

Structural and Functional Adaptations of the Auditory-Motor System: Insights from Expertise & Disorder

by
Gus F. Halwani
*Bachelor of Biopsychology,
University of South Florida, 2008*

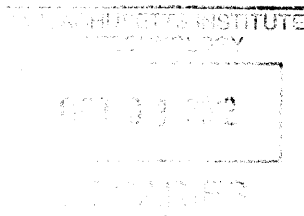
SUBMITTED TO THE DIVISION OF HEALTH SCIENCES AND TECHNOLOGY IN
PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY IN SPEECH AND HEARING BIOSCIENCE AND
TECHNOLOGY

at the
MASSACHUSETTS INSTITUTE OF TECHNOLOGY

September 2012

© 2012 Gus F. Halwani. All rights reserved.

ARCHIVES



The author hereby grants to MIT the permission to reproduce and to distribute publicly paper and electronic versions of this thesis document in whole or in part in any medium now known or hereafter created.

Digitally signed by Gus Halwani

Signature of Author:

Gus F. Halwani,
Harvard – MIT Division of Health Sciences & Technology

Certified by:

Gottfried Schlaug, M.D., Ph.D.
Associate Professor of Neurology, Harvard Medical School
Thesis Supervisor

Accepted by:

Arup Chakraborty, PhD
Director, Institute for Medical Engineering
and Sciences / Harvard-MIT Program in Health Sciences and Technology

Structural and Functional Adaptations of the Auditory-Motor System: Insights from Expertise & Disorder

by
Gus F. Halwani

ABSTRACT

While evidence from clinical and functional neuroimaging domains converges on a notion that auditory-motor networks can be remodeled functionally and structurally in response to experiences, studies that seek to evaluate these hypotheses by combining behavioral, functional, and structural measures are rare. Given relatively recent advances in neuroimaging, e.g. diffusion-tensor imaging (DTI) and functional neuroimaging methods (fMRI), it is now possible to structurally and functionally analyze these networks, as well as make inferences about them in situations where the networks are either functionally compromised by an auditory-motor feedback disorder, or structurally enhanced by an intense long-term auditory-motor training regimen.

To this end, a three-fold course of study has been undertaken:

- (1) a between-group comparison of the structural aspects of the arcuate fasciculus (a prominent white-matter fiber tract that reciprocally connects the temporal and inferior frontal lobes and is thought to be important for auditory-motor interactions) of singers and those of matched non-singing musicians, in order to evaluate the hypothesis that singers will exhibit structural differences specifically for aspects of vocal output that require rapid temporal processing and precise sound-motor matching.
- (2) a within-subject fMRI comparison of responses of young adults (non-musicians) to auditory feedback that is either unperturbed or shifted in pitch while they perform a pitch-matching task, to ascertain a functional network related to perceiving and perhaps compensating for mismatched auditory feedback.
- (3) a within-subject pilot study of the network ascertained in (2), now in a smaller group of young adults with an auditory-motor disorder/disconnection syndrome commonly referred to as tonedeafness (TD) or congenital amusia (a condition marked by a high pitch discrimination threshold as well as readily apparent difficulty in matching pitches), in order to provide insight into how this network might behave in a state of long-term disorder.

While this work corroborates previous work in clinical, behavioral, and neuroimaging domains, and sheds light on the organization of these auditory-motor networks (structurally and functionally) in the normal population, it also aids in understanding how these networks may be remodeled and optimized (structurally) in response to intense long-term training, how they adapt to an acutely compromised state (i.e. when input to the network is compromised or perturbed), as well as how they may adapt functionally in a chronically compromised state (i.e. tonedeafness). Taken together, these observations help to explain the functioning of the auditory-motor network in normal individuals and those with communication disorders, as well as shedding light on possible mechanisms of recovery as they participate in an intensive long-term auditory-motor therapy program.

Thesis Supervisor: Gottfried Schlaug, M.D., Ph.D.

Title: Associate Professor of Neurology

BIOGRAPHICAL NOTE

Gus F. Halwani
77 Massachusetts Ave., MIT Room 36-569, Cambridge, MA 02139
halwani@mit.edu

EDUCATION

- 2008-2012 Ph.D., Speech and Hearing Bioscience and Technology
Massachusetts Institute of Technology, Cambridge, MA
2004-2008 B.A., Biopsychology, *magna cum laude*
University of South Florida, Tampa, FL

EXPERIENCE

- 2009-2012 Graduate Research Assistant
Music & Neuroimaging Laboratory, PI: Gottfried Schlaug, M.D., Ph.D.
Beth Israel Deaconess Medical Center / Harvard Medical School
2009-2011 Teaching Assistant
HST. 590: Topics in Bioengineering, Biomedical Research, and Bioethics
Massachusetts Institute of Technology, Cambridge, MA
2006-2008 Research Assistant
Brain-to-Computer Interface Laboratory, PI: Emanuel Donchin, Ph.D.
University of South Florida, Tampa, FL
2005-2007 Research Assistant
Quantitative Neuromorphology
Neurostructural Research Laboratories, Inc.
University of South Florida, Tampa, FL

AWARDS

- 2008-2012 NIH-NIDCD Training Grant
2011 MIT IDEA² Fellowship for Translational Research
2006-2007 Fred L & Helen M Tharp Endowed Scholarship
2006-2007 J.O. DeLotto & Sons Inc. Endowed Scholarship
2005-2008 Honors Scholarship
2004-2008 Florida Bright Futures Scholarship (Full Tuition)

PUBLICATIONS

Halwani GF, Loui P, and Schlaug G (2012) The neural control of pitch production under perturbed auditory feedback: A simultaneous behavioral / fMRI study. (in preparation)

Halwani GF, Loui P, Rüber T and Schlaug G (2011) Effects of practice and experience on the arcuate fasciculus: comparing singers, instrumentalists, and non-musicians. *Front. Psychology* 2:156. doi: 10.3389/fpsyg.2011.00156

SELECTED POSTERS / PRESENTATIONS

Halwani, GF (2012) Music, Neuroscience, and Education: What can We Learn from the Spaces in-Between? Invited oral presentation given at **TEDxAbuDhabi**, U.A.E.

Halwani, G.F., Zhu, L., Norton, A., Loui, P., Winner, E., and Schlaug, G. (2010) White matters: musical training and temporo-frontal fiber tracts in children & adults. Poster presented at the **Organization for Human Brain Mapping** annual meeting, Barcelona, Spain.

Halwani, G.F., Zhu, L., Norton, A., Loui, P., Winner, E., and Schlaug, G. (2010) White matters: musical training and temporo-frontal fiber tracts in children. Oral presentation given at the Psychonomics' Society's **Auditory Perception-Cognition-Action Meeting** (APCAM) in Boston, MA.

Halwani, G.F. and Mervis, R. (2007) The effect of chronic lithium chloride on dendritic branching in the adult rat neocortex and hippocampus. Poster presented at the **Society for Neuroscience** annual meeting, in San Diego, CA.

ACKNOWLEDGEMENTS

Firstly, I would like to thank my thesis supervisor, Gottfried Schlaug, who has taught many lessons that I could not have learned in any classroom, both explicitly and implicitly. He is a prime example of maintaining the balance between being a physician, scientist, and mentor. Our numerous interactions in various contexts have taught me much about science and medicine, as well as life in general, and it's difficult to articulate the good fortune I have in being able to call him a friend.

I also thank my thesis committee members: Jennifer Melcher for her unwavering support that admirably treads the boundaries of thesis committee chair, academic advisor, and mentor, in addition to her readiness to chat about anything and offer an open door even when I arrived unannounced; Marjorie Nicholas for always lending a critical ear to my research and encouraging me to keep an eye to the clinical implications of any work that I may be doing; and Robert Hillman for always accommodating me into his schedule and setting aside time to have an in-depth discussion about anything from my thesis work, to prospective career opportunities and how to make the most out of my career trajectory.

This document would not be complete without acknowledging Nelson Kiang. Although we rarely discussed the details of my thesis or lab work, our regular meetings always served to realign my greater goals and maintain perspective. It's very difficult to articulate how much I've learned from him, and I look forward to continuing our regular meetings beyond my time with SHBT and HST.

The members of the Music & Neuroimaging Laboratory at the BIDMC have made the sometimes frustrating afternoons of sifting through data both enjoyable and rewarding. My thanks goes to Shinya Fujii and Anna Zamm, who helped me get a running start with analyzing heaps of data from the perturbed auditory feedback experiment, always willing to cook up some home-made MATLAB code and get me up and running again. I thank Psyche Loui, who always had an open and critical ear: her advice and comments will stay with me for many years. Thanks to Andrea Norton and the rest of the clinic crew for allowing me to invade their space (let alone remind them to be quiet) during my participant-training sessions. I thank Sarah Marchina for always reminding me about the world outside the lab and always helping me keep everything in perspective: her persistence and positive outlook is contagious and constructive. Also, many thanks to Xin Zheng for helping me brainstorm and troubleshoot technical hurdles when I couldn't overcome them myself: he is an exceptional scientist with abilities well beyond his current position, in addition to having a virtually-unguardable step-back jump-shot on the basketball court. Thanks also to Catherine Wan, for always being there to chat, whether about study methodology, or broader career advice. A special thank-you also goes to Courtenay Wilson, whose hard work contributed significantly to our perturbed auditory feedback study. All the other members of the Music & Neuroimaging Laboratory created a constructive atmosphere in which to write a PhD thesis, and I thank all of them. Finally, acknowledging the Longwood Medical community would not be complete without mention of Fotini Kourtelidis and Michael Mamico, without whom conducting MR experiments would have been more difficult and much less enjoyable.

My SHBT class (in no particular order: Andrew Lysaght, Sofia Vallila, Yenfu Cheng, Maria Berezina, and Bo Zhu) encouraged me to get through that difficult first year, in addition to making my life since then more enjoyable. I'd also like to thank Bertrand Delgutte and Louis Braida for unfiltered and always constructive advice and comments they contributed, in addition to always having an open ear when I needed it.

Finally, I want to thank my best friend and wife-to-be, Maria Orbita, my friends, and my family for always being there, offering support and encouragement during the lows, and organizing the best celebrations during the highs: without you, this work would simply not have been possible.

TABLE OF CONTENTS

ABSTRACT	3
BIOGRAPHICAL NOTE	5
ACKNOWLEDGEMENTS	6
TABLE OF CONTENTS	7
1: INTRODUCTION	9
2: BACKGROUND & MOTIVATION	13
Abstract	13
2.1 Insights from Expertise?	14
2.1.1 Music & the Auditory Domain	14
2.1.2 Music & the Motor Domain	18
2.1.3 Singing, Speaking, and Auditory-Motor Connectivity	20
2.2 Insights from Disorder?	23
2.2.1 Insights from a chronically-compromised auditory-motor networks (tonedeafness)	24
2.2.2 Insights from transiently-compromised auditory-motor networks (feedback perturbation)	26
2.3 Implications for communication disorders	30
3: STRUCTURAL ADAPTATIONS OF THE AUDITORY-MOTOR SYSTEM: Comparing the brains of professional singers, instrumentalists, and non-musicians.	32
Abstract	32
3.1 Introduction	33
3.2 Materials and methods	35
3.2.1 Participants	35
3.2.2 Image acquisition	36
3.2.4 Data Processing	36
3.2.5 Tractography – Arcuate Fasciculus	36
Statistical comparisons – arcuate fasciculus	38
3.3 Results	38
3.3.1 Tract statistics – arcuate fasciculus	38
3.3.2 FA along the arcuate fasciculus	41
3.3.3 Behavioral correlates of FA differences	44
3.4 Discussion	45
4: FUNCTIONAL ADAPTATIONS OF THE AUDITORY-MOTOR SYSTEM:	50
4.1 Introduction	51
4.2 Materials and Methods	54
4.2.1 Participants	54
4.2.2 Hardware	55
4.2.3 Software	55
4.2.4 Behavioral Paradigm	55
4.2.5 Behavioral Data Analysis	57
4.2.6 fMRI Data Acquisition	58
4.2.7 fMRI Data Analysis	59
4.3 Results	60
4.3.1 Behavioral Results	60

4.3.2 fMRI Results	61
4.4 Discussion	64
4.5 Long-term mismatch of auditory-motor feedback: the case of tonedeafness	68
4.5.1 Introduction	68
4.5.2 Participants	69
4.5.3 Pilot results – pitch-matching with perturbed auditory feedback in individuals with TD	69
4.5.4 Discussion and future directions – pitch-matching with perturbed auditory feedback in individuals with TD	73
5: SUMMARY & CONCLUSIONS	75
5.1 The auditory-vocal network adapts structurally in response to intense and long-term auditory-vocal training	75
5.2 The auditory-vocal network adapts functionally in response to short-term auditory feedback mismatch	76
REFERENCES	78
APPENDIX	86
A.1: Individual subject data from Ch. 4	86
A.2: Individual subject data from Ch. 3	87
A.3: Permissions	95

1: INTRODUCTION

As I type these words, I am simultaneously imagining myself speak them. I can almost hear my voice, the familiar sound that accompanies the expression of ideas. We always hear this sound when we speak, and most of the time we carry on speaking effortlessly, for the sound we hear is always expected: always in-line with our intention. We carry on, unaware of the frantic calculations that our brain is constantly making as it monitors the sound we are producing in real-time, making fine adjustments to our vocal articulators in order to ensure that the sounds that we hear ourselves make are the sounds that we intended to make in the first place.

We carry on until something unexpected (and often comical) occurs: we say something that we did not mean to say. It may have been clumsy pronunciation, or that we substituted one sound for another, or that we said the wrong word altogether. Regardless, we suddenly become aware of the aforementioned real-time monitoring and correction that our brain is engaged in. If we pause and consider how such a system might be configured, let alone how it might be implemented using organic materials (i.e. human anatomy), then the banality of hearing our own voice while we speak quickly gives way to a deep appreciation of the complex machine that is the human auditory-motor system. When Walt Whitman wrote “I sing the body electric” in 1900, he was not specifically referencing the human auditory-motor system, although the title of his famous poem summarizes exactly what one feels when considering that very topic.

Since then, our understanding of the human auditory-motor system has advanced considerably. We now know that what seemed like an effortless undertaking is actually the result of the sum effort of many discrete functional steps along a feedback chain, each using its specialized anatomy. When we speak, we affect the air around us such that correlated pressure waves are formed. Our inner ear is remarkably equipped to transduce these correlated pressure waves into correlated neural signals, which are eventually interpreted by our brain and integrated into the next set of motor commands. Our brain then sends these motor commands to the articulators of our vocal tract, continuing our speech seamlessly, always monitoring, and always making fine adjustments along the way (Denes & Pinson, 1993). Figure 1-1 summarizes this graphically.

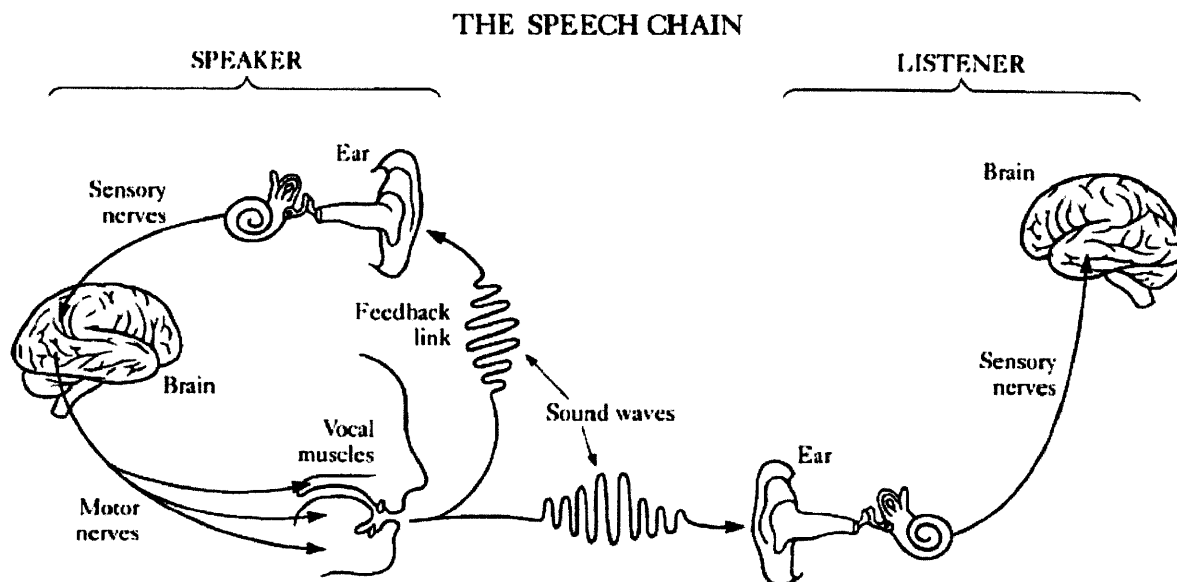


Figure 1-1. The feedback chain involved in one's own monitoring of speech is shown on the right, while the hearing chain is shown on the left. (adapted from Denes and Pinson, 1993).

Looking at this graphic, the subject of this dissertation becomes clear. Details about the mechanisms behind the transduction of air pressure waves into neural signals are outside its scope, as are details of the peripheral mechanisms that drive the musculature with motor commands from the brain. Rather, the concern of this dissertation is exactly the link in this feedback chain where sensory information and motor output is compared, integrated, and coordinated. Namely, the concern of this dissertation is auditory-motor interactions in the brain. What network of regions in the brain underlies the feedback and feedforward control of vocal output? How are the nodes of this network connected to each other? How can this network be engaged, and how can the connections between its nodes be made stronger? How does this system adapt if the sensory input is unexpectedly manipulated for a short period of time under otherwise normal circumstances? How might the auditory-motor network of someone with an auditory-motor disorder adapt under the same experimental manipulation? These are the questions that are directly considered in this dissertation.

With the advent of structural and functional magnetic resonance imaging (sMRI and fMRI, respectively), it is now possible to non-invasively examine brain structures quantitatively, as well as experimentally evaluate brain function while participants perform a pre-defined task. Using these tools, we can start to resolve the structure and function of the brain's auditory-motor system and contribute to our understanding of the most elusive part of the 'speech chain' described in fig. 1-1: the brain, in which information about what we hear is integrated into motor commands that control our vocal tract. In particular, the central concerns of this work are:

(1) Can participating in an intense and long-term auditory-vocal training regimen (such as the lifelong training of a professional vocal musician) lead to differences in neural structures that are thought to underlie auditory-vocal feedback (relative to matched individuals who have not participated in such training)? (2) Does altering the auditory feedback of participants undergoing a pitch-matching task cause them to compensate for the alteration behaviorally, and if so what are the associated functional neural correlates? (3) How do individuals with a demonstrated auditory-motor disorder (i.e., tonedeafness) react to the same experimental task (behaviorally and neurologically)?

The first investigation offers evidence that supports the notion that a) individuals participating in an intensive, long-term auditory-vocal training regimen represent a model for examining adaptations of this auditory-motor system, and b) these 'auditory-vocal athletes' exhibit structural differences (compared to controls) in certain white-matter structures thought to be important in auditory-motor function, relative to matched controls, as revealed by diffusion-tensor imaging (DTI—a magnetic resonance imaging technique that can be used to image white-matter integrity and tracts, described in more detail in chapter 3).

The second investigation proceeds to demonstrate a model for studying *short-term* functional adaptations of the auditory-vocal system by way of a perturbed auditory feedback experiment with simultaneous fMRI. While in the fMRI scanner, healthy young adults participated in a pitch-matching task under conditions of intermittent and unexpected perturbations in the fundamental frequency (F_0) of their voice. This enabled observations of behavioral compensation to the short-term perturbations (as shown by acoustic recordings made during the experiment) as well as their neural correlates (as shown by fMRI taken during the task).

Finally, the third investigation provides the first look at how a group of individuals with a demonstrated auditory-motor disorder react to the same perturbed auditory feedback experiment, enabling observations about the functional neural correlates of an auditory-motor disorder.

First, an overview of some previous experiments and paradigms used to investigate related questions is presented. This includes previous experimental studies of functional and structural adaptations in the human cortex, as well as an overview of the computational modeling literature that motivates this dissertation. This establishes the body of work that this dissertation is based on, with particular attention paid to the neuroimaging and modeling studies that provide its motivation. The motivation and background for this dissertation will be presented by illustrating (through the presentation of the relevant background literature) why it is that formally-trained musicians (particularly singers) and individuals experiencing auditory-motor feedback mismatch (whether experimentally induced or the result of a disorder) constitute useful models for studying structural and functional auditory-motor adaptations in the human cortex. Finally, the implications that such work may have on the diagnosis and treatment of several communication disorders is overviewed.

2: BACKGROUND & MOTIVATION

Abstract

In order to study the musculo-skeletal system's organization, development, and the factors that influence its recovery from injury, one might study such a system in a formally trained athlete. This provides a framework for understanding what structures and processes are unique to this area of study, and how they are remodeled in response to a finely controlled training regimen. Concurrently, one might also study the workings of this system in individuals with certain disorders, providing further insight into how such a finely-tuned system might behave in a compromised state.

Analogously, the auditory-motor system of the human cortex necessitates the use of such models. In this section, professional musicianship (particularly in the vocal domain), as well as conditions of auditory-motor feedback mismatch (whether experimentally induced or the result of a disorder), will be presented as useful models for studying structural and functional adaptations of the auditory-motor system, followed by an outline of the *Directions into Velocities of Articulators* (DIVA) model (Guenther, 2006; Guenther et al., 2006), which has received considerable attention and has been proven useful in the generation and testing of hypotheses concerning auditory and speech-motor interactions. Finally, the significance of such work will be overviewed by highlighting the role of auditory-motor interactions in various communications disorders.

2.1 Insights from Expertise?

Apart from being fascinating in their own right and captivating the imagination of audiences generation after generation, musicians also form an important model for neuroimaging researchers who are interested in auditory-motor interactions in the human cortex. Whether one is singing praise at church, dancing to the rhythms in a nightclub, or learning a favorite folk song on guitar, the neural underpinnings of such tasks and the way auditory information is coordinated with motor processing constitutes fertile ground for novel empirical questions. For questions of auditory-motor processing particularly, musicians form a special cohort from which much can be learned.

Some factors that contribute to the usefulness of a musicians' brain as a model for studying auditory-motor adaptations are inherent in music itself (e.g., training rhythm, timing, pitch perception, motor coordination, etc), while other factors are related to the fact that musical training is most often started very early in childhood, while the brain's ability to organize adapt to auditory-motor function may be at its highest (Hensch, 2004). Furthermore, this skill is continuously practiced throughout adolescence and into adult life, providing opportunities for examining the interaction between brain and behavior at various developmental stages.

2.1.1 Music & the Auditory Domain

Performing music successfully requires reliable representation of the auditory environment, exceptional motor acuity, as well as an ability to keep the former and the latter tightly coordinated. It requires the ability to adhere to rigid rhythmic structures and keep track of subtle changes in timing, while manipulating rich information in the frequency domain (frequency ratios form the basis of consonance in music) (Zatorre et al., 2007).

A musician's ear is sensitive to extracting pitch faithfully from the environment, as pitch is a valuable feature of any music and forms the basis from which its tonality is derived. However, what we call 'pitch' is not so simple. Pitch is the perceptual correlate of sound periodicity (Penagos et al, 2004), although many arrangements of sound can give rise to the same perceived pitch. Although

frequency extraction starts in the peripheral auditory system, primate studies have shown that populations of neurons lateral of the primary auditory cortices of marmosets respond preferentially to the fundamental frequency (F0) of a tone regardless of whether it is a pure tone or harmonic complex, offering a possible explanation for why the perceived pitch can be extracted given varying degrees of pitch salience (Bendor & Wang, 2005). Indeed, evidence of non-primary auditory cortex involvement in pitch extraction has also been observed in humans (Patterson et al., 2002; Penagos et al., 2004). This suggests that the neural correlates of pitch perception are organized hierarchically such that more basic features of a stimulus are extracted early in the processing chain, while more derived features are extracted later in the processing chain. However, the subtle nuances of how this information is coded are relatively poorly-understood, especially in the context of rich environmental sounds. Thus, music offers a more manageable and finite system with which pitch processing in the brain can be studied (i.e., melodies). In particular, one case in which musicianship contributes valuable information about auditory function in the cortex is the case of absolute pitch.

Absolute pitch (AP) is the ability to name or produce a musical tone without the aid of a

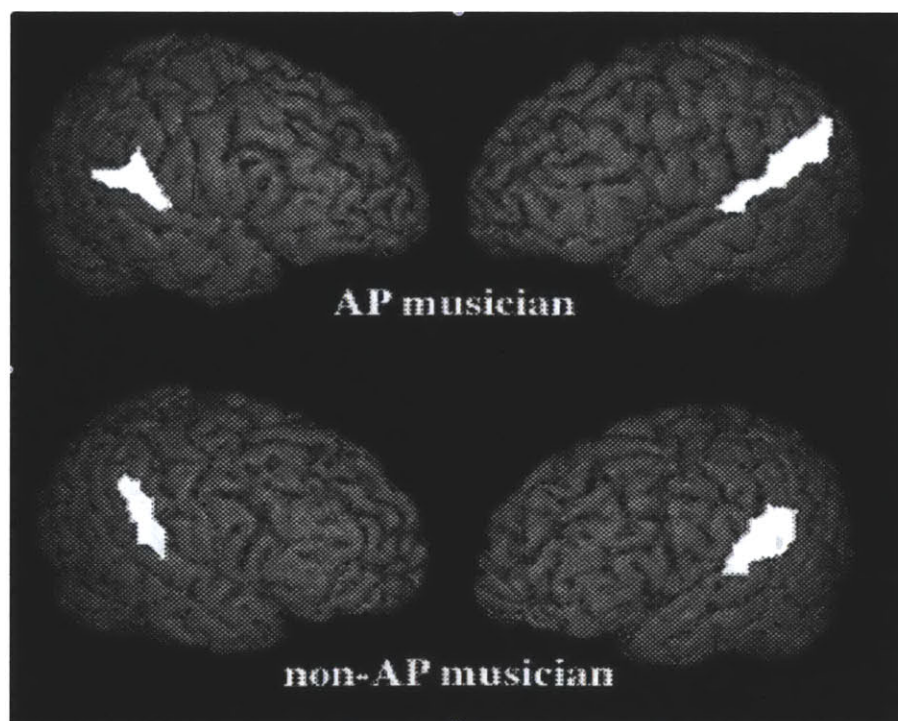


Fig. 2-1: anatomical asymmetry of the planum temporale in AP-musicians relative to non-AP musicians. Note the increased leftward lateralization in AP musicians (adapted from Schlaug, 2001).

reference tone. Possessors of this ability represent an opportunity to identify regions in the brain that are related specifically to pitch encoding and recall. Structurally, the brain of individuals with absolute pitch exhibit an enlarged planum temporale (PT), and that this contributes to an increased leftward lateralization as compared to a control group of musicians without AP (see fig. 1). The extent of lateralization of the PT has been closely associated with handedness and language lateralization (Steinmetz & Seitz, 1991; Steinmetz et al., 1991), further linking musical processing to the importance of language hemispheric dominance and laterality in the cortex (Schlaug, 2001).

In addition to structural correlates to abilities that are special even among musicians (AP), there are also more basic ways in which music drives the auditory networks, and this may be seen very early in musical training. For example, children who are engaged in a musical training regimen are actively forming important connections between regions in the brain that subserve auditory perception, timing, and motor functions, suggesting functional differences between the brains of children involved in musical training and those who are not. Indeed, studies have shown that children involved in musical training show significant differences in functional activation when

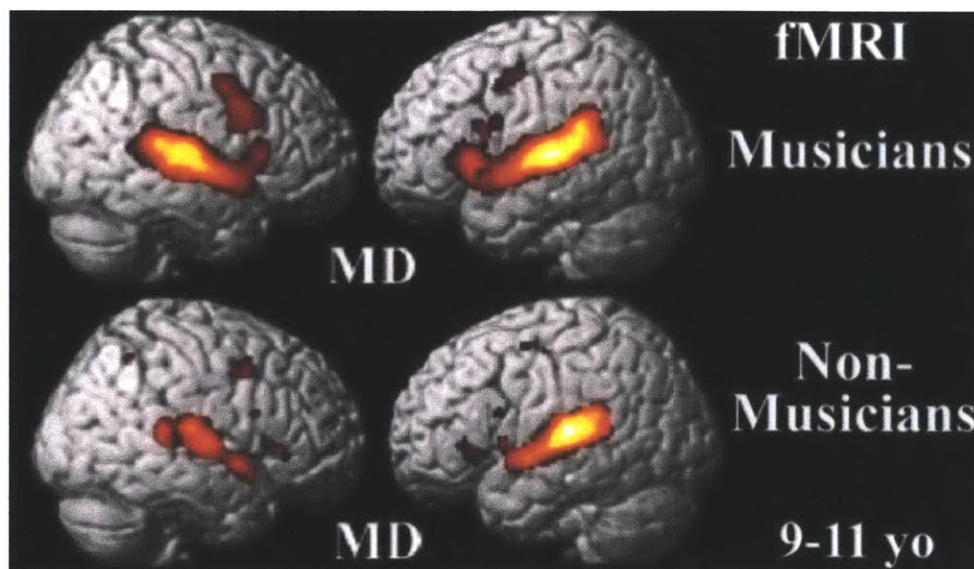


Fig. 2-2: differing activation patterns among musically trained and musically naïve children (adapted from Schlaug et al., 2005).

performing auditory tasks relative to musically-naïve controls (Schlaug, 2005). Figure 2-2 compares the activations of musically trained children to non-musicians during a melody discrimination task.

In addition to inducing the short-term functional adaptations seen above, musicianship may also contribute to changes in brain structure over time. One study investigated this by using a longitudinal design with deformation-based morphometry (DBM) an automated technique that provides a method of measuring structural differences in a brain over time (Hyde et al., 2009). Concurrently, the group also assessed the children’s musical skills behaviorally by using a musically relevant test that non-musicians could also perform (e.g., a motor-sequencing test in which the children are required to repeat a prescribed button-combination as accurately and as many times as possible during a 30s period). The results of the study showed that after 15 months of musical training, children undergoing musical training during that period showed alterations in brain structure that were not present in the control group. These changes were particular to auditory and motor regions of the cortex, and were correlated with higher scores on auditory and motor behavioral tasks.

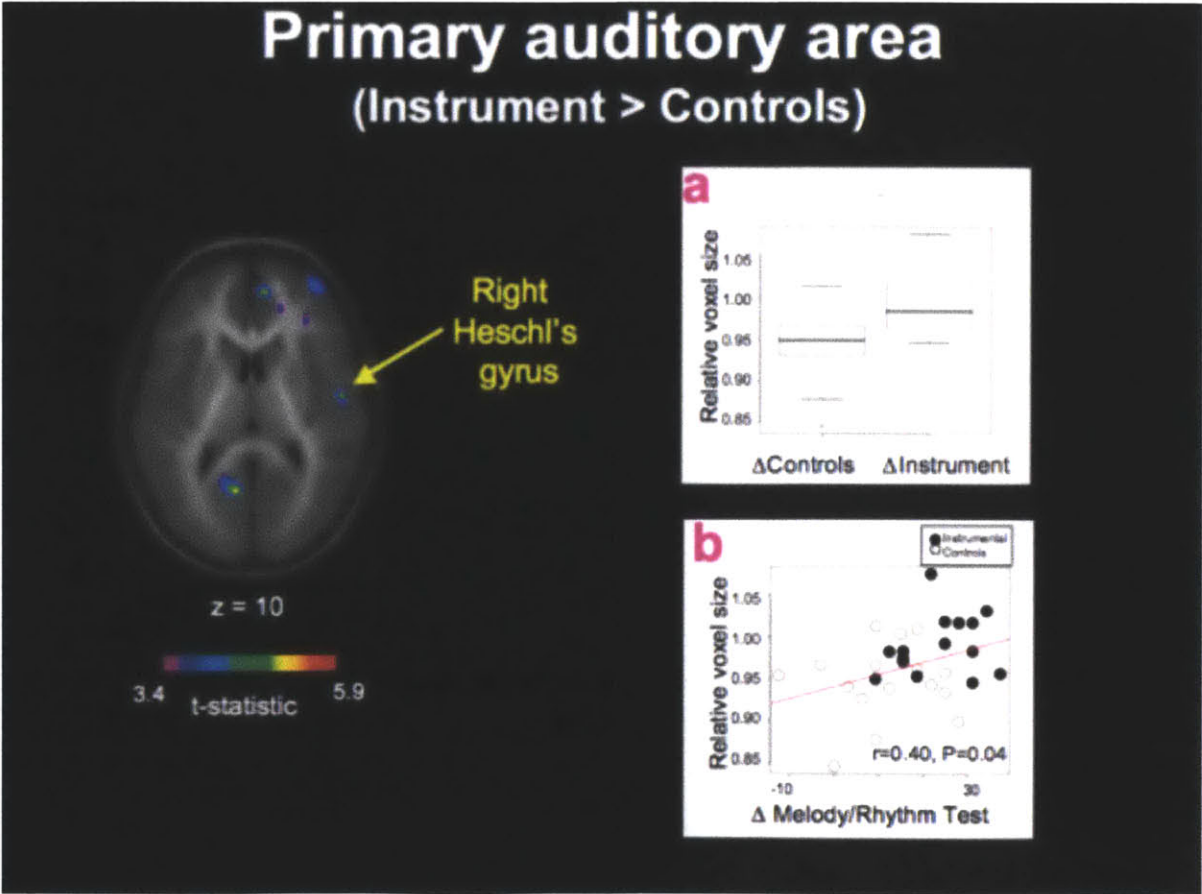


Fig. 2-3: significant differences between relative voxel size (a) in the auditory areas of musically-practicing and non-practicing children 15 months from the baseline scan, as well as the correlation between relative voxel size and performance on auditory perception tests(b) (Hyde et al., 2009).

The above figure shows the regions of significant difference in relative voxel size (15 months after initial scan) between the musically-practicing and non-practicing groups. The musically-practicing group shows a significantly higher relative voxel in the primary auditory area, and this difference is accompanied by a correlation with behavioral scores on a listening test (this significant correlation is observed in the musically-practicing group but not in controls). These results suggest that even in the early stages of musical training (barely beyond the first year), it is possible to observe structural changes in the cortex that cannot be attributed to the natural course of development. The observation of this change in the auditory areas confirms the notion that musical experience drives functional and structural adaptations of certain brain structures, supporting the notion that musical training and musicianship provide useful models in the study of auditory-motor interactions.

2.1.2 Music & the Motor Domain

In addition to demanding exceptional listening abilities, musicianship also necessitates a very high level of fine motor coordination. Although the precise nature of this can vary according to the instrument of specialization (e.g., a keyboard player's hands vs. a singer's vocal apparatus), it is safe to assume that all musical abilities necessitate great dexterity in fine motor skills. Studies that investigated the relationship between musical training and the structure of the primary motor cortex confirm this. Children who are actively engaged in a musical training regimen show changes in the right precentral gyrus after 15 months that are not present in control participants who did not receive musical training over the same period of time.

Such changes in brain structure over time are consistent with previous literature that compares the brains of adult musicians and non-musicians (Gaser & Schlaug, 2003; Lee, et al, 2003; Schmithorst & Wilke, 2002), in addition to adding support to the notion that these differences observed in adulthood are, at least in part, due to training-induced plasticity concurrent with an intensive and long-term training regimen that has been practiced since childhood. Since musicianship is a longitudinally developed skill, it is tempting to assume that the differences observed between adult musicians and non-musicians are completely due to practice, although this would be erroneous. In fact, the data only show that children who are practicing music exhibit specific structural adaptations that facilitate auditory-motor function. These adaptations can be

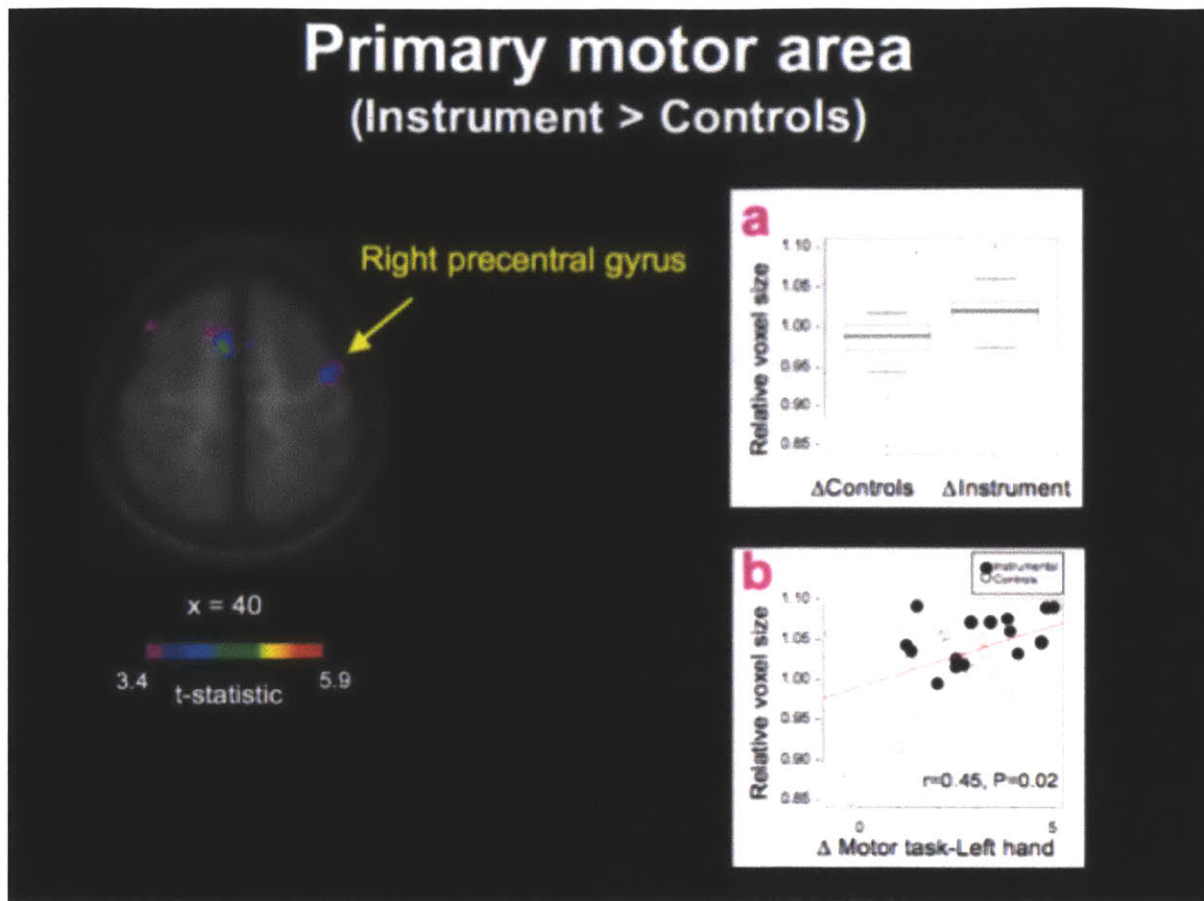


Fig. 2-4: significant differences between relative voxel size (a) in the motor areas of musically-practicing and non-practicing children 15 months from the baseline scan, as well as the correlation between relative voxel size and performance on the left-hand motor sequence task(b) (Hyde et al., 2009).

the result of intensive and long-term practice, although they could also reflect genetic predispositions, and/or a combination thereof. While it may be difficult to determine the extent to which these children's brains are changing structurally in response to the musical training, or if this cohort had already possessed some genetic factors that facilitated their attraction to music and musical training, such studies suggest that intense and long-term training (whether or not one starts with a genetic advantage) will likely lead to brain changes.

Figure 2-4 provides the motor counterpart to the figure displayed previously. Here, the study emphasizes the change in the structure of the right precentral gyrus in musically-practicing children. The relative voxel size after 15 months of training is significantly different between groups, suggesting that there are structural changes, detectable within one year, that cannot be explained by the normal course of development and, given the behavioral correlations, may be specific to the auditory-motor domain and thus induced by musical training. This provides another example of the

utility of music and musical training as a tool for studying auditory-motor interactions in the cortex, as well as how they may be remodeled with respect to time. Although the effects of musical training may be seen separately in the auditory and motor regions of the brain, music is an activity that emphasizes efficient communication between auditory and motor modules, thus necessitating exceptional abilities in two-way auditory-motor coordination. Indeed, this ability is also important for speech, another form of highly coordinated auditory-motor function. In the next section, the importance of auditory-motor connectivity in music and speech will be summarized by a discussion of the similarities and differences between speaking and singing, as well as the anatomical and functional neural substrates that underlie them.

2.1.3 Singing, Speaking, and Auditory-Motor Connectivity

While speaking and singing are thought to share some functional processing resources, relatively little is known about the structural underpinnings of these auditory-motor networks, and how they may function when auditory feedback is mismatched with motor planning.

Understanding the extent to which the neural substrates of speaking and singing are distinct depends on a grounded understanding of the lateralization of speech function in the brain, as well as the constraints that dictate this functional lateralization. Speech can be decomposed according to the time scale associated with the occurrence of its acoustic components. Formant transitions, consonant-vowel (CV) transitions, and other rapid changes in the articulation of the vocal tract can be thought of as the fast components of speech (occurring on the order of tens of milliseconds), whereas processing syllables and prosody (the fundamental frequency envelope of speech in time) can be thought of as the slow components of speech (occurring on the order of hundreds of milliseconds) (Abrams et al., 2003). This necessitates a localization of functions involving the resolution of very fine and rapid temporal changes in the signal to one hemisphere, considering a delay of more than 25ms for interhemispheric, transcallosal transfer in humans (Aboitiz et al, 1992; Ringo et al, 1994). The application of these observations to speech processing supports the notion that tasks involving short temporal integration windows (tens of milliseconds) would preferentially recruit the left hemisphere or only one hemisphere (Poeppel, 2003), whereas tasks involving temporal integration windows on the order of hundreds of milliseconds might be processed in both hemisphere or may preferentially activate structures in the right hemisphere considering the right

hemisphere's preferred role in integrating information over time (Abrams et al., 2008).

Indeed, functional neuroimaging studies show that tasks involving the rapid articulation of phonemes (such as CV-transitions) and the modulation of prosody are correlated with temporo-frontal activation (TFA) patterns that are somewhat distinct both in terms of lateralization and dorso-ventral distribution, depending on the task. Specifically, bilateral-dorsal and right-ventral TFA are implicated in CV-transition and prosodic processing, respectively (Glasser & Rilling, 2008).

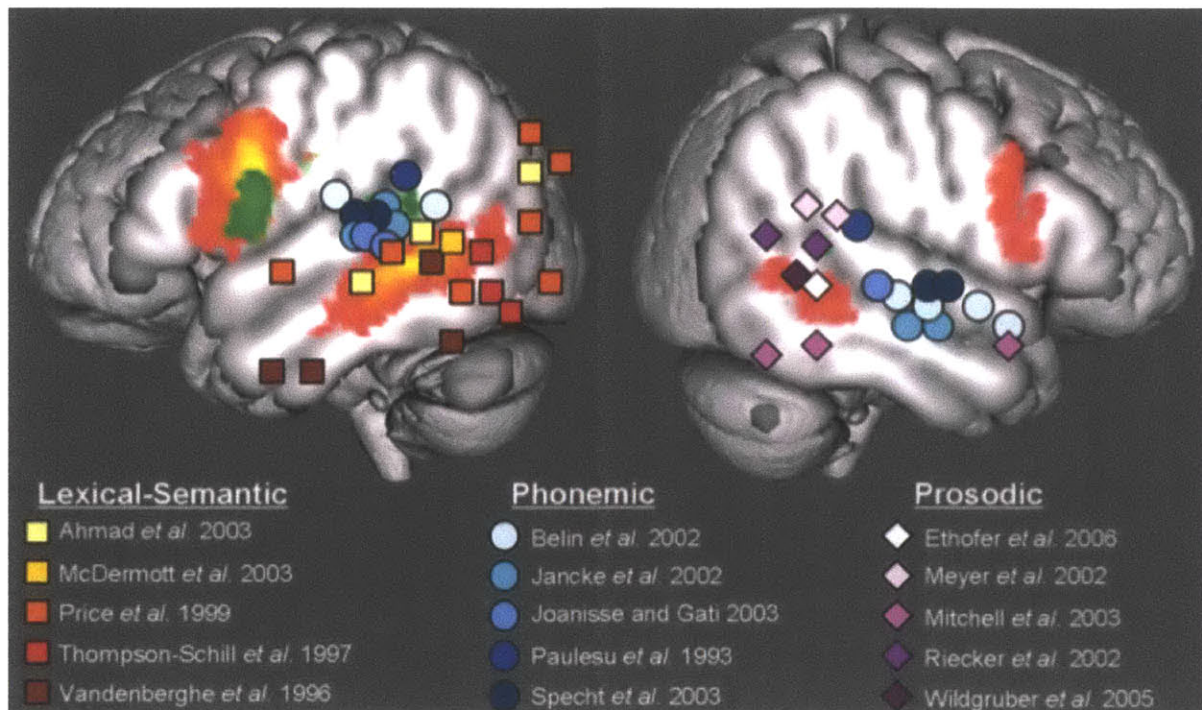


Fig. 2-5: aggregation of functional neuroimaging results from studies of various types of speech-language tasks (lexical-semantic, phonemic, and prosodic), showing hemispheric and dorso-ventral preferences for differing task demands (Glasser & Rilling, 2008).

In accord with these observations, cerebrovascular accidents (CVAs) that result in left temporo-frontal lesions lead to aphasias, an impairment in communication, whose symptoms correspond with the particular lesion location in this temporo-frontal network (Catani & Mesulam, 2008). Taken together, these lines of evidence support the notion that processing pathways for prosody (a slow component of speech) and CV-transitions (one example of a fast component of speech) are somewhat distinct, both structurally and functionally. Furthermore, the observation that individuals engaged in a long-term vocal training regimen have more accurate control of their vocal

output than individuals lacking this training suggests that it may be possible that these structural centers of vocal control adapt in response to intensive long-term training. With this in mind, it is prudent to provide structural corroboration to these notions by studying the arcuate fasciculus (AF),

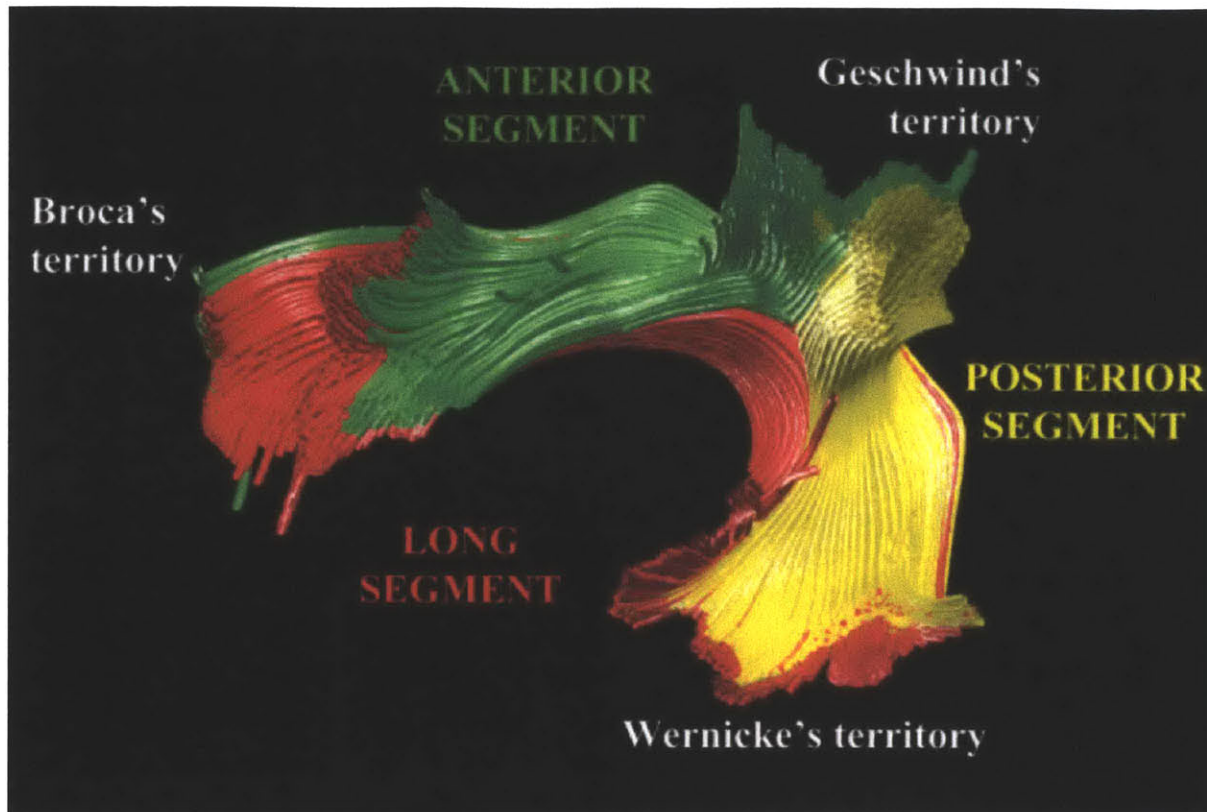


Fig. 2-6: Tractographic reconstruction of the AF, showing the direct branch, reciprocally connecting Broca and Wernicke's areas, as well as the indirect branches, connecting each via Geschwind's territory et al., 2004; Friederici, 2009)

a prominent white-matter fiber tract that connects the various nodes of these networks and acts as a “transmission line” between them (Glasser & Rilling, 2008), and how it may exhibit adaptations as a result of lifelong auditory-motor training regimen (i.e. vocal training). Secondly, functional evidence that demonstrates how these networks may adapt when auditory feedback is perturbed (both acutely and chronically) would also aid in understanding mechanisms of auditory-motor remodeling by providing insight into short-term compensatory reorganization of these networks.

Model systems that disentangle these two components (fast and slow components of speech) would benefit our understanding of the neural mechanisms that underlie separate stages of auditory-motor perception and production in healthy individuals, as well as providing insight into the

mechanisms behind clinical interventions for aphasia syndromes (e.g. melodic intonation therapy for Broca's aphasia). In particular, two model systems are required: one that will provide insights into structural, long-term auditory-motor adaptations, and one that will provide insights into functional, short-term auditory-motor adaptations.

In order to study structural remodeling of the arcuate fasciculus, individuals with intensive long-term auditory-vocal training (i.e. professional singers) may serve as one 'model system', since their lifelong training can be thought of as an intensive long-term auditory-vocal mapping and sensorimotor control program, one whose goal is to optimize the interactions between the nodes of the AF, the auditory-motor mapping regions and the sensory feedback regions, such that the perception and execution of complex and finely-adjusted vocal-motor routines is possible (this subject is treated more comprehensively in chapter 3). Conversely, healthy non-musicians may be a suitable 'model system' for a functional investigation of short-term adaptations of the auditory-motor system while engaging in a pitch-matching task under conditions of intermittent pitch-shifted auditory feedback (this subject is treated comprehensively in the first part of chapter 4). Under this experimentally-induced short-term auditory-motor feedback mismatch, insight is gained into the short-term functional adaptations of the auditory-motor system under conditions of experimentally-induced 'disorder' in the network.

2.2 Insights from Disorder?

'Disorder' is a broad term that is used here to refer to long-term disorders (functional and/or anatomical) in the auditory-motor network (such as those occurring in tonedeafness) as well as short-term, experimentally-induced conditions of auditory-motor feedback mismatch (such as those occurring during a pitch matching task with real-time perturbation of auditory feedback). Such conditions offer a unique look at the structure of the auditory-motor system in states of long-term disorder (e.g., the structure of the AF in tonedeaf individuals), as well as the functioning of the auditory motor system in states of long-term disorder (e.g., the behavioral and neurological responses of tonedeaf individuals undergoing a pitch-matching task with and without auditory feedback perturbation).

2.2.1 Insights from a chronically-compromised auditory-motor networks (tonedeafness)

Tonedeafness (also referred to as congenital amusia in some literature), has been characterized psychophysically by a pitch discrimination deficit, although it is not clear where in the auditory pathway this arises, since anatomical and physiological markers of primary auditory cortex are intact, arguing against the notion that TD is due to a malfunction in processing fine-grained pitch information (Peretz et al, 2005). Phenotypically, the disorder is characterized by an inability to sing in tune or to match a reference pitch. This suggest that the disorder could be due to perceptual problems (e.g., not forming or storing a template for the vocalizations or not having a mechanism that compares auditory feedback with the templates (e.g., a disorder of auditory error cells).

Another theory contests that the deficits demonstrated by individuals with TD arise from a disorder in spatial processing. A recent study showed that performance on mental rotation in a visual task was significantly impaired in people with TD (Douglas & Bilkey, 2007). While the notion that the auditory-motor aspects of TD may be related to deficits in other modalities is inspiring and may lead to some interesting insights, this study does not convincingly describe the link between spatial processing and the auditory-motor domain. Furthermore, the group with tonedeaf individuals could have been better matched with the control group, making the findings much more convincing. Nevertheless, this study introduces the idea that TD may have some correlates in other modalities, although the extent of this remains to be seen.

The most convincing hypothesis surrounding the etiology of tonedeafness posits a disorder in auditory-motor feedback. This is also the most recent theory, and thus requires more data to substantiate. For example, while this view states that one or several modules along the auditory-motor feedback network may be impaired, it is not clear how many, and which ones. Certainly, this could include a disorder in pitch processing (i.e., auditory state cells according to DIVA), in auditory target formation (i.e. the auditory target cells), or feedback-dependent control (i.e., auditory error cells and the feedback control subsystem) but it is difficult to determine which modules are affected in a purely behavioral experiment, since malfunction of one of the modules could produce the symptom of other malfunctioning modules indirectly (for example, a disorder in auditory target formation and auditory perception could appear identical symptomatically), and more neuroimaging data on auditory-motor function in TD is needed to help clarify and tease apart these different

possible etiologies. Nevertheless, the fact that there is no convincing evidence that shows that a possible etiology underlying this disorder originates in the primary auditory cortex (Mandell et al., 2007; Peretz et al., 2005) supports the hypothesis of a disorder somewhere in the connectivity of the feedback and feedforward system. Concurrently, functional, structural as well as electrophysiological studies have suggested that the abnormality might be outside the primary auditory region and involve auditory-association regions and auditory-motor mapping regions involved in auditory-motor feedback and feedforward tasks (e.g. Loui et al, 2009, Mandell et al, 2007). This work aims to contribute to this dialog by contributing more neuroimaging data from individuals with TD performing a pitch-matching task under conditions of perturbed auditory feedback.

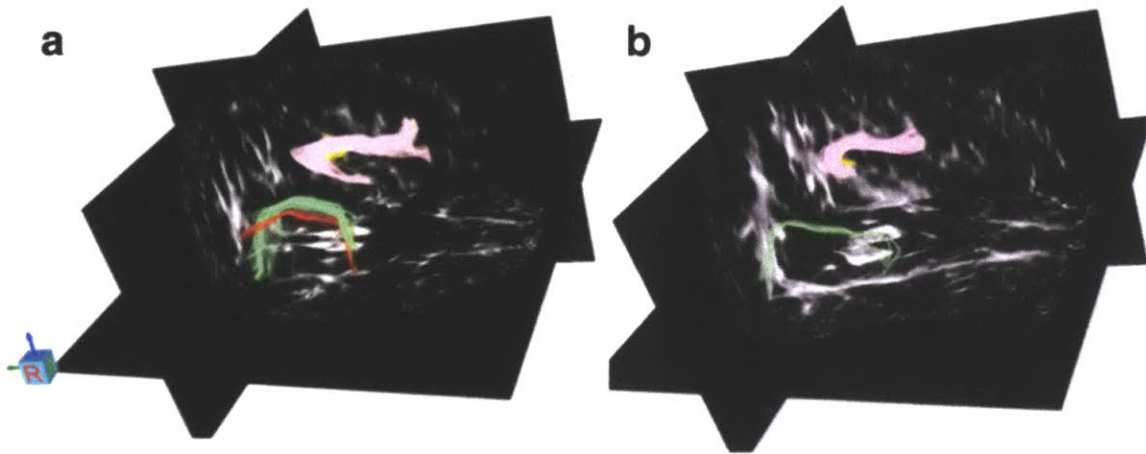


Fig. 2-7: Tractographic reconstructions of the arcuate fasciculi of normal (a) and tonedeaf individuals (b). The right-hemisphere AF of tonedeaf individuals is significantly lower in volume relative to controls, especially in the branch connecting the right superior temporal gyrus to the right inferior frontal gyrus. This right-dorsal branch of the AF is visible in red (a), but is virtually undetectable in this group of tonedeaf subjects (b) (Loui et al., 2009).

The case of tonedeafness offers a unique way to glimpse into auditory-motor processing in a pathological state. By administering a pitch-matching task with simultaneous fMRI in tonedeaf individuals, it is possible to compare their auditory-motor activation networks relative to those of control participants and make hypotheses about which nodes of the network may be incapacitated, or somehow functioning abnormally, in conditions of chronic auditory-motor compromise. Furthermore, it is possible to compare how normal and tonedeaf individuals react to auditory-feedback perturbation (behaviorally and neurologically). Comparing the behavioral (direction and magnitude of compensation for pitch-perturbation during a pitch-matching task), as well as neurological (areas of activation associated with this compensation) measurements taken from

tonedeaf individuals to those from controls will lend further insight to mechanisms to short-term adaptations in the auditory-motor system (compensating for pitch shifts), as well as how this network may function in a chronically compromised state (tonedeafness).

2.2.2 Insights from transiently-compromised auditory-motor networks (feedback perturbation)

Neurologically normal individuals change their vocal patterns when confronted with perturbed auditory feedback of their voice. This is indeed verified in recent studies of pitch-perturbed auditory feedback (Burnett et al, 1998), in which subjects altered their F0 output in a direction inversely related to that of the experimental perturbation, as long as the magnitude of the perturbation was moderate (subjects begin to ‘follow’ the direction of the shift as the perturbation magnitude is increased from .25 semitones to 3 semitones).

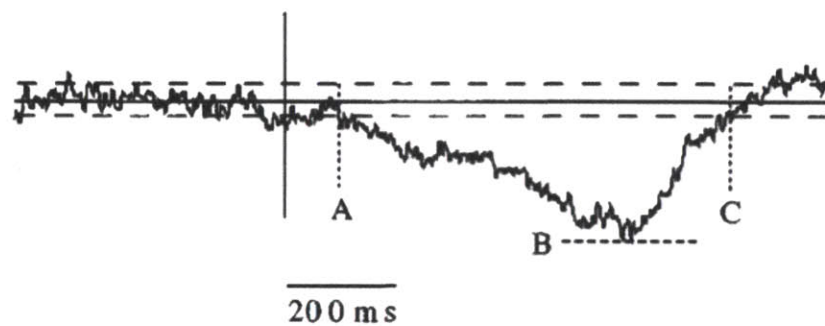


Fig. 2-8: F0 with respect to time of a subject compensating for an upward pitch-perturbation by adjusting F0 output to be lower than normal (i.e., opposing the experimental manipulation). The solid horizontal line represents the mean F0 before the onset of the perturbation (± 2 SDs indicated by dashed horizontal lines) which is indicated by the solid vertical line. A refers to the time of the onset of the compensation. B marks the peak magnitude of that response, and C indicates the offset of the response (Burnett et al., 1998).

Similar studies have been done with simultaneous fMRI acquisition. These studies report increased activity in the dorsal premotor cortex (PMC) in response to expected F0 perturbations in non-musicians, and increased activity in PMC, superior temporal gyrus / sulcus (STG / STS), and anterior cingulate cortex (ACC) in response to expected F0 perturbations in singers (Zarate & Zatorre, 2008).

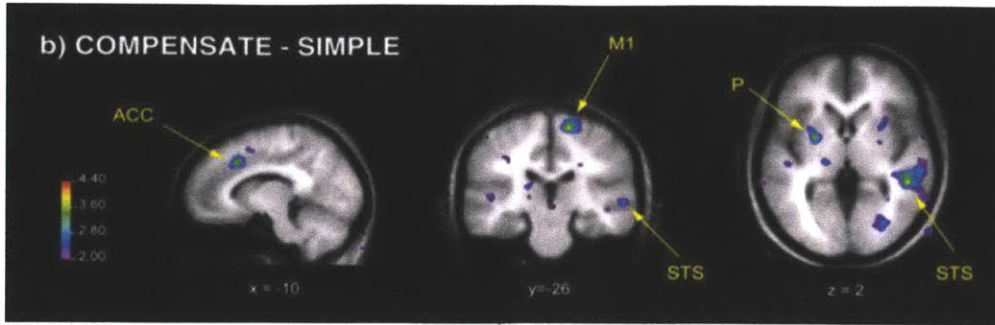


Fig. 2-9: Regions of activation differences between singers and non-musicians during conditions of expected F0 perturbations (Zarate & Zatorre, 2008).

Others have observed increased activity in superior temporal gyrus (STG) and right prefrontal cortex (PFC) and rolandic cortex (RC) in response to unexpected F1 perturbations (Tourville et al., 2008).

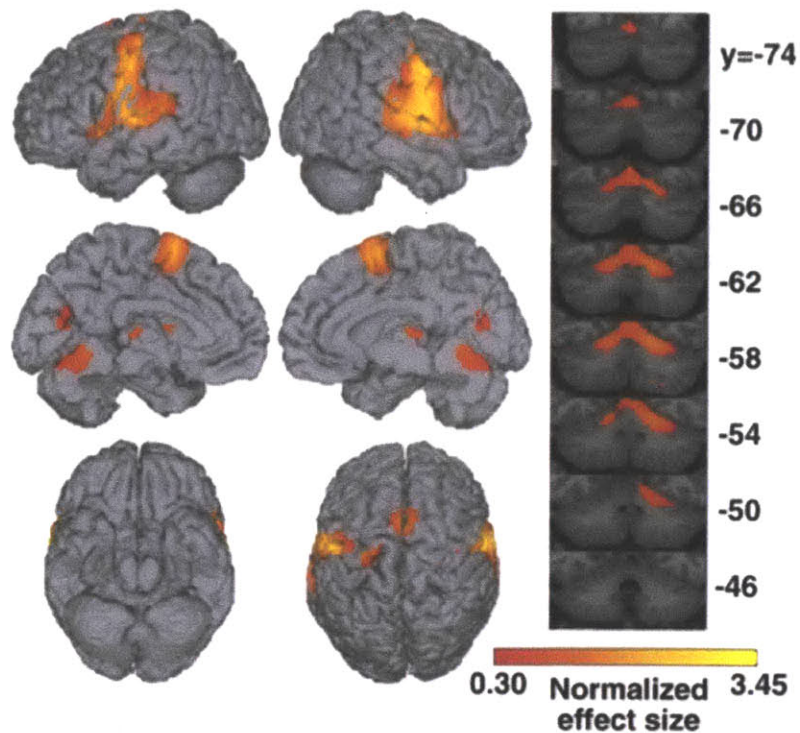


Fig. 2-10: BOLD responses of subjects to shifted F1 relative to a silent baseline task, showing responses from superior temporal regions bilaterally, superior cerebellar regions bilaterally (Tourville et al., 2008).

These experimental results were used to test the accuracy of the *Directions into Velocities of*

Articulators (DIVA) model (Guenther, 2006; Guenther et al., 2006), a computational model of vocal-motor interactions which has received considerable attention and has been proven useful in the generation and testing of hypotheses concerning auditory and speech-motor interactions. This model segregates the information processing required for vocal-motor action into two broad sub-systems: feedforward control and feedback control, the functional components of which are distributed over thirteen processing modules, each corresponding to a certain function and cortical region based on previous functional neuroimaging literature (Golfnopoulos, Tourville, & Guenther, 2010).

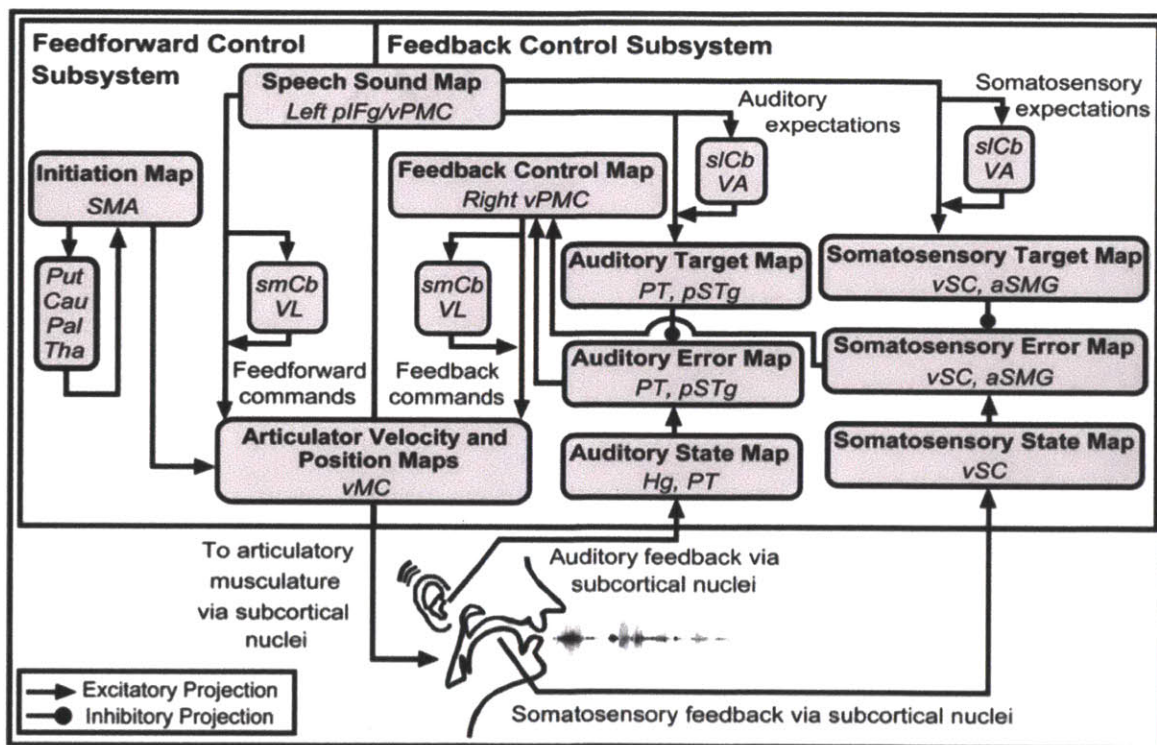


Fig. 2-11: Overview of the DIVA model, with each module corresponding to an group of neurons (based on findings of previous functional literature and labeled anatomically). The modules are connected by inhibitory or excitatory projections, shown here as lines with differing arrowheads (Golfnopoulos et al., 2010).

Apart from providing a synthesis of previous literature related to the subject of auditory-vocal control and a useful starting point for generating hypotheses and experimental designs, the model also allows for the visualization of each module's output onto a rendered brain in MNI space, allowing for direct comparisons between predicted and experimentally observed neurological responses. For the task reviewed in the previous experiment, the DIVA model predicts increased

activity in bilateral peri-sylvian cortex (the model's 'auditory error cells') and bilateral ventral-rolandic cortex (the model's 'motor correction cells') during the perturbations (Golfinopoulos et al., 2011; Guenther, 2006; Tourville et al., 2008), generally agreeing with the experimentally gathered data. This model will play a significant role in interpreting the results gathered in the primary studies that constitute this dissertation. Thus, references will be made to the model throughout. Although it is continuously refined as new data and insights become available, it represents a valuable reference point that can be used to design new experiments as well as interpret new data concerning auditory-vocal interactions (such as the investigations that follow this section) in the context of the existing literature.

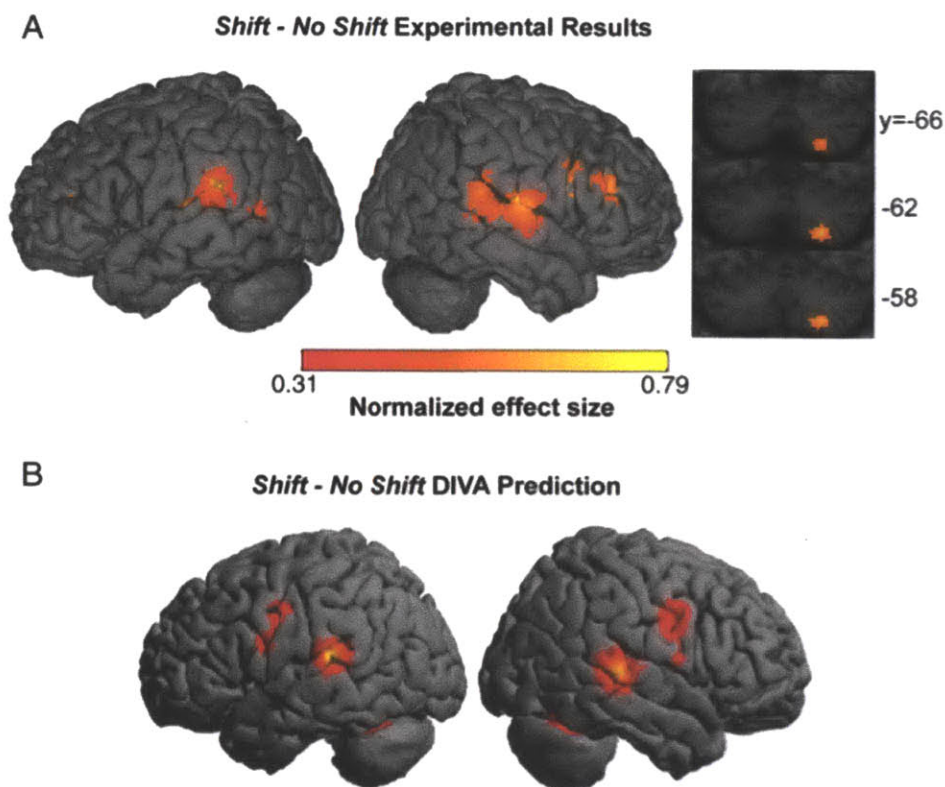


Fig. 2-12: comparison between DIVA model predictions and experimental results, showing general agreement between the model and the experimental results (Tourville et al., 2008).

Taken together, using transiently compromised auditory-motor networks (as is the case in perturbed auditory feedback experiments) and referring to models such as DIVA for interpretation comprises a prudent strategy for drawing new insights from new data such as those described in the subsequent chapters. These new insights will aid not only in understanding the organization of the auditory-motor system generally, but also in understanding certain communication disorders, whose

etiologies may include a significant auditory-motor feedback component.

2.3 Implications for communication disorders

It should first be noted that while auditory-motor interventions aim to reduce the severity of several communication disorders, they most likely do so by addressing the auditory-motor aspects of the disorder (e.g. apraxia of speech), and not the language aspects of such disorders (e.g. lexical access). For example, Broca's aphasia results from lesions in or in the vicinity of Brodmann's area (BA) 44 and 45, in the inferior frontal regions of the left hemisphere, and results in difficulties in the planning and execution of the motor aspects of language and speech (A. R. Damasio, 1992; A. R. Damasio & Geschwind, 1984; Dronkers et al., 2004; Kreisler et al., 2000). Wernicke's aphasia results from disruptions in processing in and around the left posterior superior part of the temporal lobe, and lead to significant deficits in the comprehension of language. Deficits in these areas comprise a major symptom of the Autism Spectrum Disorders (ASD), as 25% of individuals with ASD face significant difficulties in producing speech (Pickett et al., 2009; Sherer & Schreibman, 2005; Wan et al., 2011). Deficits of auditory-motor function are thought to play a role in the etiology of non-verbal autism (Wan et al., 2011), as individuals with this condition also suffer from difficulties in linking auditory percepts to motor actions. Auditory-motor training therapies that aim to help strengthen auditory-motor function in such individuals would do so by engaging the speech-related functional network and encouraging plasticity in anatomical pathways that connect its various nodes (described above in the review of the DIVA model).

The major fascicle that reciprocally connects the nodes of this network is the AF. The AF is typically involved, to some degree, in lesions that affect the Broca or Wernicke regions. However, an isolated lesion of the AF leads to a particular disorder which is commonly referred to as conduction aphasia, a rare condition characterized by intact speech comprehension and production, but impaired speech repetition capability (A. R. Damasio & Geschwind, 1984; H. Damasio & A. R. Damasio, 1980; McCarthy & Warrington, 1984; Warrington et al., 1971). Thus, investigating the structural adaptations of the AF in response to long-term auditory-vocal training (i.e. in professional singers: chapter 3), the behavioral and functional correlates of this auditory input into the system is perturbed (i.e., in chapter 4) as well as when the network is in a chronically compromised state (i.e., in tonedeafness) will contribute to the understanding of the mechanisms of the aphasias and other

communication disorders (e.g. non-verbal autism), and may help to evaluate therapies that purportedly alleviate symptoms resulting by using a new communication strategy (i.e. singing) and thus seeking an ‘alternate route’, effectively circumventing the areas or networks that may be directly affected by the disorder.

Melodic Intonation Therapy (MIT) and Auditory-Motor Mapping Therapy (AMMT) are speech-language rehabilitation techniques that introduce candidate aphasia and non-verbal autistic patients to melodically intoning their speech by using very elementary ‘melodies’ (this is typically just using two notes -one higher than the other). The rationale behind this states that this may facilitate recovery because singing has been shown to engage right-hemisphere networks more relative to speaking. There are different explanations for this observed effect. Firstly: singing slows down articulation and connects the individual phonemes into a larger ‘chunks’. Second: the use of contour and melody (which are inherent in singing), engages more right hemisphere structures and plays into one of the preferred roles of the right hemisphere (i.e., integrating information over hundreds of milliseconds or seconds, vs tens of milliseconds; Poeppel, 2003) . Third: the use of left hand rhythmic tapping may prime a right-hemisphere sensorimotor network involved in control of vocal output (Norton et al., 2009; Patel et al., 1998; Schlaug, et al., 2009).

Although there is some work that suggests promise for this therapeutic method (Schlaug et al., 2009), the reasons for it’s efficacy are still somewhat unclear. In cases where patients undergoing the therapy are improving, it is unclear why they are improving (i.e. there is a deficit in anatomical data explaining this improvement). Thus, characterizing the AFs in both hemispheres of subjects immersed in musical training will help to show how a brain may exhibit adaptations for fine auditory-motor control (chapter 3), and how a brain may function (and how the subject behaves) when the input to the networks governing this control is disrupted acutely (as in the case of perturbed feedback –chapter 4) and chronically (as in the case of tonedeafness). This will contribute useful evidence to ongoing studies of novel therapies such as MIT and AMMT, as well as acting as a harbinger for using training regimes that strengthen auditory-motor networks differentially (e.g. separate training regimens for slow/fast components of speech), towards other novel clinical interventions that aim to circumvent, or compensate for, symptoms of various communication disorders(Wan et al., 2010).

3: STRUCTURAL ADAPTATIONS OF THE AUDITORY-MOTOR SYSTEM: Comparing the brains of professional singers, instrumentalists, and non-musicians.

Abstract

Structure and function of the human brain, in particular frontal and temporal brain regions, are affected by training in both linguistic and musical domains, although the extent to which the white matter tracts that connect these regions can be affected by training is still not known. Individuals with intensive vocal musical training provide a useful model for investigating neural adaptations of learning in the vocal-motor domain and can be compared with learning in a more general musical domain. Here we confirm general differences in macrostructure (tract volume) and microstructure (fractional anisotropy (FA)) of the arcuate fasciculus (AF), a prominent white-matter tract connecting temporal and frontal brain regions, between singers, instrumentalists, and non-musicians.. Both groups of musicians differed from non-musicians in having larger tract volume and higher FA values of both the right and left AF. The AF was then subdivided in a dorsal (superior) branch connecting the superior temporal gyrus and the inferior frontal gyrus, and a ventral (inferior) branch connecting the middle temporal gyrus and the inferior frontal gyrus. Relative to instrumental musicians, singers had a larger tract volume but lower FA values in the left dorsal AF, and a similar trend in the left ventral AF. This between-group comparison controls for the general effects of musical training, although FA was still higher in singers compared to non-musicians. Both musician groups had higher tract volumes in the right dorsal and ventral tracts compared to non-musicians, but did not show a significant difference between each other. Furthermore, in the singers' group, FA in the left dorsal branch of the AF was inversely correlated with the number of years of participants' vocal training. The present findings suggest that long-term vocal-motor training might lead to an increase in volume and microstructural complexity of specific white matter tracts connecting regions that are fundamental to sound perception, production, and its feedforward and feedback control which can be differentiated from a more general musician effect that goes beyond specific tracts.

Key words: plasticity, white matter, arcuate fasciculus, auditory-motor interactions, tractography, music, singing

3.1 Introduction

In recent years, there has been increased interest in the use of musicians to examine brain adaptation in response to intense and long-term training of musical skills (Trainor & Desjardins, 1998; Ross et al, 2003; Bengtsson et al, 2005; Koelsch et al, 2005; Zatorre et al, 2007; Moreno et al, 2008; Schlaug et al, 2009; Hyde et al, 2009; Oechslin et al, 2010; Wan and Schlaug, 2010). Although most of the previous work has focused on instrumental training, one type of musical training that may provide additional insights in brain adaptation is training in the vocal auditory-motor domain (Zarate and Zatorre, 2008; Kleber et al, 2009; Zarate, Wood & Zatorre, 2010). Singing is an example of intensive auditory-vocal training which is typically started later in childhood or adolescence compared to instrumental music training, suggesting that simply being genetically predisposed to auditory-motor skills is not enough to make one an accomplished performer. Singing as an activity has also received a lot of attention recently, since forms of singing have been shown to have positive effects on various neurological disorders (Wan et al., 2010).

Regions in the superior temporal lobe, inferior frontal areas, and the associated premotor and motor regions are involved in the feedforward and feedback control of singing (Brown et al, 2004; Levitin and Menon, 2003; Maess et al, 2001; Pantev et al, 1998; Ozdemir et al, 2006). This fronto-temporal network of brain regions is connected via the arcuate fasciculus (AF), a prominent white-matter tract which, in its horizontal part, may share some components with the superior longitudinal fasciculus (SLF). The AF has direct fibers connecting the middle and superior temporal gyrus with inferior frontal regions, but may also have an indirect fiber system connecting the temporal lobe with the inferior parietal lobulus and then the inferior parietal lobulus with frontal lobe regions (Catani et al., 2005; Glasser and Rilling, 2008). It should be noted that these putative 'tracts' in fact represent tractography-derived pathways, and thus their fidelity to the anatomy is continuously contested, in particular with regards to whether or not the AF consists of direct fronto-temporal fibers or indirect fibers with synapses and relay stations in the parietal lobule (Catani et al., 2005; Glasser and Rilling, 2008; Frey et al., 2008). The AF and SLF have already been implicated in normal and abnormal vocal-motor activities. Fiber volume in the AF, and regional fractional anisotropy (FA—a measure of the degree of directional preference of water diffusion and therefore of how well fibers are aligned in one direction (Basser, 1995) - values along its midpoint, are both lower in tone-deaf individuals (Loui et al., Schlaug, 2009). The phenotypical characteristic of tone-deaf individuals

is that they cannot sing in tune and are not aware of their vocal feedback. The impairment of the AF in tone-deaf subjects supports its presumed role in the feedforward and feedback control of vocal output.

In learning to associate motor actions with sounds and in training an auditory-motor feedback loop connecting the temporal with the frontal lobe, white matter fiber bundles between these regions might change in size, volume, and composition. One common DTI-derived measure, fractional anisotropy, is a normalized measure expressing the directional diffusion of water protons; the more aligned fibers are within a tract, the higher the FA value. FA changes within-group and FA differences between-group can be regarded as a surrogate marker of structural adaptation in the white matter. Adaptations of the arcuate fasciculus have been described as a function of normal development (Barnea-Goraly et al, 2005; Ashtari et al, 2007), and developmental delay has been found to be associated with disordered morphology of the AF, possibly reflecting delayed myelination (Sundaram et al, 2008).

Previous research has identified regions that may control and be strengthened by vocal training (Zarate et al, 2008, 2009). In addition to the STG and its reciprocal connections with the inferior premotor and posterior IFG, the middle temporal gyrus (MTG) also has prominent connections with the inferior frontal gyrus (IFG). These two branches can be thought of as two separate branches with possibly slightly different functions in the auditory-motor mapping and auditory-motor control system.

Since the *connectivity between* STG, MTG, and IFG allows for the planning of complex motor sequences as well as the monitoring and correction of feedback and feedforward motor commands (Guenther et al, 2006), we hypothesized that the connectivity between these regions will be enhanced in musicians as a result of training-dependent or use-dependent plasticity in auditory-motor integration. Furthermore, we hypothesized that connectivity between these regions in singers may be enhanced even relative to instrumental musicians matched for duration of musical training, given their specific *auditory-vocal* training requiring intense and precise auditory-motor feedforward and feedback control. We examined the connectivity of the AF and its dorsal and ventral branch, which connects the STG, MTG, and IFG, using diffusion tensor imaging (DTI), an MR imaging technique that enables the visualization and quantitative assessment of white matter pathways in the

brain (Basser et al, 1994; Makris et al, 1997; Basser et al, 2000; Catani et al, 2008; Makris et al, 2005). Since fine-grained perception and feedback control of pitch and motor actions are both important aspects of musical training, we hypothesized that singers and instrumental musicians would exhibit structural adaptations in the AF relative to non-musicians, although the AF and its subdivisions in both hemispheres might be differentially affected considering the fine-grained sensory-motor mapping of sounds to articulation which we assumed is an important role for the dorsal branch of the AF.

3.2 Materials and methods

3.2.1 Participants

Twenty-two musicians were recruited through posting ads on Craigslist, bulletins at local music conservatories, and choral groups in the greater Boston area. Eleven of these individuals were either professional singers or reported to be in training to be professional singers; these singers did have some experience in playing musical instruments, such as piano ($n = 5$), cello (2), trombone (1), trumpet (1), flute (1), and clarinet (1) but were not actively practicing these musical instruments at the time of this study or in the year prior to enrollment. This group of singers was contrasted with a group of eleven instrumental musicians who did not report singing as a primary musical activity, did not have any formal singing training and were not part of any singing group, but had an equal amount of musical experience as determined by their number of years of musical training. This group's instruments included piano ($n = 4$), violin (4), cello (1), and trombone (2). These two groups of eleven musicians each were contrasted with a third group of eleven participants without any significant instrumental music training (defined as less than 1 year of instrumental music training throughout their life, but not in the year before enrollment in this study), any formal singing training, and no participation in any singing groups. This group of non-musicians was recruited through the same mechanisms as the other groups and was matched to the musician groups with regards to age, gender, and IQ. Singers, instrumental musicians, and non-musicians were similar in the mean age (singers = 25.3 (SD = 2.7) years; instrumental musicians = 27.7 (SD 7.6) years; non-musicians = 27.5 (SD 10.3) years), and gender (5m/6f for instrumentalists, 3m/8f for singers, and 5m/6f for non-musicians). Singers and instrumentalists were matched for number of years in musical training (singers' mean = 15, SD = 5; instrumentalists' mean = 14.3, SD = 9.09) and age of training onset

(singers' mean = 6.6, SD = 2.4; instrumentalists' mean = 7.4, SD = 4.4). The three groups were also matched with regards to their IQ as assessed by Shipley's verbal and abstract scaled composite score (Shipley, 1940) (singers' mean = 111, SD = 14, instrumentalists' mean = 114, SD = 10, non-musicians' mean = 111, SD = 13). This study was approved by the Institutional Review Board of the Beth Israel Deaconess Medical Center and all participants provided written informed consent.

3.2.2 Image acquisition

MR images were obtained using a 3-Tesla General Electric scanner. MR sequences included a strongly T1-weighted data set with a voxel resolution of 0.93 x 0.93 x 1.5 mm. DTI was performed using a diffusion-weighted, single-shot, spin-echo, echo-planar imaging sequence (TE1 = 86.9ms, relaxation time = 10,000ms, field of view = 240mm, matrix size = 94 x 94 voxels, no skip, NEX = 1, axial acquisition, voxel dimensions = 2.5 x 2.5 x 2.6mm). Thirty noncollinear directions with a b value of 1000 s/mm² and six volumes with a b value of 0 s/mm² were acquired.

3.2.4 Data Processing

FMRIB's FSL suite was used for pre-processing of raw images (Smith et al, 2004). A 3D affine registration was applied to correct for eddy currents and head motion followed by BET for brain extraction (Smith, 2002). Eigenvectors and eigenvalues of diffusion tensors were estimated at each voxel and FA was calculated using the *dtifit* function in FSL. Axial diffusivity, a parameter reflecting the principal direction of diffusion in white matter (Song et al, 2002), was estimated using the first eigenvalue of the diffusion tensor, λ_1 . The second and third eigenvalues were averaged and referred to as the radial diffusivity, $(\lambda_2 + \lambda_3)/2$ (Basser, 1995; Xue et al., 1999; Basser et al., 2000; Song et al, 2002). Following this, a probability distribution for fiber direction was calculated for each brain voxel using the *bedpostx* function in FSL (Behrens et al, 2003). To allow for fiber crossings, estimates of two directions per voxel were allowed (Behrens et al, 2007).

3.2.5 Tractography – Arcuate Fasciculus

Regions of interest (ROIs) were drawn by hand, on a single sagittal slice of the native FA image of each subject, according to major anatomical landmarks, shown in figure 3-1. For each

hemisphere, ROIs were drawn on white matter underlying the grey matter in three regions: posterior superior temporal gyrus (pSTG), posterior middle temporal gyrus (pMTG), and posterior inferior frontal gyrus (pIFG). Two separate one-way ANOVAs (with the dependent measure of ROI volume for one, and FA for the other) showed no significant effect of group on either: ROI mean volumes for singers: 124.2mm^3 , (SD = 41.7); instrumentalists' = 136mm^3 , (SD = 39); non-musicians' mean = 124.1mm^3 (SD = 41.7). FA values: singers' mean = .411, SD = .067, instrumentalists' mean = .422, SD = .059, non-musicians' mean = .401, SD = .062).

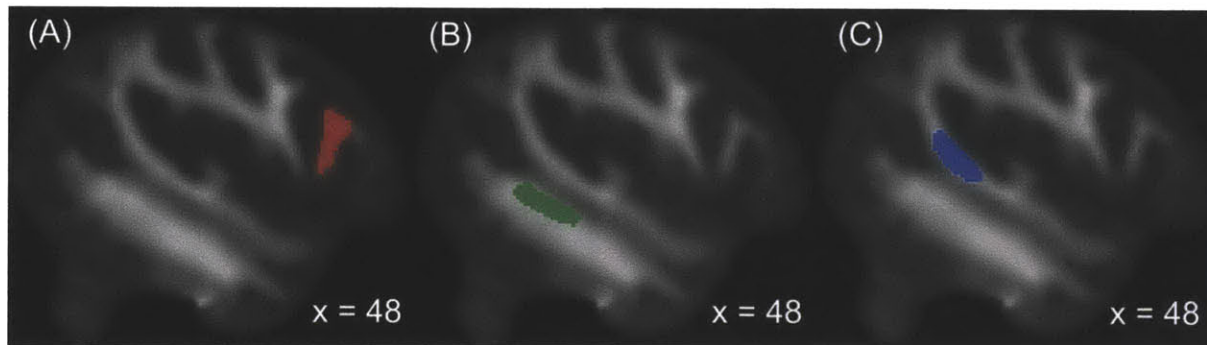


Fig. 3-1 ROI locations on the FA map: (A) IFG, (B) MTG, (C) STG.

Probabilistic tractography was applied to constrain white matter tracts to the dorsal and ventral branches of the AF in each hemisphere. Tractography was initiated from one seed region to one waypoint mask region using the *probtrackx* function in FSL in two separate steps: 1) Tracts traced from the seed region of STG to the waypoint mask of IFG were identified as the dorsal AF. 2) Tracts traced from the seed region of MTG to the waypoint mask of IFG were identified as the ventral AF. These resulting tracts were further masked by setting an intensity threshold of the median intensity values of each tract, and eliminating voxels with intensity values below that threshold. While this provides a way to threshold the tracts similarly across subjects, choosing a cut-off intensity value is somewhat arbitrary, and since there is currently no convention for setting this value (Giorgio et al., 2010), we chose the median intensity value for each tract. To compute tract volume, we used the number of voxels in each tract after applying the cut-off intensity value and multiplied the number of voxels by the voxel size (Loui et al, 2011).

Statistical comparisons – arcuate fasciculus

For each tract (dorsal AF, ventral AF) in each hemisphere, measures of volume and FA were extracted and compared using a three-way ANOVA with the between-subjects factor of Group (with three levels: singers, instrumentalists, and non-musicians) and the within-subject factors of Hemisphere (left vs. right) and Tract (dorsal vs. ventral).

As a control for results from tractography of the AF, we extracted mean FA and volume for non-zero voxels from each subjects' whole-brain FA image, and compared the three groups' means to control for possible whole-brain differences between groups using two one-way ANOVAs (one for FA and one for volume).

3.3 Results

3.3.1 Tract statistics – arcuate fasciculus

Tract volume was largest in singers, especially in the left hemisphere. This was confirmed using a three-way ANOVA on the dependent variable of tract volume with the between-subjects factor of Group (with three levels: singers, instrumentalists, and non-musicians) and the within-subject factors of Hemisphere (left vs. right) and Tract (dorsal vs. ventral). This ANOVA revealed an overall significant effect of Group ($F(2,120) = 9.8, p < 0.001$), confirming that tract volume was highest in singers, second-highest in instrumentalists, and lowest in non-musicians. Furthermore, the same ANOVA revealed a significant main effect of Hemisphere ($F(1,120) = 9.2, p = 0.003$), with tract volume being higher in the left than in the right hemisphere. Finally, the interaction between Group and Hemisphere was significant ($F(2,120) = 4.4, p = 0.014$), confirming that the tract volume in the left hemisphere was especially higher among singers relative to the other two groups. These results are summarized in figure 3-2.

In order to ascertain that tract volume in the left hemisphere was especially higher among singers relative to the other two groups, we performed pairwise post-hoc comparison for each tract between singers and instrumentalists, singers and nonmusicians, and between instrumentalists and nonmusicians applying appropriate Bonferroni corrections. The dorsal branch of the left AF showed a significantly higher volume in singers relative to instrumentalists ($t(10) = 3.36, p = .007$), surviving Bonferroni corrections for two hemispheres and two branches of the AF in each hemisphere. The same branch's volume is also significantly higher in singers relative to

nonmusicians ($t(10) = 3.76, p = .004$), also surviving post-hoc corrections for the four branches of the AF.

Tract FA was lower in singers than in instrumentalists, especially in the dorsal branch of the left hemisphere. This was tested using a three-way ANOVA on the dependent variable of FA with the between-subjects factor of Group and the within-subjects factors of Hemisphere and Tract. The main effect of Group was significant ($F(2,120) = 8.174, p < 0.001$), confirming that FA was highest in instrumentalists, followed by singers and then by non-musicians, although this finding did not survive strict correction for multiple tests. The main effect of Tract was significant ($F(1,120) = 12.49, p = 0.001$), confirming that tract FA was lower in the dorsal branch relative to the ventral branch. Finally, an interaction between Group and Hemisphere showed a trend towards significance ($F(2,120) = 2.73, p = 0.069$), showing that FA was lower in the left hemisphere of singers compared to both hemispheres of instrumentalists. These results are summarized in Figure 3-3.

To explore the potentially differing contributions of axial and radial diffusivities to the observed FA difference between singers and instrumentalists, we extracted the singers' and instrumentalists' left dorsal AF's mean axial (λ_1) and radial ($(\lambda_2 + \lambda_3)/2$) diffusivities. A direct comparison of these parameters between singers and instrumentalists suggested that the finding of lower FA was strongly due to higher radial diffusivity ($(\lambda_2 + \lambda_3)/2$) in singers relative to instrumentalists ($t(20) = 2.7, p = .01$), and not due to differences in axial diffusivity ($t(20) = 1.01, p = .33$).

To test whether the between-group differences in the arcuate fasciculus could be explained by whole-brain differences in FA or volume, separate one-way ANOVAs were conducted on the dependent variables of FA and volume. Results showed no significant between-group differences in whole-brain FA or volume (all p 's > 0.1), suggesting that differences in the arcuate fasciculus cannot be explained by whole-brain differences.

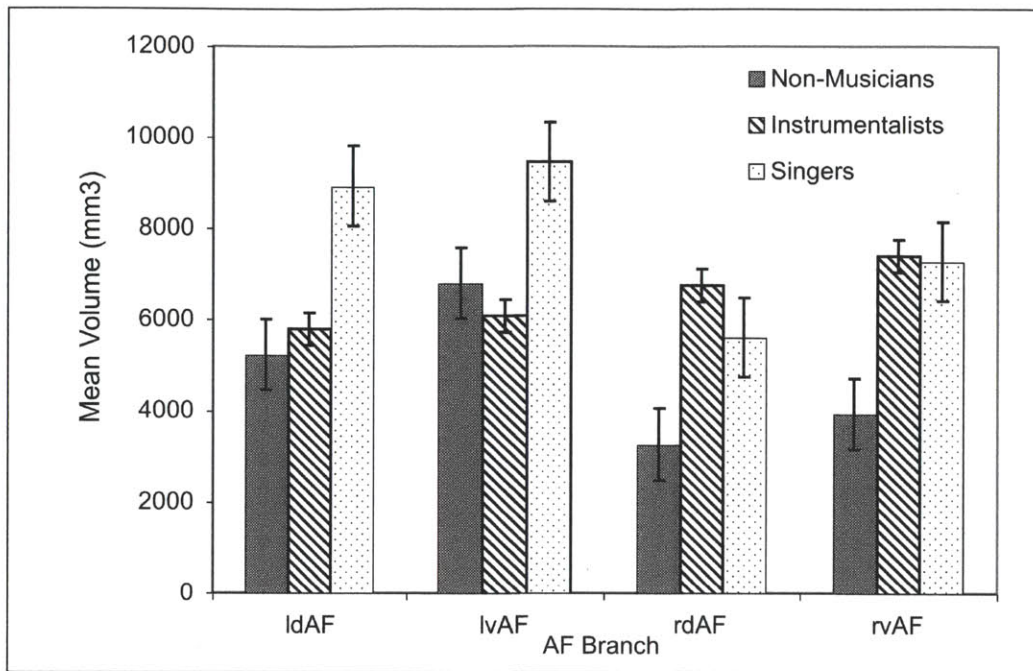


Fig. 3-2 Mean volume for all branches of the AF in both hemispheres for all groups (l = left, r = right, d = dorsal, v = ventral). Error bars represent standard error of the mean.

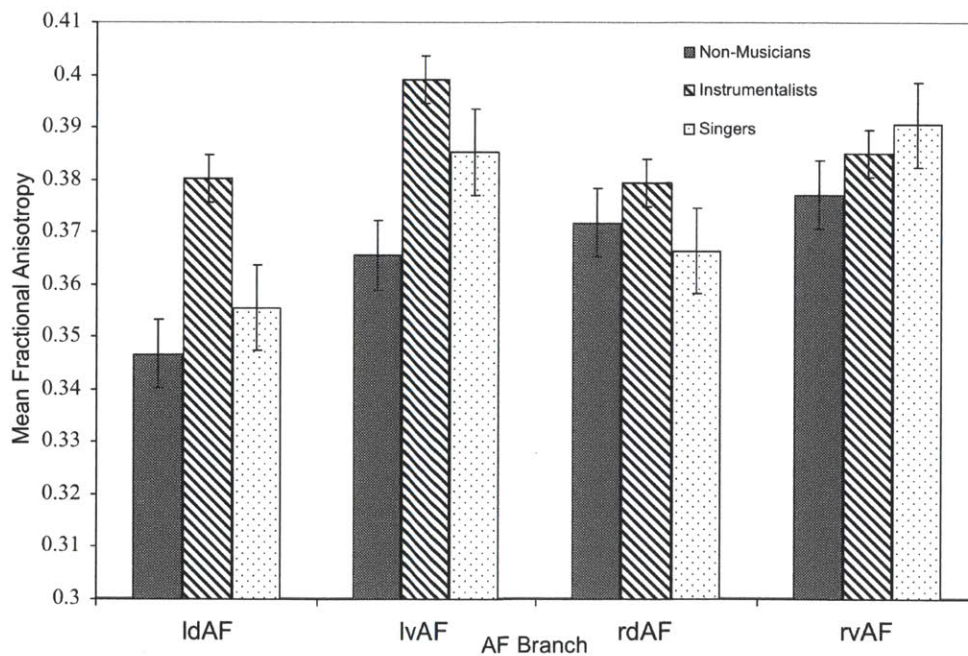


Fig. 3-3 Mean FA for all branches of the AF in both hemispheres for all groups (l = left, r = right, d = dorsal, v = ventral). Error bars represent standard error of the mean.

3.3.2 FA along the arcuate fasciculus

Having identified the left dorsal AF as the main tract of interest that showed differences between singers and matched instrumental musician controls, we further sought to identify the region along the AF that shows maximal between-group differences. Visual comparison of the FA maps of tracts identified in singers and instrumentalists (figure 3-4) suggested that a part of the longitudinal portion of the left dorsal AF showed the strongest FA differences between groups.

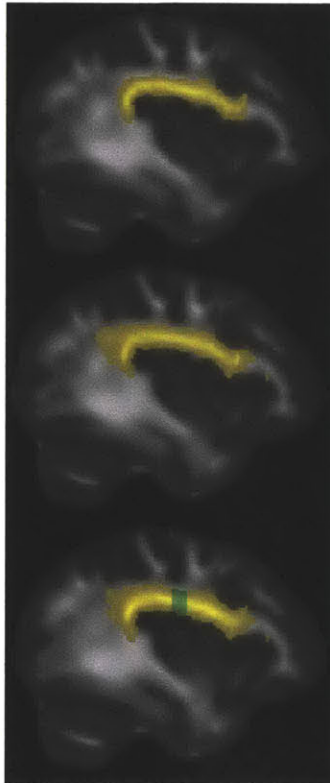


Fig. 3-4 Sagittal slice $x=38\text{mm}$, showing left dorsal AF in yellow: Instrumental controls (top). Singers (middle). All musicians (bottom), with region showing significant FA differences at $y= -22$ to -13mm , shown in green.

To explore this observed difference along the tract, the longitudinal portion of the left dorsal AF was divided into 4 bins of 10 coronal slices each and the mean FA from each bin (mean FA of 10 coronal slices) was extracted for each subject, and compared between singers and instrumentalists using a two-tailed t-test. The comparison revealed significantly *lower* FA for the singers in bin 3 ($y= -22\text{mm}$ to $y= -13\text{mm}$, $t(9) = 4.29$, $p = .002$), around the mid-point of the longitudinal portion of the left dorsal AF. Figure 3-5 shows bin-by-bin comparisons between singer and instrumental groups in the longitudinal portion of the left dorsal AF, whereas Figures 3-6 and 3-7 show the entire left dorsal AF tract in axial (fig. 3-6) and sagittal (fig. 3-7) views, highlighting the section that is

significantly lower in FA in singers than controls: on average, singers possessed lower FA in the longitudinal portion of the left dorsal AF, and more specifically in bin 3 (from $y = -22\text{mm}$ to $y = -13\text{mm}$).

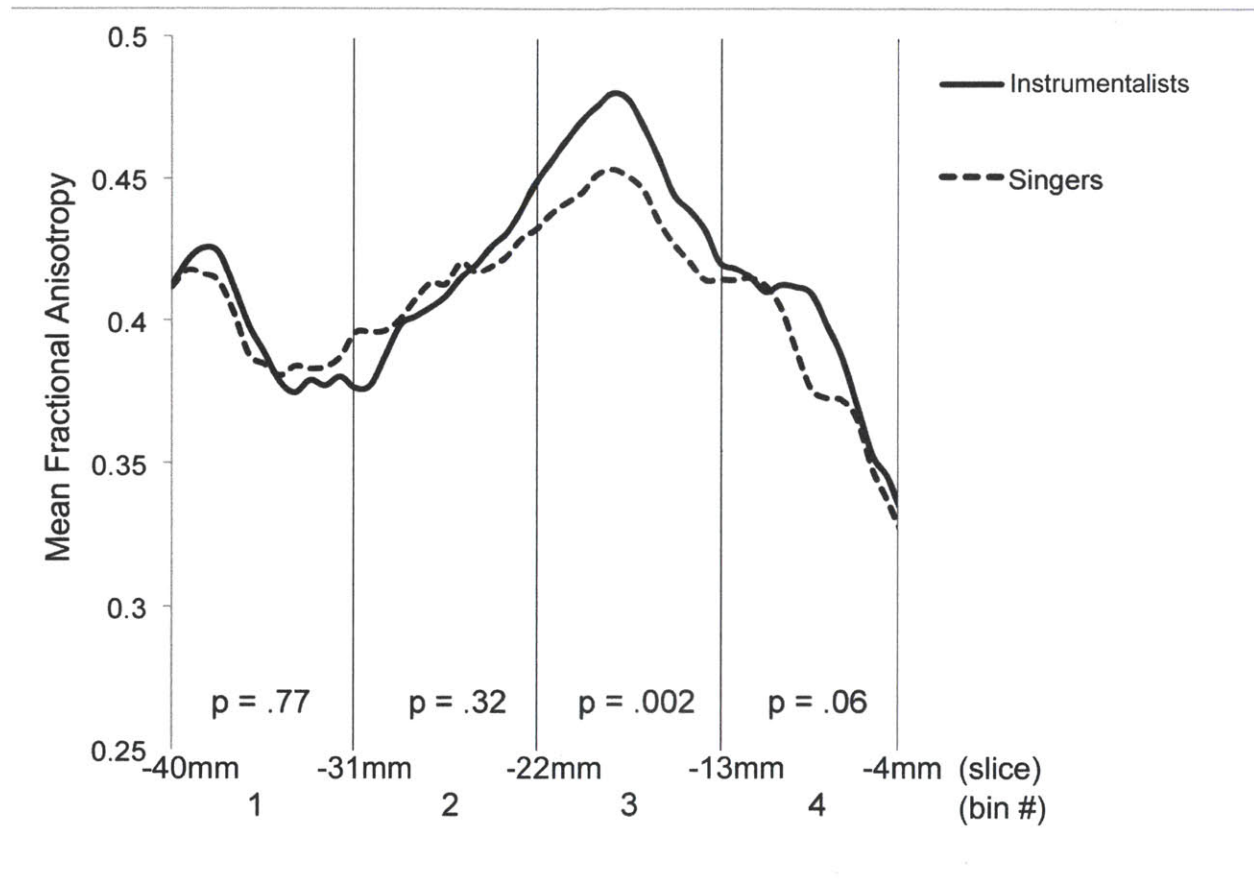


Fig. 3-5: mean FA by bin number for left dorsal AF of singers and instrumental musician controls.

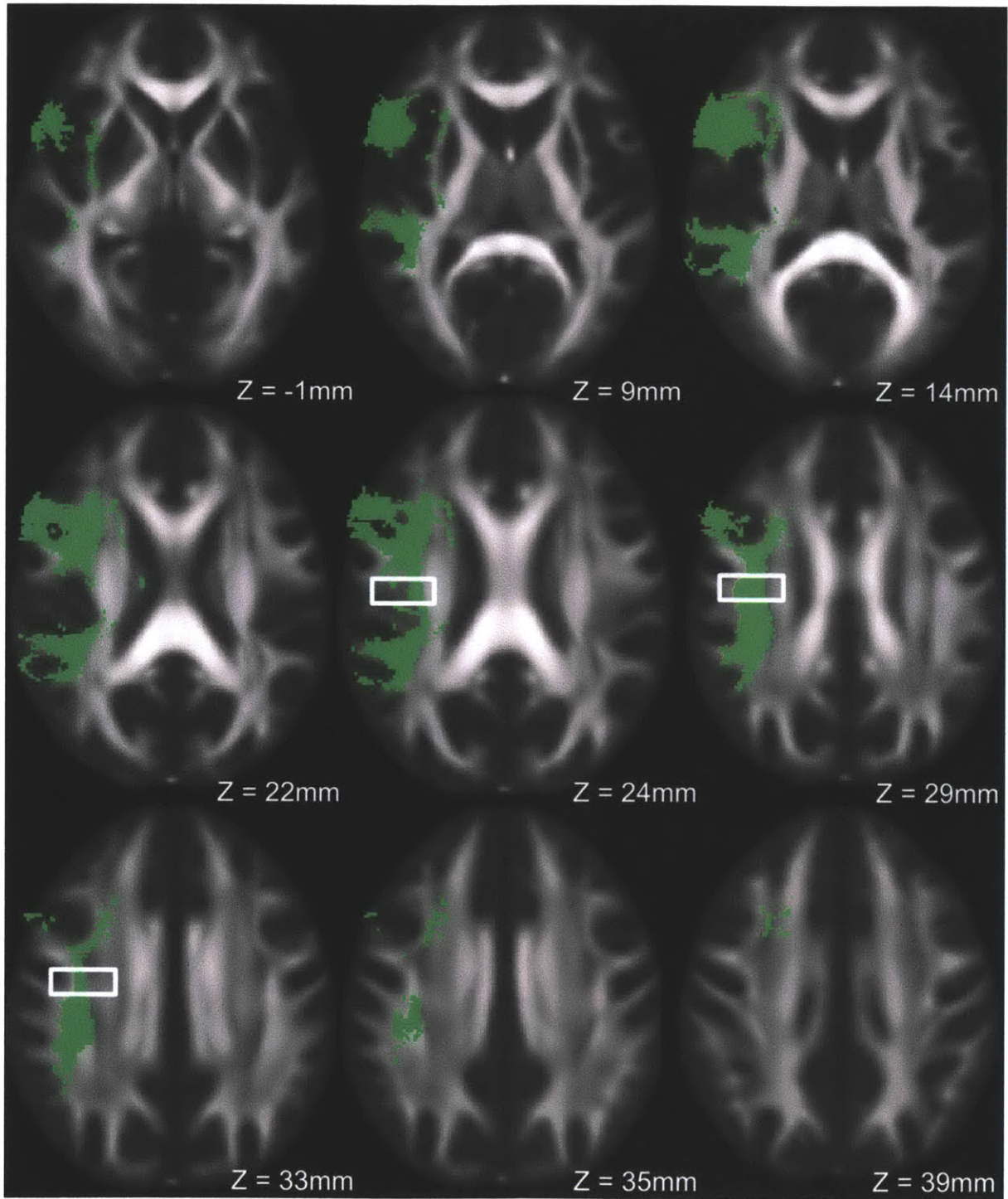


Fig. 3-6: axial view of left dorsal AF across all subjects in green, with region showing significant between-group FA differences indicated by the box.

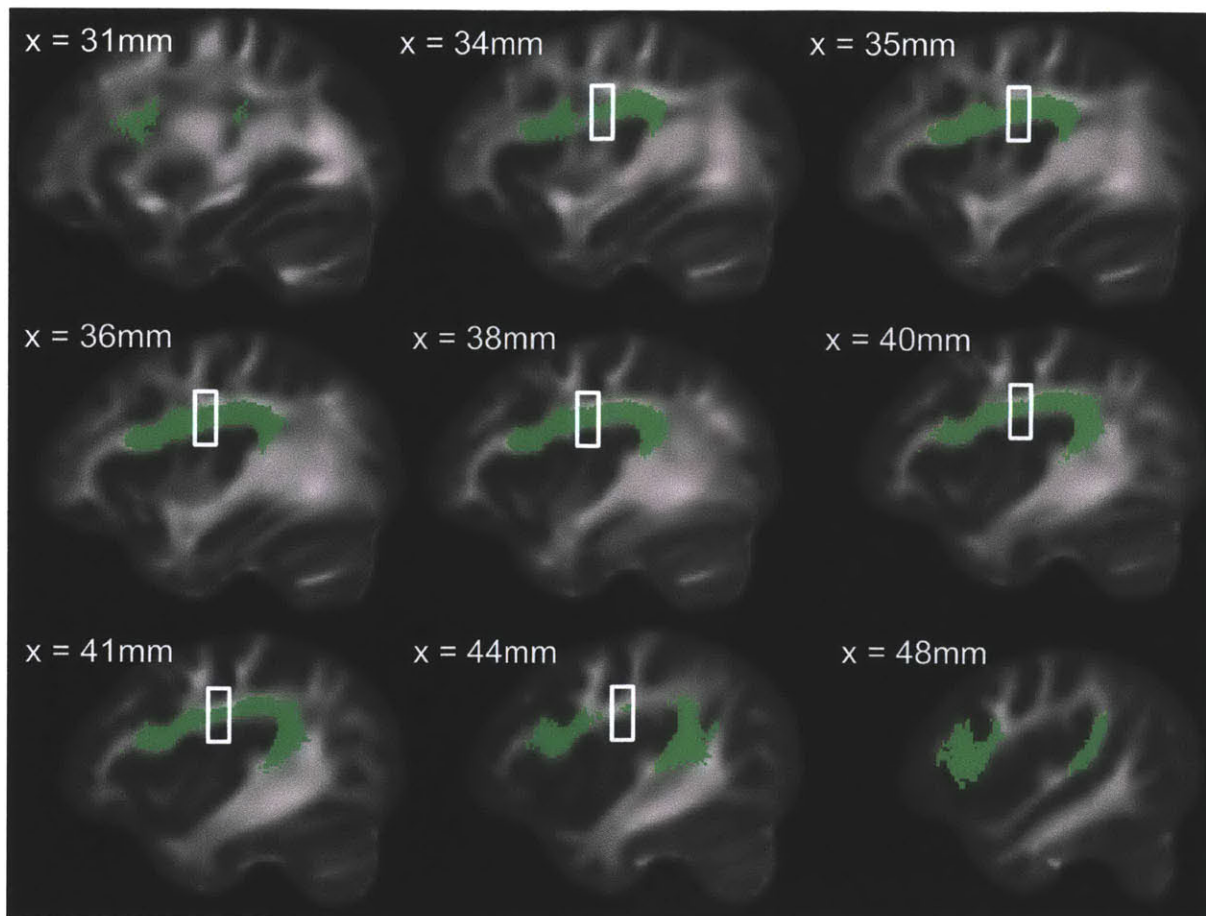


Fig. 3-7: sagittal view of left dorsal AF across all subjects in green, with region showing significant between-group FA differences indicated by the box.

3.3.3 Behavioral correlates of FA differences

To explore the relationship between singers and FA values in the left dorsal AF, we tested the hypothesis that the number of years of singing training is predictive of FA value for the left dorsal AF using a linear regression (shown in figure 3-8). Within the singer group only, the reported number of years of singing training inversely predicted the FA value of each individual's left dorsal AF ($R^2 = -.387$, $p = .04$). For both FA and volume, a similar relationship was not observed in the left dorsal AF of control musicians ($R^2 = -.08$, $p > .1$), nor for any other tracts in both singers' and instrumentalists (all $|R^2|$'s $< .16$, all p 's $> .2$).

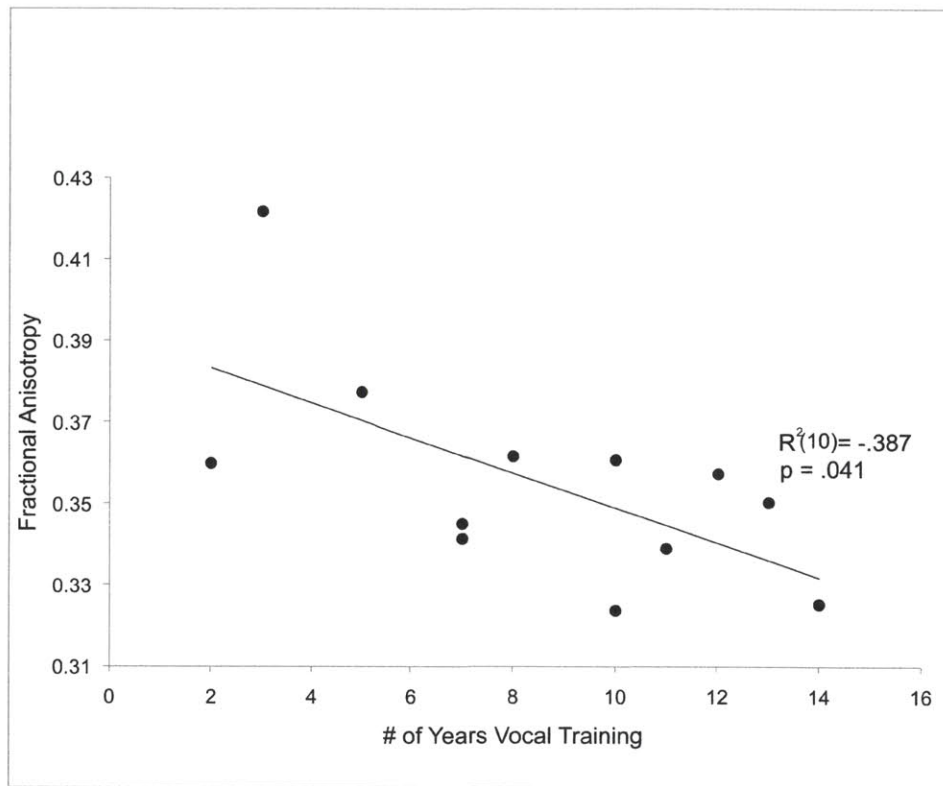


Fig. 3-8: Numbers of years of vocal training (singers' group only) inversely predicts mean FA value of the left dorsal AF.

3.4 Discussion

We report a DTI comparison between singers, instrumental musicians, and non-musicians. Our results showed that the AF, a bundle of white matter fibers that connects regions of the brain known to be involved in sound perception and production as well as the feedforward and feedback control of vocal output, has a larger volume and higher FA values in musicians (both singers and instrumentalists) relative to non-musicians. Among musicians, singers showed significantly higher volume in the dorsal and ventral branches of the left AF, and *lower* FA in the left dorsal AF, relative to instrumentalists. In contrast, group had no effect on whole-brain FA measures between the three groups, suggesting that effects could not be explained by whole brain differences. A bin-by-bin analysis of FA differences in the longitudinal portion of the AF among musicians shows significantly lower FA among singers along the midpoint of the left dorsal AF, relative to instrumentalists.

The finding of higher FA in musicians compared to non-musicians, but lower FA in singers relative to instrumental musicians provides support for auditory-motor training-induced differences in the AF for musicians in general and singers in particular. The lower FA may reflect less aligned fibers or more fiber crossings among singers along the course of the arcuate fasciculus. While DTI does not resolve the directionality of fiber tracts, tractography methods make it possible to infer tract volume based on identified tracts that connect several endpoints of grey matter (Giorgio et al. 2010). By using seed regions in the superior and middle temporal gyri, and waypoint masks in the inferior frontal gyrus of each hemisphere in each brain, we were able to identify the dorsal and ventral branches of the left and right AF. Both dorsal and ventral branches of the left AF were identified as being larger in singers than in instrumentalists, with stronger effects in the dorsal branch. Interestingly, this effect was only observed in the left hemisphere.

Previous research has shown that individuals with difficulties in pitch perception and production, i.e. tone-deaf individuals, have diminished white matter volume in their right AF, with pitch perception abilities being correlated with the dorsal branch of the right AF and pitch perception-production mismatch being correlated with the right ventral branch (Loui et al, 2009), suggesting that fine-grained control of pitch perception and production abilities are related to the dorsal branch (i.e., STG-IFG connections). In contrast, both singers and instrumental musicians in this study have expertise in pitch perception and production, as the instrumental group is matched for number of years of musical training. It is only when both the singers and instrumentalists are compared with non-musicians that differences in the right AF are observed. This might suggest that the right AF shows more of a domain general adaptation effect in activities that involve matching sounds with actions independent on whether these actions are articulatory actions or hand actions. The left AF and in particular the dorsal branch of the left AF showed the most profound differences comparing singers with instrumentalists. Although this finding is somewhat surprising, it suggests that the left AF, which already shows an adaptation when individuals acquire language (Barnea-Goraly et al, 2005; Ashtari et al, 2007) and is usually larger and more complex than the right AF (Glasser and Rilling, 2008, Vernooij et al, 2007), might be the structure that adapts the most to the specific requirements of vocal-motor and auditory-motor integration.

Furthermore, it is also possible that the dorsal (STG-IFG) and ventral (MTG-IFG) branches have different functions and therefore show different adaptations. The ventral (MTG-IFG) branch

could be part of a fast and coarse system that does not rely on precise auditory feedback while the dorsal (STG-IFG) branch could be part of a slower, more precise system that is under conscious control and heavily relies on auditory feedback to make adjustments in the auditory-motor mapping of vocal output.

Similar findings of lower FA values in white-matter regions have been reported in other studies comparing experts in a particular domain with non-experts. For example, simultaneous interpreters (individuals who translate a source's speech in real-time) were reported to have lower FA relative to controls, in subregions of their corpus callosum, as well as in the white matter underlying the left anterior insula and inferior parietal lobe, regions thought to be involved in articulatory control and sensory-motor mapping for speech (Elmer et al, 2010).

DTI provides *in vivo* measures of white matter connectivity through its parameters of FA, axial diffusivity, radial diffusivity, and shape and volume of white matter tracts. FA is a scalar measure that characterizes the degree of directional preference in diffusion of water, and is affected by the degree of myelination and axonal coherence. Axial diffusivity is said to be related to the integrity of the axons, whereas radial diffusivity is said to be related to the degree of myelination (Song et al, 2002; Schaectel et al, 2009). However there is much debate about the validity of these associations especially when applied to grey-white matter boundaries or regions with multiple crossing fibers (Wheeler-Kingshott and Cercignani, 2009).

The finding of lower FA due to higher radial diffusivity in singers, in particular in bin 3 of the tract (around the mid-point of the longitudinal portion of the AF, most proximal to regions of the motor and somatosensory cortices) suggests that the singers' AFs may be adapted to allow for more connectivity between the primary nodes of the AF (STG and IFG), the motor/somatosensory system, and/or the inferior parietal lobule via the AF's putative "indirect pathway" (as described in Catani et al, 2005). Since the FA difference is most strong in bin 3 and bin 3 roughly coincides with the location of the pre- and postcentral gyrus, this suggests that at least part of the increase in radial diffusivity in singers may be reflective of less alignment in one direction and possibly more branching in other directions (e.g. perpendicular to the axial plane of the tract, towards the pre- and postcentral gyrus). Differences in white-matter microstructure of this kind (increased radial diffusivity with no difference in axial diffusivity) are most frequently interpreted as indicating

differences in myelination (Song et al, 2002; Alexander et al., 2007; Jito et al., 2008), but changes in myelin or axon density due to axonal sprouting are also possible (Dancause et al., 2005; Carmichael, 2006), although the extent to which DTI is sensitive to such phenomena is not known. Nevertheless, enhanced connectivity of this kind in singers might be an adaptation for increased sensitivity for feedback information from the inferior parts of the somatosensory cortex (homuncular representations of sensory feedback from speech areas, e.g. proprioception of jaws, tongue, and lips), as well as feedforward information provided to the inferior regions of the inferior motor/premotor strip (homuncular representations of the tongue, jaw, lips, and larynx). This interaction of feedback and feedforward information in which the AF may play a critical role has been described in detail in Guenther et al. (2006) for syllable production in speaking and might be similar for intoned syllable production in singing. Functional neuroimaging studies have shown an extended activation after vocal skills training involving inferior motor/premotor and somatosensory regions (Kleber et al, 2010). In contrast to instrumental musicians, who exercise fine non-vocal motor control while engaging their vocal system minimally during a performance, singers must always monitor their breathing as well as proprioception from their vocal apparatus. This added cognitive demand necessitates stronger connectivity between temporal, inferior frontal, as well as inferior motor/premotor, and inferior somatosensory regions; this may be reflected in differing white matter architecture in the AF of singers, relative to instrumentalists.

Our results suggest that musical training, particularly vocal training, is associated with structural adaptations in the AF: a tract that is important for linguistic as well as musical functions. In individuals who receive primarily vocal musical training, adaptations are observed especially in the left dorsal AF, which is larger in volume but lower in FA among singers (relative to instrumentalists). This combination of DTI differences may reflect more fiber crossings in white matter regions between superior temporal gyrus and inferior frontal gyrus, possibly reflecting a more complex pattern of connectivity for the AF that may be associated with vocal training as compared to other kinds of musical training.

The present study provides further support for the use of musically trained individuals, especially singers, as a model for structural as well as functional adaptations of the auditory-motor system (Schlaug, 2001) by showing structural differences between the brains of those engaged in specific types of musical training (vocal vs. instrumental). The intensive training that is typical in

learning to sing may be translated into neurorehabilitation programs for aphasic patients and other groups of impaired vocal output (Schlaug et al, 2008; Wan and Schlaug, 2010; Wan et al, 2010), whose white matter pathways in the undamaged hemisphere show adaptations in response to intense intonation-based speech therapy (Schlaug et al, 2009; Wan et al, 2010). By characterizing the differences in white matter connectivity between singers and non-singer controls who are matched in musical training, the present study suggests that intense musical training, particularly vocal-motor training, has an effect on the macro- and microstructural anatomy of vocal-motor networks.

4: FUNCTIONAL ADAPTATIONS OF THE AUDITORY-MOTOR SYSTEM:

Cortical mechanisms regulating feedback-dependent control of vocal pitch in normal and tonedeaf subjects.

Abstract

Perceiving and responding to auditory feedback of one's own voice is important for speech, music, and auditory-motor functions. We investigated cortical mechanisms underlying the processing of vocal feedback in an fMRI study.

A short-term auditory-motor feedback mismatch was induced in a pitch matching task by playing back the fundamental frequency (F0) of subjects' vocalizations shifted up or down by 1 or 2 semitones (ST). Behavioral results showed that participants compensated for the -1 and +1ST perturbations by varying their F0 production in the direction opposite to the experimental manipulation, while not consistently compensating for the -2 and +2ST perturbations. fMRI results comparing production and no-production control trials showed widespread activations in the temporal gyri, precentral gyrus, and inferior and middle frontal gyri (IFG, MFG). A comparison between activations for perturbed and non-perturbed vocal feedback revealed increased activations during perturbed feedback in the left middle frontal gyrus and premotor cortex (PMC), supplementary motor area (SMA), left superior temporal gyrus and sulcus (STG, STS), left middle temporal gyrus (MTG), and left inferior parietal lobule (IPL). Results confirm earlier fMRI studies that implicate these regions in the auditory feedback control of vocal production and lend support to the notion that each hemisphere can potentially engage the pSTG-PMC network to register and correct for auditory-motor feedback mismatch, depending on the specific demands of the task.

As a pilot study on how this network may differ in individuals with a long-term auditory-motor disorder, the same assessment was repeated in a smaller group of individuals with tonedeafness. The behavioral and neurological results of this pilot study are presented subsequent to the discussion of the main experiment, followed by suggestions for future investigations.

Key words: auditory feedback; nonmusicians; pitch-perturbed feedback; functional magnetic resonance imaging; auditory motor feedback mismatch; tonedeafness

4.1 Introduction

While the execution of a relatively simple motor action, such as reaching for a target, seems independent of the need for sensory feedback, such behaviors are only possible after the buildup of a reliable internal model and sensory feedback that guides the action. This model is the result of ongoing integration of sensory feedback (visual, somatosensory, and proprioceptive) and consequent fine-motor correction in order to guide limb movements towards the target (Bendor & Wang, 2005; Seidler et al., 2004). During this learning process, the sensory system continuously monitors for errors while the motor system makes minute corrections in real-time (feedback-dependent control), eventually leading to the buildup of the internal model that allows for the execution of the desired action in a manner that requires less sensory feedback, relative to the time prior to the internal model (feedforward control). Together, these feedback and feedforward modes of control ensure that the system continues to function efficiently while fulfilling the objective and adjusting to any environmental changes (Desmurget & Grafton, 2000; Patterson et al., 2002; Penagos et al., 2004). Similarly, highly coordinated vocal-motor actions, such as speaking and singing, are thought to develop along a similar trajectory (J. A. Jones & K. Munhall, 2005; Penagos et al., 2004).

One common requisite for both speaking and singing is reliable auditory feedback. Reliable and predictable auditory feedback is important for both singing and speaking due to the demand for real-time monitoring of the auditory stream and, when necessary, correction of vocal-motor output (Bauer et al., 2006; Golfinopoulos et al., 2011; Guenther, 2006; Schlaug, 2001; Xu et al., 2004; Zarate & Zatorre, 2008). In addition, the reliability of this auditory feedback contributes significantly to how new motor sequences can be learned, internalized, and stored for later feedforward execution (Bauer et al., 2006; Purcell & K. G. Munhall, 2006; Schlaug, 2005).

A computational model can aid in the understanding of the possible ways in which the cortex can implement the functions described above. One prominent model which has received considerable attention and has been proven useful in the generation and testing of hypotheses concerning auditory and speech-motor interactions is the *Directions into Velocities of Articulators* (DIVA) model (Guenther, 2006; Guenther et al., 2006, Golfinopoulos et al., 2010). This model separates the information processing required for speech production into two broad sub-systems:

feedforward control and feedback control, the functional components of which are distributed over thirteen processing modules, each corresponding to a certain function and cortical region based on previous functional neuroimaging literature (Golfinopoulos et al., 2010). Each of these functional components is connected to others via modeled one-way or two-way excitatory or inhibitory projections. The feedforward and feedback subsystems' function is integrated, and thus the model can 'learn' to speak fluently by starting with a babble, and then iteratively monitoring and correcting its output until it converges on a given auditory target. Importantly, the model makes specific predictions, based on previous neuroimaging findings, for brain regions activated by each of its functional components. Thus, the DIVA model represents a valuable tool in the generation and testing of hypotheses that concern auditory-vocal interactions, and enables comparison of simulated fMRI data and iterative refinement of the model based on data acquired from human subjects during the same task. This enables comparison of predicted neurological and behavioral results to experimentally acquired data in a given experimental design, e.g. perturbed auditory feedback during a behavioral task (with or without simultaneous fMRI acquisition).

The effects of perturbed auditory feedback on human vocal production are well demonstrated behaviorally. Persons communicating in natural environments will vary the amplitude of their vocalizations according to the ambient noise level, increasing the amplitude as the noise level increases to compensate for masking of their speech, and subsequently restoring the amplitude as the ambient noise level diminishes again. This automatic compensatory action, known as the Lombard effect, has been experimentally verified since 1911 (Hensch, 2004; Lane & Tranel, 1971). Conversely, in what is known as the side-tone amplification effect, participants provided with *amplified* auditory feedback of their voice significantly decrease the amplitude of their vocalizations. Both of these procedures have the aim of adjusting vocal output to increase communicability to listeners (Siegel & Pick, 1974).

Other observations of compensation for perturbed auditory feedback can be found when auditory feedback is temporally delayed. Normal speakers are found to exhibit decreased fluency when their auditory feedback is delayed, committing errors such as pronounced slowness in speech, repetition of phonemes, and other features of speech that resemble stuttering, while individuals who stutter are found to have increased fluency when provided with delayed auditory feedback of their vocalizations (Black, 1951; Stuart et al., 2002).

The effects of auditory feedback perturbation on vocal output can also be observed in the pitch domain. Experimental manipulation of vocal pitch, whether to the fundamental frequency (F0) or first formant (F1), results in participants compensating for the perturbation by biasing their output in a direction opposite to that of the perturbation, in an effort to achieve the intended auditory target (Burnett et al., 1998; Houde, 1998; Liu & Larson, 2007; Purcell & K. G. Munhall, 2006), even when participants report that they are unaware of the perturbation in auditory feedback (Hafke, 2008).

Several studies have investigated the neural correlates of perturbed auditory feedback using functional neuroimaging with sparse sampling acquisition designs to minimize the confounding effects of scanner noise on the BOLD signal. These studies reported increased activity in the dorsal premotor cortex (PMC) in response to *expected* F0 perturbations in *non-musicians*, and increased activity in PMC, superior temporal gyrus / sulcus (STG / STS), and anterior cingulate cortex (ACC) in response to *expected* F0 perturbations in *singers* (Zarate & Zatorre, 2008). Others have observed increased activity in STG and right prefrontal cortex (PFC) and rolandic cortex (RC) in response to *unexpected* F1 perturbations (Tourville et al., 2008). The aforementioned DIVA model predicts increased activity in bilateral peri-sylvian cortex (the model's 'auditory error cells') and bilateral ventral-rolandic cortex (the model's 'motor correction cells') during the perturbations (Golfinopoulos et al., 2011; Guenther, 2006; Tourville et al., 2008), generally agreeing with the experimentally gathered data.

One important motivation driving these investigations is the role of auditory-motor feedback mismatch in the pathophysiology of several conditions (Ardila, 2010; Habib, 2000; Heilman, Voeller, & Alexander, 1996; Loui et al., 2009; Loui, Guenther, Mathys, & Schlaug, 2008; Wan & Schlaug, 2010), as well as the role of auditory feedback in developing training regimens that aim to remap auditory-motor interactions in an effort to maximize the reliability of auditory feedback and thus increase intelligible vocal output (Norton et al., 2009; Schlaug et al., 2009; Wan et al., 2011).

Despite insights from clinical, experimental, and modeling approaches, a general consensus concerning the organization of cortical mechanisms that govern involuntary, feedback-dependent control of vocal pitch in the healthy population remains elusive. While others have tested behavioral

and neurological responses to expected perturbations of F0 in vocally-trained participants and non-musicians (Zarate & Zatorre, 2005; 2008), unexpected perturbations in F0 in vocally-trained participants (Zarate, Wood, & Zatorre, 2010), and unexpected perturbations of F1 in non-musicians (Tourville et al., 2008), results that report the behavioral and neurological response to *unexpected* F0 perturbations in *non-musicians* are lacking.

To this end, the current study investigates behavioral and neurological responses to unexpected perturbations of F0 in normal, musically untrained subjects via a pitch-matching task in the fMRI environment, using a sparse sampling acquisition to permit simultaneous recording of vocal and fMRI responses without the interference of scanner-noise. An MR-compatible microphone and headphones enabled participants to receive and respond to auditory feedback while they heard their own vocal output in near real-time (perturbed or unperturbed). Offline analyses enabled comparisons of acoustic and neurological responses across perturbation conditions.

4.2 Materials and Methods

4.2.1 Participants

19 right-handed volunteers, 10 males and 9 females (age range = 18-34, mean = 24.2, SD = 4.3) were recruited through online advertisements and bulletin advertisements at college campuses in the greater Boston area. Average IQ, as assessed by Shipley's verbal and abstract scaled composite score (Shipley, 1940) was 117.9 (range = 111 - 130, SD = 4.3).

None of the participants had any significant musical training (defined by no training other than mandatory music classes in primary school). Conversely, none of the participants showed evidence of any auditory or auditory-motor difficulties in perceiving or producing tonality, as assessed by the average score of the first three sub-tests of the Montreal Battery for Amusia (mean = 81.9% correct, range = 70 - 91.4%, SD = 6.7%) and psychophysical tests for perceiving and producing pitch-interval directionality (as described in (Loui et al., 2008); perception mean = 5.5Hz, SD = 3.8Hz ; production mean = 7.7Hz, SD = 5.Hz).

None of the participants reported any neurological / psychiatric conditions, and all passed the "Screening for Hearing Impairment in Adults", as described in the American Speech-Language-

Hearing Association's Guidelines for Audiologic Screening (American Speech-Language-Hearing Association, 1997). The study was approved by the Institutional Review Board of Beth Israel Deaconess Medical Center (BIDMC). All participants gave written informed consent and received monetary compensation for their participation.

4.2.2 Hardware

A notebook computer (Lenovo Thinkpad T-400), running Windows XP Professional was used as a platform to run the experiment. In order to minimize latency, audio processing was performed using a dedicated external USB audio processor (TASCAM US-122 - <http://tascam.com/product/us-122/>), and a XENYX Behringer mixer / amplifier was used to amplify/attenuate/route the signal as needed (<http://www.behringer.com/EN/Products/802.aspx>). Participants' vocalizations were recorded using a Shure (SM-93 - <http://www.shure.com/americas/products/microphones/sm/sm93-lavalier-microphone>) pro-audio microphone (cabling shielded for the MR-scanner environment), and they received near real-time auditory feedback through MR-compatible earphones (Sensimetrics MRI-Compatible Insert Earphones - Model S14 <http://www.sens.com/s14/index.htm>). Figure 4-1 shows the experimental hardware setup.

4.2.3 Software

In order to achieve the lowest latency possible while preserving the quality of the audio signal, a sample rate of 44.1kHz and a buffer size of 2048 samples was used (introducing a total latency of approximately 45 ms). MATLAB (version 2010a -<http://www.mathworks.com/products/matlab/>) was used with a compiled C++ program to run the pitch-perturbation algorithm (<http://www.dspdimension.com>).

4.2.4 Behavioral Paradigm

Before performing any tasks in the scanner, participants first came in on a separate day to train on the behavioral task. They were first instructed to hum for 3s in their speaking voice (not unnaturally low or high for their voice). This was recorded and subsequently used to ascertain each

participant's center fundamental frequency (F0).

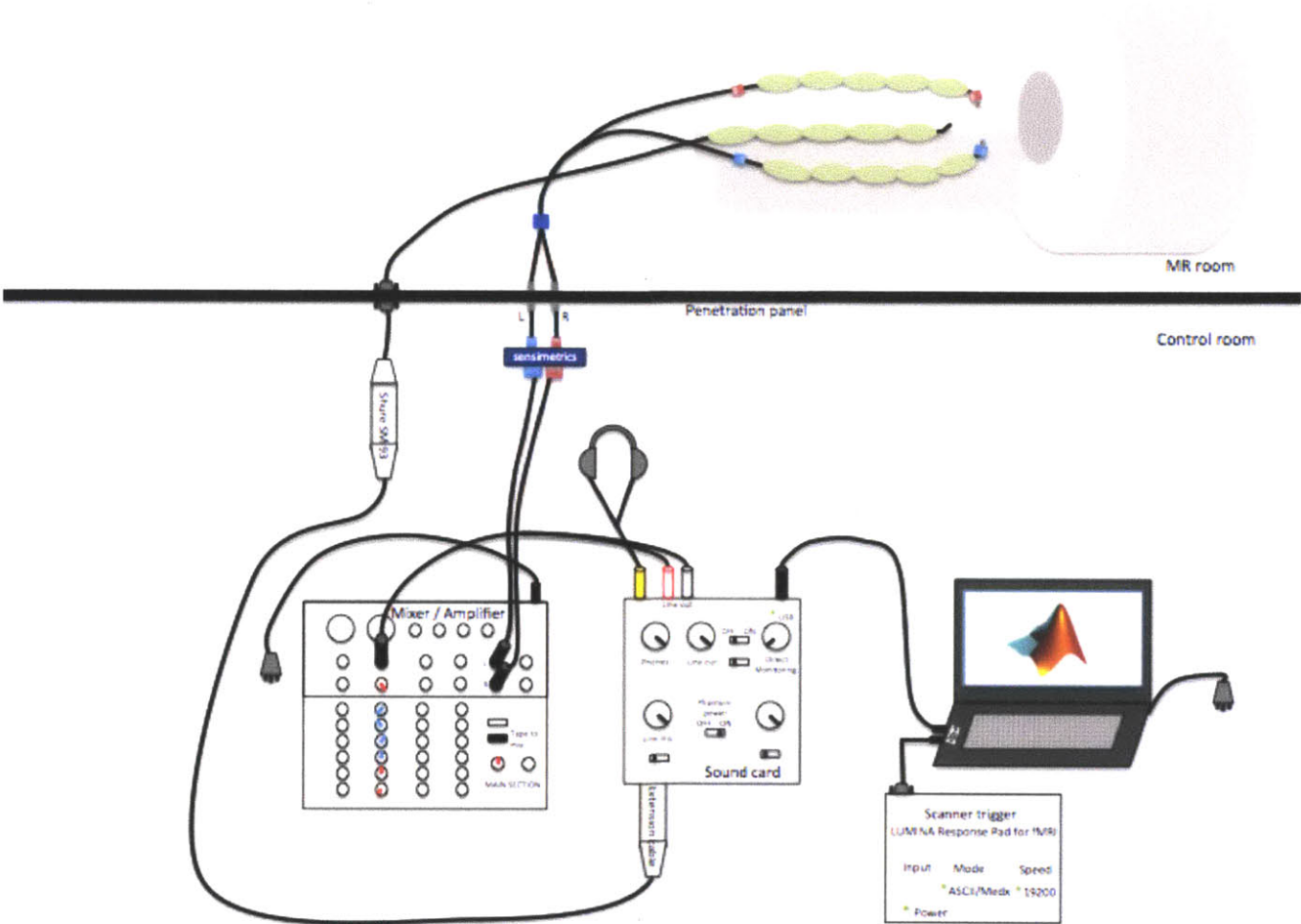


Fig. 4-1: diagram showing hardware setup in scanning environment

On trials in which the participants were to hum, they were told that they would first hear a brief noise cue (NC1 -a 50ms band-passed noise burst centered at 500Hz, including 10ms rise/fall cosine squared ramps) followed by a “target tone” (TT- a randomized presentation of one of 4 pure tones, differing in 5Hz steps equally around the participant’s recorded F0) for 1.5s including 10ms of cosine squared ramps, then NC1 again, to cue the onset of the participants’ humming. The participant was instructed to hum the same pitch as that heard in the TT. The participants hummed during a 2s response period (RES), after which they heard a third NC1, indicating that they should stop humming.

While humming, subjects received near real-time auditory feedback of their vocalization. Auditory feedback was either: not perturbed (no-pert: no shift in f_0), shifted up by 1 semitone (+1ST), shifted down by 1 semitone (-1ST), shifted up by 2 semitones (+2ST), or shifted down by 2 semitones (-2ST). These five conditions (no-pert, +1ST, -1ST, +2ST, -2ST) represented our set of active conditions. In addition, there was a sixth, passive, control condition in which subjects were instructed not to vocalize (no-voc). This condition was indicated by a different brief noise cue than the aforementioned NC1 (NC2 - a 50ms band-passed noise burst centered at 3.5kHz including 10ms cosine squared rise/fall ramps). Figure 4-2 summarizes the study paradigm. There were 24 trials in total: 4 repetitions of each of the six conditions, which constituted one run.

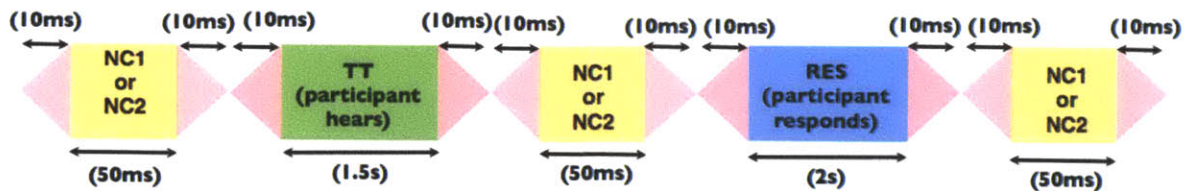


Fig. 4-2: diagram showing the behavioral paradigm. In each trial participants first heard one of two noise bursts (NC1 or NC2) to announce the beginning of a trial, after which they heard the target tone (TT) while inhaling in preparation for the response. They then heard another noise burst to cue their response. They then responded (RES), humming or exhaling silently (in condition 6), depending on which noise cue was heard, before hearing a third noise burst to announce the end of the trial.

Participants heard a total of 24 trials per run (1 run = 6.5mins). For the training session, we asked the participant about the levels of the sounds they heard in order to ascertain that (1), the acoustic presentations were at a comfortable listening level, and that (2), the auditory feedback heard through the earphones was the dominant percept (i.e., “it is important that you not ignore the audio from the headphones during vocalization, is it loud enough to ensure that?”).

4.2.5 Behavioral Data Analysis

The F_0 stream was recorded from each trial and then analyzed offline using custom code in MATLAB. The produced stream of F_0 values in each trial was normalized by its target F_0 , onset-aligned, and averaged within each condition and across subjects to obtain a cents-deviation value from the target F_0 in each condition. Mean deviations in the time window from 1000ms to 1500ms after production onset were selected for statistical analyses to minimize the effects of wavering of

F0s at the onset and release of each vocalization. The average frequency deviation in this 500ms window was calculated across subjects for each condition to allow comparison of the extent of compensation between conditions. The average of each participant's deviations within the no-pert condition was considered an index of their accuracy, and was examined to confirm that the subjects could reasonably match the target without perturbation.

4.2.6 fMRI Data Acquisition

Functional MR data was obtained using a GE 3T MRI scanner. A gradient-echo EPI-sequence with a repetition time (TR) of 15s, echo time (TE) of 25ms, acquisition time (TA) of 1.8s, and a matrix of 64 x 64 was used. Using a midsagittal scout image, a total of 28 axial slices with a voxel size of 3.75 x 3.75 x 4mm were acquired after each trial. Initiation of the first set of slices was synchronized with the stimulus presentation using custom software coded in the MATLAB environment. The order in which the conditions were presented was randomized across trials. Although the TR was held constant at 15s, the delay between the participants' responses and the onset of the scanner acquisition was varied by moving the experimental tasks within the 15s time frame. This resulted in sets of images with delays of .4s, 1.4s, 2.4s, and 3.4s from the end of each trial. Combining data from these four time-points ensured the capture of the peak hemodynamic response while allowing for variations in timing between participants, as well as differing perfusion rates between different brain regions.

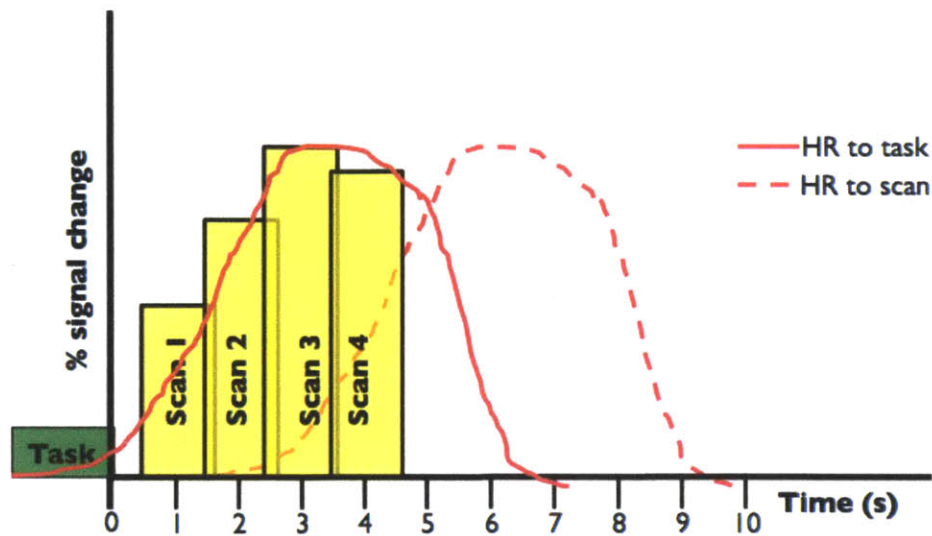


Fig. 4-3: a diagram of the sparse sampling method with jittered acquisition, showing the hemodynamic response (HR) to the task and to the scan. Although 4 scans are shown in the illustration, this represents the 4 possible scan delays after the end of each trial (only one of these scan delays occurs after each trial). This maximizes the acquisition of the response of interest (HR to task) while minimizing the acquisition of HR due to the noise generated by the scanner (HR to scan).

4.2.7 fMRI Data Analysis

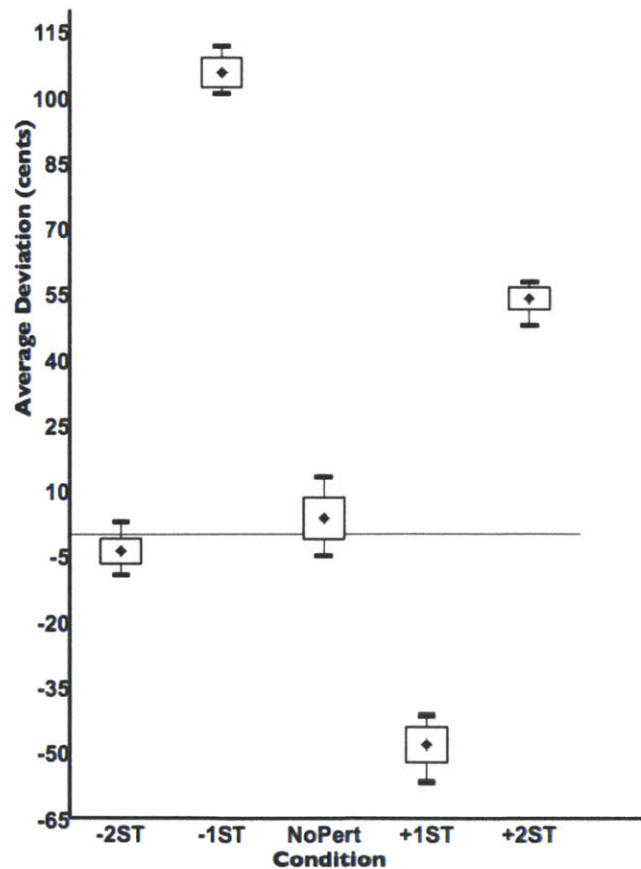
fMRI data were analyzed using SPM5 software (Institute of Neurology, London, UK). Preprocessing the data included image realignment, spatial normalization, and smoothing (8mm Gaussian kernel). Condition effects were estimated using General Linear Models (Friston, Ashburner, Kiebel, Nichols, & Ashburner, 2006). Each scan was scaled globally in order to normalize the effects across subjects and avoid the effects of global intensity differences, and data were not convolved with the hemodynamic response function (HRF). Combining all individual imaging time points yielded a 1st-level design matrix. This was used to examine the effects of each condition (no production, unperturbed production, +1ST perturbed production, +2ST perturbed production, -1ST perturbed production, and -2ST perturbed production) for individual subjects. A contrast was calculated for all production conditions vs. no production (prod > noprod), in addition to one for all the perturbed production conditions vs. unperturbed production (pert > nopert). Each subject's prod>noprod contrast image was then entered into a one-sample t-test to compare the production and no production conditions (prod > noprod) at the second level. Similarly, each subject's pert>nopert contrast image was entered into a one-sample t-test to compare activations between perturbed and non-perturbed production (pert > nopert) at the second level. A threshold

of $P < .05$ (FDR-corrected) was applied, and no masking was applied to limit the volume being considered for comparisons.

4.3 Results

4.3.1 Behavioral Results

On average, participants successfully matched the randomized target pitches (mean deviation = 3.62 cents, range = 18.5 cents). Participants showed evidence of compensation during -1ST and +1ST conditions by opposing the experimental manipulation, (mean deviation = 105.56 cents and -48.13 cents, respectively; range = 10.94 and 15.08 cents, respectively) while this result was not observed for the -2ST and +2ST conditions (mean deviation = -3.85 and 53.77 cents, respectively; range = 11.31 and 18.51 cents, respectively). For each condition, figure 4-4 shows a boxplot (mean, +/- s.d., min/max) of the participants' average cents-deviation from the target during the stable 500ms window.



4.3.2 fMRI Results

The production vs. no-production contrast (prod > noprod, 2nd-level, FDR-corrected at $P < .05$, -see figure 4-5) revealed functional activations that included bilateral ventral motor and somatosensory cortices, bilateral inferior frontal regions, and bilateral auditory cortices. This is consistent with neuroimaging studies on vocalization and has been observed in previous studies of our own group (Ozdemir et al., 2006), as well as other groups

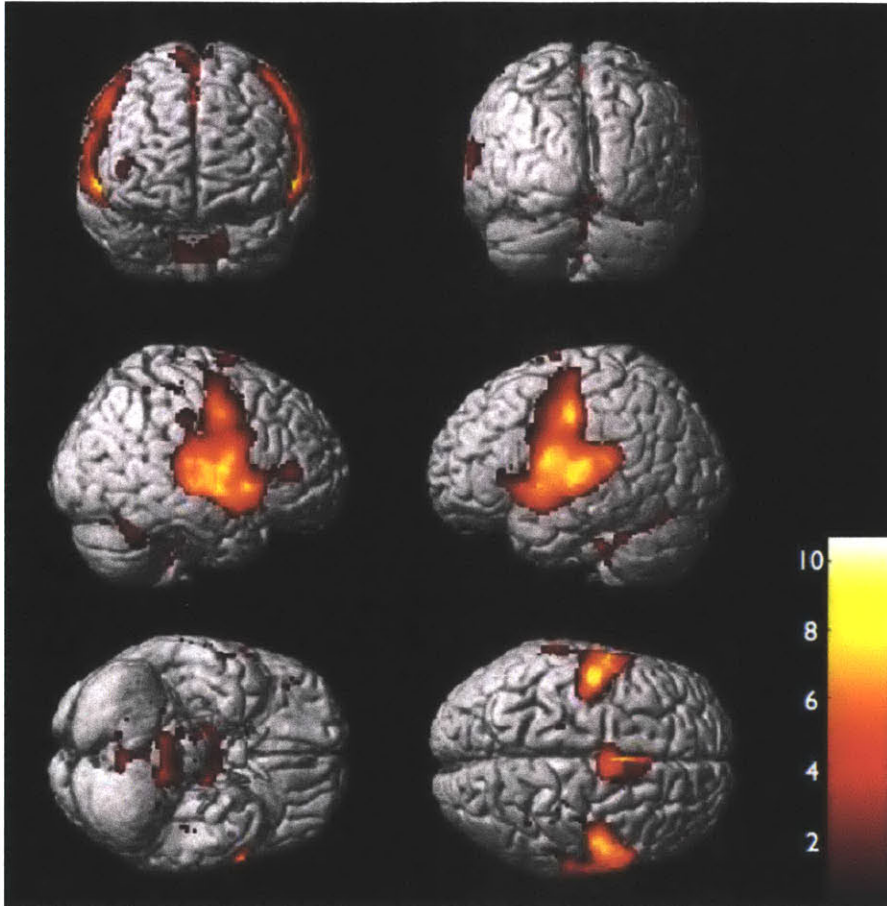


Fig. 4-5: prod > no production contrast ($p < .05$, FDR-corrected)

The effect of perturbation (pert > nopert, 2nd-level, FDR-corrected at $P < .05$, see figure 4-6i) recruited a functional network with peak activations centering around the left PMC and MFG, as well as the left STG and STS. Other active regions included SMA and IPL. Figures 4-7i and 4-7ii shows sections with the relevant structures labeled.

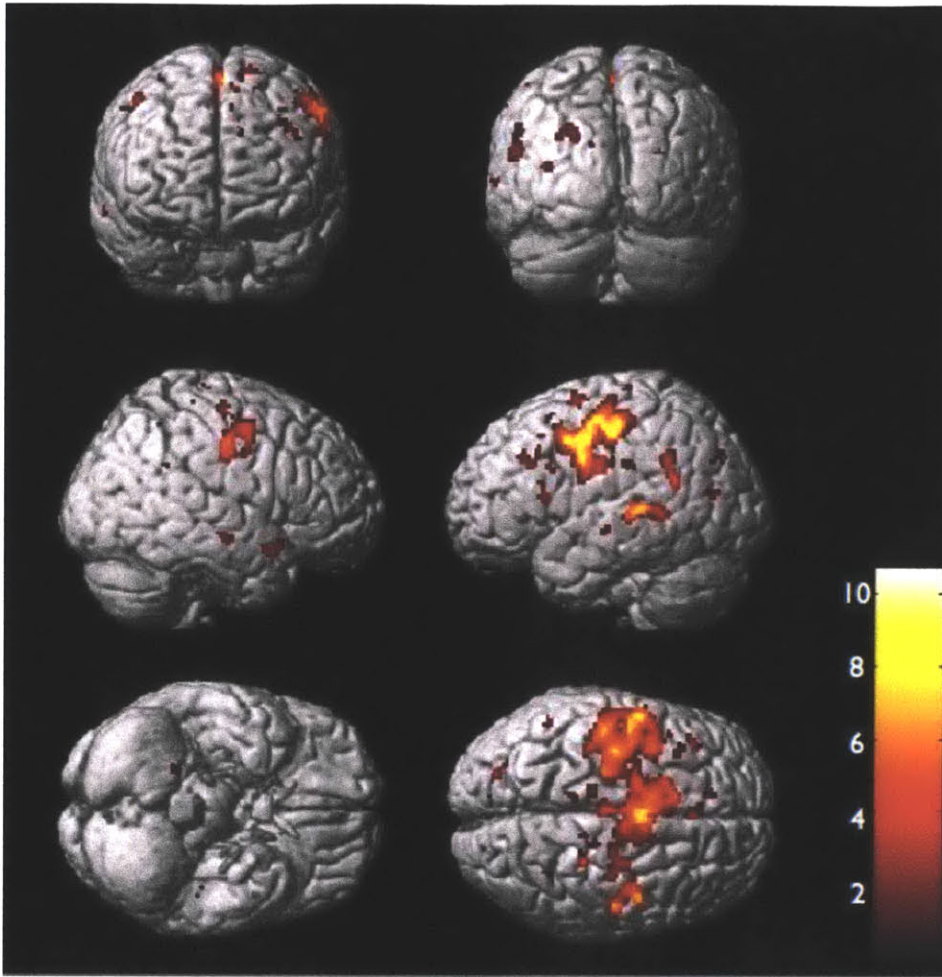


Fig. 4-6i: perturbation > no perturbation contrast ($p < .05$, FDR-corrected)



Fig 4-6ii: perturbation > no perturbation contrast showing only the left MFG –PMC activation ($p < .05$, FWE-corrected)

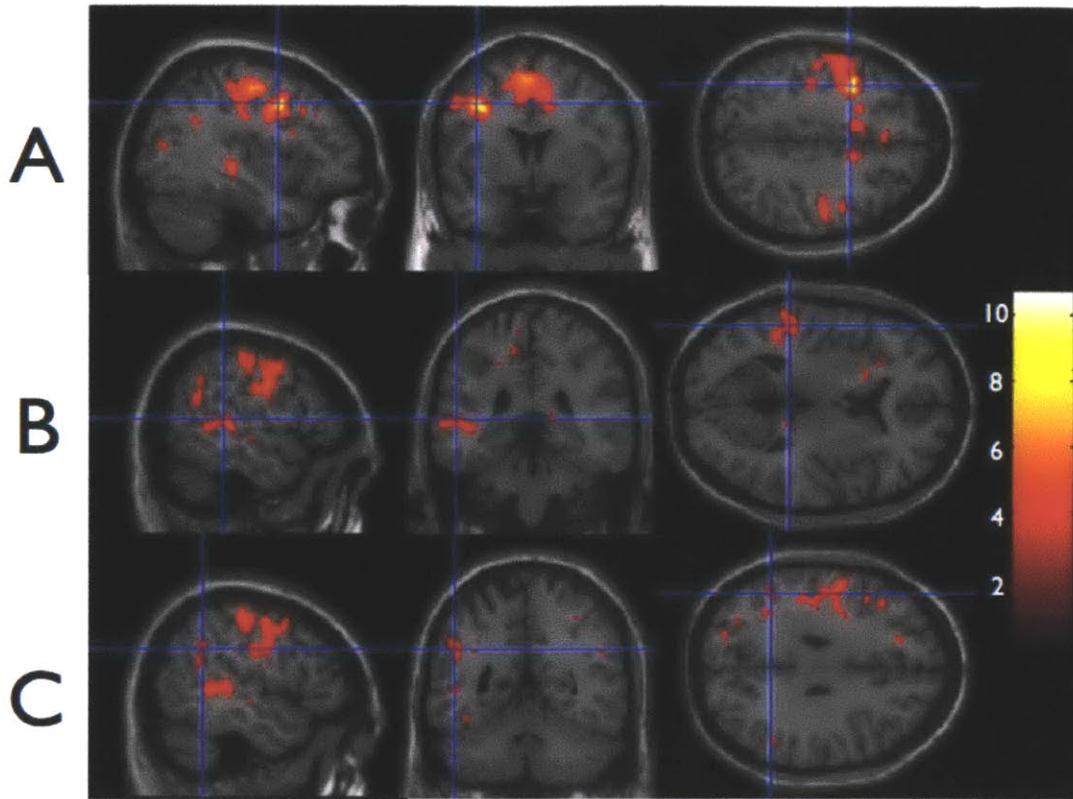


Fig. 4-7i: sections from perturbation > no perturbation contrast ($p < .05$, FD-corrected), showing the more medial activations for MFG-PMC (A), STG and STS (B), and IPL (C).

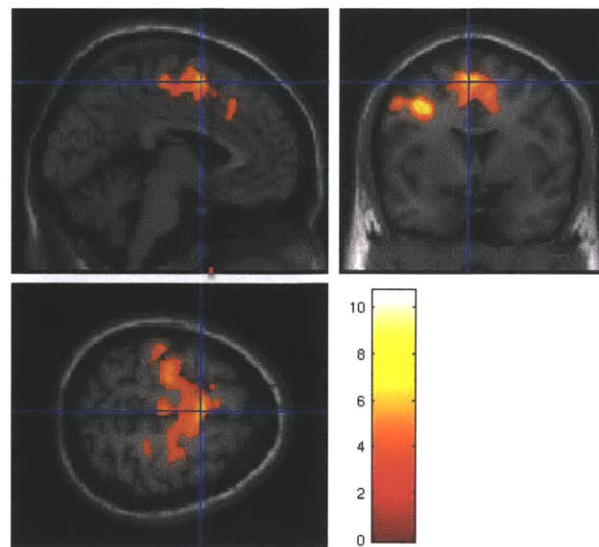


Fig. 4-7ii: sections from perturbation > no perturbation contrast ($p < .05$, FDR-corrected), showing the more medial activations for SMA. The blue crosshair indicates the location of peak activation, while the red vertical line in the sagittal image (perpendicular to the AC-PC line) marks the boundary between SMA (posterior to red line) and pre-SMA (anterior to red line) (Zilles et al., 1996).

4.4 Discussion

A left-hemispheric cortical network including STG-STS, SMA, and PMC is involved in perceiving and responding to pitch-shifted auditory feedback to the voice. Behavioral results showed that participants modulated their vocal pitch in response to the F0 perturbation across the -1ST and +1ST conditions, compensating for the effect of the perturbation and resulting in a percept in their headphones which matches the target tone. A similar observation was not made across the -2ST and +2ST conditions, suggesting that participants may have faced more difficulty in performing this task under conditions where their auditory feedback was more profoundly perturbed, resulting in a different percept from their own voice. Specifically, participants ignored the -2ST condition but followed the perturbation in the +2ST condition.

This finding is consistent with other studies, suggesting that participants respond differently to perturbed F0 depending on the magnitude of the perturbation (Burnett et al., 1998; Liu & Larson, 2007). When the magnitude of the perturbation is subtle, participants oppose the perturbation, while they tend to disregard the perturbation as its magnitude increases. This suggests that the auditory-motor system may be uniquely adapted to compensate automatically for small deviations from expected output, as these deviations are likely to be generated endogenously, as opposed to larger mismatches, which might indicate interference from environmental sounds. By not correcting for larger perturbations of auditory feedback, the auditory-vocal system may protect itself against erroneously correcting for feedback that is influenced by other environmental sounds (Liu & Larson, 2007). A more peripheral contributor to this effect may also involve the perception of the sounds by way of bone conduction rather than through the air. The subjects' percept of their own voice through bone conduction is not perturbed, unlike the air-conducted feedback coming in through the headphones. Thus, in conditions when the air-conducted feedback is more than a semitone or so apart from the bone-conducted feedback, this may cause some confusion in subjects with regards to which tone to focus on for the task. In situations where the auditory-feedback level is set too low, the bone-conducted feedback may become the dominant one, causing the subject to attend to the bone-conducted signal rather than the signal coming through the headphones.

Although the finding that participants compensated more for subtle F0 perturbations than for

profound ones is consistent with other results, this does not explain the asymmetry in results in the +/- 2 ST conditions, where participants ignored the -2ST perturbation, responding virtually as if there is no perturbation, while they tended to follow the +2ST perturbation by adjusting their vocal pitch in the same direction as perturbation. Although the precise reason behind this 'following' behavior is not known, one explanation might be related to the participants' misattribution of positive perturbed feedback (that is well above their center F0) as the target tone, and thus recalibrating their F0 to the received auditory feedback, effectively rendering it the new reference pitch (Hain et al., 2000; Liu & Larson, 2007).

Although the likelihood of 'following' the perturbation seems to increase with the magnitude of the perturbation, this effect seems only to be observed in the +2ST but not the -2ST condition of this experiment. Rather, the participants seemed to ignore the perturbation in that condition, vocalizing as if they were only hearing their unperturbed auditory feedback.

One likely explanation for this result is related to the way in which the center F0 for each participant was ascertained: Participants were instructed to hum for 3 seconds in their natural speaking voice. F0 for speaking is often lower than F0 for singing (Natke et al., 2003), and this may have resulted in some target frequencies that approach the lower limit of some participants' vocal range, making it much less likely for them to 'follow' the -2ST perturbation relative to the +2ST perturbation. Nevertheless, one might expect that participants would still attempt to follow, and that this would be reflected in the average cents-deviation in the averaging window, suggesting that other factors may have also contributed to this response.

One other explanation is that the feedback in the -2ST condition is, given the employed pitch-processing algorithm, more susceptible to being tainted by artifacts relative to feedback that is shifted up +2ST. This is particularly pronounced in male participants whose F0 is already near 100Hz. If participants heard auditory feedback with enough artificial degradation due to the processing, they may have de-identified with the signal, no longer regarding it as their own auditory feedback, but instead hearing it as external sound, independent from their vocalization, thus explaining the apparent 'ignore' behavior during the -2ST trials but not during +2ST.

In order to function effectively, the auditory-vocal system must differentiate continuously between sounds coming from the environment and sounds that are generated endogenously

(Behroozmand & Larson, 2011). To accomplish this differentiation, efference copies of the vocal output are constantly compared to the perceived auditory feedback. During this process, the system may initiate a correction of F0 output when the auditory feedback doesn't match the efference copy that it corresponds with. However, if the efference copy and the auditory feedback are too disparate (as seems to be the case in the -2ST condition), then the system does not initiate any involuntary correction, treating this sensory input as originating from the environment, independent of the vocal-motor action (Behroozmand & Larson, 2011; Houde et al., 2002; Poulet & Hedwig, 2002).

FMRI results comparing all production conditions with the no-production condition revealed a functional network that includes the cerebellum, bilateral primary and secondary auditory cortices, ventral motor and somatosensory cortices, as well as inferior frontal regions. These regions are consistent with other studies comparing vocalization to rest (Kleber et al., 2007; Ozdemir et al., 2006; Price, 2000). Furthermore, this network of regions is also in agreement with computational models of speech-motor interactions (Guenther, 2006). According to these models, activations in these regions indicate that auditory state, target and error maps are engaged in the process of cross-referencing the auditory target (pSTG) with the sensory input (A1) and encoding any discrepancies in the auditory error map (pSTG). Information about the position and movement trajectories of vocal articulators is, according to the model, localized to the ventral motor cortex (vMC), while the left ventral premotor cortex (vPMC) houses the *speech sound map*, responsible for the tuning of auditory targets (Golfinopoulos et al., 2010). This network is likely always engaged during vocalization, but certain nodes might become more active as demands dictate (e.g., auditory error cells might be preferentially activated when there is discord between the output of the auditory target and state cells).

Contrasting all perturbed production conditions with the unperturbed auditory feedback condition removes all activations due to simple vocal perception and production and reveals the network that is active particularly when participants are faced with auditory-vocal feedback mismatch. In this contrast, robust activation is seen in a region in the left PMC. In addition, strong activation is observed in the left pSTG and STS and IPL. Nearly homologous activation is also observed in the right hemisphere, although not as robust.

The network of activations in response to perturbation includes regions involved in

monitoring the perceived auditory feedback as well as the expected auditory feedback to one's voice, and correcting for the mismatch between expected and perceived feedback. The posterior STG/STS is activated in many auditory tasks (Ozdemir et al., 2006) but importantly, is activated in perturbed vocal feedback studies, regardless of whether perturbation was applied to fundamental frequency (Zarate et al., 2010; Zarate & Zatorre, 2008) or to formants (Golfinopoulos et al., 2010; Tourville et al., 2008). In perturbed auditory feedback studies, activity observed in these regions is linked to auditory error correction in the auditory error map (Tourville et al., 2008). In this study, a similar activation pattern is observed, although it is a complex of STG and STS and not only STG, differing somewhat from a result that the computational model (Golfinopoulos et al., 2010) might predict (STG and PT). Furthermore, the model suggests that IPL may be more involved in detecting and correcting for feedback perturbations in the somatosensory domain, relative to the relative to auditory, although this study, and others from our group (Schulze et al., 2009; Ellis et al., 2012), has suggested that it plays a role in auditory-motor interactions.

The DIVA model also hypothesizes projections from this auditory error map to the feedback control map (localized according to the model in right vPMC). Although the model hypothesizes that projections from the auditory error cells would engage the feedback control map (in the *right* vPMC) in order to relay corrective motor commands to the vMC, no robust activation was found in the *right* vPMC in our study. Rather, the strongest response is centered around the left MFG or PMC, contralateral to the model's prediction, with additional surrounding activation in the vMC as well as parts of the IFG (pars opercularis), as well as some activation in the SMA. These findings are consistent with other empirical results during perturbed F0 (Zarate et al., 2010; Zarate & Zatorre, 2008), but not with studies investigating responses to perturbed formant frequencies (Golfinopoulos et al., 2010; Tourville et al., 2008).

Similar task-dependent-distinctions have been observed between the lateralization of PMC activation in other studies: participants recruit the *right* PMC when instructed to ignore the feedback perturbation, while recruiting the *left* PMC when instructed to compensate (Zarate & Zatorre, 2008). At the same time, other studies have found that while PMC and inferior parietal areas may be involved in spatial processing related to judging the direction of perturbation (Beurze et al., 2007; Chouinard & Paus, 2006; Zarate & Zatorre, 2008), *left* PMC may aid in low-level correction based on raw sensorimotor input (such as varying phonation frequency based on incoming F0 stream), while

right PMC might be engaged when the correction involves modifying a learned motor program, or selecting a different learned program entirely (Mars et al., 2007). This distinction may be applied to the difference between an F0-matching task and one when the target is a vowel. Perturbation of F0 will necessitate a correction along the same plane of perturbation, relying on the raw sensorimotor association and resulting in predominantly *left* PMC activation, while correcting for formant perturbations (i.e., vowel perturbations) may necessitate correction by modifying the motor program for a learned vowel, or by articulating a different vowel altogether, thereby leading to predominantly *right* PMC activation (Mars et al., 2007).

Taken together, the present study shows behavioral compensation in response to small changes in fundamental frequency of auditory feedback, accompanied by increased activations in a predominantly left-hemispheric network including pSTG, STS, PMC, and SMA during the processing of these feedback perturbations. Behavioral compensations for perturbations occurred only during small shifts resulting in feedback that was acceptable as natural alterations to one's own voice. A widespread network of auditory and motor regions was activated during production tasks; this network was refined and limited to specific auditory and premotor regions during the controlled manipulation of auditory feedback. In conclusion, results show that the functional auditory-motor network that controls auditory feedback in non-musicians who are not tonedeaf is sensitive to the degree of mismatch as well as the type of auditory information being controlled.

4.5 Long-term mismatch of auditory-motor feedback: the case of tonedeafness

4.5.1 Introduction

While the results discussed above shed light on the function of the auditory-vocal network during conditions of short-term 'disorder' (i.e., experimentally-induced auditory-vocal mismatch), studying the same network in conditions of long-term disorder (i.e., tonedeafness) will provide insight into the neural correlates of the poor auditory-motor performance that is regularly observed in individuals with tonedeafness. In addition to demonstrating that individuals with TD experience difficulty in matching pitches vocally, assessing them using the above-described methods will also determine whether or not they are sensitive to perturbations of their auditory feedback (i.e., how

they behaviorally react to the experimental manipulations relative to the results described in section 4.3). Finally, investigating the neural correlates of their reaction will provide neurological context to their performance on the pitch matching task, relative to the results described in section 4.3. Taken together, this pilot study provides preliminary data on the behavioral and neurological correlates of TD and offers an introductory look at auditory-motor function (behaviorally and neurologically) in individuals with TD, as compared to those not showing evidence of TD. This serves to motivate future studies of long-term deficit in auditory-vocal function and may establish TD as a model for studying long-term deficits in auditory-vocal function as well as any associated compensatory mechanisms.

4.5.2 Participants

Following a general consensus that recruiting individuals with TD is best done by way of screening those who self-identify as tonedeaf, and/or report difficulties in singing (Mandell et al., 2007; Peretz, 2001), advertisements were made online, asking individuals who report difficulty in singing to inquire about participating. The individuals who agreed to be part of the study were then subjected to the same audiometric evaluation used in the main experiment, including the first three sub-tests of the Montreal Battery for Evaluation of Amusia (MBEA) (Peretz et al., 2003), a psychophysical test for pitch-interval directionality (for perception and production).

Of the participants screened for this study to date, 5 fit our criteria for TD (3f, 2m; mean age = 28, s.d. = 8). All had normal IQ (mean = 117, s.d. = 5) as assessed by verbal and abstract IQ measures (Shipley, 1940), scored an average of 73% (s.d. = 9%) on the first three sub-tests of the MBEA and showed an average results of 31Hz (s.d. = 14Hz) and 45Hz (s.d. = 10Hz) on the psychophysical tests for pitch-interval directionality (for perception and production, respectively), placing them in the range of psychophysical criteria for TD used in previous studies (Loui et al., 2009). They then each participated in the same experimental protocol described in section 4.2.

4.5.3 Pilot results – pitch-matching with perturbed auditory feedback in individuals with TD

On average, participants with TD failed to successfully match the randomized target pitches

(mean deviation = -94 cents, range = 14 cents) in the 500ms 'stable window' during the unperturbed condition. The same participants showed similar performance regardless of perturbation condition, consistently singing back around -1ST of the target pitch regardless of the direction of the perturbation, suggesting that they ignored or were unaware of the perturbed feedback. For each condition, figure 4-8 shows a boxplot (mean, +/- s.d., min/max) of the participants' average cents-deviation from the target during the stable 500ms window. The data from section 4.3 has been reproduced in this plot in black, whereas the data from participants with TD is shown in red. Figure 4-9 shows a contrast of all perturbation conditions – no perturbation.

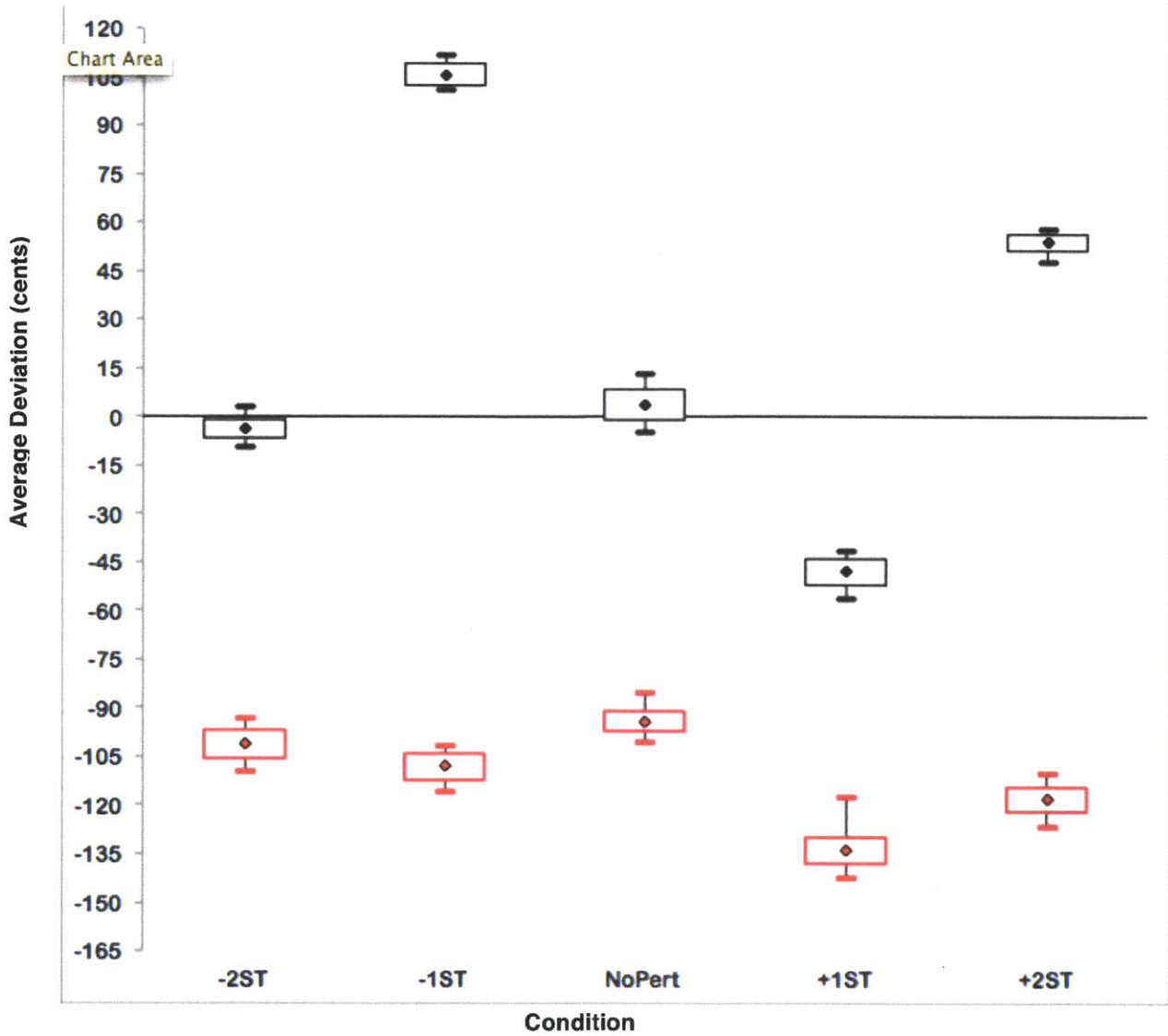


Fig. 4-8: average cents-deviation re: perturbation condition for individuals with TD (red boxes). The data from section 4.3 (performance of normal participants under the same experimental conditions) were reproduced here and shown for reference (black boxes).

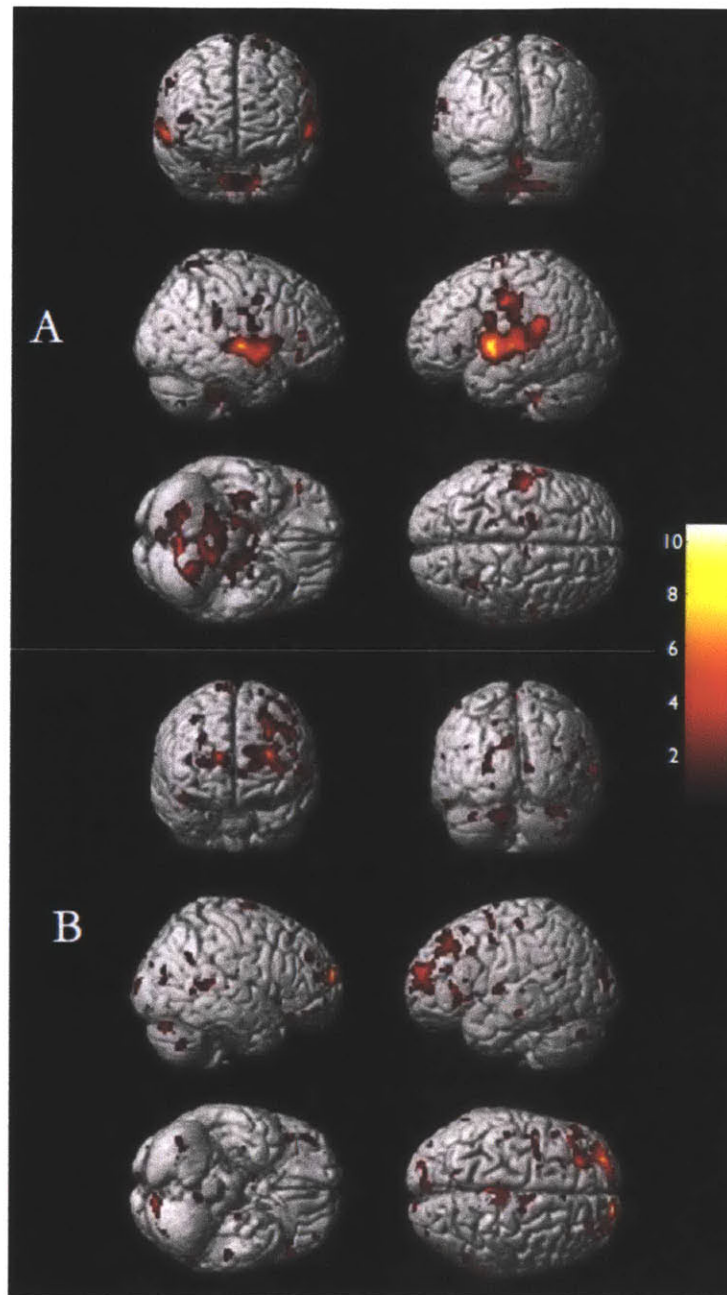


Fig 4-9: panel (B) shows the perturbed > unperturbed contrast for TD participants ($p < .05$, uncorrected). For reference, panel (A) shows the contrast for production > no production ($p < .05$, uncorrected) for the same participants, suggesting that even though a typical activation pattern for vocalization is emerging (considering $n=5$), the loci of activation for the perturbed > unperturbed contrast do not begin to converge near any of the loci seen in normal subjects (fig. 4-6). Instead, TD subjects exhibit a much more frontal activation pattern relative to normal subjects, possibly indicating increased cognitive load while attempting the pitch-matching task.

4.5.4 Discussion and future directions – pitch-matching with perturbed auditory feedback in individuals with TD

As expected, TD participants performed poorly on the pitch-matching task, relative to participants not showing evidence of TD. This was demonstrated on their average performance on the task in the no-perturbation condition (averaged across all non-perturbed trials and all TD participants). This reinforces the notion that a primary behavioral marker for TD is the inability to accurately produce vocal pitch that matches an external target (Ayotte et al., 2002; Peretz et al., 2009; Loui et al., 2009). With regards to the perturbed auditory feedback conditions, TD participants seemed to be unaware of the perturbation in feedback, despite being instructed to maintain attentiveness to the sound of their voice in the headphones. This is in agreement with other studies that have found that individuals with TD not only perform poorly on such tasks, but are often unaware of their performance (Peretz et al., 2009). Although a wider range of produced pitches would have been expected (greater variability relative to non-TD participants), this was not observed, most likely due to the smaller sample size relative to the group in section 4.3.

Although the sample size used in this pilot study severely limits interpretation of the neuroimaging findings (Desmond et al., 2002; Hayasaka et al., 2007), it offers a preliminary look at the function of the auditory-motor network in a state of long-term disorder. Having isolated a candidate network for processing auditory-feedback mismatch in the previous experiment (a predominantly left-hemispheric network including pSTG-STS, PMC, and SMA), it is notable that (assuming this general trend of activation continues as more participants are added to the analysis) TD participants do not show significant activation in the same network while engaged in the same task, relative to non-TD participants. Figure 4-9 suggests no qualitative left-lateralization in function for TD participants, contrary to non-TD participants. Additionally, the strong activation around the left PMC observed in the previous experiment is also absent, as is any significant activation of STG and IPL in either hemisphere. Importantly, the absence of strong activation in the relevant auditory areas seen in the previous experiment may indicate a disorder in functional connectivity between the auditory state, auditory error, and/or auditory target maps represented by the DIVA model (Golfinopoulos et al., 2010).

The network of activation observed in fig. 4-9B includes regions involved in monitoring the

perceived auditory feedback as well as the expected auditory feedback to one's voice, and correcting for the mismatch between expected and perceived feedback. The absence of strong posterior STG or STS activation in TD-participants could explain their negligence of the feedback perturbation conditions, as these regions are strongly implicated with monitoring auditory feedback (Ozdemir et al, 2006, Golfopoulos et al., 2010). In other similar studies, activity observed in pSTG is linked to auditory error correction in the auditory error map, as confirmed by the model as well as experimental results (Tourville et al, 2008).

The DIVA model also hypothesizes that projections from this auditory error map to the feedback control map (localized according to the model in right vPMC) trigger the engagement of the feedback control map (hypothesized in the model to be in the right PMC although results from section 4.3 suggest otherwise, see section 4.4 for discussion of this finding). Engagement of this module would in turn relay corrective motor commands to the vMC (subserving movements of the vocal apparatus), ultimately leading to a correction in vocal output that would be reflected behaviorally as a compensation to the perturbation of F0 feedback. This behavioral response, as well as any hypothesized neural correlate of this response, is absent in TD participants. With the assumption that this general activation trend continues as more subjects are added to the analysis, this pilot study confirms that TD may serve as a model for studying long-term auditory-vocal disorder in the otherwise healthy population. Future work will evaluate these claims by more individuals with TD to the analysis.

5: SUMMARY & CONCLUSIONS

5.1 The auditory-vocal network adapts structurally in response to intense and long-term auditory-vocal training

In chapter 3, the results of a comparison of the AF of non-musicians, instrumental musicians, and vocalists were reported, showing that the AF has a larger volume and higher FA values in musicians (both singers and instrumentalists) relative to non-musicians. Among the 21 musicians who participated in the study, singers showed significantly higher volume in the dorsal and ventral branches of the left AF, and *lower* FA in the left dorsal AF, relative to instrumentalists. Conversely, the three groups' whole-brain FA measures did not differ, suggesting that the observed structural differences are not due to whole-brain differences and may be specific to anatomical regions that subserve auditory-motor interactions. Assessing the FA of different regions of the AF in singers showed that one particular region contributed the bulk of the FA difference, and that the observed lower FA in singers was in fact driven by higher radial diffusivity and not lower axial diffusivity, relative to instrumentalists, suggesting that the difference was observed due to greater connectivity from the AF to regions in the ventral motor and somatosensory cortices, which are heavily implicated in controlling the vocal apparatus.

In summary, the results suggest that musical training, particularly vocal training, is associated with structural adaptations in the AF: a tract that is important for linguistic as well as musical functions, providing further support for the use of musically trained individuals, especially singers, as a model for structural adaptations of the auditory-motor system (Schlaug, 2001). The long-term and intensive nature of a formal vocal training regimen means that components of these training regimens may be incorporated into a rehabilitation programs for aphasic patients and other groups with impaired vocal output (Schlaug et al, 2008; Wan & Schlaug, 2010; Wan et al, 2010).

Indeed, individuals in such groups show neurological adaptations in response to intense intonation-based speech therapy (Schlaug et al, 2009; Wan et al, 2010). By characterizing the differences in white matter connectivity between singers and non-singer controls who are matched in musical training, the study presented in chapter 3 suggests that intense, long-term musical training (particularly vocal-motor training) has an effect on the anatomy of vocal-motor networks.

5.2 The auditory-vocal network adapts functionally in response to short-term auditory feedback mismatch

In chapter 4, normal, non-musician participants were subjected to a pitch-matching task under conditions of intermittent auditory feedback perturbation (via shifting their F0 up or down up to 2 semitones). Behavioral results showed that participants modulated their vocal pitch in response to the F0 perturbation across the -1ST and +1ST conditions, compensating for the effect of the perturbation and resulting in a percept in their headphones which matches the target tone. A similar observation was not made across the -2ST and +2ST conditions, consistent with other studies, suggesting that participants respond differently to perturbed F0 depending on the magnitude of the perturbation. When the magnitude of the perturbation is subtle, participants oppose the perturbation, while they tend to disregard the perturbation as its magnitude increases.

Neurologically, a left-hemispheric network including pSTG-STS, SMA, and PMC (involved in perceiving and responding to pitch-shifted auditory feedback to the voice) was found to be especially activated under conditions of perturbed auditory feedback. These regions are consistent with other studies comparing vocalization to rest. Furthermore, this finding is also in agreement with computational models of speech-motor interactions (Guenther, 2006). These regions are involved in monitoring the perceived auditory feedback, and correcting for the mismatch between expected and perceived feedback. The same behavioral and neurological responses were not observed in a pilot study involving 5 participants with TD.

Taken together, the results presented in chapter 4 show behavioral compensation in response to small changes in fundamental frequency of auditory feedback, accompanied by increased activations in a predominantly left-hemispheric network including pSTG-STS, PMC, and SMA during the processing of these feedback perturbations in normal individuals, whereas the same was not observed in a pilot study with participants with TD. The results suggest that (1) the auditory-motor network can quickly adapt to short-term auditory-feedback mismatch and (2) that individuals with TD may represent a model for studying long-term auditory-motor feedback mismatch in otherwise healthy individuals.

REFERENCES

- Aboitiz, F., Scheibel, A. B., Fisher, R. S., & Zaidel, E. (1992). Fiber composition of the human corpus callosum *Brain research*, 598(1-2), 143–153.
- Abrams, D., Nicol, T., & Zecker, S. (2008). Right-Hemisphere Auditory Cortex Is Dominant for Coding Syllable Patterns in Speech. ... *Journal of Neuroscience*.
- Alexander, A. L., Lee, J. E., Lazar, M., and Field, A. S. (2007). Diffusion tensor imaging of the brain. *Neurotherapeutics* 4, 316–329.
- American Speech-Language-Hearing Association (1997). *Guidelines for audiologic screening* (p. 60). American Speech-Language-Hearing Association.
- Ardila, A. (2010). A review of conduction aphasia *Current neurology and neuroscience reports*, 10(6), 499–503. doi:10.1007/s11910-010-0142-2
- Ashtari, M., Cervellione, K. L., Hasan, K. M., Wu, J., Mcilree, C., Kester, H., Ardekani, B. A., Roofeh, D., Szeszko, P. R., and Kumra, S. (2007). White matter development during late adolescence in healthy males: a cross-sectional diffusion tensor imaging study. *Neuroimage* 35, 501–510.
- Ayotte, J., Peretz, I., & Hyde, K. (2002). Congenital amusia: a group study of adults afflicted with a music-specific disorder *Brain : a journal of neurology*, 125(Pt 2), 238–251.
- Barnea-Goraly, N., Menon, V., Eckert, M., Tamm, L., Bammer, R., Karchemskiy, A., Dant, C. C., and Reiss, A. L. (2005). White matter development during childhood and adolescence: a cross-sectional diffusion tensor imaging study. *Cereb. Cortex* 15, 1848–1854.
- Basser, P. J. (1995). Inferring micro-structural features and the physiological state of tissues from diffusion-weighted images. *NMR Biomed.* 8, 333–344.
- Basser, P. J., Mattiello, J., and Lebihan, D. (1994). MR diffusion tensor spectroscopy and imaging. *Biophys. J.* 66, 259–267.
- Basser, P. J., Pajevic, S., Pierpaoli, C., Duda, J., and Aldroubi, A. (2000). In vivo fiber tractography using DT-MRI data. *Magn. Reson. Med.* 44, 625–632.
- Bauer, J. J., Mittal, J., Larson, C. R., & Hain, T. C. (2006). Vocal responses to unanticipated perturbations in voice loudness feedback: an automatic mechanism for stabilizing voice amplitude *The Journal of the Acoustical Society of America*, 119(4), 2363–2371.
- Behrens, T. E., Berg, H. J., Jbabdi, S., Rushworth, M. F., and Woolrich, M. W. (2007). Probabilistic diffusion tractography with multiple fibre orientations: what can we gain? *Neuroimage* 34, 144–155.
- Behrens, T. E., Woolrich, M. W., Jenkinson, M., Johansen-Berg, H., Nunes, R. G., Clare, S., Matthews, P. M., Brady, J. M., and Smith, S. M. (2003). Characterization and propagation of uncertainty in diffusion-weighted MR imaging. *Magn. Reson. Med.* 50, 1077–1088.
- Behroozmand, R., & Larson, C. R. (2011). Error-dependent modulation of speech-induced auditory suppression for pitch-shifted voice feedback *BMC Neuroscience*, 12, 54. doi:10.1186/1471-2202-12-54
- Bendor, D., & Wang, X. (2005). The neuronal representation of pitch in primate auditory cortex *Nature*, 436(7054), 1161–1165. doi:10.1038/nature03867
- Bengtsson, S. L., Nagy, Z., Skare, S., Forsman, L., Forssberg, H., and Ullen, F. (2005). Extensive piano practicing has regionally specific effects on white matter development. *Nat. Neurosci.* 8, 1148–1150.

- Beurze, S. M., de Lange, F. P., Toni, I., & Medendorp, W. P. (2007). Integration of target and effector information in the human brain during reach planning *Journal of Neurophysiology*, *97*(1), 188–199. doi:10.1152/jn.00456.2006
- Black, J. W. (1951). The effect of delayed side-tone upon vocal rate and intensity *The Journal of speech disorders*, *16*(1), 56–60.
- Brown, S., Martinez, M. J., Hodges, D. A., Fox, P. T., and Parsons, L. M. (2004). The song system of the human brain. *Brain Res. Cogn. Brain Res.* *20*, 363–375.
- Burnett, T. A., Freedland, M. B., Larson, C. R., & Hain, T. C. (1998). Voice F0 responses to manipulations in pitch feedback. *The Journal of the Acoustical Society of America*, *103*(6), 3153–3161.
- Carmichael, S. T. (2006). Cellular and molecular mechanisms of neural repair after stroke: making waves. *Ann. Neurol.* *59*, 735–742.
- Catani, M., & Mesulam, M. (2008). What is a disconnection syndrome *Cortex; a journal devoted to the study of the nervous system and behavior*, *44*(8), 911–913. doi:10.1016/j.cortex.2008.05.001
- Catani, M., Jones, D. K., & ffytche, D. H. (2004). Perisylvian language networks of the human brain. *Annals of Neurology*, *57*(1), 8–16. Wiley Subscription Services, Inc., A Wiley Company. doi:10.1002/ana.20319
- Chouinard, P. A., & Paus, T. (2006). The primary motor and premotor areas of the human cerebral cortex *The Neuroscientist : a review journal bringing neurobiology, neurology and psychiatry*, *12*(2), 143–152. doi:10.1177/1073858405284255
- Damasio, A. R. (1992). Aphasia. *The New England journal of medicine*, *326*(8), 531–539. doi:10.1056/NEJM199202203260806
- Damasio, A. R., & Geschwind, N. (1984). The neural basis of language. *Annual review of neuroscience*, *7*, 127–147. doi:10.1146/annurev.ne.07.030184.001015
- Damasio, H., & Damasio, A. R. (1980). The anatomical basis of conduction aphasia. *Brain : a journal of neurology*, *103*(2), 337–350.
- Dancause, N., Barbay, S., Frost, S. B., Plautz, E. J., Chen, D., Zoubina, E. V., Stowe, A. M., and Nudo, R. J. (2005). Extensive cortical rewiring after brain injury. *J. Neurosci.* *25*, 10167–10179.
- Denes, P., & Pinson, E. (1993). *The Speech Chain: The Physics and Biology of Spoken Language* (Second Edition. p. 246). Worth Publishers.
- Desmond, J. E., & Glover, G. H. (2002). Estimating sample size in functional MRI (fMRI) neuroimaging studies: statistical power analyses. *Journal of neuroscience methods*, *118*(2), 115–128.
- Desmurget, M., & Grafton, S. (2000). Forward modeling allows feedback control for fast reaching movements *Trends in Cognitive Sciences*, *4*(11), 423–431.
- Dronkers, N. F., Wilkins, D. P., Van Valin, R. D., Redfern, B. B., & Jaeger, J. J. (2004). Lesion analysis of the brain areas involved in language comprehension. *Cognition*, *92*(1-2), 145–177. doi:10.1016/j.cognition.2003.11.002
- Ellis, R. J., Norton, A. C., Overy, K., Winner, E., Alsop, D. C., & Schlaug, G. (2012). Differentiating maturational and training influences on fMRI activation during music processing *NeuroImage*, *60*(3), 1902–1912. doi:10.1016/j.neuroimage.2012.01.138
- Elmer, S., Hanggi, J., Meyer, M., and Jancke, L. (2010). Differential language expertise related to white matter architecture in regions subserving sensory-motor coupling, articulation, and interhemispheric transfer. *Hum Brain Mapp.* PMID: 21162044.
- Frey, S., Campbell, J. S., Pike, G. B., and Petrides, M. (2008). Dissociating the human language pathways with high angular resolution diffusion fiber tractography. *J. Neurosci.* *28*, 11435–11444.
- Friederici, A. D. (2009). Pathways to language: fiber tracts in the human brain. *Trends in Cognitive Sciences*, *13*(4), 175–181. doi:10.1016/j.tics.2009.01.001

- Friston, K. J., Ashburner, J. T., Kiebel, S. J., Nichols, T. E., & Ashburner, J. T. (2006). *Statistical Parametric Mapping: The Analysis of Functional Brain Images*. (W. D. Penny, K. J. Friston, J. T. Ashburner, S. J. Kiebel, & T. E. Nichols, Eds.) (1st ed. p. 656). Academic Press.
- Gaab, N., Gaser, C., Zaehle, T., Jancke, L., & Schlaug, G. (2003). Functional anatomy of pitch memory--an fMRI study with sparse temporal sampling *NeuroImage*, *19*(4), 1417–1426. doi:10.1016/S1053-8119(03)00224-6
- Gaser, C., & Schlaug, G. (2003). Gray matter differences between musicians and nonmusicians *Annals of the New York Academy of Sciences*, *999*, 514–517.
- Giorgio, A., Santelli, L., Tomassini, V., Bosnell, R., Smith, S., De Stefano, N., and Johansen-Berg, H. (2010). Age- related changes in grey and white matter structure throughout adulthood. *Neuroimage* *51*, 943–951.
- Glasser, M. F., & Rilling, J. K. (2008). DTI tractography of the human brain's language pathways. *Cerebral Cortex*, *18*(11), 2471–2482. doi:10.1093/cercor/bhn011
- Golfinopoulos, E., Tourville, J. A., & Guenther, F. H. (2010). The integration of large-scale neural network modeling and functional brain imaging in speech motor control. *NeuroImage*, *52*(3), 862–874. doi:10.1016/j.neuroimage.2009.10.023
- Golfinopoulos, E., Tourville, J. A., Bohland, J. W., Ghosh, S. S., Nieto-Castanon, A., & Guenther, F. H. (2011). fMRI investigation of unexpected somatosensory feedback perturbation during speech. *NeuroImage*, *55*(3), 1324–1338. doi:10.1016/j.neuroimage.2010.12.065
- Guenther, F. H. (2006). Cortical interactions underlying the production of speech sounds *Journal of communication disorders*, *39*(5), 350–365. doi:10.1016/j.jcomdis.2006.06.013
- Guenther, F. H., Ghosh, S. S., & Tourville, J. A. (2006). Neural modeling and imaging of the cortical interactions underlying syllable production *Brain and language*, *96*(3), 280–301. doi:10.1016/j.bandl.2005.06.001
- Habib, M. (2000). The neurological basis of developmental dyslexia: an overview and working hypothesis *Brain : a journal of neurology*, *123 Pt 12*, 2373–2399.
- Hafke, H. Z. (2008). Nonconscious control of fundamental voice frequency *The Journal of the Acoustical Society of America*, *123*(1), 273–278. doi:10.1121/1.2817357
- Hain, T. C., Burnett, T. A., Kiran, S., Larson, C. R., Singh, S., & Kenney, M. K. (2000). Instructing subjects to make a voluntary response reveals the presence of two components to the audio-vocal reflex *Experimental brain research Experimentelle Hirnforschung Expérimentation cérébrale*, *130*(2), 133–141.
- Halwani, G. F., Loui, P., Rüber, T., & Schlaug, G. (2011). Effects of practice and experience on the arcuate fasciculus: comparing singers, instrumentalists, and non-musicians *Frontiers in psychology*, *2*, 156. doi:10.3389/fpsyg.2011.00156
- Hayasaka, S., Peiffer, A. M., Hugenschmidt, C. E., & Laurienti, P. J. (2007). Power and sample size calculation for neuroimaging studies by non-central random field theory. *NeuroImage*, *37*(3), 721–730. doi:10.1016/j.neuroimage.2007.06.009
- Heilman, K. M., Voeller, K., & Alexander, A. W. (1996). Developmental dyslexia: A motor-articulatory feedback hypothesis. *Annals of Neurology*, *39*(3), 407–412. doi:10.1002/ana.410390323
- Hensch, T. K. (2004). Critical period regulation *Annual review of neuroscience*, *27*, 549–579. doi:10.1146/annurev.neuro.27.070203.144327
- Houde, J. F. (1998). Sensorimotor Adaptation in Speech Production. *Science*, *279*(5354), 1213–1216. doi:10.1126/science.279.5354.1213
- Houde, J. F., Nagarajan, S. S., Sekihara, K., & Merzenich, M. M. (2002). Modulation of the auditory cortex during speech: an MEG study *Journal of cognitive neuroscience*, *14*(8), 1125–1138.

doi:10.1162/089892902760807140

- Hyde, K. L., Lerch, J., Norton, A., Forgeard, M., Winner, E., Evans, A. C., & Schlaug, G. (2009). Musical training shapes structural brain development. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, 29(10), 3019–3025. doi:10.1523/JNEUROSCI.5118-08.2009
- Jenkinson, M., and Smith, S. (2001). A global optimisation method for robust affine registration of brain images. *Med. Image Anal.* 5, 143–156.
- Jito, J., Nakasu, S., Ito, R., Fukami, T., Morikawa, S., and Inubushi, T. (2008). Maturational changes in diffusion anisotropy in the rat corpus callosum: comparison with quantitative histological evaluation. *J. Magn. Reson. Imaging* 28, 847–854.
- Jones, J. A., & Munhall, K. (2005). Remapping Auditory-Motor Representations in Voice Production. *Current Biology*, 15(19), 1768–1772. doi:10.1016/j.cub.2005.08.063
- Kleber, B., Birbaumer, N., Veit, R., Trevorrow, T., & Lotze, M. (2007). Overt and imagined singing of an Italian aria. *NeuroImage*, 36(3), 889–900. doi:10.1016/j.neuroimage.2007.02.053
- Kleber, B., Veit, R., Birbaumer, N., Gruzelier, J., and Lotze, M. (2010). The brain of opera singers: experience-dependent changes in functional activation. *Cereb. Cortex* 20, 1144–1152.
- Koelsch, S., Gunter, T. C., Wittfoth, M., and Sammler, D. (2005). Interaction between syntax processing in language and in music: an ERP Study. *J. Cogn. Neurosci.* 17, 1565–1577.
- Kreisler, A., Godefroy, O., Delmaire, C., Debachy, B., Leclercq, M., Pruvo, J. P., & Leys, D. (2000). The anatomy of aphasia revisited. *Neurology*, 54(5), 1117–1123.
- Lane, H., & Tranel, B. (1971). The Lombard Sign and the Role of Hearing in Speech. *Journal of Speech and Hearing Research*, 14(4), 677. ASHA.
- Lee, D. J., Chen, Y., & Schlaug, G. (2003). Corpus callosum: musician and gender effects *Neuroreport*, 14(2), 205–209. doi:10.1097/01.wnr.0000053761.76853.41
- Levitin, D. J., and Menon, V. (2003). Musical structure is processed in “language” areas of the brain: a possible role for Brodmann Area 47 in temporal coherence. *Neuroimage* 20, 2142–2152.
- Lindenberg, R., Renga, V., Zhu, L. L., Betzler, F., Alsop, D., and Schlaug, G. (2010). Structural integrity of corticospinal motor fibers predicts motor impairment in chronic stroke. *Neurology* 74, 280–287.
- Liu, H., & Larson, C. R. (2007). Effects of perturbation magnitude and voice F0 level on the pitch-shift reflex *The Journal of the Acoustical Society of America*, 122(6), 3671–3677. doi:10.1121/1.2800254
- Loui, P., Alsop, D., & Schlaug, G. (2009). Tone Deafness: A New Disconnection Syndrome *The Journal of neuroscience : the official journal of the Society for Neuroscience*, 29(33), 10215–10220. doi:10.1523/JNEUROSCI.1701-09.2009
- Loui, P., Guenther, F. H., Mathys, C., & Schlaug, G. (2008). Action-perception mismatch in tone-deafness *Current biology : CB*, 18(8), R331–2. doi:10.1016/j.cub.2008.02.045
- Loui, P., Li, H. C., Hohmann, A., and Schlaug, G. (2011a). Enhanced cortical connectivity in absolute pitch musicians: a model for local hyperconnectivity. *J. Cogn. Neurosci.* 23, 1015–1026.
- Loui, P., Li, H. C., and Schlaug, G. (2011b). White matter integrity in right hemisphere predicts pitch related grammar learning. *Neuroimage* 55, 500–507.
- Maess, B., Koelsch, S., Gunter, T. C., and Friederici, A. D. (2001). Musical syntax is processed in Broca’s area: an MEG study. *Nat. Neurosci.* 4, 540–545.
- Makris, N., Kennedy, D. N., Mcinerney, S., Sorensen, A. G., Wang, R., Caviness, V. S. Jr., and Pandya, D. N. (2005). Segmentation of subcomponents within the superior longitudinal fascicle in humans: a quantitative, in vivo, DT-MRI study. *Cereb. Cortex* 15, 854–869.
- Makris, N., Worth, A. J., Sorensen, A. G., Papadimitriou, G. M., Wu, O., Reese, T. G., Wedeen, V. J.,

- Davis, T. L., Stakes, J. W., Caviness, V. S., Kaplan, E., Rosen, B. R., Pandya, D. N., and Kennedy, D. N. (1997). Morphometry of in vivo human white matter association pathways with diffusion-weighted magnetic resonance imaging. *Ann. Neurol.* 42, 951–962.
- Mandell, J., Schulze, K., & Schlaug, G. (2007). Congenital amusia: an auditory-motor feedback disorder *Restorative neurology and neuroscience*, 25(3-4), 323–334.
- Mars, R. B., Piekema, C., Coles, M. G. H., Hulstijn, W., & Toni, I. (2007). On the programming and reprogramming of actions *Cerebral Cortex*, 17(12), 2972–2979. doi:10.1093/cercor/bhm022
- McCarthy, R., & Warrington, E. K. (1984). A two-route model of speech production. Evidence from aphasia. *Brain : a journal of neurology*, 107 (Pt 2), 463–485.
- Moreno, S., Marques, C., Santos, A., Santos, M., Castro, S. L., and Besson, M. (2009). Musical training influences linguistic abilities in 8-year-old children: more evidence for brain plasticity. *Cereb. Cortex* 19, 712–723.
- Natke, U., Donath, T. M., & Kalveram, K. T. (2003). Control of voice fundamental frequency in speaking versus singing *The Journal of the Acoustical Society of America*, 113(3), 1587–1593.
- Norton, A., Zipse, L., Marchina, S., & Schlaug, G. (2009). Melodic intonation therapy: shared insights on how it is done and why it might help. *Annals of the New York Academy of Sciences*, 1169, 431–436. doi:10.1111/j.1749-6632.2009.04859.x
- Oechslin, M. S., Imfeld, A., Loenneker, T., Meyer, M., and Jancke, L. (2009). The plasticity of the superior longitudinal fasciculus as a function of musical expertise: a diffusion tensor imaging study. *Front. Hum. Neurosci.* 3:76. doi: 10.3389/neuro.09.076.2009
- Ozdemir, E., Norton, A., & Schlaug, G. (2006). Shared and distinct neural correlates of singing and speaking *NeuroImage*, 33(2), 628–635. doi:10.1016/j.neuroimage.2006.07.013
- Pantev, C., Oostenveld, R., Engelien, A., Ross, B., Roberts, L. E., and Hoke, M. (1998). Increased auditory cortical representation in musicians. *Nature* 392, 811–814.
- Patel, A. D., Peretz, I., Tramo, M., & Labreque, R. (1998). Processing prosodic and musical patterns: a neuropsychological investigation. *Brain and language*, 61(1), 123–144. doi:10.1006/brln.1997.1862
- Patterson, R. D., Uppenkamp, S., Johnsrude, I. S., & Griffiths, T. D. (2002). The processing of temporal pitch and melody information in auditory cortex *Neuron*, 36(4), 767–776.
- Penagos, H., Melcher, J. R., & Oxenham, A. J. (2004). A neural representation of pitch salience in nonprimary human auditory cortex revealed with functional magnetic resonance imaging *The Journal of neuroscience : the official journal of the Society for Neuroscience*, 24(30), 6810–6815. doi:10.1523/JNEUROSCI.0383-04.2004
- Peretz, I. (2001). Brain specialization for music. New evidence from congenital amusia. *Annals of the New York Academy of Sciences*, 930, 153–165.
- Peretz, I., Brattico, E., & Tervaniemi, M. (2005). Abnormal electrical brain responses to pitch in congenital amusia *Annals of Neurology*, 58(3), 478–482. doi:10.1002/ana.20606
- Peretz, I., Brattico, E., Jarvenpaa, M., & Tervaniemi, M. (2009). The amusic brain: in tune, out of key, and unaware. *Brain : a journal of neurology*, 132(5), 1277–1286. doi:10.1093/brain/awp055
- Peretz, I., Champod, A. S., & Hyde, K. (2003). Varieties of musical disorders. The Montreal Battery of Evaluation of Amusia *Annals of the New York Academy of Sciences*, 999, 58–75.
- Pickett, E., Pullara, O., O'Grady, J., & Gordon, B. (2009). Speech acquisition in older nonverbal individuals with autism: a review of features, methods, and prognosis *Cognitive and behavioral neurology : official journal of the Society for Behavioral and Cognitive Neurology*, 22(1), 1–21. doi:10.1097/WNN.0b013e318190d185
- Poeppl, D. (2003). The analysis of speech in different temporal integration windows: cerebral lateralization as “asymmetric sampling in time.” *Speech Communication*, 41(1), 245–255.

- doi:10.1016/S0167-6393(02)00107-3
- Poulet, J. F. A., & Hedwig, B. (2002). A corollary discharge maintains auditory sensitivity during sound production *Nature*, *418*(6900), 872–876. doi:10.1038/nature00919
- Price, C. J. (2000). The anatomy of language: contributions from functional neuroimaging. *Journal of anatomy*, *197 Pt 3*, 335–359.
- Purcell, D. W., & Munhall, K. G. (2006). Compensation following real-time manipulation of formants in isolated vowels *The Journal of the Acoustical Society of America*, *119*(4), 2288–2297.
- Ringo, J. L., Doty, R. W., Demeter, S., & Simard, P. Y. (1994). Time is of the essence: a conjecture that hemispheric specialization arises from interhemispheric conduction delay *Cerebral cortex (New York, NY : 1991)*, *4*(4), 331–343.
- Ross, D. A., Olson, I. R., and Gore, J. C. (2003). Cortical plasticity in an early blind musician: an fMRI study. *Magn. Reson. Imaging* *21*, 821–828.
- Schaechter, J. D., Fricker, Z. P., Perdue, K. L., Helmer, K. G., Vangel, M. G., Greve, D. N., and Makris, N. (2009). Microstructural status of ipsilesional and contralesional corticospinal tract correlates with motor skill in chronic stroke patients. *Hum. Brain Mapp.* *30*, 3461–3474.
- Schlaug, G. (2001). The brain of musicians. A model for functional and structural adaptation *Annals of the New York Academy of Sciences*, *930*, 281–299.
- Schlaug, G. (2005). Effects of Music Training on the Child's Brain and Cognitive Development. *Annals of the New York Academy of Sciences*, *1060*(1), 219–230. doi:10.1196/annals.1360.015
- Schlaug, G., Marchina, S., & Norton, A. (2008). From Singing to Speaking: Why Singing May Lead to Recovery of Expressive Language Function in Patients with Broca's Aphasia *Music perception*, *25*(4), 315–323. doi:10.1525/MP.2008.25.4.315
- Schlaug, G., Forgeard, M., Zhu, L., Norton, A., and Winner, E. (2009a). Training- induced neuroplasticity in young children. *Ann. N. Y. Acad. Sci.* *1169*, 205–208.
- Schlaug, G., Marchina, S., & Norton, A. (2009b). Evidence for Plasticity in White-Matter Tracts of Patients with Chronic Broca's Aphasia Undergoing Intense Intonation-based Speech Therapy. *Annals of the New York Academy of Sciences*, *1169*(1), 385–394. doi:10.1111/j.1749-6632.2009.04587.x
- Schulze, K., Gaab, N., & Schlaug, G. (2009). Perceiving pitch absolutely: comparing absolute and relative pitch possessors in a pitch memory task *BMC Neuroscience*, *10*, 106. doi:10.1186/1471-2202-10-106
- Schmithorst, V. J., & Wilke, M. (2002). Differences in white matter architecture between musicians and non-musicians: a diffusion tensor imaging study *Neuroscience letters*, *321*(1-2), 57–60.
- Seidler, R., Noll, D., & Thiers, G. (2004). Feedforward and feedback processes in motor control. *NeuroImage*, *22*(4), 1775–1783. doi:10.1016/j.neuroimage.2004.05.003
- Sherer, M. R., & Schreibman, L. (2005). Individual behavioral profiles and predictors of treatment effectiveness for children with autism *Journal of consulting and clinical psychology*, *73*(3), 525–538. doi:10.1037/0022-006X.73.3.525
- ShIPLEY, W. (1940). A self-administering scale for measuring intellectual impairment and deterioration. *The Journal of Psychology*.
- Siegel, G. M., & Pick, H. L. (1974). Auditory feedback in the regulation of voice *The Journal of the Acoustical Society of America*, *56*(5), 1618–1624.
- Smith, S. M. (2002). Fast robust auto- mated brain extraction. *Hum. Brain Mapp.* *17*, 143–155.
- Smith, S. M., Jenkinson, M., Woolrich, M. W., Beckmann, C. F., Behrens, T. E., Johansen-Berg, H., Bannister, P. R., De Luca, M., Drobnjak, I., Flitney, D. E., Niazy, R. K., Saunders, J., Vickers, J., Zhang, Y., De Stefano, N., Brady, J. M., and Matthews, P. M. (2004). Advances in functional and structural MR image analysis and implementa- tion as FSL. *Neuroimage* *23*(Suppl. 1), S208–

S219.

- Song, S. K., Sun, S. W., Ramsbottom, M. J., Chang, C., Russell, J., and Cross, A. H. (2002). Dysmyelination revealed through MRI as increased radial (but unchanged axial) diffusion of water. *Neuroimage* 17, 1429–1436.
- Steinmetz, H., & Seitz, R. J. (1991). Functional anatomy of language processing: neuroimaging and the problem of individual variability *Neuropsychologia*, 29(12), 1149–1161.
- Steinmetz, H., Volkman, J., Jäncke, L., & Freund, H. J. (1991). Anatomical left-right asymmetry of language-related temporal cortex is different in left- and right-handers *Annals of Neurology*, 29(3), 315–319. doi:10.1002/ana.410290314
- Stuart, A., Kalinowski, J., Rastatter, M. P., & Lynch, K. (2002). Effect of delayed auditory feedback on normal speakers at two speech rates *The Journal of the Acoustical Society of America*, 111(5 Pt 1), 2237–2241.
- Sundaram, S. K., Sivaswamy, L., Makki, M. I., Behen, M. E., and Chugani, H. T. (2008). Absence of arcuate fasciculus in children with global developmental delay of unknown etiology: a diffusion tensor imaging study. *J. Pediatr.* 152, 250–255.
- Tourville, J. A., Reilly, K. J., & Guenther, F. H. (2008). Neural mechanisms underlying auditory feedback control of speech. *NeuroImage*, 39(3), 1429–1443. doi:10.1016/j.neuroimage.2007.09.054
- Trainor, L. J., Desjardins, R. N., and Rockel, C. (1999). A comparison of contour and interval processing in musicians and non-musicians using event-related potentials. *Aust. J. Psychol.* 51, 147–153.
- Vernooij, M. W., Smits, M., Wielopolski, P. A., Houston, G. C., Krestin, G. P., and Van Der Lugt, A. (2007). Fiber density asymmetry of the arcuate fasciculus in relation to functional hemispheric language lateralization in both right- and left-handed healthy subjects: a combined fMRI and DTI study. *Neuroimage* 35, 1064–1076.
- Wan, C. Y., & Schlaug, G. (2010). Neural pathways for language in autism: the potential for music-based treatments *Future neurology*, 5(6), 797–805.
- Wan, C. Y., Bazen, L., Baars, R., Libenson, A., Zipse, L., Zuk, J., Norton, A., et al. (2011). Auditory-motor mapping training as an intervention to facilitate speech output in non-verbal children with autism: a proof of concept study *PLoS ONE*, 6(9), e25505. doi:10.1371/journal.pone.0025505
- Wan, C. Y., Rüber, T., Hohmann, A., & Schlaug, G. (2010a). The Therapeutic Effects of Singing in Neurological Disorders *Music perception*, 27(4), 287–295. doi:10.1525/mp.2010.27.4.287
- Wan, C. Y., Demaine, K., Zipse, L., and Schlaug, G. (2010b). From music making to speaking: engaging the mirror neuron system in autism. *Brain Res. Bull.* 82, 161–168.
- Warrington, E. K., Logue, V., & Pratt, R. T. (1971). The anatomical localisation of selective impairment of auditory verbal short-term memory. *Neuropsychologia*, 9(4), 377–387.
- Wheeler-Kingshott, C. A., and Cercignani, M. (2009). About “axial” and “radial” diffusivities. *Magn. Reson. Med.* 61, 1255–1260.
- Xu, Y., Larson, C. R., Bauer, J. J., & Hain, T. C. (2004). Compensation for pitch-shifted auditory feedback during the production of Mandarin tone sequences *The Journal of the Acoustical Society of America*, 116(2), 1168–1178.
- Xue, R., Van Zijl, P. C., Crain, B. J., Solaiyappan, M., and Mori, S. (1999). In vivo three-dimensional reconstruction of rat brain axonal projections by diffusion tensor imaging. *Magn. Reson. Med.* 42, 1123–1127.
- Zarate, J. M., & Zatorre, R. J. (2005). Neural substrates governing audiovocal integration for vocal pitch regulation in singing. *Annals of the New York Academy of Sciences*, 1060, 404–408.

doi:10.1196/annals.1360.058

Zarate, J. M., & Zatorre, R. J. (2008). Experience-dependent neural substrates involved in vocal pitch regulation during singing *NeuroImage*, *40*(4), 1871–1887.

doi:10.1016/j.neuroimage.2008.01.026

Zarate, J. M., Wood, S., & Zatorre, R. J. (2010). Neural networks involved in voluntary and involuntary vocal pitch regulation in experienced singers *Neuropsychologia*, *48*(2), 607–618.

doi:10.1016/j.neuropsychologia.2009.10.025

Zatorre, R. J., Chen, J. L., & Penhune, V. B. (2007). When the brain plays music: auditory-motor interactions in music perception and production. *Nature Reviews Neuroscience*, *8*(7), 547–558.

doi:10.1038/nrn2152

Zilles, K., Schlaug, G., Geyer, S., Luppino, G., Matelli, M., Qü, M., Schleicher, A., et al. (1996). Anatomy and transmitter receptors of the supplementary motor areas in the human and nonhuman primate brain *Advances in neurology*, *70*, 29–43.

APPENDIX

A.1: Individual subject data from Ch. 4

Below is a table of individual subject data from Chapter 4. Column headings are descriptive (The columns 'Perc_test' and 'Prod_test' are the listening and humming subsets of pitch-discrimination test (least distinguishable interval value in Hertz). Cond_ columns indicate the frequency ratio (produced / target), calculated in the 500ms stable window, for each condition, for each subject. Subjects 20-24 were enrolled as tonedeaf subjects, according to their MBEA / discrimination tests.

SUBJ.											
ID	Age	Gender	IQ	MBEA	Perc_test	Prod_test	Cond_-2ST	Cond_-1ST	Cond_NoPS	Cond_+1ST	Cond_+2ST
1	27	F	119	91.4	2.9	3.5	0.997663855	1.00351254	0.98504118	0.977966513	0.9776324
2	27	F	119	90.3	1.88	2	1.011574435	1.003694351	1.007038216	1.011876827	1.005686492
3	22	F	130	89.2	5.3	3.3	1.012486018	1.025820308	1.003144602	1.001205802	1.001763953
4	29	M	120	89.2	8.5	6.8	0.990160498	1.090535759	0.985912883	0.99331026	0.996145215
5	26	M	114	88.7	1.56	7.28	0.906779837	1.000782218	1.000440641	0.992974292	1.004401079
6	22	F	112	83.8	3.5	6.5	1.047671063	1.187361251	1.001443559	0.985389294	1.169187082
7	19	F	121	81.7	15	17	0.914409133	1.029613486	1.005888073	1.000162055	0.987698242
8	26	M	113	78.5	6	18	1.036964816	1.075268233	0.993408971	0.93466032	1.102824725
9	22	F	122	77.4	11.51	14.88	0.97915736	1.267078931	1.002623483	0.942451173	0.985272091
10	20	M	117	76.3	3.6	2.9	1.048284547	1.106550878	1.013475698	1.023842173	1.085384088
11	25	M	116	73.1	4.81	1.53	0.958599639	1.026401436	1.002037273	0.960126342	0.952081546
12	25	M	116	78.5	3.875	8.375	0.956830259	1.106325165	1.019011822	0.926222594	1.113026622
13	30	F	116	78	9	13	1.021805459	1.102914527	0.988287992	0.991639056	0.972018604
14	20	M	119	70	5.75	14.5	1.077976965	1.143760755	1.012258851	0.968418276	1.198067147
15	27	M	111	86	1.625	11	1.031328529	1.047979073	1.001634678	0.876802225	1.0572773
16	34	M	113	75	1.7	2.31	0.991626648	1.002197014	1.001039597	0.998106264	0.995077471
17	18	F	114	84.9	4.25	7.5	0.998922576	0.993591259	0.989843724	1.008117753	1.028102061
18	21	M	121	75	3.18	4.69	0.970031	0.976277976	1.001858479	0.882009361	0.977593539
19	20	F	128	90.3	10.5	2.6	1.005534853	1.00496103	1.005470622	1.003826036	0.990171419
20	26	F	121	72	37.08	42.1	0.991532994	1.008979037	0.990605316	0.989142613	0.997693448
21	20	F	111	64.5	44	42	1.003019329	1.010268255	1.006877114	1.006528727	1.004026367
22	37	M	115	64.5	7.75	45.16	0.839968428	0.839038381	0.888029663	0.808613706	0.81020951
23	21	M	115	77.4	41	34	0.865027127	0.826401436	0.838556558	0.815898191	0.85544351
24	37	F	124	85	25.5	64	1.016530831	1.012573692	1.01152079	1.00765832	1.002958153

A.2: Individual subject data from Ch. 3

A.2.1: Demographic and music practice data.

Subject #	Group	Gender	Age at scan	Instrument	Years Practice
1	1	F	33	Piano	15
2	1	M	19	Cello	15
3	1	M	31	Violin	26
4	1	F	23	Piano	12
5	1	F	24	Violin	8
6	1	M	15	Violin	8
7	1	F	26	Violin	6
8	1	F	32	Piano	26
9	1	F	32	Piano	8
10	1	M	43	Trombone	28
11	1	M	27	Trombone	15
1	2	M	32	Voice	14
2	2	F	26	Voice	14
3	2	F	22	Voice	12
4	2	F	26	Voice	11
5	2	F	25	Voice	13
6	2	F	25	Voice	7
7	2	F	22	Voice	22
8	2	F	25	Voice	22
9	2	M	24	Voice	12
10	2	M	25	Voice	22
11	2	F	27	Voice	16
1	3	M	25		n/a
2	3	M	31		n/a
3	3	M	24		n/a
4	3	F	19		n/a
5	3	M	22		n/a
6	3	F	24		n/a
7	3	M	20		n/a
8	3	F	27		n/a
9	3	F	28		n/a
10	3	F	55		n/a
11	3	F	27		n/a

A.2.2: Mean intensity from tractographic measurements.

Subject #	Grp	ISTG<->IIFG	IMTG<->IIFG	rSTG<->rIFG	rMTG<->rIFG
1	1	132.925343	43.900752	16.123855	62.218335
2	1	31.716857	24.590102	96.308025	68.91255
3	1	43.707057	53.290403	5.795057	62.05708
4	1	70.098525	35.740741	11.518329	91.801956
5	1	93.721532	31.639522	15.421013	91.338666
6	1	23.381316	18.648132	1.996374	68.789538
7	1	51.018973	38.246594	4.912539	8.006152
8	1	13.653371	15.918728	2.258199	1.704583
9	1	29.493464	127.201848	15.141409	4.596244
10	1	17.872008	20.129604	2.7116	8.516909
11	1	79.859563	6.87564	7.020243	1.491176
1	2	163.16009	332.651273	1.965239	1.841036
2	2	119.625352	42.779713	2.714286	30.901914
3	2	135.090993	144.794323	20.88092	63.880998
4	2	17.849853	55.317887	7.519892	4.823684
5	2	79.775401	1.660944	1.894149	5.425997
6	2	91.32978	45.115804	8.371067	147.218849
7	2	23.911714	15.419182	5.392029	13.139359
8	2	76.945258	121.150564	20.915104	99.326189
9	2	8.468336	14.94696	1.620785	2.375
10	2	96.298364	10.711661	19.855854	78.838327
11	2	306.284759	207.085339	92.778387	63.212722
1	3	103.404968	79.325435	10.579813	19.842473
2	3	98.156239	244.718996	15.347266	57.552607
3	3	140.528629	87.449429	17.755955	17.599228
4	3	51.105858	110.335367	3.382424	7.585889
5	3	64.359411	36.34273	3.857368	19.540615
6	3	24.70243	67.802216	4.419045	17.666005
7	3	47.342355	38.06142	1.732545	6.119707
8	3	3.206043	1.623131	14.597739	3.756991
9	3	107.726317	200.246237	33.84255	9.88987
10	3	40.132001	140.445973	1.683072	5.153459
11	3	4.699982	39.964082	66.921272	83.604399

A.2.3: Mean FA from tractographic measurements.

Subject #	Grp	ISTG<->IIFG	IMTG<->IIFG	rSTG<->rIFG	rMTG<->rIFG
1	1	0.358232	0.384658	0.393565	0.377389
2	1	0.36616	0.385492	0.353599	0.361448
3	1	0.409093	0.414672	0.421134	0.386564
4	1	0.385117	0.39591	0.346548	0.337092
5	1	0.333497	0.36187	0.366018	0.370699
6	1	0.360032	0.368298	0.403188	0.360795
7	1	0.393741	0.426582	0.359142	0.391265
8	1	0.404333	0.383732	0.421148	0.464585
9	1	0.385729	0.385645	0.37229	0.387924
10	1	0.376319	0.419411	0.386925	0.404292
11	1	0.406714	0.463809	0.369844	0.410647
1	2	0.361846	0.377426	0.385058	0.412819
2	2	0.325496	0.357878	0.368645	0.373064
3	2	0.323934	0.337134	0.356238	0.362356
4	2	0.360962	0.369252	0.368665	0.436871
5	2	0.350514	0.400179	0.374152	0.39298
6	2	0.341545	0.381175	0.373521	0.367187
7	2	0.37747	0.413705	0.348444	0.366493
8	2	0.360192	0.361224	0.353812	0.355566
9	2	0.35774	0.376603	0.388474	0.407164
10	2	0.421852	0.455075	0.414044	0.413888
11	2	0.339304	0.346793	0.319297	0.390747
1	3	0.362855	0.38106	0.377021	0.395479
2	3	0.370118	0.378575	0.347237	0.361415
3	3	0.344799	0.376402	0.391875	0.400461
4	3	0.325959	0.344972	0.383391	0.375352
5	3	0.380593	0.395703	0.408939	0.390286
6	3	0.352332	0.363701	0.37083	0.372063
7	3	0.322244	0.348952	0.382685	0.382509
8	3	0.316195	0.375864	0.353939	0.388271
9	3	0.347438	0.360792	0.364204	0.385115
10	3	0.321056	0.327129	0.365926	0.364848
11	3	0.353912	0.356752	0.336425	0.342549

A.2.4: Mean Volume from tractographic measurements.

Subject #	Grp	ISTG<->IFG	IMTG<->IFG	rSTG<->rIFG	rMTG<->rIFG
1	1	7988.901367	7598.140137	5239.860352	8425.366211
2	1	9014.936523	8496.206055	11617.72754	12490.65625
3	1	4922.223633	5500.367676	2218.885498	6245.328125
4	1	4337.230469	4072.1521	5797.446289	8411.667969
5	1	8649.311523	4209.255371	3066.677979	11855.38379
6	1	5381.547852	5137.035645	3151.233154	3756.800293
7	1	6142.505371	10063.83691	13978.31348	6686.373047
8	1	5728.887695	9700.489258	3832.20752	5484.375977
9	1	4195.544434	4698.27832	4282.380371	2920.427979
10	1	4392.067871	4901.657227	10696.81055	8784.135742
11	1	5125.609863	3123.811279	4515.472656	3107.815186
1	2	13260.77344	12568.37012	3681.389893	4499.476562
2	2	5678.618164	5249.008301	2255.451172	2865.588379
3	2	12380.98731	16021.24414	4970.219238	5952.837402
4	2	6985.71875	14449.03418	3388.884766	6946.871094
5	2	4273.246094	3727.093018	4296.097656	5326.704102
6	2	12860.86133	11306.95508	5591.77832	10086.68164
7	2	6652.09082	8553.34082	10836.21289	9051.504883
8	2	12022.2002	14995.18652	10847.62988	20470.41797
9	2	14145.1084	5600.914551	3320.330078	2924.998291
10	2	7819.800293	6094.508301	10130.0918	8466.499023
11	2	8546.479492	11487.47363	2918.142822	2191.463623
1	3	10240.00781	11284.09473	4409.206543	8011.181641
2	3	7934.640625	10222.08398	3416.882813	5489.521485
3	3	6824.615235	7602.710449	3813.352295	6212.193848
4	3	5909.419434	6367.593262	3068.39624	2105.202149
5	3	5909.419434	6367.593262	3068.39624	2105.202149
6	3	4137.275879	6909.170899	2561.660645	4026.445801
7	3	3545.994385	3869.344238	1014.610291	1794.420532
8	3	2514.814453	2178.325195	7882.074707	3227.783203
9	3	3968.171387	4630.866211	2975.271729	2910.144776
10	3	4946.789063	7391.333496	766.0982055	1362.52356
11	3	3092.387695	11006.45508	5210.15625	8232.84668

A.2.5: Mean λ 1 from tractographic measurements.

Subject #	Grp	ISTG<->IIFG	IMTG<->IIFG	rSTG<->rIFG	rMTG<->rIFG
1	1	0.001103	0.001083	0.001072	0.001075
2	1	0.00105	0.00106	0.001042	0.00105
3	1	0.001101	0.001087	0.001004	0.001065
4	1	0.001077	0.001088	0.001015	0.001011
5	1	0.000983	0.001019	0.000961	0.001005
6	1	0.001056	0.001053	0.001041	0.001072
7	1	0.000985	0.001003	0.001019	0.001025
8	1	0.001036	0.001031	0.001094	0.00112
9	1	0.001135	0.001144	0.001047	0.001069
10	1	0.000954	0.001017	0.001004	0.001024
11	1	0.00104	0.001071	0.001003	0.00106
1	2	0.001102	0.001091	0.001012	0.00107
2	2	0.001072	0.001074	0.001031	0.001081
3	2	0.001033	0.001068	0.001002	0.001039
4	2	0.001083	0.001124	0.001001	0.001062
5	2	0.001046	0.001044	0.001022	0.001018
6	2	0.001084	0.001064	0.001068	0.001101
7	2	0.001078	0.001087	0.001037	0.00105
8	2	0.001071	0.00109	0.001074	0.001107
9	2	0.001042	0.001043	0.001032	0.001027
10	2	0.001031	0.001019	0.001012	0.001021
11	2	0.001079	0.001066	0.001097	0.001113
1	3	0.001048	0.001045	0.001033	0.001034
2	3	0.001071	0.001108	0.00104	0.001089
3	3	0.001031	0.00102	0.001031	0.001032
4	3	0.000969	0.000987	0.001001	0.001008
5	3	0.00102	0.001024	0.000983	0.001018
6	3	0.001025	0.001054	0.00107	0.001062
7	3	0.001018	0.001023	0.000963	0.001008
8	3	0.001179	0.001204	0.001191	0.001205
9	3	0.001042	0.001031	0.000985	0.001003
10	3	0.001042	0.001059	0.001012	0.001033
11	3	0.001142	0.001213	0.001161	0.001184

A.2.6: Mean λ_2 from tractographic measurements.

Subject #	Grp	ISTG<->IIFG	IMTG<->IIFG	rSTG<->rIFG	rMTG<->rIFG
1	1	0.000774	0.000722	0.00071	0.000717
2	1	0.000738	0.000715	0.000747	0.000735
3	1	0.00076	0.00072	0.00065	0.000713
4	1	0.000741	0.000721	0.000702	0.00072
5	1	0.000696	0.000695	0.000667	0.000674
6	1	0.000746	0.000727	0.000687	0.000722
7	1	0.000689	0.000648	0.000688	0.000675
8	1	0.000695	0.000695	0.000694	0.000631
9	1	0.000785	0.000806	0.000751	0.000714
10	1	0.000667	0.000657	0.000679	0.000677
11	1	0.000694	0.000628	0.000683	0.000671
1	2	0.000794	0.000756	0.000673	0.000669
2	2	0.000784	0.00075	0.000714	0.000726
3	2	0.000772	0.00077	0.000708	0.000722
4	2	0.00078	0.00077	0.000705	0.000663
5	2	0.000742	0.000665	0.000689	0.000661
6	2	0.000776	0.000713	0.000745	0.000768
7	2	0.000764	0.000716	0.000735	0.000725
8	2	0.000763	0.000761	0.000759	0.000767
9	2	0.00072	0.000699	0.000691	0.000657
10	2	0.000678	0.000624	0.000655	0.000661
11	2	0.000776	0.000754	0.000812	0.000713
1	3	0.000722	0.000702	0.000698	0.000678
2	3	0.000726	0.000731	0.000733	0.000745
3	3	0.000727	0.000688	0.00069	0.00068
4	3	0.000709	0.000693	0.000662	0.000669
5	3	0.000667	0.000658	0.000652	0.000679
6	3	0.000717	0.000716	0.000728	0.000717
7	3	0.00074	0.000716	0.00065	0.000677
8	3	0.000851	0.000798	0.000817	0.00078
9	3	0.000746	0.000715	0.000707	0.00068
10	3	0.000759	0.000757	0.000729	0.000738
11	3	0.000791	0.000815	0.000828	0.000829

A.2.7: Mean λ_3 from tractographic measurements.

Subject #	Grp	ISTG<->IIFG	IMTG<->IIFG	rSTG<->rIFG	rMTG<->rIFG
1	1	0.000577	0.000534	0.000508	0.000537
2	1	0.000514	0.000496	0.00053	0.000526
3	1	0.00051	0.000499	0.000428	0.000511
4	1	0.00051	0.0005	0.000512	0.000523
5	1	0.0005	0.0004	0.0004	0.000473
6	1	0.000521	0.000508	0.000465	0.000547
7	1	0.000454	0.000422	0.000509	0.000471
8	1	0.000474	0.000496	0.000487	0.000439
9	1	0.000558	0.000567	0.00051	0.000493
10	1	0.000446	0.000434	0.000463	0.000454
11	1	0.000466	0.000412	0.000483	0.000466
1	2	0.000576	0.00055	0.000464	0.000468
2	2	0.000583	0.000537	0.000503	0.00054
3	2	0.00058	0.000586	0.000507	0.000525
4	2	0.000561	0.000575	0.000475	0.000427
5	2	0.000539	0.000475	0.000482	0.000456
6	2	0.000581	0.000515	0.000536	0.000576
7	2	0.00052	0.000481	0.000524	0.000509
8	2	0.00054	0.000552	0.000545	0.000566
9	2	0.000522	0.000499	0.00048	0.000452
10	2	0.000456	0.000406	0.000444	0.000453
11	2	0.000583	0.000563	0.00062	0.000548
1	3	0.000527	0.000498	0.000497	0.000474
2	3	0.000528	0.000548	0.000539	0.000554
3	3	0.000537	0.000487	0.000469	0.000461
4	3	0.000516	0.000505	0.000466	0.000484
5	3	0.000487	0.000469	0.000421	0.000471
6	3	0.000513	0.000519	0.000521	0.000512
7	3	0.000564	0.000534	0.000449	0.00048
8	3	0.000646	0.000576	0.000603	0.000559
9	3	0.000555	0.000529	0.00049	0.000473
10	3	0.000577	0.00058	0.000495	0.000513
11	3	0.000566	0.000612	0.00061	0.000619

A.2.8: Mean radial diffusivity from tractographic measurements.

Subject #	Grp	ISTG<->IIFG	IMTG<->IIFG	rSTG<->rIFG	rMTG<->rIFG
1	1	1.632864545	1.724522293	1.760262726	1.714513557
2	1	1.677316294	1.750619323	1.631949883	1.665344964
3	1	1.733858268	1.78342904	1.86270872	1.740196078
4	1	1.721822542	1.782145782	1.672158155	1.626709574
5	1	1.643812709	1.861187215	1.80131209	1.752397559
6	1	1.666929755	1.705263158	1.807291667	1.689519307
7	1	1.723534558	1.874766355	1.702589808	1.788830716
8	1	1.77245509	1.73131822	1.852667231	2.093457944
9	1	1.690245719	1.666423889	1.660586836	1.771333886
10	1	1.714285714	1.864344638	1.758318739	1.810786914
11	1	1.793103448	2.059615385	1.720411664	1.864555849
1	2	1.608759124	1.670750383	1.780123131	1.882145998
2	2	1.568397952	1.668997669	1.69433032	1.707740916
3	2	1.528106509	1.575221239	1.649382716	1.666399358
4	2	1.615212528	1.671375465	1.696610169	1.948623853
5	2	1.633099141	1.831578947	1.745516652	1.822739481
6	2	1.597641857	1.732899023	1.667447307	1.638392857
7	2	1.679127726	1.816207185	1.647339158	1.70178282
8	2	1.643898695	1.660319878	1.647239264	1.660915229
9	2	1.677938808	1.741235392	1.762596072	1.852119026
10	2	1.818342152	1.978640777	1.841674249	1.833034111
11	2	1.587932303	1.618830676	1.532122905	1.765265662
1	3	1.678142514	1.741666667	1.728870293	1.795138889
2	3	1.708133971	1.732603597	1.635220126	1.676674365
3	3	1.631329114	1.736170213	1.779119931	1.808939527
4	3	1.582040816	1.647746244	1.774822695	1.74848222
5	3	1.767764298	1.817213842	1.832246039	1.770434783
6	3	1.666666667	1.706882591	1.713370697	1.728234337
7	3	1.561349693	1.6368	1.752502275	1.742437338
8	3	1.575150301	1.752547307	1.677464789	1.799850635
9	3	1.601844735	1.65755627	1.645781119	1.739809193
10	3	1.55988024	1.584143605	1.653594771	1.651478817
11	3	1.683124539	1.700070077	1.614742698	1.635359116

A.3: Permissions

The author hereby declares that all figures in chapters 1 and 2 were adapted from the original publications (reference detailed in figure caption) and reproduced with written permission from the following publishers:

American Institute of Physics

John Wiley & Sons

Elsevier

W.H. Freeman & Company/Worth Publishers

Society for Neuroscience