively modulate these biomarkers for voice production is essential to a reduction in the incidence of relapse and development of a more holistic approach to voice therapy. This can facilitate development of new protocols such as those developed in physical therapy¹⁸⁻²³ to enhance clinical care and success rates amongst this population.

CONCLUSIONS AND FUTURE DIRECTIONS

The fictive paralysis model employed in this study provided a perturbation model for phonation that allowed us to examine behavioral and central neural correlates for disordered phonation in a controlled environment. The availability of baseline data for each participant was instrumental in demonstrating the significant difference in activity during iUVFP and recovery. Although this data is representative of acute changes from a transient paralysis, it provides an insight into the response of the cortex to sudden perturbation at the peripheral phonatory mechanism.

Reorganization of cortical representation after a peripheral injury can occur due to either unmasking of latent thalamocortical arbors, long term potentiation or collateral sprouting.²¹⁹ While long term potentiation and collateral sprouting occur over a period of time and may be seen in chronic vocal fold paralysis, an acute UVFP may cause cortical reorganization due to the unmasking of latent connections.^{130, 167}

The disruption in normal phonation brought about changes in the neocortical and limbic system signifying widespread activity changes of the central laryngeal system to dysphonia. The observed functional reorganization may constitute potential biomarkers, occurring within minutes of nerve blockade and recovery-related change associated with recalibration of the system after normal return of function. These regions form neural

indicators of laryngeal function and inhibitory/excitatory modulation of the activity in these regions with treatment can result in improved phonatory function. Further investigation of the effects of various treatment forms for the necessitated change is required.

The neural system, however, did not return to baseline activation on recovery even though the participants had a perceptually normal vocal quality and normative values on the behavioral measures. This phenomena may point towards a longer recovery time period necessitated for return to normal cortical activity than that indicated by behavioral measures. The current time of under an hour for the final fMRI scan after recovery demonstrated the large role played by the frontal region in recovery which may reduce once complete recovery is made, but an additional scan would target a more accurate estimate of when complete recovery occurs.

The difference in the time of recovery peripherally and at the central level was also demonstrated by limited correlations between the behavioral and fMRI variables. Alternate functional networks may have been recruited to compensate for the change in peripheral function even with a common structural network. The different functional networks involved allow the peripheral measures to demonstrate normalcy of function, even though the central measures do not indicate the same results. Further examination of these findings with a connectivity analysis between the ROI and an extension of this form of research in the true patient population is warranted to understand the time frame required for complete recovery of cortical activity. An estimate of this time frame will aid in reducing the incidence of relapse to a voice disorder due to early discharge from

treatment, based solely on perceptual voice quality and peripheral, behavioral measures used clinically.

Interestingly, the data also demonstrated distinct differences between the patterns of cortical activity in males and females. The data was limited by its small sample size in both gender groups making it difficult to strongly extrapolate the unexpected differences in the response of males and females to iUVFP despite significant interaction of gender with time for the ROI. Further study of the gender differences in the laryngeal representation of phonation will be crucial in understanding the mechanisms of disorders that are more prevalent in one population than the other, such as spasmodic dysphonia; the differential response to recovery and treatments seen in the two genders and the likelihood of a quicker, more robust recovery with a specific treatment paradigm in one gender over the other.

Only five ROI were selected in this study, however, additional regions such as the thalamus, Brodmann's area 10, supramarginal gyrus, insula and others, as indicated by previous literature, will provide better understanding of the cortical response to the iUVFP. The selected regions were also not distinguished based on their functions such as dorsal versus rostral ACC, areas 4a versus 4p or the laryngeal/ phonation area of the precentral gyrus. This distinction will allow for more in-depth understanding of the role of these regions in normal and disordered phonation.

A connectivity analysis between the various regions identified in this study and additional regions implicated in phonation not examined here will provide information critical in translating these results for treatment based clinical applications. The identification of biomarkers and a cause-effect relation between regions will help focus

modifications in current treatment protocols and develop new treatments in keeping with the core principles of neuroplasticity.^{220, 221}

This phonatory perturbation model was successful in highlighting key features in the cortical and behavioral manifestation of dysphonia in persons with a sudden onset of hoarseness, specifically secondary to a vocal fold paralysis. Continued examination of the cortical response to a phonatory perturbation and recovery, either acute or chronic is mandated for development of improved treatment protocols and clinical care in persons with voice disorders.

Consensus Auditory-Perceptual Evaluation of Voice (CAPE-V)

Name: _____

Date: _____

The following parameters of voice quality will be rated upon completion of the following tasks:

1. Sustained vowels, /a/ and /i/ for 3-5 seconds duration each.
2. Sentence production:

a. The blue spot is on the key again.	d. We eat eggs every Easter.
b. How hard did he hit him?	e. My mama makes lemon muffins.
c. We were away a year ago.	f. Peter will keep at the peak.
3. Spontaneous speech in response to: "Tell me about your voice problem." or "Tell me how your voice is functioning."

Legend: C = Consistent I = Intermittent
 MI = Mildly Deviant
 MO = Moderately Deviant
 SE = Severely Deviant

			<u>SCORE</u>
Overall Severity _____	C I	_____ /100	
MI MO SE			
Roughness _____	C I	_____ /100	
MI MO SE			
Breathiness _____	C I	_____ /100	
MI MO SE			
Strain _____	C I	_____ /100	
MI MO SE			
Pitch (Indicate the nature of the abnormality): _____	C I	_____ /100	
MI MO SE			
Loudness (Indicate the nature of the abnormality): _____	C I	_____ /100	
MI MO SE			
_____ _____	C I	_____ /100	
MI MO SE			
_____ _____	C I	_____ /100	
MI MO SE			

COMMENTS ABOUT RESONANCE: NORMAL OTHER (Provide description): _____

ADDITIONAL FEATURES (for example, diplophonia, fry, falsetto, asthenia, aphonia, pitch instability, tremor, wet/gurgly, or other relevant terms): _____

Clinician: _____

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VITA
Ashwini Joshi

Date and Place of Birth

Date of birth: December 22, 1983
Place of birth: Mumbai, India

Education

Ali Yavar Jung, National Institute for the Hearing Handicapped, Mumbai, India
Bachelor of Science (Hearing, Language Science) --- June 2001 to July 2005

Bloomsburg University, Bloomsburg, PA
Master of Science (Speech Language Pathology) --- August 2005 to May 2007
Thesis: Effects of elicitation control on the respiratory and phonatory control characteristics of voice

University of Kentucky, Lexington, KY
Doctoral Candidate (Rehabilitation Sciences)—April 2010 to current
Expected graduation date: August 2011
Dissertation: Central neural and behavioral correlates of voice secondary to induced unilateral vocal fold paralysis.

Professional positions

Graduate Assistant to Joseph C. Stemple,
Dept. of Communication Sciences and Disorders, University of Kentucky
August 2008- May 2009

Clinical Doctoral Fellow
Clinical Voice Center, University of Kentucky
July 2009- April 2011

Scholastic and professional honors

Graduate School Travel Award, University of Kentucky (4/2008, 5/2009, 10/2009, 10/2010).

Dept. of Rehabilitation Sciences Travel Award, University of Kentucky (2008, 2010).

International Conference for Advances in Laryngeal Biophysiology Travel Award (2008).

American Speech Language Hearing Association, Research Mentoring Pair Travel Award (2008).

International Student Scholarship, American Speech-Language-Hearing Foundation (2009).

Seed Grant, Center for Clinical and Translational Sciences, University of Kentucky, Central Laryngeal Representation in Temporary Induced Unilateral Vocal Fold Paralysis (2009).

University of Kentucky Research Fund- MRISC Service Center Grant (2010).

College of Health Sciences, University of Kentucky Pilot Grant (2010).

Professional Publications

Stemple, J.C, **Joshi, A.**, and Ensslen, A.J. Voice Disorders. In: Ruscello, D., ed. *Review Questions for the Speech-Language Pathology Praxis Examination*. Missouri: Mosby Elsevier; 2010:134-146.

Joshi, A., Jiang, Y., Stemple, J.C., Archer, S.M., Andreatta, R.D. Induced Unilateral Vocal Fold Paralysis and Recovery Rapidly Modulate Brain Areas Related to Phonatory Behavior: A Case Study. *J Voice*, 2011, 25 (2): e53-59.

Andreatta, R.D., Stemple, J.C., **Joshi, A.**, Jiang, Y. Task-related differences in temporo-parietal cortical activation during human phonatory behaviors. *Neurosci Lett*. Oct 22 2010;484 (1):51-55.

Dietrich, M.M., Yang, J., Andreatta, R.D., **Joshi, A.**, and Stemple, J.C. (submitted) Neuroticism and Introversion Modulate Limbic and Sensorimotor Brain Responses During Sentence Reading. *Journal of Speech, Language and Hearing Research*.

Ashwini Joshi