PERIPHERAL AND CENTRAL AUDITORY PROCESSING IN PEOPLE WITH ABSOLUTE PITCH

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GENERAL ABSTRACT

Absolute pitch (AP) is a rare ability that is defined by being able to name musical pitches without a reference standard. This ability has been of interest to researchers studying music cognition and the processing of pitch information because it is very rarely expressed and raises questions about developmental interactions between biological predispositions and musical training. This dissertation focuses mainly on the peripheral and central neural substrates and is divided into seven chapters.

The first chapter reviews the anatomy, function, and frequency resolution of the auditory peripheral and central nervous system. It includes background information pertaining to the origins of AP and describes inconsistencies reported throughout a number of studies that characterize AP emergence. Chapter two details a series of peripheral experiments on twenty AP and thirty-three control subjects recruited for testing at two locations. The goal was to test whether frequency resolution differences could be resolved at the level of the cochlea within both groups as a potential correlate for the genesis of AP.

Chapter three details two behavioural tests that were administered to assess the smallest frequency difference that AP musicians could resolve and to test how well they could detect melodic mistuning excerpts compared to non-AP musicians and controls without musical experience. Both AP musicians and non-AP musicians did significantly better in both tests compared to non-musicians. However, there were no differences between the AP and non-AP musician groups. Chapter four details a functional MRI study that measured frequency tuning in the cortex using a population receptive field (pRF) model that estimates preferred frequency bandwidth in each voxel. This method was also tested in auditory subcortical nuclei such as the inferior colliculus and medial geniculate nucleus.

Chapter five reports the neuro-anatomical correlates of musicianship and AP using structural MRI. Here we investigated cortical thickness and volume differences among the three groups and found a number of regions differed significantly. Cortical thickness was significantly greater in the left Heschl's gyrus (an area that acts as a central hub for auditory processing) in AP musicians compared to non-AP musicians and non-musicians. AP and non-AP musicians also exhibited increased cortical thickness and volume throughout their cortex and subcortex. In line

with previous studies, AP musicians showed decreased cortical thickness and volume in frontal regions such as the pars opercularis part of the inferior frontal gyrus.

Chapter six reports the neuro-anatomical correlates of musicianship and AP using diffusion tensor imaging (DTI) to measure connectivity and white matter structural integrity in regions associated with audition and language processing. Tracts connecting language processing regions were reduced in volume in AP musicians compared to their non-AP counterparts. Chapter seven includes the general discussion, which integrates the findings and results from the five experiments. Our findings indicate that the sharpness of frequency tuning did not differ in either peripheral or central auditory processing stages among AP and non-AP groups. This implies that AP possessors do not encode or represent auditory frequency any differently than other groups, from the periphery through auditory cortex; instead, the neural substrate of their abilities must lie elsewhere. The automatic and working memory independent categorization abilities in AP may reflect more refined efficiency in local but not global functional connectivity.

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LIST OF ABBREVIATIONS

A1	Primary auditory cortex
AFNI	Analysis of Functional NeuroImages
AF	Arcuate fasciculus
AG	Angular gyrus
ANOVA	Analysis of variance
AP	Absolute pitch
APE	Ability to perceptually encode
BA	Brodmann area
BW	Bandwidth
CF	Center frequency
CI	Confidence interval
CIS	Circular insular sulcus
CNS	Central nervous system
CON	Non-musicians
CS	Circular sulcus
CT	Cortical thickness
DTI	Diffusion tensor imaging
ERB	Equivalent rectangular bandwidth
EPI	Echo-planar imaging
FOV	Field of view
FA	Fractional anisotropy
fMRI	Functional magnetic resonance imaging
GM	Gray matter
GRAPPA	Generalized autocalibrating partial parallel acquisition
HG	Heschl's gyrus
HRF	Hemodynamic response function
IC	Inferior colliculus
IFOG	Inferior frontal opercular gyrus
IHC	Inner hair cell
JND	Just noticeable difference
Lp	Probe level
MEG	Magnetoencephalography
MGN	Medial geniculate nucleus
MOCS	Medial olivocochlear system
MPRAGE	Magnetization prepared rapid acquisition gradient echo
MRI	Magnetic resonance imaging
MTG	Middle temporal gyrus
MUS	Non-AP musicians
N_{SFOAE}	Stimulus frequency period delay

OAE	Otoacoustic emission
OHC	Outer hair cell
PAC	Primary auditory cortex
PC	Pericallosal sulcus
PD	Proton density
PNS	Peripheral nervous system
PP	Planum polare
pRF	Population receptive field
PT	Planum temporale
PS	Precentral sulcus
R	Rostral
ROI	Region of interest
RT	Rostral temporal
SCG	Subcallosal cingulate gyrus
SFOAE	Stimulus frequency otoacoustic emission
SOAE	Spontaneous otoacoustic emission
SLF	Superior longitudinal fasciculus
SUMA	Surface mapping with AFNI
SPSS	Statistical Package for the Social Science
SS	Suborbital sulcus
STG	Superior temporal gyrus
STS	Superior temporal sulcus
TBSS	Tract based spatial statistics
TE	Echo time
TR	Repetition time
VBM	Voxel based morphometry
VPA	Valproate
WHEPI	Whole head echo-planar image

Chapter 1

1.1 General Introduction

Absolute pitch (AP), also referred to as perfect pitch, characterizes the ability to identify or recreate a given note or collection of notes in the absence of a reference note (Ward, 1999; Deutsch, 2013). It is not simply a better ability to hear, but the ability to mentally class sounds into remembered categories. There is still debate as to whether AP is genetic or a learned ability that is linked to one's exposure to music during critical period of development. The prevalence of AP is relatively rare, with estimates of less than 1 in 10,000 reported (Bachem, 1955; Profita & Bidder, 1988; Deutsch, 2013), affecting both genders equally (Deutch et al., 2005). Additionally, higher rates of AP ability have been reported in students at music conservatories (Gregersen et al., 1999). Nonetheless, AP ability remains difficult to acquire even among expert musicians who have had the same amount of musical training, i.e., spending tens of thousands of hours practicing and reading scores (Deutsch & Dooley, 2009). Reported prevalence rates among expert musicians differed between cultures with estimates between 1–20% found in Western musicians (Vitouch, 2003) and close to 50% in musicians from Japan (Miyazaki, 1988; Gregerson et al., 1999). An explanation for this deviation stems from the Suzuki method used in Japan that trains musicians to play by ear rather than relying on sight-reading scores. In this way, this former method heavily relies on auditory feature learning that may play a role in AP development.

Since AP ability is found in only a subset of musicians, examples of noted musicians who had AP are Mozart, Bach and Beethoven, whereas Wagner and Schumann lacked AP ability (Sacks, 2007). The mechanisms underlying AP are not well understood. It is worth noting that although this ability is rare, one might wonder why being able to label a pitch without a reference tone is not universal, akin to being able to automatically label a colour one perceives. Five experiments have been outlined in this dissertation that investigate how AP ability emerges with the prospect of understanding its underlying mechanism.

The first experiment examined whether there was evidence for a peripheral (i.e., cochlear) basis of AP based upon otoacoustic emissions (OAEs, which are low-level sounds emitted by the cochlea that provide information on inner ear health). The chief motivations were that both AP and spontaneous otoacoustic emissions (SOAEs) appear to have genetic components and anecdotal

observations of prevalence in certain populations, for example, a relatively higher incidence of both in Asians (Deutch et al., 2005; Gregerson et al., 2001).

The second experiment looked at behavioural differences in AP musicians, non-AP musicians, and control groups without musical training. The idea behind using a non-AP musician group was to control for differences that may have been associated with musical training. In this way we were able to tease apart AP ability on its own. The smallest frequency difference, or just noticeable difference (JND) thresholds were determined at two different test frequencies to discern which group fared better. Melody mistuning tasks were administered that tested how well each group detected slight differences in timbre, duration, and tempo of musical excerpts that were held in working memory. This was motivated by research that found that AP possessors had an enhanced auditory digit span as compared to matched non-AP musicians, signifying that auditory working memory may be involved in AP emergence (Deutsch & Dooley, 2013).

The purpose of the third experiment was to find evidence of a central basis for AP by using functional magnetic resonance imaging (fMRI). Looking for differences in the tonotopic map would be one approach to finding if neural markers distinguishing the AP musician group compared to the non-AP musician and control groups exist. We established a tonotopic mapping protocol of the auditory cortex. Participants were subjected to an auditory stimulus consisting of pure tone logarithmic sweeps modified from DeMartino et al. (2013) and the data were analyzed using an adaptation of the population receptive field (pRF) technique developed by Dumoulin and Wandell. (2008) used initially for retinotopic mapping. The pRF approach was used to estimate different neuronal population quantities such as sound frequencies in the auditory cortex. Our model treated the pRF underlying each voxel's response as a one-dimensional Gaussian function of frequency. This technique provided an estimated sensitivity function for each voxel with a given center, or preferred frequency, and standard deviation, or tuning bandwidth. The fundamental question of how the auditory cortex is organized in AP musicians, non-AP musicians and non-musicians with different pitch discrimination abilities would help reveal differences in auditory processing abilities. This work was motivated in conjunction with the behavioural JND experiment that tested if frequency discrimination was enhanced in AP possessors. One could then predict sharper frequency tuning in AP musicians to better explain their enhanced pitch categorization ability.

This brings us to the fourth experiment that looked at cortical thickness and volume differences globally to find evidence of a central basis for AP using structural MRI. Previous studies have reported inconsistent findings based on structural differences found in AP possessors. However, the general consensus seems to suggest that cortical auditory and frontal regions are implicated in its development. We had used a larger sample size compared to previous studies and predict to find similar regions affected that are associated with AP emergence. Lastly, the fifth experiment measured the connectivity of the arcuate fasciculus (AF) that connects Wernicke's area located in the posterior section of the superior temporal gyrus (STG) of the temporal cortex, known for its role in language comprehension (Wernicke, 1875;1995) to Broca's area located in the frontal lobe, known for its role in language processing and music perception (Brown et al., 2006; Fadiga et al., 2009) using diffusion tensor imaging (DTI). The AF has not been directly studied in AP. However, a previous study found enhanced connectivity within the STG and middle temporal gyrus (MTG) of the temporal cortex in AP musicians compared to non-AP musicians using DTI (Loui et al., 2011). In contrast, another study found that the superior longitudinal fasciculus (SLF) that is comprised of the AF showed reduced white matter tract integrity (Oechslin et al., 2010a). This motivated us to look at the AF in AP since the STG is associated with one of the regions it connects with. Likewise, the AF has been looked at in congenital amusia (tone-deafness) with inconsistent findings that report it being significantly decreased in congenital amusic participants (Loui & Schlaug, 2009), whereas another study found no differences between amusics and controls (Chen et al., 2015).

Overall, the findings of all these experiments provide information that fill the gaps in current literature on the manifestation of AP ability and help tie in commonalities and discrepancies from previous studies. AP possessors are known for their enhancements in pitch categorization and perception ability that is rare in the population. In order to be able to isolate AP ability, matched musicians and controls without musical ability need to be included for testing. To understand how the human auditory system develops, we cannot do manipulative experiments, and instead rely on populations with altered ability and development. It is by studying rare populations such as AP that provides insight to the genetics and categorization of auditory processing that would add to the body of knowledge on how the normal auditory system develops and matures. Being able to detect if any subtle behavioural, peripheral, or central differences exist can be beneficial in providing a behavioural and neural marker for AP emergence and in turn may

correlate with auditory processing deficits such as amusia.

1.2 Hypotheses

We initially wanted to test if there were any peripheral differences in acoustic processing in AP possessors. There have not been any previous reports that looked at cochlear functioning via OAE measurements in AP musicians, with only inconsistent findings in non-AP musicians. For example, previous studies that looked at the medial olivocochlear system (MOCS), (a peripheral efferent neural pathway projecting from the brainstem to both cochlea) in musicians found variable results. The MOC system is thought to be modulated centrally via the descending auditory pathway as well as modulate downstream cochlear functions. It is normally measured noninvasively by the suppression of OAEs using contralateral noise (Perrot & Collet, 2014). It was previously reported that MOC activity was significantly enhanced bilaterally in musicians compared to non-musicians (Perrot et al., 1999) suggesting that musicians may have enhanced auditory selective attention, improved hearing in noise, and better protection against acoustic trauma (Perrot & Collet, 2014). However, other studies did not find significant MOC enhancements in musicians (Brashears et al., 2003; Stuart & Daughtrey, 2016) suggesting auditory processing and MOCs is similar between different levels of musicianship. Furthermore, since AP possessors and SOAEs have been linked to a higher prevalence in certain populations, and audiometric thresholds are typically lower at the frequencies SOAEs are found, we predicted to see an increase in the number of SOAEs in AP. We also measured stimulus-frequency emissions (SFOAE), which are sound delays emitted from the ear in response to an auditory stimulus. SFOAEs act as a proxy measure of peripheral frequency selectivity of the ear and we predict that AP possessors have longer delays, suggesting sharper frequency tuning of the auditory filters. If significant differences are not observed, this may then suggest that frequency selectivity does not occur at the level of the cochlea in AP and may then amplify as auditory information is processed centrally.

We then wanted to measure the smallest frequency difference that AP possessors could detect compared to non-AP musicians and non-musicians behaviourally. There has been only one previous study that looked at JND thresholds in AP that reported differences between musicians and non-musicians and no difference between AP and non-AP musician groups (Fujisaki & Makio, 2002). We wanted to replicate this study using our large data set since Fujisaki et al. (2002) did not

indicate sample size as well as a number of other factors in their study. We therefore predict that JND thresholds would be smaller in musicians compared to non-musicians, whereas AP musicians may have lower thresholds overall that may or may not be significantly different compared to non-AP musicians.

Next, we wanted to find novel evidence for a central basis of AP by using the pRF model for our fMRI experiment. We hypothesize that AP possessors have more sharply tuned pRFs that may indicate a role of the ascending pathway for its underlying mechanism. However, if differences are not found in frequency discrimination nor the degree of tuning, then perhaps AP is a more salient cognitive manifestation, and its underlying mechanism can be explained via different measures, for example differences in connectivity or neuroanatomical variations. Furthermore, this may mean that AP and control groups have the essential neural circuitry to process fine-grained pitch differences, and brain enhancements in AP might therefore lie in the fronto-temporal networks involving auditory and inferior frontal cortices. This brings us to the next central experiment which sought to determine if structural similarities and differences in cortical thickness and volume are evident in AP. There have been a number of inconsistencies reported on the neuroanatomy in AP. However, based on the general consensus we hypothesize that AP possessors have enhanced structural differences in a number of regions including auditory structures such as Heschl's Gyrus (HG) and planum temporale (PT), and decreased cortical thickness in frontal regions. Furthermore, we looked at the AF, a structure that has been implicated in tone deafness with the hypothesis that connectivity within this structure may be altered in AP. Based on previous findings, we predict that we will find either enhancements in feed-forward connections to the frontal cortex, or instead will find reduced white matter tract integrity as observed with the STG finding that Oechslin et al. (2010a) reported.

1.3 Anatomy and Function of the Auditory Peripheral Nervous System (PNS)

In human hearing, the ear is responsible for the perception of sound by converting air pressure fluctuations (compression and rarefaction of a gas) to electrical impulses that travel through the auditory nerve to the brain. The ear can be separated into three sections (outer, middle, and inner) for the process of hearing. As sound waves propagate through air, they enter through the outer ear comprised of the pinna (skin-covered cartilaginous flap) and pass through the external auditory meatus (external ear canal) traveling to the tympanic membrane (eardrum). The sound

waves cause the tympanic membrane to vibrate causing the air-filled cavity of the middle ear ossicles (three tiny bones malleus, incus and stapes) to vibrate, amplifying the sound. The ossicles link the tympanic membrane to the oval window of the cochlea and are responsible for acoustic impedance matching since the incoming sound waves propagate through air and need to be transferred to fluid within the cochlea of the inner ear. Since fluid is heavier and harder to vibrate than air, in order to hear sound, the middle ear mechanically amplifies the sound so that sound energy is sufficient when it is carried into cochlear fluids (Hamill & Price, 2014). Air pressure is equalized within the middle ear by the Eustachian tube that links the middle ear to the uppermost part of the throat.

Within the inner ear lies the cochlea, a fluid filled snail shaped organ responsible for the conversion of mechanical pressure waves into electrical signals. The movement of sound waves causes pressure imbalances in the cochlea, specifically in the scala tympani and scala vestibule. As the stapes vibrates in the oval window, the cochlear fluids in the inner ear move, and it is this motion that permits hearing. Since the fluids in the cochlea cannot be compressed, when the stapes footplate moves inward towards the inner ear, there will be a corresponding outward movement of the round window to allow for pressure relief, conversely when the stapes footplate moves outward toward the middle ear, the round window moves inwards. This inwards and outwards motion of the stapes footplate occurs at the same rate as the sound wave's frequency, for example a 2000 Hz tone would create the stapes footplate to move in and out 2000 times per second (Hamill & Price, 2014).

Inside the cochlea, the movement of fluid creates ripples on the Reisner's and the basilar membrane that cause deformations of the organ of Corti leading to the back and forth movement of the tectorial membrane. This movement is sensed by inner hair cells (IHCs) that have hair like projections (stereocilia) attached to the basilar membrane on the bottom and tectorial membrane on the top, while its nucleus lies centrally within the cell. As the basilar membrane vibrates, a shearing force is created causing the stereocilia to bend back and forth thereby converting the membrane movement into electrical signals that travel to the auditory nerve which connects to the brain for interpretation.

Outer hair cells (OHCs) differ in that they have stereocilia at the top of the cell, and a nucleus at the bottom and become stimulated by the auditory nerve causing the hair like projections to change in length with every sound wave. Their role is to change the compliance of certain sections of the tectorial membranes and by doing this some sound frequencies are amplified and some are attenuated. This allows us to hear quiet sounds that for example are used when trying to listen to a conversation or some sound of interest in a noisy environment, and is known as cochlear filter sharpening (Evans, 1975; Hamill & Price, 2014). Within each human cochlea, there are approximately 3,500 IHCs that are considered to be the primary sensory hair cells of the cochlea and are innervated by dendrites of the auditory nerve. There are more OHCs within each cochlea, approximately 11,000 in humans and are arranged in 3–4 rows (Ashmore, 2008).

1.4 Frequency Resolution: PNS

Auditory input is received from the organ of Corti in the inner ear that acts as a sound frequency analyzer. Within this region, the basilar membrane of the cochlea is made up of hair cells tuned to higher frequencies at the base and lower frequencies at the apex. The hair cells form synapses with nerve fibers retaining the tonotopic organization towards the auditory cortex. A number of tonotopic progressions can then be found in the peripheral ear followed by a number of structures of the auditory nuclei in the brainstem (cochlear nucleus CN and superior olivary complex, SOC), midbrain (inferior colliculus, IC), thalamus (MGN), and in the auditory cortex (Reese & Palmer, 2010; Saenz & Langers, 2013). Based on psychoacoustic experiments in humans, it is generally agreed that the bandwidth of the peripheral filters have a width of about a sixth of an octave, or a critical band of 10–15% of the stimulus frequency (Moore, 1982).

1.5 Anatomy and function of the Auditory Central Nervous System (CNS)

From the periphery, auditory information is sent via the auditory nerve to central nervous system (CNS), first innervating the CN that subdivides auditory information into two different streams, one for processing binaural sound localisation, and the other for sound identification. The ventral stream primarily functions on sound localization and innervates the SOC that extracts the direction of the sound source by associating timing and intensities of sound stimuli received by the two ears. The auditory information is then sent to the IC, where the dorsal stream primarily

functions in extracting temporal variation, spectral, and sound information from the CN to get mapped onto the IC. The IC combines auditory information from both streams forming a representation of an auditory object that further sends projections to the MGN. The ventral division of the MGN projects predominantly to the primary auditory cortex (A1). The IC has been designated as an essential relay for auditory input to the MGN, however it has been reported that some neurons that send projections to the MGN bypass the colliculus (Malmierca et al., 2002).

The auditory cortex is located on the upper surface of the temporal lobe in a region known as the superior temporal plane within the Sylvian fissure, also known as the lateral sulcus. The primary auditory cortex core is located in the posterior-medial part of Heschl's gyrus (Brodmann area 41 (BA41)). The auditory core region is surrounded by belt and parabelt regions. The human auditory cortex can be divided into three areas on a macroscopic scale, which includes in the anterior posterior direction, the planum polare, the transverse temporal gyrus (Heschl's gyrus (HG)), and planum temporale. The HG convolution is evolutionarily new, and has not been identified in the macaque monkey (Baumann et al., 2013), and only detected in a subset of chimpanzees (Hacket et al., 2001).

Auditory cortical cells show a variety of tuning curves that span from broad to narrow tuning, respond to single or multiple peaks in frequency sensitivity, and respond to stimuli modulated in amplitude, frequency, and sound location. Auditory cortical neurons progressively become more complex when they span from core to parabelt regions. Previous studies interpret auditory core neurons more responsive to simpler stimuli such as sound localization and detecting the direction of frequency change, whereas belt and parabelt regions respond to more complex stimuli (Pickles, 2012).

Tonotopy refers to the topographical arrangement of sound frequency responsivity in the brain. Just like with retinotopy where the organization of spatial location in the retina is preserved on the cortical surface, so is tonotopy, which reflects the frequency organization of the cochlea. Tonotopic maps provide insight as to how the auditory system is functionally organized and also allow us to subdivide the central auditory system into properties such as acoustic features and attention (Saenz and Langers, 2013). Although frequency is the main acoustic feature that is mapped, other emerging features including tuning bandwidth form complementary maps (Moerel

et al., 2012). Tonotopic mapping of the auditory cortex has proven particularly challenging for human neuroimaging. This is most likely due to the small size of the auditory cortical fields in relation to the spatial neuroimaging resolution as well as disagreements of the architectonic definition of the primary auditory cortex (A1), resulting in different interpretations of the auditory fields. Nevertheless, spatial patterns of frequency preference remain highly consistent in the human auditory cortex (Saenz & Langers, 2013).

Throughout previous studies, a substantial consensus regarding the spatial distribution of frequency tuning regions of auditory cortex surrounding HG in humans has been made. The most recent findings converge onto the interpretation of the spatial orientation of A1 in humans that is consistent with that of non-human primates (Baumann et al., 2013). In humans, the core fields A1 and R are positioned on the caudal and rostral banks of HG that spread across the HG rather than along it. According to these data, an elongated zone on HG was found to respond favourably to lower frequencies, whereas zones posterior and anterior to HG were found to respond favourably to higher frequencies (Da Costa et al., 2011; Herdener et al., 2013; Humphries et al., 2010).

1.6 Frequency Resolution: CNS

The cochlea is the first place in the auditory system where frequency resolution takes place. It resolves different frequency bands that are tonotopically organized, and this organization is maintained throughout the auditory pathways up to the primary auditory cortex. A number of studies have looked at how frequency resolution changes as auditory signals traverse the central nervous system, as well as how lateral inhibition affects the frequency resolution of individual neurons. Frequency resolution pertains to the ability of resolving a narrowband spectral element residing in a broadband stimulus, whereas frequency discrimination refers to the ability in discerning two narrowband stimuli presented one after the other. Psychoacoustical evidence suggests that the auditory frequency just noticeable difference in well-trained subjects is about 30 times smaller than the apparent bandwidth of the peripheral filters (i.e. critical bands that are around a sixth of the octave in human hearing) (Evans, 1997).

Within the brainstem auditory nucleus, the IC is subdivided into 3 sections, the central nucleus referred to as the lemniscal nucleus that receives the majority of input, and the external and

dorsal cortex referred to as the non-lemniscal nuclei, that receive more diffuse inputs that surround the central nucleus (Morest & Oliver, 1984). Previous studies reported in anaesthetized cats, the majority of central IC neurones have sharp tuning curves while a smaller subset had shallow low frequency tails to the tuning curves (Aitkin et al., 1975), while in the awake chinchilla the response areas to IC neurons was more complex categorized by more than one excitatory area and multiple areas of inhibition (Ramachandran et al., 1999). Neurons in the external and dorsal nucleus of the IC have been reported to be more broadly tuned and to habituate rapidly. Furthermore, neurons in the dorsal cortex of the IC primarily respond to monaural stimuli, whereas in the external nucleus primarily responds to binaural responses (Aitkin et al., 1975).

In primates, the MGN is organized into different sections; the ventral principle division, and adjacent posterodorsal, anterodorsal and medial divisions (Jones, 2003). Neurons in the ventral section of the MGN have sharp tuning curves as found in cats (Aitkin & Webster, 1972) and in awake marmosets (Barlett &Wang, 2011). In all species reported, the MGN neural tuning curves do not increase in width based on stimulus intensity to the same degree as in the auditory nerve. This means that within the MGN, frequency resolution is independent of stimulus intensity (Pickles, 2012). Furthermore, lateral inhibition interactions initially obtained in the dorsal CN are further enhanced by the MGN and have been reported to enhance cues for sound localization in the vertical direction (Samson et al., 2000)

Very few studies have been able to resolve the frequency resolution of auditory cortical neurons in humans. A previous study used extracellular single unit recordings of cortical neurons in Heschl's gyrus in four human epileptic patients. Electrodes were placed bilaterally in Heschl's gyrus of the primary auditory cortex. Frequency resolution of the auditory neurons was determined by matching the neural response to the auditory stimulus presented, and by changing the spacing of the tones presented. The stimulus consisted of random chord tones and speech segments from a film. These neurons could reliably distinguish frequencies of less than 3% (Bitterman et al., 2008). Their results suggest that the frequency tuning in single neurons recorded from human auditory cortex in response to random-chord stimuli is far narrower than that typically described in any other mammalian species (besides bats), and considerably surpasses that attributed to the human auditory periphery i.e., human critical bands are roughly 10–15% of the stimulus frequency

(Bitterman et al., 2008). These findings suggest the frequency tuning in humans sharpens when auditory information traverses from the peripheral to the central auditory regions.

In other non-human mammals, the frequency tuning widths in auditory cortical neurons have been reported to be much broader than in humans. For example, neuronal tuning widths ranged from one octave in anesthetised cats (Read et al., 2012) and about a fifth to a third octave in anesthetised rats (Gaese & Ostwald, 2001; Honey & Schnupp, 2015). Tuning bandwidths have repeatedly been shown to be broader in the same species of awake animals as found in cats (Qin et al., 2003) and rats (Gaese & Ostwald, 2001). In awake macaques, reported auditory cortical neuron tuning widths were typically half to one octave and very narrowly tuned neurons were reported rare (Recanzone et al., 2000). Taken together, these results suggest that the hyperacuity of frequency discrimination in humans is substantially better than other mammals with evidence that suggests our enhanced cognitive skills involving language (Benasich & Tallal, 2002), learning aptitudes, and working memory (Banai & Ahissar, 2006) may play a factor.

Previous animal studies have found that the most responsive neurons in A1 have sharp tuning with a single frequency area of maximum sensitivity as found in cats (Phillips & Irvine, 1981). In awake marmosets, approximately 27% of A1 neurons had sharper tuning than what was observed in the auditory nerve during the sustained rather than onset part of the response (Bartlett et al., 2011). In another study on awake marmosets, 20% of A1 neurons that were recorded were found to have two or more regions of maximum sensitivity, known as multi-peaked responses that in a number of cases had their peaks harmonically associated to the cell's characteristic frequency (Kadia & Wang, 2003). In cats, multi-peaked neurons were primarily found in the dorsal rather than central portion of A1 (Schreiner et al., 2000). As well, in cats and primates, A1 neurons can have broad tuning curves that span several octaves and are spatially separated from sharper tuned neurons.

Just like other regions in the auditory system, A1 neurons can be inhibited when stimulating areas outside the excitatory response region. In addition, a large number of A1 neurons can be inhibited by stimuli comprised of one or more frequency bands that are isolated from central excitatory or inhibitory regions (Kadia & Wang, 2003). Part of this inhibition is thought to reside

in cortical networks, evidenced by decreases in activity when the GABA blocker bicuculline is locally applied, based on a previous experiment in the cat auditory cortex (Yuan et al., 2011).

It should be noted that subcortical and brainstem auditory nuclei receive both reciprocal and descending (top-down) auditory inputs from higher stages of the auditory system. Auditory cortical regions send sizeable descending projections to the MGN primary from the region it received ascending inputs, and also to auditory brainstem nuclei including the IC, SOC and CN, and non-auditory regions including thalamic nuclei, the amygdala, the tegmentum, and motor nuclei of the pons and striatum (Winer, 2006; Suga, 2012). The tonotopic regions of A1 project to the tonotopic regions of the MGN, maintaining a close coupling in the loop of the afferent and efferent fibers that act as a suggested single integrated unit. As well, cortical projections to the IC terminate predominantly in the extralemniscal areas of the colliculus. As such, frequency representations in the MGN and IC can be manipulated when the auditory cortex is electrically stimulated such that their responses are enhanced at the frequencies represented in the region of the auditory cortex stimulation (Suga & Ma, 2003).

As found in single-neuron recordings of the macaque monkey auditory cortex, core neurons were found to be more narrowly tuned than surrounding belt neurons implying that voxel tuning widths may also be determined in the human auditory core (Rauschecker et al., 1995). Human fMRI data looks at each voxels BOLD response in a population of hundreds of thousands of neurons together across cortical layers and neuronal types (10^4–10^5 neurons per mm^3 in cortex), which is why correlating data from single neuron tuning widths to large populations in voxels is not very straightforward (Saenz & Langers, 2013). Nevertheless, MRI is still a valuable tool to infer how population of neurons respond to auditory stimuli non-invasively. Using a 7T scanner, a recent study in humans has demonstrated both tonotopic and tuning width maps for the human inferior colliculus and auditory cortex revealing a high-low-high frequency gradient in tonotopic maps and narrower tuning widths in A1 and R (De Martino et al., 2013).

Recent studies have used natural sound stimuli (vocal, environmental, and tool sounds) for tonotopic mapping of preferred frequency and tuning width of a population of auditory cortical neurons within each voxel (De Martino et al., 2013; Moerel et al., 2012). These studies

used natural stimuli that revealed similar frequency preference maps that were also obtained from separate scan runs that used more standard pure tone stimuli. In these studies, natural stimuli were characterized by their spectral profiles throughout 40 frequency bins using regularized regression to estimate each voxel's response to all spectral bins. Gaussian fits to the resulting response profiles allowed estimation of voxel-wise preferred frequency and tuning width. The benefit of this modelling technique enabled an extensive range of stimulus types (for example, broadband noise), without imposing constraints on stimulus order, and it also provided useful estimates of tuning width.

To date, auditory tuning width maps from human fMRI data are minimal, complex and an attractive field to study because it still remains to be seen if repeated studies reveal the same or convergent views. It still needs to be determined if special populations with different pitch discrimination abilities or deficits have differences in tonotopic and tuning width maps. The purpose of our fMRI experiment described in Chapter 4 was to determine if more expert pitch detectors as found in AP subjects have more sharply tuned auditory pRFs. Sharper tuning widths would imply an enhanced ability in pitch processing mechanisms that may relate to their better ability in pitch categorization and perception. However, not finding any differences in tuning would suggest that AP possessors have the same auditory processing mechanisms as non-AP subjects, and that their ability may be further explained by neuroanatomical differences in working memory and structure associated with higher order perceptual encoding

1.7 Background: Absolute Pitch Origins

AP ability has been debated over the past century, primarily due to the characterization of pitch class categorization and by its mechanism for development. This chapter will cover the latest findings and theories stemming from behavioral cognitive experiments to neuroimaging findings that will help uncover the debate of AP origin. These findings are based on genetic, environmental, neural, and biomechanical paradigms that may reveal scientific models of brain structure and function.

1. 8 Genetic Studies

There have been numerous genetic studies that have suggested that AP ability arises as an inherited trait and includes a genetic origin as part of it manifestation. One of the first genetic studies looked at 35 AP probands (referring to the member being studied) from 19 families. It was first suggested that due to the significant family incidence of this trait, a possible mode of AP inheritance was by an autosomal dominant gene with incomplete penetrance (referring to the proportion of individuals that have a particular genetic change or mutation of an allele i.e., one that can code for AP ability that ends up being expressed in some individuals and not in others), that has an estimated segregation ratio (AP to non-AP) between ~1:3 (.37) and ~ 1:4 (.24) (Profita and Bidder, 1988). Recently, a larger sample size of 1463 AP 1 probands yielded the segregation ratio of ~ 1:11 (.089), suggesting that AP was not inherited in a simple Mendelian fashion (referring to highly penetrant alleles that when present, generally express the phenotype). In addition, this also suggested that multiple genetic factors may be involved in acquiring AP, such as a combination of environmental and genetic factors (Theusch & Gitschier, 2011).

AP may also occur by different genetic variants at different chromosomal locations, both within and across populations of different ancestries. A genome-wide linkage study looked at 73 families of European, East Asian, Ashkenazi Jewish and Indian descent in the US and Canada. In each family there were at least 2 AP possessors. In European, Ashkenazi Jewish, and Indian AP possessors, there was linkage on chromosome 8q21.11, and 8q24.21, where one of the four genes found near the linkage peak on 8q24.21 was adenylate cyclase 8 (AC-8). AC-8 was found to be expressed almost exclusively in the brain and is implicated in learning and memory processes. The linkage region on 7q22.3 was also observed in a subset of European and East Asian ancestry (Theusch et al., 2009).

A small percentage of AP possessors have synesthesia (characterized as a neurological occurrence where the stimulation of one sensory pathway leads to the involuntary perception of another sensory pathway, i.e., blending of senses), particularly associating musical pitches with colours. Synesthesia is a rare condition and appears to have a genetic predisposition. A recent study looked at AP and synesthesia finding that 151 out of 768 individuals (20.1%) reported synesthesia where pitch and colour associations were the most common (84%), whereas the other

synesthetes with AP had synesthesia with smell, shapes and other complex sensory experiences. This study also conducted a combined linkage analyses of AP and synesthesia finding a common region of association on chromosome 6q over a 20 Mb region as well as linkage on chromosome 2. A number of candidate genes in these linked regions responsible for both phenotypes were investigated such as EPHA7 and CNR1 involved in neurodevelopment which likely reflect the common neurodevelopmental mechanisms in brain connectivity (Gregersen et al., 2013).

Further supporting evidence of genetic origins in AP ability come from studies that examined different ethnic groups. Among these, a previous study reported a higher prevalence (47.5%) in AP ability as found in Asian (Korean, Japanese, and Chinese) music theory students compared to a lower prevalence (9%) in Caucasian students (Gregerson et al., 2001). Another study found the same finding of a higher prevalence of AP in music conservatory students from China where the tonal language Mandarin is spoken compared to the US, where the non-tonal language English is spoken (Deutch et al., 2005). An explanation of the higher prevalence of AP ability in Asians described by Henthorn & Deutsch (2007) was attributed to early tonal language exposure. However, the 'tonal language' explanation may not be entirely acceptable since AP ability has been found to have a higher incidence in all Asian sub-groups, and Asian languages such as Korean and Japanese are not tone languages (Sohn, 1999; Zatore, 2003; Kubozono, 2012).

1.9 Environmental (Critical Period) Hypothesis:

Supporting evidence for the environmental mechanism suggests a critical period, or early learning hypothesis, which describes that a child must be exposed to musical training in note labeling up until the age of seven for AP ability to emerge (Levitin & Zatorre, 2003; Russo et al., 2003, Miyazaki & Ogawa, 2006; rev., Deutsch, 2013). This has been supported with studies that found that an earlier onset of musical training was linked with a higher probability of AP development (Deutch et al., 205; Miyazaki & Ogawa, 2006). Although debated, further claims that AP is linked to a critical period suggest that musical training after the age of nine very seldom leads to AP emergence, which is additionally supported by no reported cases in adults successfully developing it (Brady, 1970, Ward & Burns, 1999; Levitin & Rogers, 2005).

To further test how a critical period may be necessary for AP development, a recent study tested adult men with no musical experience by having them associate pitches with names when taking valproate (VPA), a drug commonly administered for epilepsy and bipolar disorder. VPA has been implicated in altering connections that have been established after the critical period. Those participants who took VPA learned to identify pitch significantly better in the AP task than those taking the placebo—evidence that VPA facilitated critical-period learning in the adult human brain. In this way VPA acted by altering the cellular processes of neuroplasticity by establishing perceptual preferences that were otherwise impossible to acquire after youth, further supporting the critical period hypothesis (Gervain et al., 2013).

A problematic view can arise when one questions whether musical experience is even needed for AP to manifest. This view would then suggest that a critical period alone is not essential for AP to emerge. In an extremely rare self-reported case, an individual largely musically untrained referred to as R.M had demonstrated to possess AP. A recent study devised a new paradigm that tested for AP that is pre-categorical and did not require any musical knowledge. In this test, subjects had to reproduce the target sine tone they heard which was followed by a delay filled with distractor tones and had to reproduce the original tone they heard using a digital sine function generator. R.M was able to perform a pitch memory task at a level indistinguishable from AP musicians. However, it was later described that R.M has a non-negligible history of musical training where during a note naming AP test he scored at the top end range of the non-AP musicians, as well as performed intermediate to non-AP and AP musicians on a number or tone-matching tests (Ross, 2004). Nonetheless, subject R.M's case does implicate the natural variability in the musically untrained population to extract pitch information, and further demonstrates that an early onset of music training (or any music training) may not be fully essential for AP ability to emerge (Ross et al., 2003). This may also suggest that AP and non-AP possessors may be using different pitch processing mechanisms (McLachlan et al., 2013) that in part, reflect genetically influenced neuroanatomical differences.

To further support that other factors may be involved other than a critical period alone, 20% of the AP possessors that were recruited for the studies in this dissertation pertaining to experiments 2–5 (Chapters 3–6), did not have any musical training before the age of seven (the critical period window), and only started any formal musical training and note association labeling

in their early to late teens. Our findings suggest that genetics may play a more salient role for AP ability to emerge in neurodevelopment as opposed to a critical period alone.

1.10 Central Studies

By understanding the function of AP in the brain, a number of inferences could be made about its development. These neural correlates could provide more information on how musical training, ethnicity, and language factor into its genesis as evidenced by structural and functional neuroimaging, and electrophysiology findings.

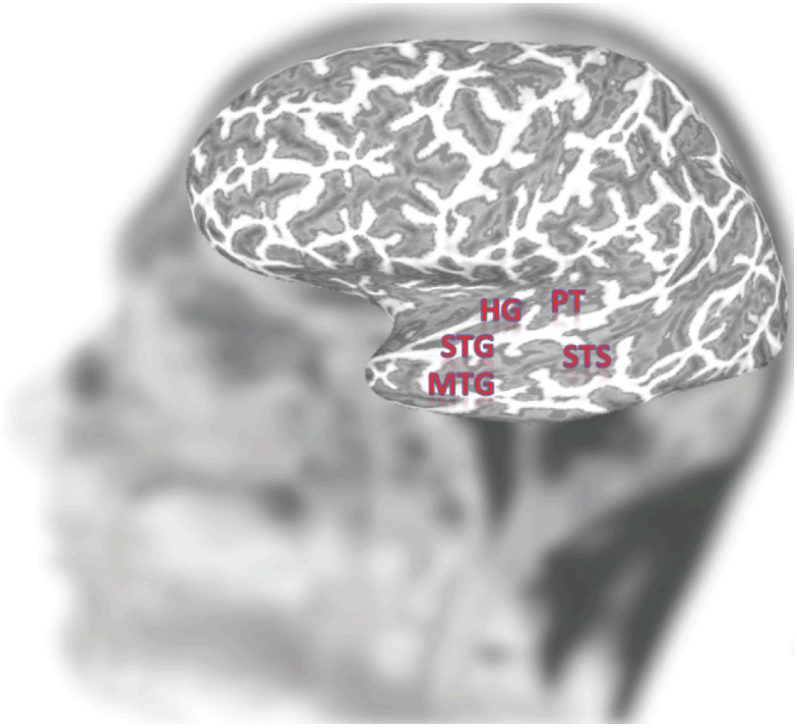

Figure 1.1 Central auditory regions associated with Absolute Pitch. Regions abbreviated in red associated with auditory processing: Heschl's Gyrus (HG), Planum Temporale (PT), Superior Temporal Gyrus (STG), Superior Temporal Sulcus (STS), Middle Temporal Gyrus (MTG). Structural MRI findings: Increased right HG volume in AP (Wengenroth et al., 2014). Increased left PT volume asymmetry compared to right PT volume in AP (Schlaug et al., 1995a; Chen et al., 2000, Keenan et al., 2001; Luders et al., 2004). No difference in left or right PT asymmetry in AP (Zatorre et al., 1998; Bermudez & Zatorre 2005; Bermudez et al., 2009). Increased cortical thickness in bilateral STG in AP (Dohn et al., 2013). Increased connectivity between left STG and

MTG (Loui et al., 2011). Increased fMRI activation, in left STG, STS, MTG (Shulze et al., 2009; Loui et al., 2012).

The following descriptions of auditory central regions associated with AP are summarized and referred to in Figure 1.1. Located within the primary auditory cortex, Heschl's gyrus (HG) also known as the transverse temporal gyrus, is the first structure within the cortex that processes auditory information. Using magnetoencephalography (MEG), differences in functional roles were found within the HG depending on the hemisphere. The left HG was implicated in a more holistic or global perception of musical information, whereas the right HG was responsible in more fine-tuned spectral sound processing of frequency information (Schneider et al., 2005). Structural MRI revealed that AP musicians had a larger right HG volume compared with non-AP musicians (implicating the relationship between the right HG and spectral sound perception). There were no differences between the left HG volumes between groups (Wengenroth et al., 2014). It is not known if the right HG enlargement is an outcome or the cause of AP and was reported as a potential structural marker for AP.

The planum temporale (PT) is a structure located in the posterior superior temporal gyrus (STG), behind the Heschl's gyrus within the Sylvian fissure that also acts as a hub of auditory processing. Structural neuroimaging data reveal discrepancies within the PT volume in AP musicians, non-AP musicians, and controls with minimal to no musical experience. In the normal population, the left PT volume on average is larger than the right (Geschwind & Levitsky, 1968; Steinmetz, 1996). This leftward asymmetry was significantly increased in AP musicians compared to non-AP musicians (Schlaug et al., 1995a; Chen et al., 2000; Luders et al., 2004) and in self-reported AP possessors (Keenan et al., 2001). Since the left planum temporale houses Wernicke's area which is involved in language comprehension, this leftward bias in AP may be indicative of the ability of verbal associations in pitch identifications found in AP. As well, it was put forth that when considering PT surface area instead of asymmetry, the absolute size of the right PT predicted musical ability. These findings suggest a possible developmental mechanism that involves pruning of the right PT that in turn results in a larger left PT volume that may act as a developmental marker in AP. In this case, the etiology of AP has been described as having both a genetic and environmental origin in that coding for hemispheric asymmetry combined with an early environmental exposure to music may be

involved for AP to manifest (Keenan et al., 2001).

In contrast, more recent studies did not find PT volume asymmetry in AP and non-AP subjects (Zatorre et al., 1998; Bermudez & Zatorre 2005; Bermudez et al., 2009), except when comparing the musician group to non-musicians i.e., AP musicians did not differ from non-AP musicians in PT volume (Burmudez & Zatorre, 2005), suggesting that the PT volume asymmetry may be due to musical ability and not an AP marker alone. As well, Zatorre et al. (1998) reported that the right PT volume asymmetry was not evident. Instead, the right PT volume was larger in the AP group, although was not significant contrary to previous findings. These discrepancies in PT asymmetry and volume may be partly due to inconsistent and arbitrary delineations of PT boundaries, human error, and morphological variability with automated methods such as cortical thickness and voxel-based morphometry VBM methods (Zatorre et al., 1998; Bermudez et al., 2009).

Further inconsistencies in whole brain gray matter (GM) structural analyses have been found. In one study, AP possessors had thinner cortex in areas that included frontal and parietal regions (Bermudez et al., 2009). However, no differences were found in AP subjects compared to non-AP musicians in another study that instead had reported increased cortical thickness (CT) in a number of regions including bilateral superior temporal gyrus (STG), left inferior frontal gyrus, and right supramarginal gyrus (Dohn et al., 2013). Furthermore, CT covariations were assessed in AP musicians compared to non-AP musicians, and non-musicians using graph theoretical analysis that found decreased global interconnectedness and increased local connectivity in peri-sylvian language regions in AP (Jäncke et al., 2012).

Another structural method that compares the microstructure of white matter connectivity has been assessed in AP subjects. Diffusion tensor imaging (DTI) is a type of MRI scan that measures the diffusion of water molecules in white matter. In one study, the superior longitudinal fasciculus (SLF) comprised of the arcuate fasciculus (AF) that connects the superior temporal lobe and frontal lobe was assessed. Fractional anisotropy (FA) is a DTI parameter that measures water molecular diffusion within white matter. A lower FA value closer to zero indicates unrestricted molecular diffusion and a higher value closer to one indicates more restricted diffusion primarily along one axis that reflects increased white matter tract integrity, myelination, fiber density and axonal diameter. FA values were increased in the left compared to

right SLF in AP subjects, however this asymmetry was not observed in non-AP musicians. As well, AP subjects had lower FA in the SLF compared to non-AP musicians, which suggests that AP subjects had lower axonal/white matter tract integrity in the region. The researchers proposed a pioneering axon theory which argues that peripheral white matter development instead of compact core white matter regions are more susceptible to environmental influences like musical training that could account for their findings of lower FA values (Oechslin et al., 2010a).

Other DTI studies revealed increased structural connectivity between the superior temporal gyrus (STG) and middle temporal gyrus (MTG) bilaterally. The volume of the tract connecting the left STG and MTG was significantly correlated with behavioral measures of AP acuity and predicted AP performance (Loui et al., 2011). However, a whole brain, tract-based-spatial-statistic (TBSS) analysis found one significant cluster in the right temporal lobe only in AP musicians compared to non-AP musicians. This study reported a rightward asymmetry with higher FA in a single significant cluster within the path of the right inferior fronto-occipital fasciculus (IFOF), the uncinate fasciculus (UF), and the inferior longitudinal fascicles (ILF) (Dohn et al., 2015). A number of explanations were proposed to describe the discrepancies found in asymmetry; Dohn et al. (2015) used a larger sample size that could have improved the power in detecting differences, had controlled for more matching criteria that could have accounted for variation in FA that may not have been related to AP ability alone, and had used different methodologies (TBSS is a whole brain analysis that corrects for multiple comparisons), suggesting that differences in the left SLF as found by Oechslin et al. (2010a) and left MTG, STG as found in Loui et al. (2011) may not be accounted for due to low effect size, or multiple comparisons.

Functional MRI (fMRI) studies reveal increased activation in the left superior temporal sulcus (STS), (a region involved in the categorization of varied sounds) in AP musicians during a pitch memory task compared to non-AP musicians. In contrast, non-AP musicians showed increased activation in the parietal lobe (which may play a role in visual-spatial mapping schemes between pitch and spatial configuration) (Schulze et al., 2009). As well, in another study, AP musicians had increased functional activations in the superior temporal gyrus (STG) (an area important for sound perception) that extended into the STS and a number of structures related to a reward-system and emotional processing (bilateral amygdala, hippocampus and

ventral tegmental area) as compared to the non-AP musicians during a music listening task. This task required the participants to focus on assessing emotional judgements to musical excerpts (Loui et al., 2012). Taken together, these studies suggest that AP musicians have enhanced capability for auditory categorical processing and that AP subjects may inherently find music listening more rewarding (Loui, 2014).

Of note, very few studies investigated if AP ability can be transferred to other skills other than music perception. In a functional study, Oechslin et al. (2010b) looked at the direct link between processing speech in AP musicians compared to non-AP musicians and non-musicians. AP subjects showed an increased left lateralized activation in the lower portion of the posterior superior temporal sulcus (STS) based on segmental speech stimuli consisting of flattened speech (comprised of pure lexical syntax information without dynamic pitch contour with and without sentence meaning), and delexicalized speech (comprised of speech prosody or pitch contour). This study supports that AP ability is not only confined to music processing, but can also transfer to speech processing.

A number of electrophysiological studies have been carried out in AP possessors that measure the event-related brain potentials (ERP) from electroencephalography (EEG) responses. ERP measures time-sensitive neural responses in relation to perceptual or cognitive stimuli such as listening to music. P300 waves are ERP components that occur in decision-making, stimulus categorization or evaluation processes. A number of these electrophysiological studies found a reduction or absence of the P300-evoked response (a positive waveform ~ 300 msec after the onset of the stimulus) in AP subjects. Interpretations of this finding suggest that AP subjects lack in updating auditory working memory, and instead use working memory independent strategies to process auditory information (Klein et al., 1984; Wayman et al., 1992; Hantz et al., 1992). Taken together, an interpretation of these results suggest that AP subjects may utilize pre-determined frameworks or pitch categories to hold pitch class information that does not depend on conventional working memory dependent mechanisms. In contrast, other studies have found that the P300-evoked response was present in AP subjects (Bischoff Renninger, et al., 2003; Hirose et al., 2002). These latter results suggest that working memory in AP may be sensitive to individual differences in the approach used to encode pitch as well as differences in task instruction (identification compared to detection of infrequent notes of the experiment (Loui,

2014)).

1.11 Conclusion

The etiology of AP has been controversial with varying models supporting different claims. To summarize, one can conclude that AP is linked to heredity and learning; AP is based on a genetically determined trait in some instances; AP is related to early musical experiences; and AP possessors must have had some musical training, where the degree of AP tended to correlate with the age of onset of musical training.

Having an enhanced auditory working memory may play a fundamental role in being able to learn AP, as evidenced by AP musicians that had a larger auditory working memory compared to matched musicians (Deutsch & Dooley, 2013). Here in lies the 'chicken or egg' problem in relation to working memory in AP. It may be that having a larger auditory working memory capacity fosters AP to develop, or it may mean that having AP in the first place is what leads to an increased auditory working memory capacity (Van Hedger et al., 2015). If it is the former, it may be the case that those rare non-musical adults with AP had increased executive functioning in the auditory domain, such as an enhanced tonal working memory that allowed them to selectively attend to pitch-chroma categories, even when presented with a number of interfering tones (Van Hedger et al., 2015).

Chapter 2

Experiment 1: Peripheral Basis for Absolute Pitch

2.1 Abstract

Absolute pitch (AP) is the ability to identify or produce the perceived pitch of a sound (e.g., fundamental frequency of a piano note) without an external reference. This ability is relatively rare (~1/10,000 individuals possess it) and the mechanisms underlying AP are not well understood. This study examined whether there was evidence for a peripheral (i.e., cochlear) basis for AP based upon otoacoustic emissions (OAEs). The chief motivations were that both AP and spontaneous emissions (SOAEs) appear to have genetic components and a higher prevalence in certain populations (e.g., relatively higher incidence of both in Asians). We examined SOAE and stimulus-frequency emissions (SFOAE) in both control ($N = 33$) and AP ($N = 22$) normal hearing populations. We found no substantial differences in SOAE activity between groups. SFOAE phase-gradient delays, measured using several probe levels (20–50 dB SPL), also showed no significant differences. This latter observation argues against sharper frequency selectivity in AP subjects. Taken together, these data support the prevailing view that AP mechanisms arise at a central nervous system processing level at the brainstem or higher.

2.2 Background: *Otoacoustic Emissions*

Otoacoustic emissions (OAEs) are the sounds produced in the inner ear canal when sound stimulates the cochlea. Healthy ears emit OAEs, typically thought to be a by-product of an underlying amplification mechanism at work in the cochlea. Although it remains uncertain exactly how auditory information is initially peripherally encoded during forward transduction, there is much agreement to date that this is based on the 'active ear' paradigm. OAEs are thought of as backward traveling waves that are generated from the energy of the cochlear amplification process in response to outer hair cell (OHC) vibration. This nonlinear amplification mechanism (i.e., reverse transduction) enhances the detection of low-level sounds that results in an almost inaudible backward traveling wave through the middle ear (Hudspeth, 2008; Bergevin et al., 2015). OAEs are measured through a probe that is inserted in the outer third of the ear canal. The probe contains a loudspeaker that generates sounds and a microphone that measures the resulting

OAE's produced in the cochlea that are reflected back through the middle ear into the outer ear canal. The resulting sound that is picked up by the microphone is digitized and processed by specially designed hardware and software. The very low-level OAEs are separated by the software from both the background noise and from the evoked stimulus.

In this way, OAEs act as non-invasive probes of cochlear mechanics and can infer an indirect monitor of the amount of cochlear amplification (Shera & Guinan, 2007). Therefore, to obtain an OAE one needs an unobstructed outer ear canal, absence of significant middle ear pathology, and functioning cochlear OHCs. OAEs are useful to measure since their detection allows for characterization of auditory function and dysfunction. Their detection has been an essential component for audiological diagnostic test batteries in that they help screen for differences in cochlear status and are useful in differentiating sensory from neural disorders. As well, they provide evidence of how sound stimulation interacts with the cochlea (Kemp, 2008). To date there have been two theoretical approaches as to how they arise.

First, the local-oscillator model predicts that OAEs occur solely through the local, self-directed oscillation of OHCs within the organ of Corti (e.g., the active process underlying the cochlear amplifier). The 'local' aspect to this model predicts that these oscillators are directly coupled to their nearest neighbours. As such, this model assumes that OHC movement produces spontaneous movement of the basilar membrane, which in turn creates a traveling wave towards the base of the cochlea generating emissions (Gold, 1948; Martin & Hudspeth, 2001; Hudspeth, 2008; Vilfan & Duke, 2008; Dierkes et al., 2008; Gelfand et al., 2010).

Second, another view describes a global standing-wave model to explain OAEs. It presumes that OAEs can also be induced by spontaneous movements of the OHCs, but in contrast to the first model, dismisses that they themselves generate the OAEs. This model assumes that the actual emissions are generated by cochlear standing waves created by multiple internal reflections within the cochlea (Shera, 2003). In this analogy, impedance differences at the organ of Corti can be attributed to hair cell movement at the location of the basilar membrane where a forward traveling wave is at its maximum. When these differences build up at this frequency location on the basilar membrane, forward traveling wave reflections can arise. When

they do, they also will be partly reflected into the cochlea again due to impedance differences between the middle and inner ear. A forward traveling wave will be produced, amplified, and reflected back at the same location on the basilar membrane where impedance differences of OHCs took place. When enough of these traveling waves become in phase, a standing wave can arise within the cochlea and becomes emitted as an OAE (Kemp, 1979; Kemp, 1986; Davis, 1983; Zweig, 1991; Talmadge & Tubis, 1993; Zweig & Shera, 1995; Talmadge et al., 1998, Shera & Guinan, 1999; Shera, 2003; Duke & Jülicher, 2003; Ku et al., 2009; Epp et al., 2010; Bergevin et al*.,* 2015). There are different types of OAEs, two of which are described in the following section that were collected on control and AP subjects.

2.3 Spontaneous otoacoustic emissions *(SOAEs)*

Spontaneous otoacoustic emissions (SOAEs) are low-intensity sounds emitted by the inner ear in the absence of any stimulus. Their prevalence is in about 40–60% of normal hearing people (Talmadge et al., 1993; Snihur & Hampson, 2011). Roughly 80% of all emitting ears have more than one SOAE, with a median of 5 SOAEs per emitting ear (Talmadge et al., 1993). The prevalence of SOAEs is more frequent in women than in men and more frequent in the right than in the left ear (Bilger et al., 1990; Penner et al., 1993; Talmadge et al., 1993; Penner & Zhang, 1997; Snihur & Hampson, 2011). The presence of SOAE's is usually considered to be a sign of cochlear health, but the absence of SOAE's is not necessarily a sign of abnormality. They are unique to each individual, just like a fingerprint. Previous studies on subjects with and without SOAEs found sharper tuning in ears with emissions based on psychophysical tuning curves (PTC) measurements. PTCs represent masker levels required to mask a tonal probe fixed in frequency and level as a function of varied masker frequencies. Subjects with SOAEs had sharper PTCs at 2 kHz, however there were no differences at 1 kHz or 4 kHz frequencies (Micheyl & Collet 1994). In addition, subjects who had SOAEs tended to have lower auditory thresholds at the SOAE peak, i.e., subjects could hear softer pure tones at the SOAE frequency (Baiduc et al., 2014). Therefore, we predicted that there might be more SOAEs in subjects with AP relating to sharper tuning at those frequencies.

2.4 Stimulus frequency otoacoustic emissions *(SFOAEs)*

Stimulus frequency otoacoustic emissions (SFOAEs) are sound delays (latencies) evoked from the ear in response to pure tones. They provide a measure of mechanical delay within the cochlea and are related to the frequency selectivity of the ear (Kemp 1986; Shera & Guinan 2003; Joris et al., 2011). SFOAEs do not act as a mere echo of the applied sound stimulus (even though they are similar in acoustic characterization), but rather act as a complex transformation of it. They arise due to linear discontinuities within the cochlea, typically impedance mismatches, resulting from the coherent scattering of cochlear traveling waves off small, random perturbations in the mechanical properties of the cochlea (Shera, 2002). A previous study found that when SOAEs were observed, then SFOAEs demonstrated a localized increase at the SOAE peak. However, the opposite was not always the case, i.e., you can have robust SFOAEs in the absence of SOAEs (Bergevin et al., 2012).

2.5 Methods: Participants

Prior to OAE testing, each participant filled out an ethics and questionnaire describing the protocol. We examined SOAEs and SFOAEs in both control (N = 33, 40 ears) and AP (N = 20, 31 ears) normal hearing populations. Data were collected independently at the University of Western Ontario (UWO) [control (N = 26, 26 ears) and AP (N = 9, 9 ears)] and York University [control (N = 7, 14 ears) and AP (N = 11, 21 ears)] with comparably sized pools using the same acquisition parameters and data analysis. A majority of subjects only had their dominant ear tested due to time constraints particularly at the UWO location, as well as other factors that hindered usable data from noisy measurements. Cumulatively from both testing locations, sixteen participants were excluded from further analyses due to either hearing loss, too much ear wax build-up obstructing proper OAE extraction, or no usable data from noisy measurements. AP participants were recruited from notices at University music departments and by word of mouth. More females were tested in each group due to a higher incidence of SOAEs found (Table 2.1). The present study was approved by the University Ethics Committees at York University and Western University.

A standardized AP test was given for all participants [http://www.musicianbrain.com/aptest/] developed in lab of Gottfried Schlaug, allowing for objective classification of AP status. The AP test consisted of 24 sine wave tones taken from the chromatic scale (C4–B4 repeated twice and randomized per trial). Data were collected on four trials (for a total of 96 tones presented). AP ability was confirmed if the accuracy was 90% or above on the responses given that were within one semitone difference from the presented tone (Miyazaki 1998; Zatorre & Becket 1989; Hamilton et al., 2004). Normal audiometric thresholds were confirmed for each participant using an audiometer. During the recording sessions, the subjects remained awake sitting quietly on a chair in a double-walled acoustic chamber (Istrial Acoustics Co.).

Table 2.1
Participant background information

Group	***AP***			***Controls***		
	York U	***UWO***	***Total***	***York U***	***UWO***	***Total***
Number of subjects	11	9	**20**	7	26	**33**
Number of ears tested	22	9	**31**	14	26	**40**
Gender (male/female)	5/6	3/6	**8/12**	1/6	2/24	**3/30**
Age (Mean ± SD)	25 (9.5)	22.6 (4)	**24.5 (3.4)**	26 (4.51)	24.2 (3)	**24.1 (7.4)**
Handedness						
Right-handed	9	6	**15**	6	25	**31**
Left-handed	1	3	**4**	1	1	**2**
Ambidextrous	1	—	**1**	—	—	—
AP Test (Mean ± SD)	98.5 (2.8)	100	**99.2 (2.2)**	14.2 (7.2)	18.2 (13.1)	**17.3 (12.8)**

2.6 Methods: Data Acquisition and Measurements

Right ears were typically tested first due to a higher incidence of OAEs (Snihur & Hampson, 2011) unless audiometric thresholds and ear preference were markedly better for the left ear. All subjects included here had normal audiometric thresholds. OAEs were measured by an Etymotic ER-10C probe that contained the two stimulus transducers (loudspeakers that generated the sounds) and a microphone that measured the resulting OAEs. The resulting sound was picked up by the microphone was digitized and processed using signal averaging methodology using Matlab (Figure 2.1).

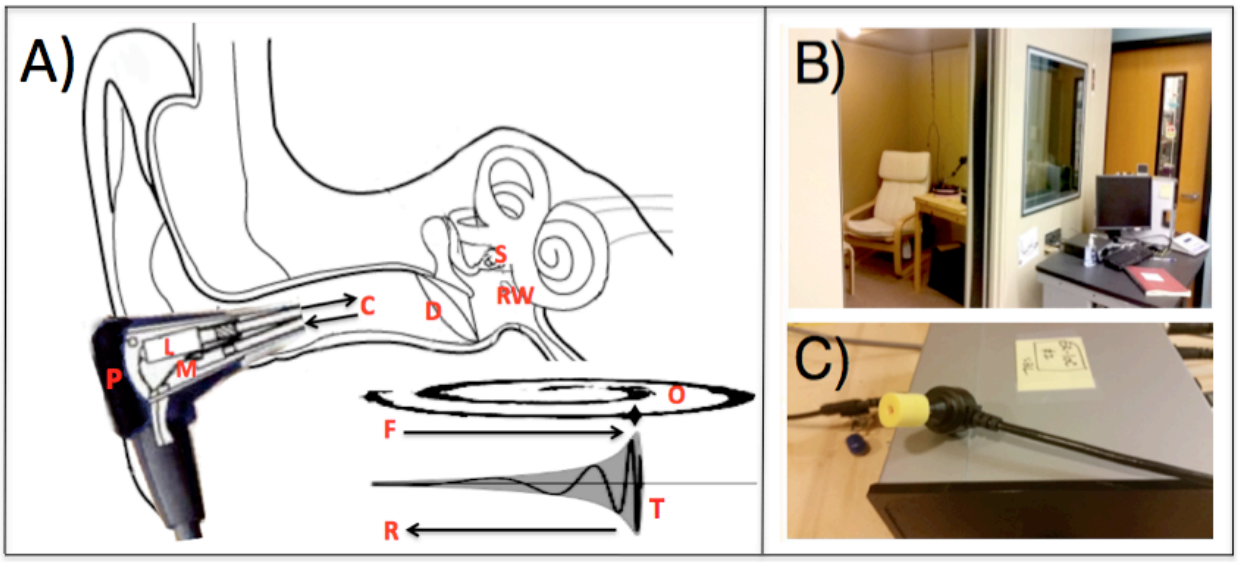

Figure 2.1 Illustration of an otoacoustic emission recording and images of the set-up procedure. (A) Each participant had their ear sealed with a soft plastic tip probe (P). It contained the loudspeaker (L) that provided the auditory stimulus, and a microphone (M) that recorded the emissions within the sealed ear canal (C). Emissions were recorded from spontaneous otoacoustic emissions (SOAEs) that arose from vibrations of the eardrum (D) driven by the cochlea through the middle ear that connects the stapes (S) with the eardrum (D). With evoked OAEs such as stimulus frequency otoacoustic emissions (SFOAEs), a continuous pure tone produced by the loudspeaker at a specific frequency caused a traveling wave to oscillate the stapes (S). This in turn displaced cochlear fluid that produced a traveling wave (T) along the basilar membrane in the forward direction (F). The traveling wave (T) excites the sensory hair cells within the spiral organ of Corti (illustrated as a cross-section from an electron micrograph image (O)). With SFOAEs, there is a distinct area where the maximum vibration of the BM happens just basal to an area where the energy is absorbed and the wave is halted. Around this peak, some wave energy is retransmitted back to the base of the cochlea described as a reverse traveling wave in the direction (R). This reverse traveling wave then stimulates the stapes (S) and round window (RW) due to cochlear fluid vibration, causing the vibration of the middle ear bones, which in turn stimulate the eardrum (D). This results in sound pressure to be recorded as the resulting emissions of the same frequency as the stimulus. (B) Image of the double-walled acoustic chamber and testing station at York University (C) Image of a probe used for recording OAEs.

2.7 Methods: Procedure *SOAEs*

Canal calibration was confirmed throughout the experiment to ensure proper probe and suppressor coupling. SOAE measurements were taken at the beginning and end of each experiment per ear. If SOAEs were present, a 120s waveform at Sample Rate (SR) = 44.1kHz was taken. The SR was needed to determine the frequency bins. For SOAE analysis, the SOAE spectrum (Figure 2.2.B) was obtained by spectrally averaging 60 samples of sounds. We used 60 sample buffers (32,768 points per buffer), i.e., the number of points in the FFT buffer for the averaged spectrum.

2.8 Methods: Procedure *SFOAEs*

Four SFOAE swept tone measurements were acquired that ranged from 0.5–6 kHz, with 30 logarithmic steps, at probe levels ranging from 20–50 Hz with a suppressor level of +15 Hz per probe level. For example, if the probe level was 30 Hz, the suppressor level was 45 Hz that was used to suppress the OAE. 34 averages were taken with 367,920 points per buffer.

To measure SFOAEs, swept tones were presented as a single probe tone alone, or with the addition of a second suppressor tone that was slightly higher in level and nearby in frequency (Shera and Guinan, 1999; Brass & Kemp 1993; Neely et al., 2005; Kalluri & Shera, 2013). The separation of the emission from the stimulus is a challenge for SFOAE measurements because they occur at the same frequency. This was achieved by the vector subtraction of the stimulus component from the signal containing both the stimulus and SFOAE. For example, from the SFOAE run, the red and blue traces show the microphone response at the probe frequency when the tone was presented at a constant level (L_p = 30 dB SPL) for two conditions: probe alone (blue curve) and probe and suppressor (red curve; suppressor level 45 dB SPL and 40 Hz higher in frequency) (Figure 2.2.A).

When the suppressor was also presented (red trace), it inhibited the cochlear generation of the SFOAE and caused the SFOAE measured in the ear canal to be reduced or eliminated. SFOAE presence can be interpreted as a backward-traveling wave within the cochlea. The

residual SFOAE (blue trace Figure 2B) can be extracted from the response interval without the suppressor by subtracting the response in the interval with the suppressor (Neely et al., 2005). The magnitude indicates the size of the SFOAE (Figure 2.2.B.) and the slope of the phase curve with respect to frequency reveals the delay, also called the phase-gradient delay (Figure 2.2.C).

We then calculated SFOAE group delays, defined as the negative of the slope of the emission-phase (in cycles) versus frequency function—from unwrapped phase responses and expressed them in dimensionless form as the equivalent number, N_{SFOAE}, of stimulus periods (Shera et al., 2002). Phase gradient delays are a proxy measurement of tuning. A longer delay reflects a higher store of energy; where the longer the delay, the sharper the tuning. These delays are hypothesized as the build-up time toward the steady state response of the underlying filters. Furthermore, these delays can be thought of as the energy spread comprising a round-trip delay, that is, a delay that is relative to the stimulus for a specific frequency to reach its characteristic frequency region, as well as the delay for the OAE coming from the characteristic frequency cochlear region to propagate to the ear canal (Neely et al., 1988). Mathematically, these delays are related to the rate of change of the phase with frequency based on the signal frequency (Goodman et al., 2004).

Phase-gradient delays were computed from the slope of the unwrapped phase (Fig 2.2.C) using peak-picking algorithms (Shera & Bergevin, 2012) (Figure 2.3). Otoacoustic trend lines were computed using locally linear regression, with confidence intervals determined using bootstrap resampling.

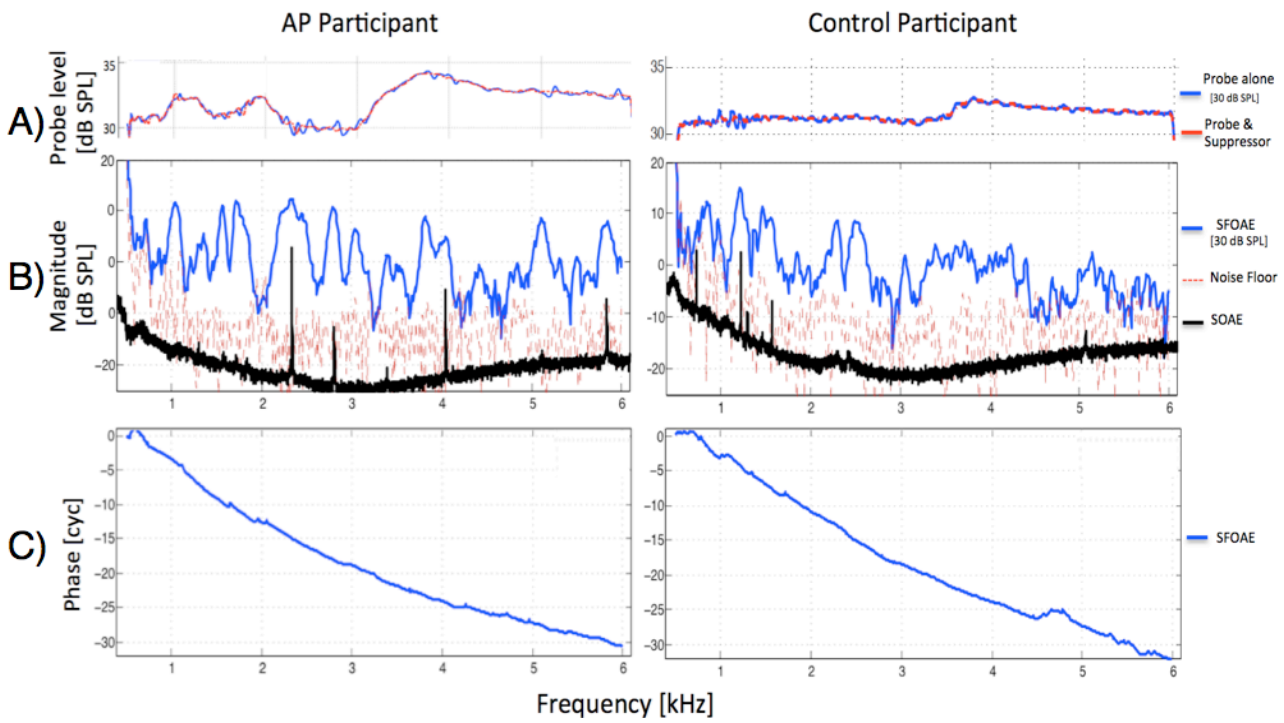

Figure 2.2 OAE data from a representative absolute pitch (AP) participant [male, age 21] in the first column, and control participant [female, age 26] in the second column. In this example, OAEs recorded from the right ears are displayed in both participants. SFOAEs were measured when swept tones were presented as a single probe tone alone, and with the addition of a second suppressor tone slightly higher in level and nearby in frequency.

2.2.A) The probe-alone condition (blue trace) depicts the measured pressure at the stimulus frequency as a combination of both the stimulus and the emission, whereas when the suppressor is also presented (red trace), the interference at the probe frequency diminishes, indicating greater dominance of the stimulus.

2.2.B) SFOAEs (blue curve), were extracted by comparing the complex-valued spectral response at the probe frequency between the two conditions. The magnitude indicates the size of the emission. As well, SOAE spectrums, which are the emissions in the absence of any stimuli are overlaid (black curves). They were taken just before the SFOAE run.

2.2.C) The SFOAE (unwrapped) phase (L_p = 30 dB SPL). The slope of the phase curve with respect to frequency reveals the delay (also known as the phase-gradient delay).

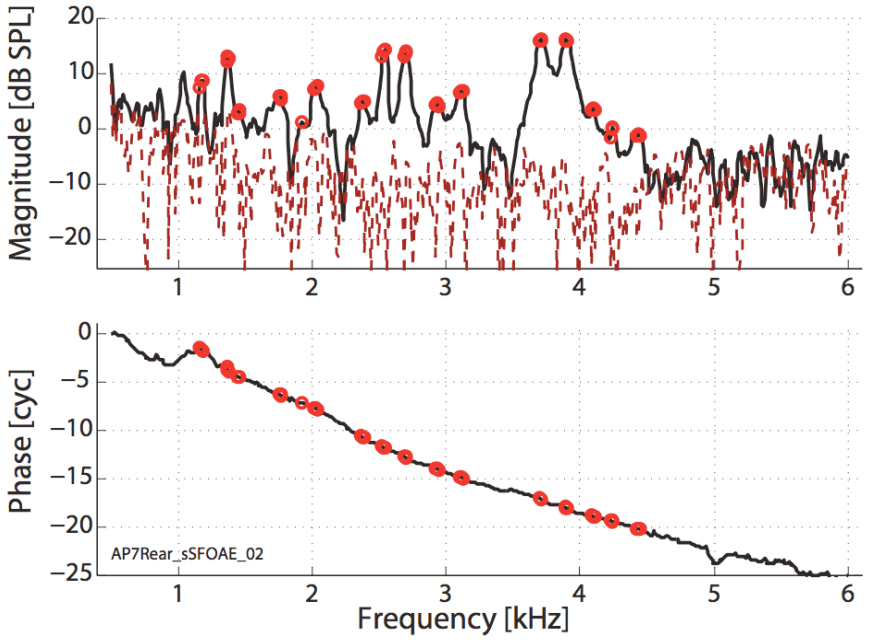

Figure 2.3 Representative SFOAE data from a single ear showing the "peak-picking" algorithm used for extracting SFOAE phase gradient delays [denoted as open red circles].

2.9 Results

Our results indicate no obvious/salient differences in the amount of SOAEs in AP compared to controls based on our pooled SOAE count differences in AP ($N = 20$, 31 ears) and control ($N = 33$, 40 ears) subjects (Figure 2.4). SOAE incidence was similar in comparison between both groups, with a median of 2 SOAEs in both AP and non-AP groups. Figure 2.5 shows an example of an AP and control subject with robust SOAEs compared to an AP and control subject with no SOAEs.

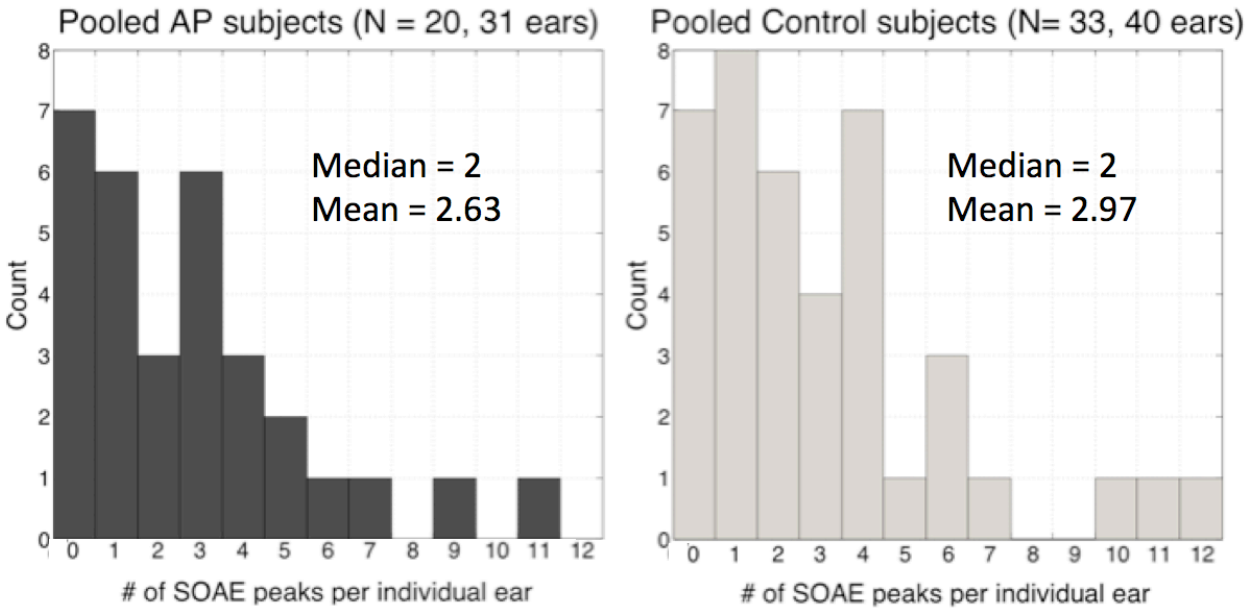

Figure 2.4 SOAE count differences in AP (N = 20, 31 ears) and control (N = 33, 40 ears) subjects. SOAE incidence was similar in comparison between both groups, as well as compared when including the same number of unique ears and the same subject pool sample size.

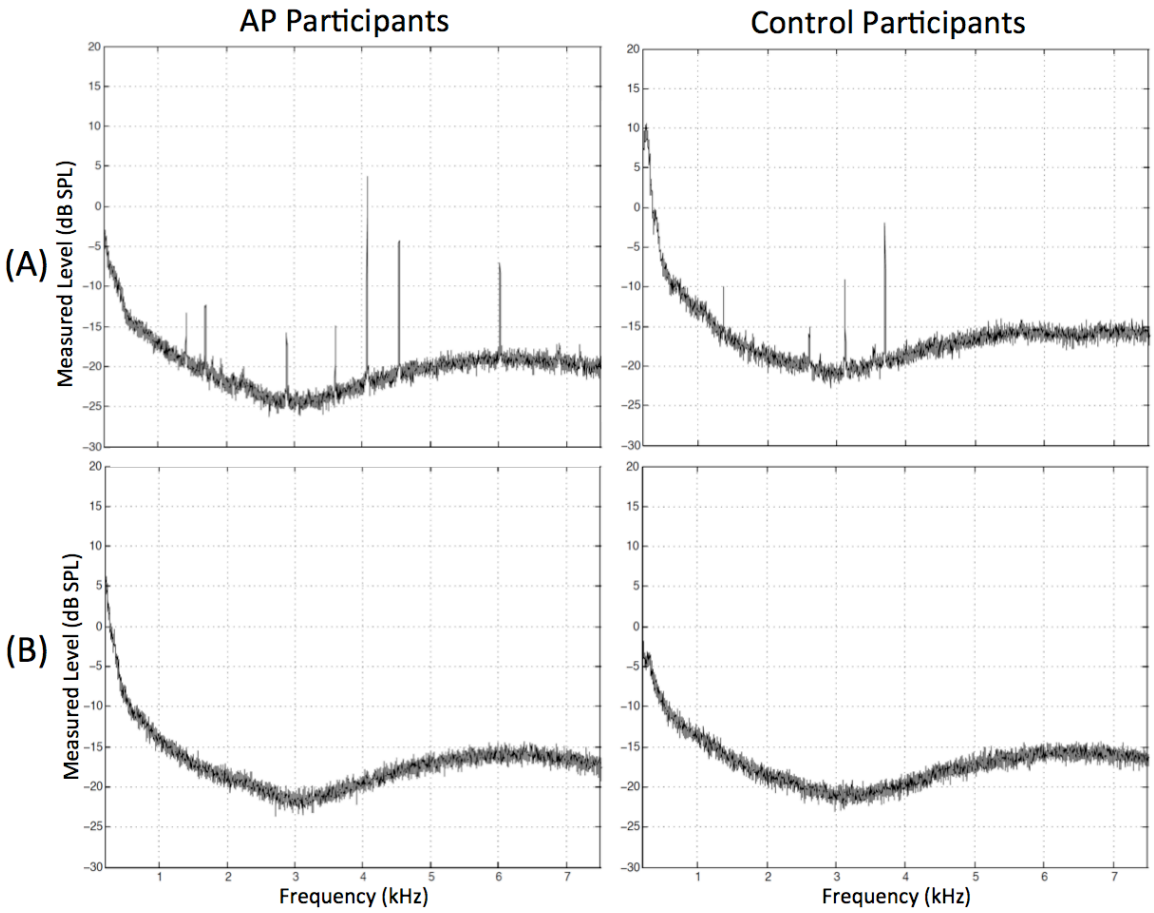

Figure 2.5 SOAE differences in representative control and AP subjects. Panel 2.5.A) illustrates robust SOAE peaks, whereas Panel 2.5.B) illustrates no SOAE peaks present in both control and AP subjects.

SFOAEs delays in dimensionless form (N_{SFOAE}), represent the delay in periods on the stimulus frequency. SFOAE delays (and thereby a proxy measure of peripheral tuning) were similar between both AP and control groups. The trend across frequency is quite robust; the scatter apparent in the data is typical of SFOAEs and does not arise from pathology or measurement noise (the measurements are quite reproducible) but reflects the role of mechanical irregularity inherent in the process of emission generation (Shera et al., 2008; Joris et al., 2011).

With respect to the pooled N_{SFOAE} results from control (seven ears from York, 26 ears from UWO; $N = 33$) and AP (eleven ears from York, nine ears from UWO; $N = 20$) unique individuals, to the first order we observed no substantial differences between AP and control groups. Interestingly, there may be some slight difference at the lower frequencies, which may

suggest minor frequency-dependent differences between groups (Figure 2.6). If these differences do exist, then they may get amplified as one ascends the central nervous system (CNS).

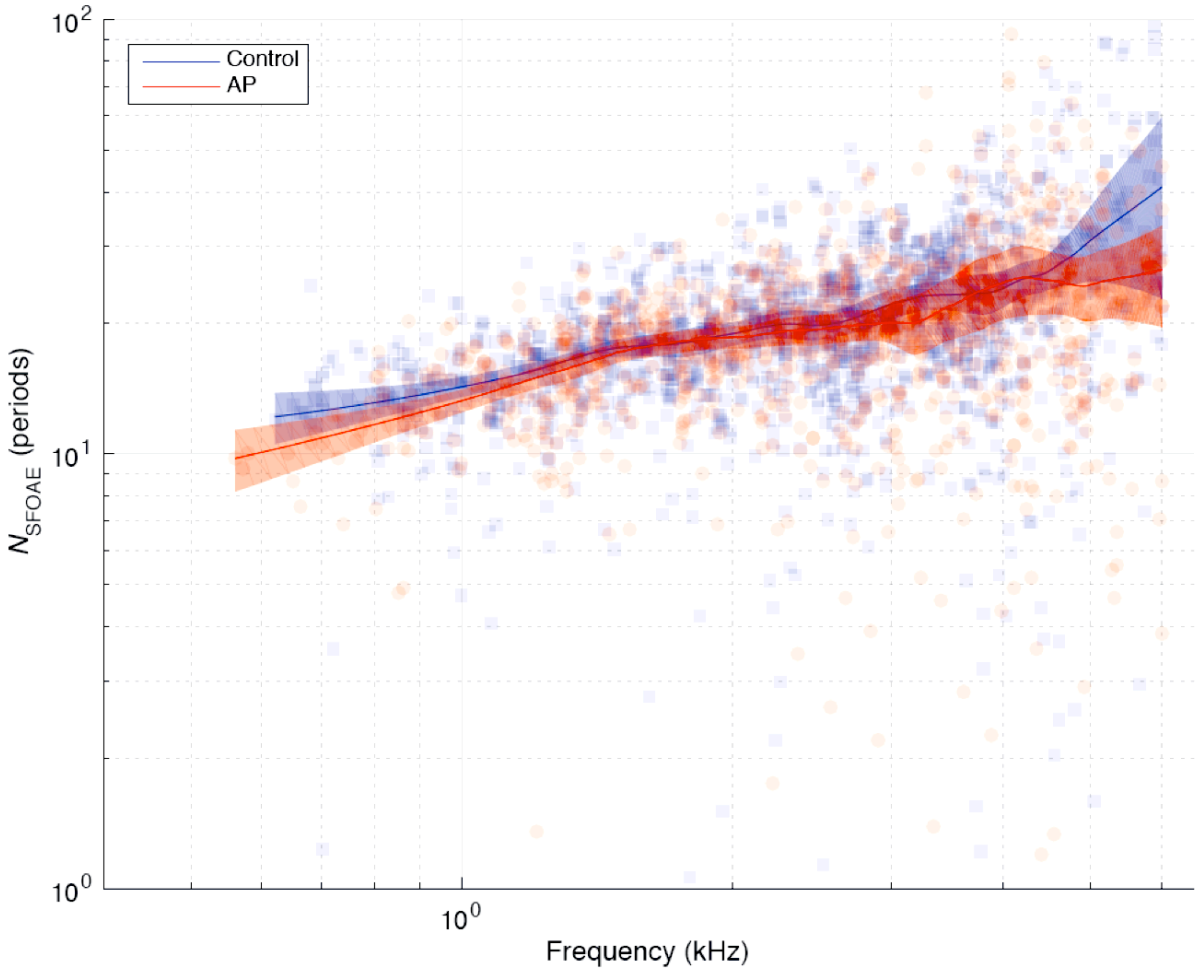

Figure 2.6: Number of stimulus periods of delay (N_{SFOAE}) extracted from phase-gradient delays in pooled Control (N = 33) and AP (N = 20) unique individual ears, L_p = 30 dB SPL. Shaded areas indicate a 95% confidence interval (CI) via bootstrapping across subjects. Results suggest no overall improved frequency selectivity in AP subjects. Similar relationship exists at other stimulus levels, although delays get progressively longer for lower stimulus levels.

2.10 Discussion and Conclusion

Scientific findings chiefly revolve around the notion of neuroanatomical differences found in AP. For example, at the level of the central nervous system, structural differences reveal an increased leftward asymmetry of the PT volume in subjects with AP compared to controls (Keenan, 2001), and enhanced functional networks at the cortical level (Schulze et al., 2009; Loui et al., 2012). Our primary question regarded whether cortical/cognitive differences were sufficient to explain AP development, or if there were other differences that could be found downstream. We examined whether there was evidence for a peripheral (i.e., cochlear) basis of AP based upon OAEs. The predominant motivations were that both AP and SOAEs appear to have genetic components and a higher prevalence in certain populations, for example there is a relatively higher incidence of both in Asians (Deutch et al., 2005; Gregerson et al., 2001). We sought to address if SOAEs were more prevalent in AP subjects. Using SFOAE delays as a proxy measure for frequency tuning, we tested if AP subjects exhibit differences in selectivity.

This has been the first study to measure SOAEs and SFOAEs in AP participants. A possible limitation in our study was not controlling for musicianship. This would have been achieved by including a separate group that had musical experience without AP. However, a previous study found no significant difference in the mean evoked OAE amplitude between musicians and non-musicians (Perrot et al., 1999), further supporting our findings of no OAE differences in our AP musician group. Furthermore, Perrot et al. (1999) also reported increased activity in the bilateral medial olivocochlear system bundle (MOCS) (a region that comprises a large number of fibers originating in the medial nuclei of the superior olivary complex (SOC) that reach the OHCs within the cochlea), in musicians compared to non-musicians using a broadband auditory stimulus. The MOCS is found in the final chain of the descending auditory pathways beginning in the auditory cortex (Huffman & Henson, 1990). Therefore, it has been stipulated that the differences between the musician and non-musician groups may have been attributed to more central auditory structure activations, which are in line with our findings.

In conclusion, our results indicate no obvious/salient differences in the amount of SOAEs in AP compared to controls (e.g., no evidence for one or more strong SOAEs that could act as a cue). For both groups, SFOAE delays continually got larger with decreasing frequency down to at least L_p = 20 dB SPL.

SFOAE phase-gradient delays, measured using several probe levels ranging from 20–50 dB SPL, also showed no significant differences (Figure 2.6). These findings suggest that tuning may amplify as auditory information is processed towards the CNS. Taken together, these data support the prevailing view that AP mechanisms arise at a processing level in the central nervous system at the brainstem or higher. Therefore, we conclude that OAEs suggest no clear peripheral difference between AP and non-AP participants. Instead, we argue that the required mechanisms lie centrally.

Chapter 3

Experiment 2: Behavioural Mechanism for Absolute Pitch

3.1 Abstract and Background

For the following experiment, we looked at behavioural differences in AP musicians, non-AP musicians, and control groups without musical training. Described next is a brief background in musical characteristics that will help address further concepts. In a musical scale, there are 12 semitones within an octave and a semitone is made up of 100 cents where 1 cent equates to 1% of a semitone. Pitch is perceived logarithmically in relation to frequency. For example A4 = 440 Hz, and to find the frequency of a semitone above of A#4 you would multiply 440 Hz by ($2^{1/12}$) or 1.05946 since there are 12 notes within an octave, to get 466.16 Hz. Since pitch is spaced logarithmically on the basilar membrane, music is perceived as a ratio between frequencies. For example, A3 = 220 Hz to A4 = 440 Hz is the same interval as A = 440 Hz to A5= 880 Hz even though the pairs have different frequency ranges between them, they still share the same frequency ratio of 2:1. Cents are a measurement unit between intervals and cannot be converted to Hz because they are not a measurement of frequency. The advantage of using the cents notation allows every tempered semitone to be the same, whereas expressing semitones as Hz creates differences in semitone. Stated another way, 1 just noticeable difference (JND) roughly equals 4.3 cents, approximately 0.36 Hz within an octave of 1000–2000 Hz, whereas 1 JND roughly equals 40 cents, approximately 2 Hz within an octave of 62–125 Hz.

The JND limit is closely related to the critical band characteristic of the auditory system. Critical bands refer to the frequency bandwidth of the auditory filter within the cochlea, whereas equivalent rectangular bandwidths (ERBs) refer to the association between the auditory filter, critical bandwidth and frequency such that as center frequency increases so does the ERB. Previously Zwicker et al. (1957) ran a psychoacoustic experiment that used sinusoidal stimuli that had fixed wave shapes and constant sound intensity level and duration. They reported that the JND was approximately one thirtieth of the critical bandwidth across the hearing range (musically equivalent to ~one twelfth of a semitone). This tells us that the JND in pitch is much smaller than the resolution of the analysis filters (critical bandwidth—which is around a third of an octave for much of the frequency range, but is greater at lower frequencies). Furthermore,

Zwicker et al. (1957) reported that throughout most of the frequency ranges from 60–10,000 Hz, there are roughly 30 JNDs in one critical band.

In normal hearing human adults, pitch differences tend to be reliably differentiated at 25 cents (1/4 semitone), whereas adults with congenital amusia, have trouble differentiating pitches of 100 cents (1 semi-tone) or more (Peretz & Hyde, 2003). A previous study looked at JND thresholds in Mandarin speaking controls and congenital amusics that found the JND average for controls to be ~6 Hz (a third of a semitone) compared to the JND in amusics with tone agnosia ~21 Hz (1.25 semitones) when the test tone of 250 Hz was used (Huang et al., 2015). Expert musicians were found to have JNDs reported between 10–16 cents (which relates to 1/6 to 1/10 of a semitone (Burns, 1999).

3.2 Just Noticeable Difference (JND) Test

Each of the sixty-one subjects participated in the JND in frequency threshold test to determine the smallest detectable difference between two pitches. Human hearing ranges from 20 Hz–20 kHz, with the greatest sensitivity in the 200–2000 Hz range, which occupies up to two-thirds of the basilar membrane (Kollmeier, 2008). The JND threshold for pitch depends on the frequency of the tone and sound level, as well as duration and the suddenness of the frequency change. Previous studies described that a stronger familiarity and experience with a particular musical timbre would affect AP performance (a pianist would recognize piano target tones better than stringed tones for example (Bahr et al., 2005; Brammer, 1951). As such, two pure tones were used for testing AP ability for the JND test, one at 1 kHz and the other at 987.76 kHz. The latter tone is equivalent to an equitempered note (B5), which was used to test if the musician groups performed better with the familiar frequency. As well, pure tones were used in order to remove any biases an AP possessor may have had to an instrumental timbre as a function of experience.

3.3 Methods: Participants

A total of 61 participants were recruited for the behavioural and central studies for Experiments 2–5: 20 AP musicians (AP) (mean age (± SD) 25.2 ± 7.6 years, 13 males), 20 non-

AP musicians (MUS) (mean age 25.5 ± 7.4 years, 13 males) and 20 non-musicians with minimal to no musical background (mean age 25.4 ± 7.4 years, 13 males) matched for age ($F(1,59) = 0.011$, $p = .99$), gender ($F(1,59) = 0$, $p = 1$), handedness ($F(1,59) = 0.38$, $p = .69$), and number of languages spoken ($F(1,59) = 0.66$, $p = .52$) (Table 4.1). Each group had 3–4 participants who spoke a tonal language (e.g. Mandarin). An additional musician participant was considered a special case in that she did not realize she had AP, denoted as quasi-AP (q-AP). This participant did not score as high on the AP test, and unlike the other AP subjects, she had used a tonal reference for one note (middle C) for solving the AP test tones by using relative pitch comparisons to the reference tone she could mentally class. The ability to judge one note in relation to another given a reference tone is known as relative pitch (RP). RP is very common, and all musicians (those with and without AP) reported having RP in this study. AP musicians, and non-AP musicians were recruited from notices advertised in university music departments and by word of mouth.

AP musicians and non-AP musicians were matched on their primary instrument, onset age of musical training ($F(1,39) = 1.26$, $p = .27$) , and the number of hours of musical training per week ($F(1,39) = 2.40$, $p = .44$). In the control group, minimal musical training was defined as not having any current musical training in any instrument and having less than three years of any musical training and exposure overall. Out of the 20 control participants, 11 had no musical training or exposure to any instrument, while 9 control subjects had minimal exposure, less than 3 years and practice under 6 hours/week during that time. All of the participants had normal structural MRI scans, did not have any hearing impairments, and did not suffer from any neurological disorders. York University's Human Participants Review Committee approved the study.

Prior to the collection of data, written informed consent was obtained from each participant after detailed explanation of the experimental procedure. A comprehensive auditory questionnaire was collected for each participant that pertained to musical background, education, primary instrument/voice, age of onset of musical training and AP (Table 3.1).

Table 3.1 **Participant demographics**				
Group	**AP**	**MUS**	**CON**	**q-AP**
Number	20	20	20	1
Gender (male/female)	13/7	13/7	13/7	Female
Age (years)	25.2 ± 7.6	25.5 ± 7.4	25.4 ± 7.4	22
Handedness				
Right-handed	17	15	16	—
Left-handed	2	3	3	1
Ambidextrous	1	2	1	—
Languages spoken				
Monolingual	11	10	9	—
Bilingual	7	7	8	1
Trilingual	2	3	3	—
Tonal languages spoken	4	3	3	—
Years of formal education	16.3 ± 2.1	16.8 ± 2.81	17.1 ± 2.24	15
Age of musical training onset (years)	5.7 ± 3.3	6.8 ± 3.1	—	6
Hours of practice per week	11.9 ± 7.6	9.6 ± 5.1	—	8
Primary Instrument				
Piano	17	17	—	1
Guitar	2	2	—	—
Trombone	1	1	—	—

A standardized AP test was given for all participants developed in the lab of Gottfried Schlaug [http://www.musicianbrain.com/aptest/], allowing for objective classification of AP status. The AP test consisted of 24 sine wave tones taken from the chromatic scale (C4–B4 repeated twice and randomized per trial). Data were collected on four trials (for a total of 96 tones presented). AP ability was confirmed if the accuracy was 90% or above on the responses given that were within one semitone difference from the presented tone (Miyazaki 1998; Zatorre & Becket 1989; Hamilton et al., 2004). Normal audiometric thresholds were confirmed for each participant using an audiometer. Data were further analyzed using SPSS 23 for Mac.

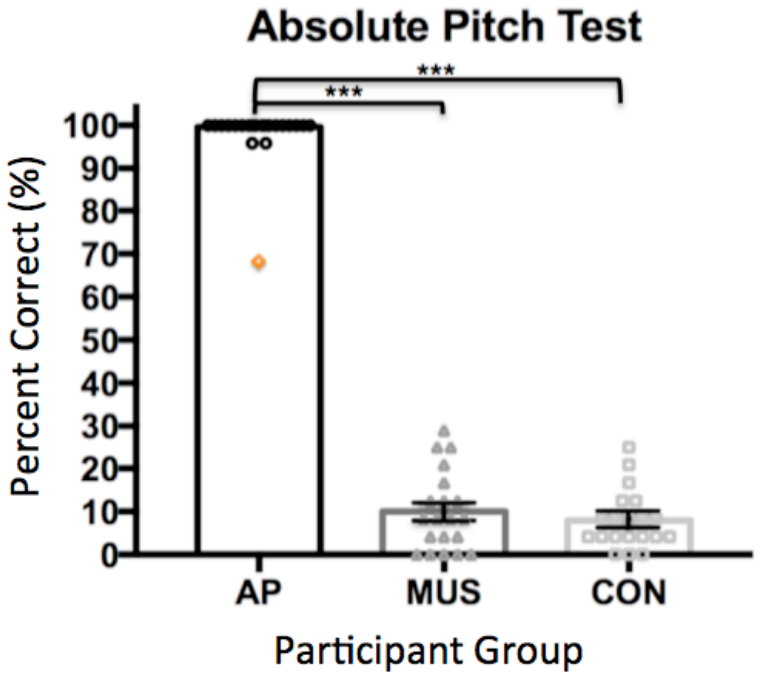

Figure 3.1 Absolute pitch test scores (mean ± SEM) for AP (black open circles), musician (MUS) (dark gray open triangles), and control (CON) (light gray open square) participants (N = 60). The quasi-AP subject (N = 1) is denoted by the open filled orange diamond symbol. AP subjects did significantly better on the AP test compared to musician and controls. ***ps < .001.

A one-way ANOVA revealed a significant main effect of group ($F(1,59) = 1248.6$, $p <$ .001) between AP-musicians, non-AP musicians and non-musician control groups for the AP test. Post hoc Bonferonni tests for multiple comparisons revealed significantly increased scores for AP musicians compared to non-AP musicians and AP musicians compared to non-musician

controls 1000 Hz tone ($p < .001$). There were no significant differences between non-AP musician and non-musician control groups ($p = .977$). The AP test average score in AP musicians was (mean ± SD) 99.6 ± 1.2%, in non-AP musicians was 10.0 ± 9.1% and in non-musician controls was 7.9 ± 6.7 %.

3.4 Method: JND Test

The JND experiment was programmed in Matlab using the Psychoacoustics Toolbox and consisted of two tones played in succession. Pitch discrimination thresholds were determined by a 250 ms pure tone at 1000 Hz and 987.76 Hz (the equitempered tone of B5) using a two-alternative forced choice task, where the subject pressed 1 or 2 to indicate the temporal position of the higher pitch. Thresholds were estimated using the Maximum Likelihood Procedure (MLP) toolbox (Grazi & Soranzo, 2009; 2014). For each testing frequency, there were 5 blocks presented consisting of 30 trials per block. Data were further analyzed using SPSS 23 for Mac.

3.5 Results

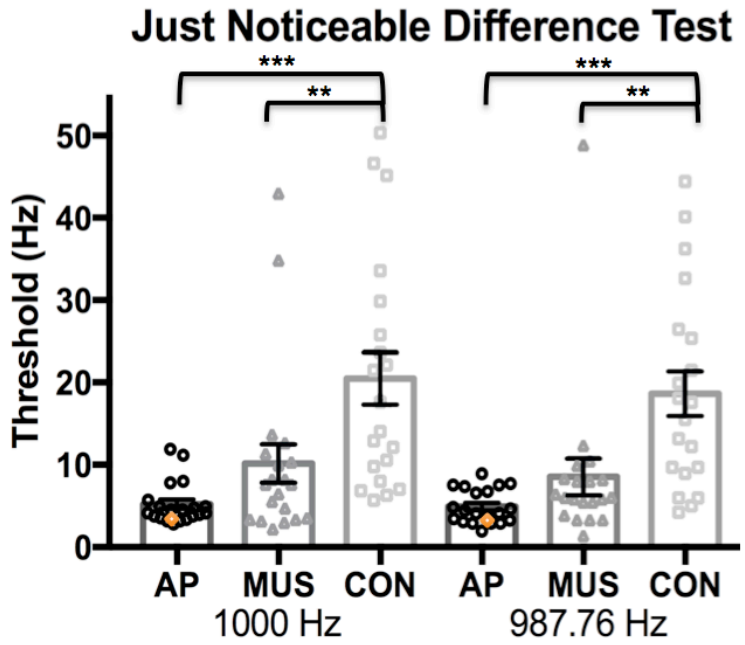

Figure 3.2: JND thresholds (mean ± SEM) for AP (black open circles), musician (MUS) (dark gray open triangles), and control (CON) (light gray open square) participants ($N = 60$). The quasi-AP subject ($N = 1$) is denoted by the orange open diamond symbol. AP and musician

subjects did significantly better at discerning the smallest frequency at both tones compared to controls. ** $p < .01$, *** $p < .001$.

A 3 × 2 mixed model analysis of variance (ANOVA), with group (AP, MUS, and CON) as the between-groups variable and JND threshold for each condition (1000 Hz and 987.76 Hz) as the within-group variable revealed a significant main effect of group ($F(1,57) = 13.0$, $p < .001$) between AP musician (AP), non-AP musician (MUS), and non-musician (CON) groups for the JND test at 1000 Hz and 987.76 Hz. Post hoc pairwise comparisons (Bonferroni adjusted alphas = .025) revealed significantly increased scores for 1000 Hz tone and 987.76 Hz tone (ps < .001) in AP musicians compared to control participants, and significantly increased scores for 1000 Hz ($p = .002$) and 987.76 Hz ($p = .001$) tones in non-AP musicians compared to controls. There were no significant differences in scores for the 1000 Hz tone ($p = .13$) or 987.76 Hz tone ($p = .217$) in AP compared to musicians. There were no significant differences between the 1000 Hz and 987.76 Hz tone in AP musician ($p = .84$), non-AP musician ($p = .23$), and non-musicians control ($p = .174$) groups, meaning the equitempered 987.76 Hz equivalent to a B5 tone did not fare better than the 1 kHz tone.

In AP participants, the JND at 1000 Hz averaged (mean ± SD) 5.2 ± 2.6 Hz, and at 987.76 Hz was 4.9 ± 2.1 Hz. In non-AP musicians, the JND at 1000 Hz averaged 10 ± 10 Hz, and at 987.76 Hz was 8.5 ± 9.9 Hz. In non-musician controls, the JND at 1000 Hz averaged 20 ± 14 Hz, and at 987.76 Hz was 19 ± 12 Hz.

3.6 Melody Mistuning (MM) Test

An additional behavioural test was administered pertaining to melody mistuning/tone-deafness detection developed by Dr. Mandell (online source: http://jakemandell.com/tonedeaf/). The test involved 36 short musical phrases that repeated twice. The participant would then indicate if the melodies were both the same or different. The test was made purposefully difficult such that expert musicians on averaged scored 75% correct. Each melodic excerpt ranged in musical timbre, duration, and tempo.

3.7 Results

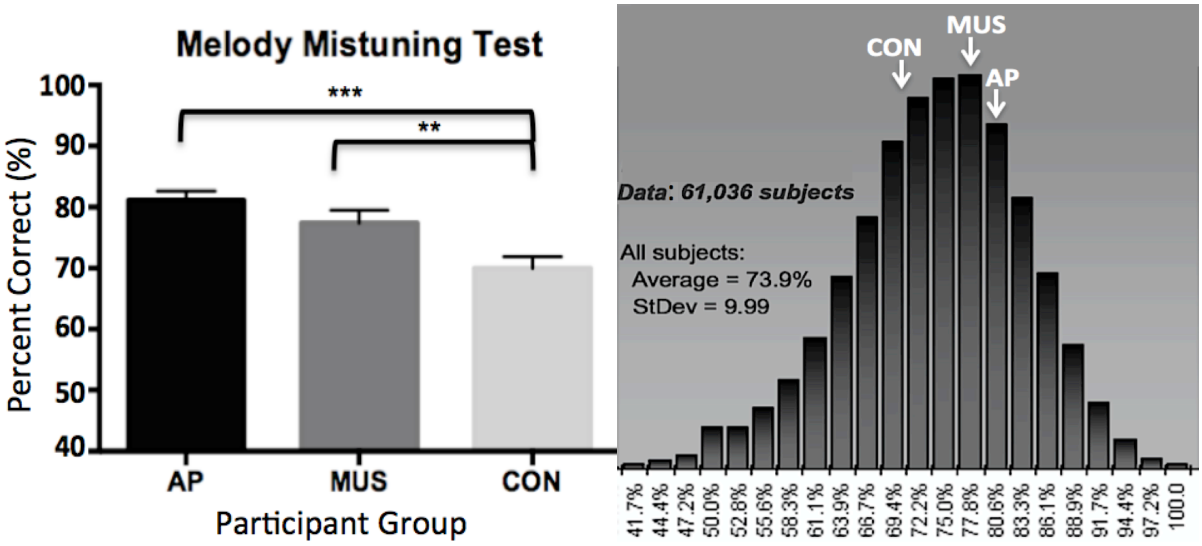

Figure 3.3 Melody mistuning detection test results. The first panel shows the melody mistuning detection test (mean ± SEM) for AP, musician (MUS) and control (CON) groups. Both AP and musicians did significantly better than controls $^{**}p < .01$, $^{***}\ p < .001$. The second panel shows data from over 61,000 participants that had taken the online test that shows where AP, musician, and control subjects fared overall.

A one-way ANOVA revealed a significant main effect of group ($F(1,59) = 9.27$, $p < .001$) for the melody mistuning test. Post hoc Bonferonni tests for multiple comparisons revealed significantly increased scores for AP musicians compared to non-musician controls ($p < .001$) and non-AP musicians compared to non-musician controls ($p = .021$). There were no significant differences between AP and non-AP musicians ($p = .47$). The AP test average score in AP participants was (mean ± SEM) 81.1 ± 1.4%, in non-AP musicians was 77.4 ± 2.1% and in non-musician controls was 70.0 ± 1.8%.

3.8 Discussion

Processing pitch is essential not only in understanding musical perception, but also in speech processing, particularly useful for tone languages. Our initial behavioral test looked at the smallest frequency that could be detected (JND) by playing two tones in quick succession with

the listener being asked if there was a difference between the two pitches. Here, we report significant differences in JND thresholds in AP musicians and non-AP musicians compared to non-musician control groups at both 1000 Hz and 987.76 Hz testing frequencies. Although the AP subjects did better than musicians, it was not significant. Also, there were no significant differences between testing tones, meaning that neither group fared better at 1000 Hz, a frequency of B5 on the equitempered Western scale, compared to a tone that is not equitempered.

A number of behavioural and neurophysiological studies have recognized quasi-absolute pitch (q-AP) musicians who had limited AP ability in that they did not score as high on AP tests and who commonly had a tonal reference for white notes of the piano or the strings of their primary instrument (Bermudez & Zatorre, 2009; Wilson et al., 2009). Similar to the q-AP subject who was tested in our experiment, these musicians often rely on RP judgements for pitches that they cannot label right away and therefore have less associations between verbal pitch category labels and the stimulus representation (McLachlan et al., 2013). Accordingly, the q-AP musicians may then have fewer templates to categorize verbal labels with than AP musicians do. We took into consideration where the q-AP subject ranked, which was more similar to the AP group than the musician group.

A number of studies have compared JND thresholds at various test tones in musicians compared with non-musicians and all reported consistent results that showed musicians had enhanced pitch discrimination ability (smaller JNDs) than non-musicians. The differences in thresholds were increased in musicians by a factor of 2 (Spiegel & Watson, 198; Kishon-Rabin et al., 2001), and in another study by a factor of 6 (using 330 Hz i.e., E4 on the equitempered Western scale as their test tone). The explanation for the larger JND difference in musicians was thought to be due to the stringent selection criteria among both musician and non-musician groups as compared to the previous studies (Micheyl et al., 2006). However, a recent study using a 1 kHz test tone found very similar JND thresholds in musician (JND = ~10 Hz) and non-musician (JND = ~25 Hz) groups (Kuhnis et al., 2013). Our results found that the JND thresholds were larger in the control group with no musical experience (JND = ~20 Hz) which significantly differed by a factor of two compared to the non-AP musician group (JND = ~10

Hz). Our AP group (JND = ~5 Hz) on average did better than the non-AP musician group although not significant.

There has been only one other reported study that looked at JND thresholds in AP subjects. They used the same test tones (1000 Hz and 987.76 Hz) and did not find significant differences between groups (AP, q-AP, and non-AP musicians had JND thresholds ~20 Hz and controls had JND thresholds of ~25 Hz for both test tones) concluding that AP possessors may not have particularly 'good ears' (Fujisaki & Makio, 2002). What was interesting still was that the controls were not significantly different than any musician group, while all other studies reported significant differences. There were a number of gaps in this study in that they did not report the sample size of subjects within each group, age, gender, ethnicity, and did not elaborate on the methodology in enough detail. The main consensus still holds—JND differences were not significant in AP musicians compared to non-AP musicians as found within our study, which further suggests that other salient features may be responsible in AP manifestation than difference limen alone.

A proposed model of AP ability has been explained as a hierarchical two-stage model where pitch representation in long term memory is the first stage and pitch labeling is the second stage (Levitin & Rogers, 2005). The overall representation of pitch in fixed classes has been considered common to all humans, however the association between pitch and the labels assigned to them grouped into nominal categories is thought to result in only a few select individuals—those with AP (Zatorre, 2003). An additional part to this model can encompass an enhancement in auditory working memory as evidenced in AP musicians compared to non-AP musicians (Deutsch & Dooley, 2013). As was demonstrated in our second behavioural task, AP subjects did significantly better in holding a melodic excerpt that differed in timbre, duration and tempo in working memory to detect if differences exist as compared to controls. Although AP subjects did better than the musician group, this difference was not significant.

Nevertheless, another study described an opposing viewpoint that suggested AP possessors have note categories that are plastic and not fixed in absolute frequency referents as established early in age. In this study, AP subjects listened to music detuned in steps that was below the JND that permitted the subtle change in perceptual frequency experience without the

subject being aware. In just 45 minutes, AP subjects showed significant changes in the tuning of their note categories when they heard detuned music by a fraction of a semitone (Hedger et al., 2013). Furthermore, this study suggests that the stability of AP categories may not be related to a critical period of early musical exposure, and instead by cultural norms accepted for tuning music (Hedger et al., 2013). Taken together, the behavioural tests in this study report that AP subjects along with non-AP musicians did fare significantly better in difference limen thresholds and compared melodic mistuning excerpts better in working memory than their non-musical counterparts. Although musicianship did play a factor, the underlying AP marker may be more representative in central studies as described in the upcoming sections.

Chapter 4

Experiment 3: Central Basis for Absolute Pitch (functional MRI)

4.1 Abstract

The focus of our study was to determine whether central differences in the precision of frequency representation might account for the special abilities in AP. Advancements in fMRI have established tonotopic mapping in the human auditory cortex. To date, there still remains a debate of where the exact orientations of the primary gradients occur in Heschl's gyrus (HG) of the primary auditory cortex (A1) (Saenz & Langers, 2014). As well, there is limited data on the tonotopic organization of subcortical auditory structures: the inferior colliculus (IC) and medial geniculate nucleus (MGN), which are harder to resolve due to their small volumes.

Previous fMRI studies revealed an increase in activation in the left superior temporal sulcus in AP musicians during a pitch memory task compared to controls (Schulze et al*.,* 2009), and increased functional activations in the STG, bilateral HG, and middle temporal gyrus (MTG) in the AP group compared to control group during a music listening task (Loui et al*.,* 2012). These studies suggest that AP subjects have improvements in sound processing and perception compared to controls.

What is not known is if there exist differences in the sharpness of tuning between AP musicians, non-AP musicians, and non-musician control groups. We approached this question by the use of the population receptive field (pRF) model and tonotopic/tuning width analysis of the auditory cortex. Our goal was to determine the center frequency and tuning width of the auditory regions (A1), rostral (R) and rostral-temporal (RT) regions of the cortex, with the prediction that AP musicians had sharper frequency selectivity than non-AP musicians and controls without musical training.

4.2 Methods: Participants

Before performing our pRF protocol on the AP-musician, non-AP musician, and non-musician control subjects, we had initially experimented with a number of stimuli in order to

reliably identify tonotopic and tuning curve maps in the cortex and subcortex, including the MGN and IC. With further refinements of the stimulus, sixty-one participants were scanned with a modified protocol in order to detect differences in CF and BW in cortical auditory regions Participant information is described in Table 3.1.

4.3 Method: Data Acquisition, Processing, and Measurements

All images were acquired using a 3T Siemens Trio MRI scanner with a 32-channel head coil at York University. To reduce head motion, cushions were placed around the participants' heads. Each participant was instructed to listen to the auditory stimulus they heard.

Participants were presented with an auditory stimulus consisting of pure tone logarithmic sweeps and the data were analyzed using an adaptation of the population receptive field (pRF) technique developed by Dumoulin and Wandell (2008), used initially for retinotopic mapping. The pRF approach was used to estimate different neuronal population quantities such as sound frequencies in the auditory cortex. Our model treated the pRF underlying each voxel's response as a one-dimensional Gaussian function of frequency. This technique provided an estimated sensitivity function for each voxel with a given center, or preferred frequency, and sigma, or tuning bandwidth. Sigma was computed as one standard deviation of the normal distribution. The sharpness of tuning (Q) was computed as the ratio between center frequency CF and bandwidth of the Guassian response function (full width at half maximum (FWHM) that was centered about the CF. For each voxel this was defined as CF/FWHM, where FWHM = 2.355 * SD). This means that sharper tuning relates to a higher Q value, whereas broader tuning relates to a lower Q value. The SD was the sigma or tuning width parameter computed from the pRF model.

A high resolution T1 weighted three-dimensional MPRAGE scan of the entire head was collected on every subject with the following parameters: TR = 1.9 s, TE = 2.52 ms, 1 mm thick slices, 256 × 256 matrix (1 mm^3 isotropic voxel size).

A whole head echo-planar image (WHEPI) was collected that was used for registration with the following parameters: acquisition time 30 s, 128 × 128 matrix, seventy-seven 2 mm thick slices, TR = 7 s, TE = 30 ms, flip angle = 90°.

For control participants that had their subcortex analyzed, a proton density weighted (PD) scan was acquired to delineate subcortical ROIs of the MGN and IC. Forty (PD) weighted images were acquired with the following parameters: 89 s acquisition time, 192 mm field of view (FOV), up-sampled to a 512 × 512 matrix (0.375 × 0.375 × 1 mm^3 voxel size), concatenated, motion corrected, and averaged using FSL. Future PD scans will use a different protocol to reduce scan time to ~15 min. Following this protocol, only a minimum of 5 PD scans would be required using the following parameters: acquisition time 179 s, acquisition matrix 512 × 512 (0.3 × 0.3 × 1 mm^3 voxel size), TR = 3.25 s, TE = 32 ms, flip angle = 120°, interleaved slice acquisition, FoV read = 160 mm, FoV phase = 100%, parallel imaging (GRAPPA) with an acceleration factor of 2, bandwidth 40 Hz/pixel, 18 slices, each 1 mm thick, FOV = 160 mm, as described in McKetton et al. (2015).

The first auditory stimulus was used to test whether we could achieve reliable tonotopic maps of the subcortex. We initially used an auditory stimulus that consisted of eight 32 s logarithmic sweeps from 20 Hz–20 kHz (4:16 min each run). Within one session, between 10–15 functional runs were collected. Functional EPI (echo-planar imaging) parameters: 4:16 min acquisition time, 192 mm FOV and 128 × 128 matrix (1.5 × 1.5 × 2 mm^3 voxel size resampled to 0.75 mm isotropic), TR = 2 s, TE = 30 ms, twenty-two 2 mm thick slices per slab (Figure 4.1 b). In the example showing the subcortex, at least three sessions worth of data were required (~35 scans) for reliable tonotopic and tuning width maps. For cortical data, a minimum of one session (10 scans) was necessary.

The second auditory stimulus was modified to include blanks. This allowed us to model the hemodynamic response function (HRF) delay better, resulting in an improved signal-to-noise ratio (SNR). We used this stimulus for collecting functional data on the 61 participants for the study. The second auditory stimulus consisted of 6 ascending and 6 descending 24 s long sweeps from 20 Hz-10 kHz jittered with four 8 s blanks. Ten functional runs were collected per session

with the following parameters: 5:20 min acquisition time, 192 mm FOV, 128 matrix (1.5 × 1.5 × 2 mm^3 voxel size resampled to 0.75 mm), TR = 2 s, TE = 30 ms, twenty-two 2 mm thick slices.

ROIs were traced in surface inflated space by a rater blind to group membership following boundaries of auditory regions consistent with interpretations from (Moerel et al., 2014; Kaas & Hackett 2000).

4.4 Data Analysis

Data were preprocessed using Matlab, Freesurfer, and AFNI [http://afni.nimh.nih.gov/afni/]. Data were deskulled, and the functional runs were time shifted, deobliqued, upsampled to twice the resolution, motion corrected, highpass filtered, and registered to the WHEPI within the session, and then to the master WHEPI that was then registered to the anatomical T1. MGN ROIs were delineated from the PD weighted mean (Figure 4.1 c–e), IC ROIs were delineated from T1 weighted scans (Figure 4.2 a–b) both using FSL [http://fsl.fmrib.ox.ac.uk/fsldownloads/fsldownloadmain.html], whereas functional cortical ROIs were delineated using the AFNI surface mapper SUMA [http://afni.nimh.nih.gov/afni/suma] (Figure 4.2 d).

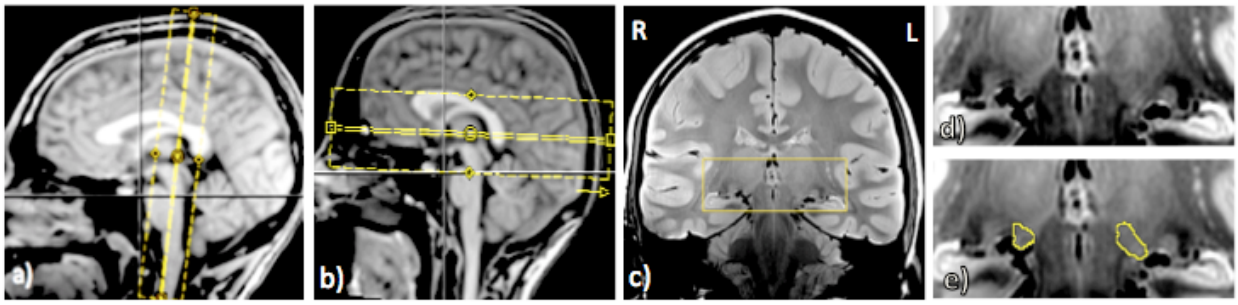

Figure 4.1

Neuroimaging slice selection plan and MGN localization. a) Sagittal view of a T_1 weighted image displaying the slice selection box (yellow) used as a template for collecting the PD slab used for MGN ROIs. b) Slice selection box used as template for collecting functional runs covering auditory cortex and subcortex. c) Coronal PD averaged slab (512 matrix) of a control. The yellow box encloses both the right and left MGN. d) Zoomed view. e) Outline of the right and left MGN ROI.

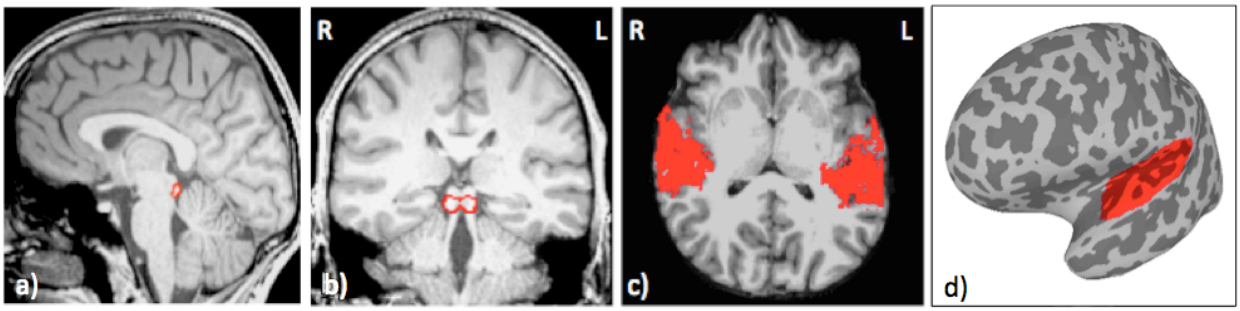

Figure 4.2 IC and auditory cortex localization. a) Sagittal and b) Coronal T_1 weighted view of the IC ROI outline (red). c) Axial and d) sagittal view of the functional auditory cortex ROIs.

4.5 pRF Model

Data were analyzed using an adaptation of the pRF technique from the pRF code developed by Kevin DeSimone [http://kdesimone.github.io/popeye/]. This model treated the pRF underlying each voxel's response as a 1D Gaussian function of frequency providing an estimated sensitivity function for each voxel with a given center, or preferred frequency, and standard

deviation, or tuning bandwidth (Figure 4.3). pRF maps were thresholded at $r^2 = .0625$ ($r = .25$), $p = .01$. Cortical data were further 3D visualized with AFNI's surface mapper SUMA.

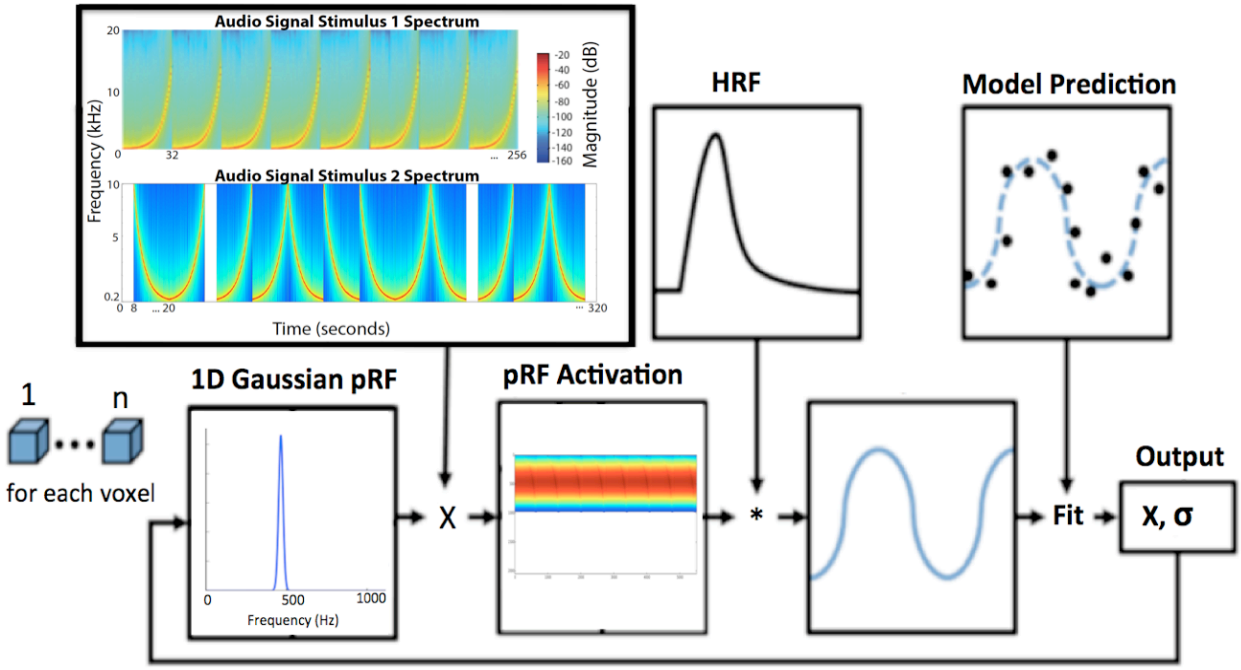

Figure 4.3 Population receptive field (pRF) model used in fMRI data collection to establish the tonotopic mapping of cortex and subcortex. This model provides an estimated sensitivity function for each voxel with a given center frequency and bandwidth.

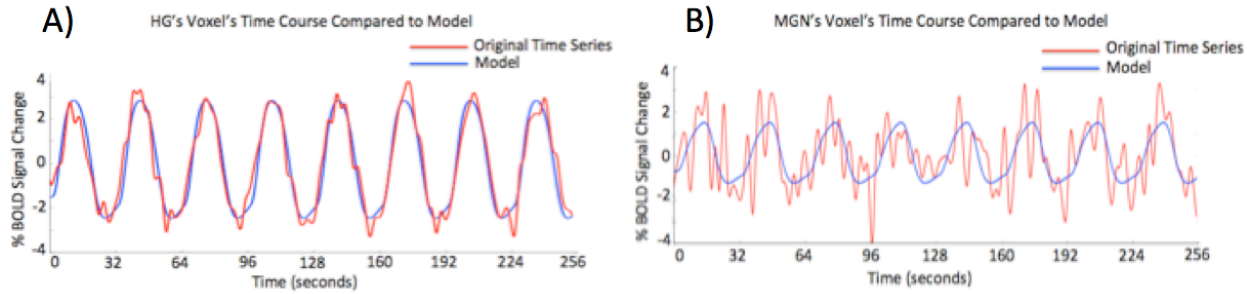

Figure 4.4 Auditory voxel time course compared to model in A) HG of the auditory cortex, and B) MGN of the subcortex. Threshold: $r^2 = .0625$ ($r = .25$), $p = .01$.

4.6 Subcortical Results

We applied our pRF model that estimated the best frequency tonotopic maps and tuning bandwidth maps of the auditory cortical and subcortical (IC, MGN) regions in healthy control human subjects that listened to the first auditory stimulus. Cortical data were consistent with previous findings that showed lower frequencies on the crest of HG that were flanked by two high-frequency zones posteromedially towards the planum temporale and anteromedially towards the circular sulcus. Consistent with the current paradigm, this gives rise to at least two primary tonotopic gradients oriented in a distinct V-shaped high-low-high frequency pattern (Figure 4.5).

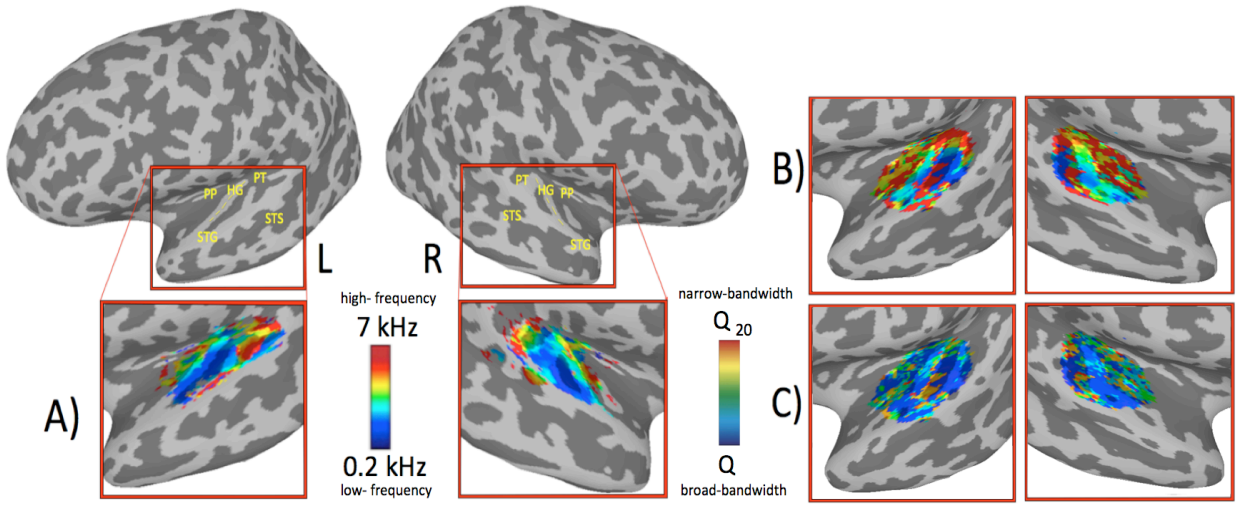

Figure 4.5 Tonotopic pRF and tuning curve map of the auditory cortex using auditory Stimulus 1 on controls as a proof of concept that our model worked. Center frequency gradient and tuning curve maps were plotted on the unfolded cortical surface for each hemisphere. Left and right hemispheres of the primary A1 that colocalise with Heschl's gyrus (HG), a transverse superior temporal gyrus, that separates the planum polare (PP) on the anterior side from the planum temporale (PT) posteriorly. Panel A shows the left and right hemisphere from a control subject from 3 sessions of data (35 functional runs). Panel B shows left and right hemisphere pRF maps and C) tuning sharpness (Q) maps from a control subject from 1 session of data (10 functional runs). All data show significant voxels thresholded at $r^2 = .0625$ ($r = .25$), $p = .01$.

The tonotopic map of the IC displays a high-to-low frequency gradient from the ventral (V) to dorsal (D) orientation in the sagittal plane consistent with one other study (DeMartino et al., 2013) (Figure 6.6). Moving through the slice selection from (a–c; [anterior-posterior direction]), we interpret a low-to-high-to-low tonotopic gradient that starts to emerge in the superior-inferior direction (Figure 4.7).

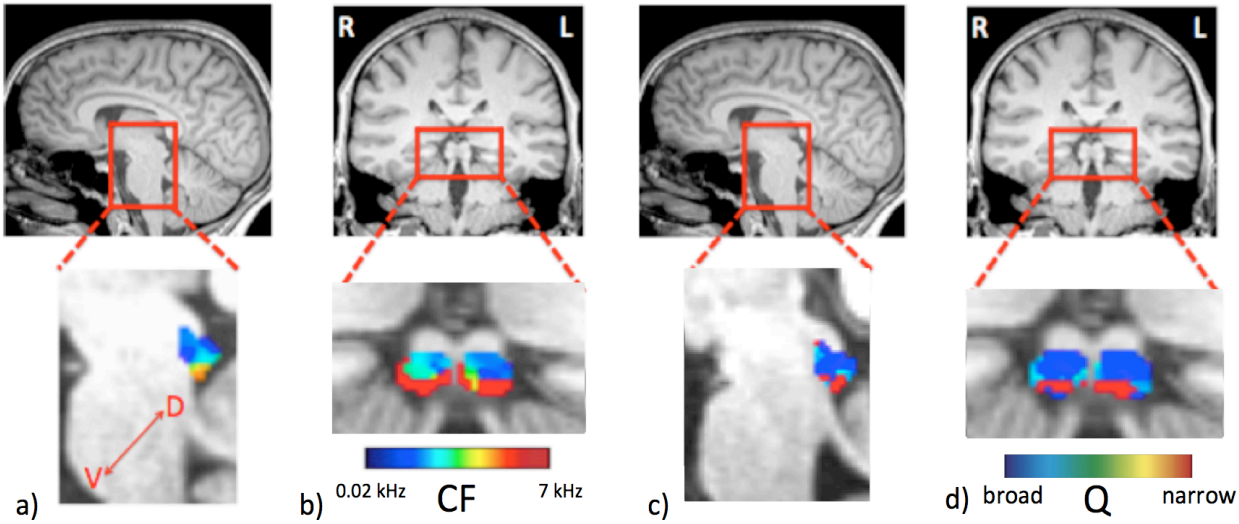

Figure 4.6 Tonotopic and Tuning Width Maps of the IC.

a) (Top) Sagittal, (bottom) zoomed in view of the IC displaying the Center Frequency (CF) tonotopic maps showing the high-to-low frequency gradient from the ventral (V) to dorsal (D) orientation.
b) (Top) Coronal, (bottom) zoomed in view of the right and left tonotopic maps of the IC.
c) (Top) Sagittal, (bottom) zoomed in view of the IC displaying tuning sharpness (Q) maps.
d) (Top) Coronal, (bottom) zoomed in view of the right and left tuning sharpness maps of the IC.

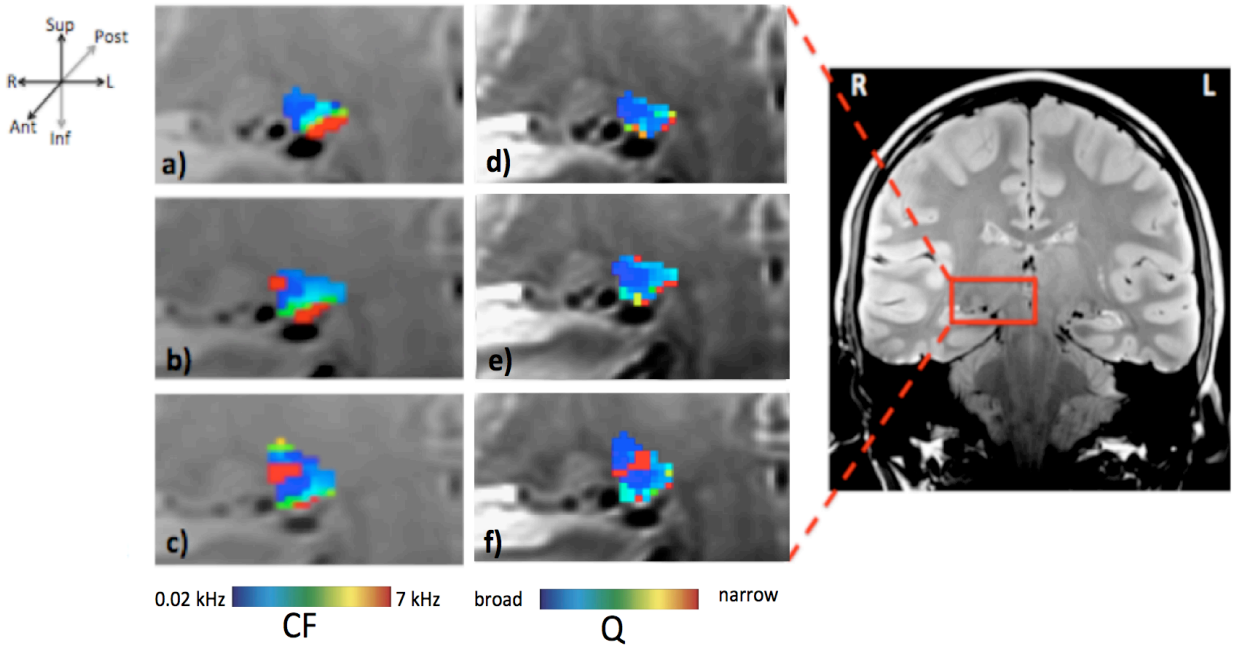

Figure 4.7 Tonotopic map of the MGN. Panels (a–c) display the tonotopic organization and (d–f) display the tuning sharpness (Q) maps of the right MGN.

4.7 AP Results

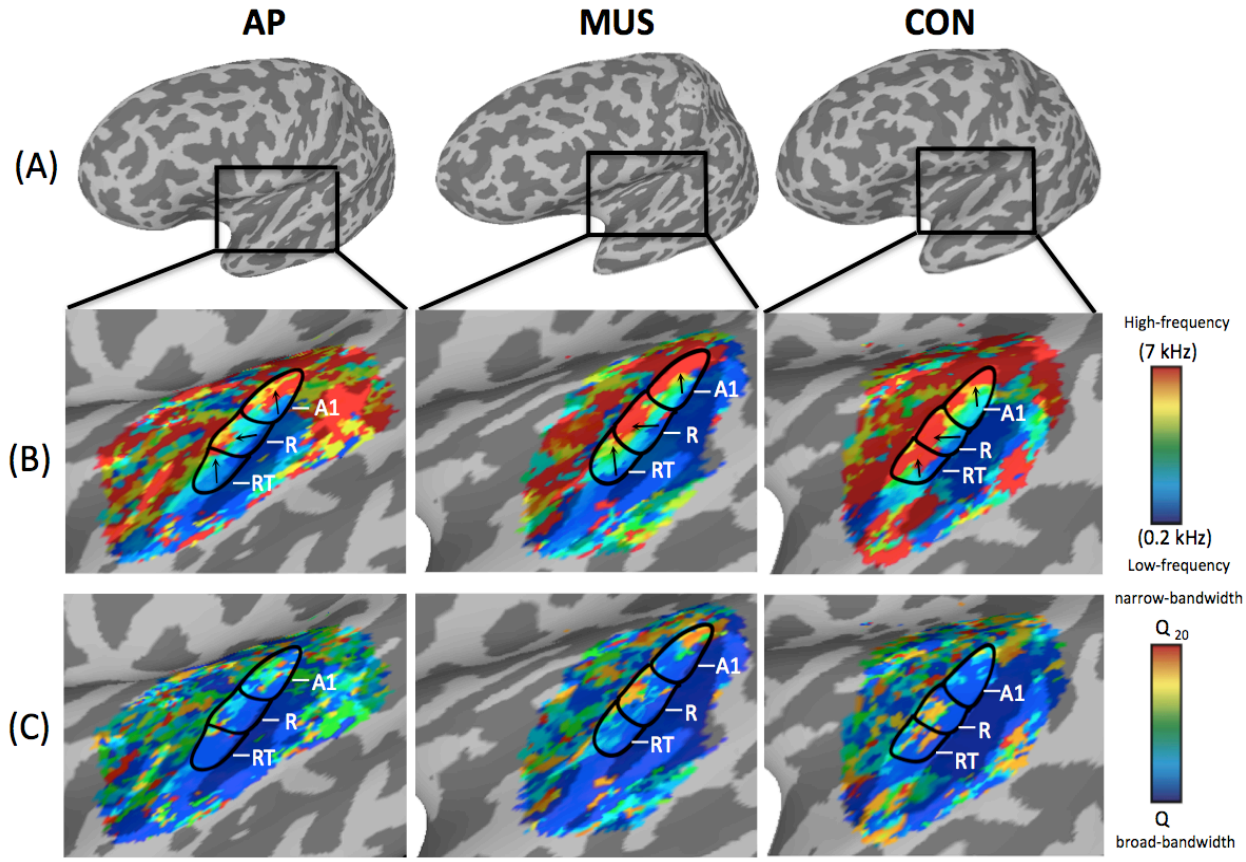

Figure 4.8 Tonotopic pRF and tuning curve map of the auditory cortex in representative subjects from the absolute pitch (AP) musician group (1st column), musician without AP group (2nd column), and control participant without musical training (3rd column) from 1 session. Panel (A) shows left surface inflated hemispheres. Panel (B) shows the left zoomed in view of the pRF map for A1, R, RT and belt regions. Solid black lines indicate boundaries between tonotopic maps, and black arrows indicate direction of tonotopic gradient (low-high) consistent with interpretations from (Moerel et al., 2014; Kaas & Hackett 2000). Panel (C) shows the left zoomed in view of the tuning sharpness maps (Q) for A1, R, RT and belt regions.

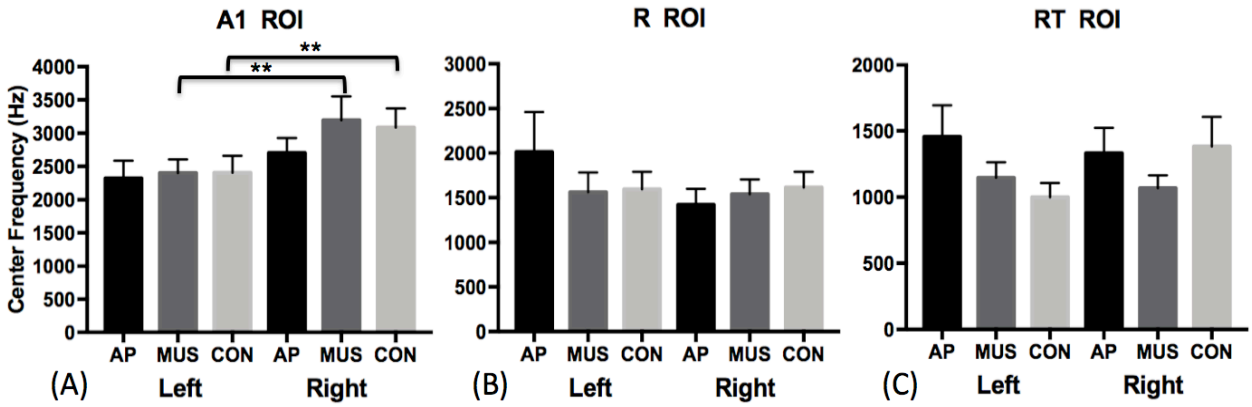

Figure 4.9 Center frequency (CF) means ± SEM for auditory ROIs in musicians with absolute pitch (AP) non-AP musicians (MUS), and controls without any musical background (CON). Only significant voxels corresponding to the auditory stimulus were used in the analyses (r^2 = .0625, $p < .05$). Panel (A) shows left and right primary auditory cortex (A1) region of interest (ROI). Panel (B) shows left and right rostral core (R) ROIs. Panel (C) shows left and right rostral-temporal core (RT) ROIs.

Center frequency (CF) for each auditory ROI was subjected to a 3 × 2 mixed model analysis of variance (ANOVA), with group (AP, MUS, and CON) as the between-groups variable and hemisphere as the within-group variable. There were no significant group by hemisphere interactions for the A1 ($F(1,57) = .74$, $p = .48$), R ($F(1,57) = 1.31$, $p = .28$), or RT ($F(1,57) = 1.96$, $p = .15$) ROIs. There was a significant effect of hemisphere in A1 ($F(1,57) = 18.5$, $p < .001$), but not in the R ($F(1,57) = 1.33$, $p = .25$) or RT ($F(1,57) = 0.28$, $p = .60$) ROIs. There was no effect of group in the A1 ($F(1,57) = 0.74$, $p = .48$), R ($F(1,57) = .18$, $p = .83$), or RT ($F(1,57) = 0.18$, $p = .83$) ROIs.

Post hoc pairwise comparisons (Bonferroni adjusted alphas = .025) revealed no significant differences in CF in the A1 ROI for the left ($p = .82$) or right ($p = .37$) hemispheres in AP subjects compared to musicians, the left ($p = .81$) or right ($p = .24$) hemispheres in AP subjects compared to controls, or the left ($p = .99$) or right ($p = .79$) hemispheres in musicians compared to controls. There were no significant differences in the R ROI for the left ($p = .30$) or right ($p = .62$) hemispheres in AP subjects compared to musicians, the left ($p = .33$) or right ($p = .43$) hemispheres in AP subjects compared to controls, or the left ($p = .94$) or right ($p = .76$)

hemispheres in musicians compared to controls. Likewise, there were no significant differences in the RT ROI for the left (p = .19) or right (p = .30) hemispheres in AP subjects compared to musicians, the left (p = .06) or right (p = .84) hemispheres in AP subjects compared to controls; or the left (p = .53) or right (p = .22) hemispheres in musicians compared to controls. There was a significant difference between the left and right hemipheres in A1 for both musician and control groups (ps < .01), where CF was larger in the right hemisphere, but not in the AP group (p = .13). There were no significant differences between the left and right hemispheres in R for AP (p = .06), musician (p = .94), or controls (p = .95) groups. Likewise, there were no significant differences between hemispheres in RT for AP (p = .54), musician (p = .69), or control (p = .06) groups.

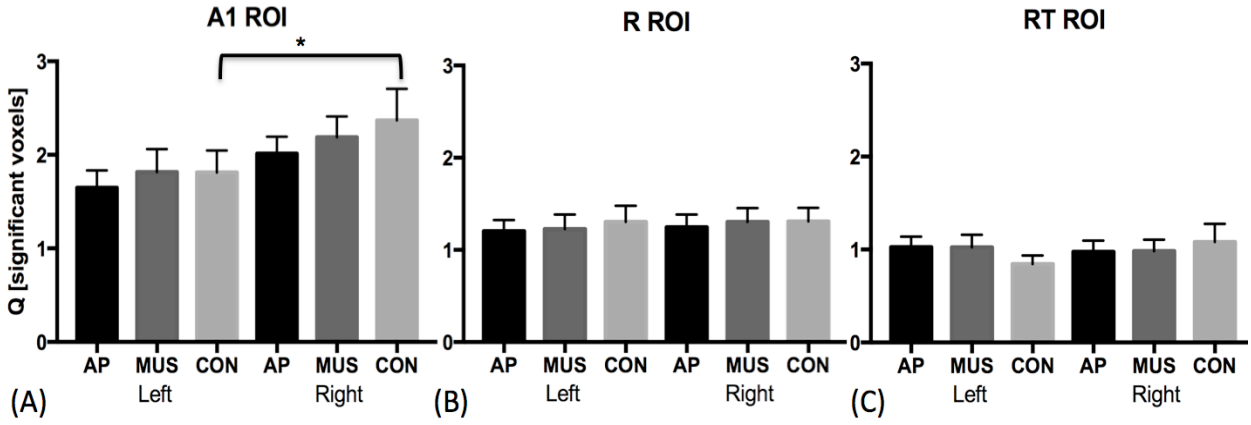

Figure 4.10 Tuning sharpness (Q) (means ± SEM) for auditory ROIs in musicians with absolute pitch (AP), musicians without AP (MUS), and controls without any musical background (CON). Only significant voxels corresponding to the auditory stimulus were used in the analyses (r^2 = .0625, p < .05). Panel (A) shows left and right primary auditory cortex (A1) region of interest (ROI). Panel (B) shows left and right rostral core (R) ROIs. Panel (C) shows left and right rostral-temporal core (RT) ROIs. *p < .05.

Tuning sharpness (Q) for each auditory region ROI was analyzed with a 3 × 2 mixed model analysis of variance (ANOVA), with group (AP, MUS, and CON) as the between-groups variable and hemisphere as the within-group variable. It revealed no significant group by hemiphere interactions in the A1 (F(1,57) = 0.20, p = .82), R (F(1,57) = 0.053, p = .95), or RT (F(1,57) = 0.74, p = .48) ROIs. However, there was a significant effect of hemisphere in A1,

($F(1,57) = 9.41$, $p = .003$), but not in the R ($F(1,57) = 0.21$, $p = .65$) or RT ($F(1,57) = 0.20$, $p = .66$) ROIs. There were no significant effects of group for the A1 ($F(1,57) = 0.20$, $p = .82$), R ($F(1,57) = 0.053$, $p = .95$), or RT ($F(1,57) = 0.74$, $p = .48$) ROIs.

Post hoc pairwise comparisons (Bonferroni adjusted alphas = .025) revealed no significant differences in tuning sharpness (Q) in the A1 ROI for the left ($p = .60$) or right ($p = .63$) hemispheres in AP subjects compared to musicians, the left ($p = .61$) or right ($p = .33$) hemispheres in AP subjects compared to controls, or in the left ($p = .99$) or right ($p = .62$) hemispheres in musicians compared to controls. There were no significant differences for the left ($p = .92$) or right ($p = .78$) hemispheres in AP subjects compared to musicians; the left ($p = .64$) or right ($p = .76$) hemispheres in AP subjects compared to controls, or in the left ($p = .72$) or right ($p = .98$) hemispheres in musicians compared to controls. Likewise, there were no significant differences in the RT ROI for the left ($p = .98$) or right ($p = .97$) hemispheres in AP subjects compared to musicians, the left ($p = .27$) or right ($p = .62$) hemispheres in AP subjects compared to controls, or the left ($p = .28$) or right ($p = .64$) hemispheres in musicians compared to controls.

There was a significant difference between hemispheres in A1 for controls ($p = .026$), but not for the AP ($p = .14$) or musician ($p = .13$) groups. There were no significant differences between hemispheres in R for AP ($p = .79$), musician ($p = .98$), or control ($p = .63$) groups. Likewise, there were no significant differences between hemispheres in RT for AP ($p = .79$), musician ($p = .83$), or control ($p = .22$) groups.

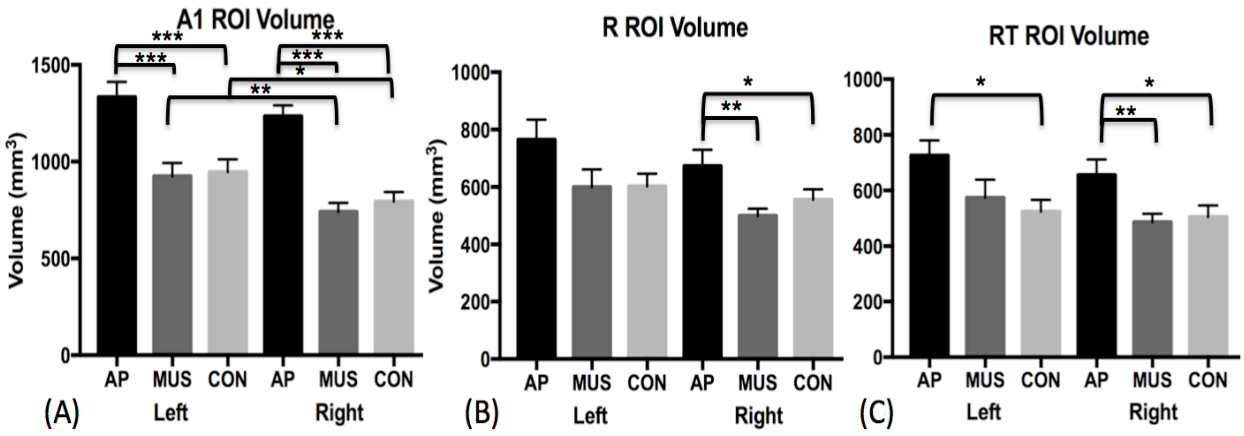

Figure 4.11 Volume of Auditory ROIs (means ± SEM) in musicians with absolute pitch (AP) non-AP musicians (MUS), and controls without any musical background (CON). Only significant voxels corresponding to the auditory stimulus were used in the analyses (r^2 = .0625, p < .05). Panel (A) shows left and right primary auditory cortex (A1) region of interest (ROI). Panel (B) shows left and right rostral core (R) ROIs. Panel (C) shows left and right rostral-temporal core (RT) ROIs. ***ps < .001, **ps < .01, *ps < .05.

The volume of each auditory ROI was analyzed with a 3 × 2 mixed model analysis of variance (ANOVA), with group (AP, MUS, and CON) as the between-groups variable and hemisphere as the within-group variable. It revealed no significant group by hemisphere interaction in the A1 (F(1,57) = 0.49, p = .61), R (F(1,57) = 0.19 , p = .83), or RT (F(1,57) = 0.35, p = .70) ROIs; however, there was a significant effect of hemisphere in A1 (F(1,57) = 16.6, p < .001) and R (F(1,57) = 4.57, p = .037), but not in RT (F(1, 57) = 2.91, p = .093) ROIs. There was a significant effect of group in A1 (F(1,57) =21.8, p < .001), R (F(1,57) = 5.12, p = .009), and RT (F(1,57) = 6.08, p = .004) ROIs.

Post hoc pairwise comparisons (Bonferroni adjusted alphas = .025) revealed significant differences between the volumes of the A1 ROIs for the left and right hemispheres in AP subjects compared to musicians and AP subjects compared to controls (ps < .001), but not between the left (p = .83) or right (p = .47) hemispheres in musicians compared to controls. There was a significant difference in volume in R for the right (p = .005) hemisphere and approaching significance for the left hemisphere (p = .055) in AP subjects compared to musicians. There was a significant difference in the right (p = .049) hemisphere R volume and

approaching significance in the left (p = .059) hemisphere in AP subjects compared to controls. There were no significant differences in R ROI volume for the right (p = .35) or left (p = .97) hemispheres in musicians compared to controls. There was a significant difference in the RT ROI volume for the right (p = .008) hemisphere and marginal significance for the left (p = .056) hemisphere in AP subjects compared to musicians. There were significant differences in volume for both the left (p = .012) and right (p = .018) hemispheres in AP subjects compared to controls, but no significant differences in RT volumes for either the left (p = .52) or right (p = .76) hemispheres in musicians compared to controls. There were no significant differences in the left or right A1 volume for AP (p = .12); however there were differences between the musician (p = .004), and control (p = .016) groups where the left side was larger. There were no significant differences in the left and right R volumes for AP (p = .16), musicians (p = .13), or controls (p = .47), nor the left or right RT volumes for the AP (p = .25), musician (p = .15), or control (p = .75) groups.

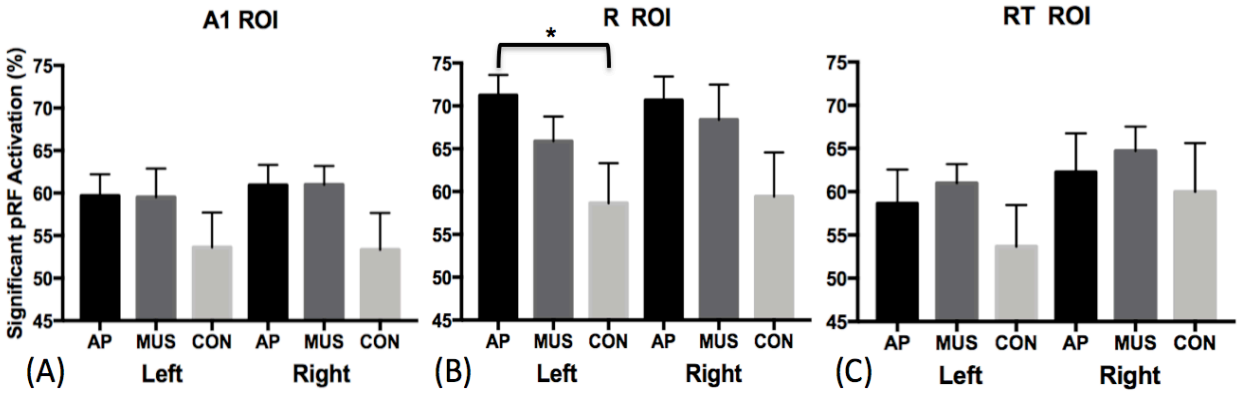

Figure 4.12 Percentage of significant pRF activation means ± SEM for auditory ROIs in musicians with absolute pitch (AP), non-AP musicians (MUS), and controls without any musical background (CON). Only significant voxels corresponding to the auditory stimulus were used in the analyses (r^2 = .0625, p < .05). Panel (A) shows left and right primary auditory cortex (A1) region of interest (ROI). Panel (B) shows left and right rostral core (R) ROIs. Panel (C) shows left and right rostral-temporal core (RT) ROIs. *ps < .05.

The percentage of voxels with significant pRF activation (r^2 = .0625, p < .05) for each auditory ROI was subjected to a 3 × 2 mixed model analysis of variance (ANOVA) with group (AP, MUS, and CON) as the between-groups variable and hemisphere as the within-group

variable. It revealed no significant group by hemisphere interaction in the A1 ($F(1,57) = 0.19$, $p = .83$), R ($F(1,57) = 0.15$, $p = .86$), or RT ($F(1,57) = 0.059$, $p = .94$) ROIs, and no significant effects of hemisphere in A1 ($F(1,57) = 0.001$, $p = .98$), R ($F(1,57) = 1.51$, $p = .70$), or RT ($F(1,57) = 2.45$, $p = .12$) ROIs. There were no significant effects of group in A1 ($F(1,57) = 0.001$, $p = .98$) or RT ($F(1,57) = 0.60$, $p = .56$) ROIs, but there were in R ($F(1,57) = 3.56$, $p = .035$).

Post hoc pairwise comparisons (Bonferroni adjusted alphas = .025) revealed no significant differences in A1 for the left ($p = .59$) or right ($p = .99$) hemispheres in AP subjects compared to musicians, the left ($p = .092$) or right ($p = .09$) hemispheres in AP subjects compared to controls, or in the left ($p = .248$) or right ($p = .088$) hemispheres in musicians compared to controls. There were no significant differences in R for the left ($p = .28$) or right hemisphere ($p = .70$) in AP subjects compared to musicians. However, there was a significant difference in the left ($p = .012$) and marginally significant in the right ($p = .058$) hemisphere for AP subjects compared to controls, but no significant difference in the left ($p = .14$) or right ($p = .13$) hemispheres in musicians compared to controls. Likewise, there was no significant difference in RT for the left ($p = .88$) or right ($p = .70$) hemispheres in AP subjects compared to musicians, the left ($p = .44$) or right ($p = .72$) hemispheres in AP subjects compared to controls, or the left ($p = .35$) or right ($p = .46$) hemispheres in musicians compared to controls. There were no significant differences between the left and right hemispheres in A1 for AP ($p = .68$), musician ($p = .66$), or control ($p = .93$) groups, in R for AP ($p = .89$), musician ($p = .54$), or controls ($p = .86$) groups, or in RT for AP ($p = .52$), musician ($p = .36$), or control ($p = .26$) groups.

Since there were no significance differences between hemispheres for the percentage of pRF activation for either auditory ROI, we collapsed the hemispheres for further analyses.

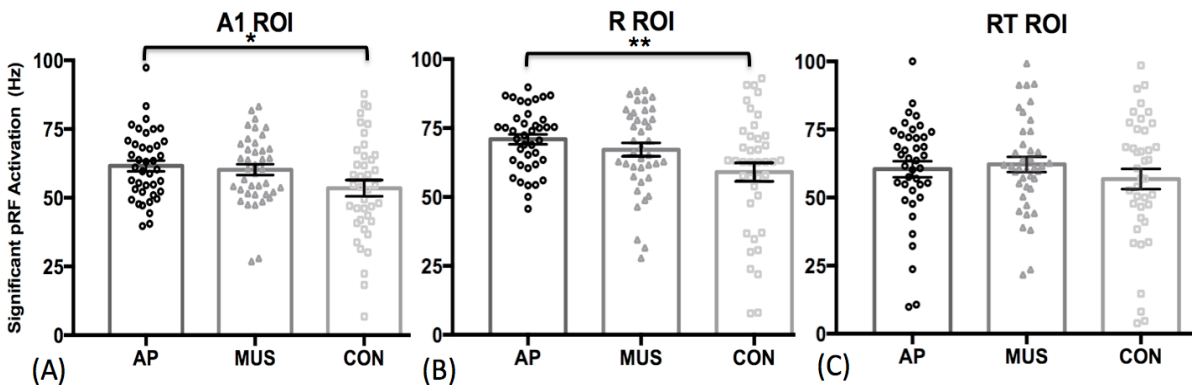

Figure 4.13 Percentage of significant pRF activation (means ± SEM) for auditory ROIs in musicians with absolute pitch (AP) non-AP musicians (MUS), and controls without any musical background (CON), collapsed across hemispheres. Only significant voxels corresponding to the auditory stimulus were used in the analyses (r^2 = .0625, p < .05). Panels (A–C) shows each subjects data point for the A1, R, and RT ROI respectively. **p < .01 , * p < .05.

There was a significant main effect of group for the percentage of pRF activation in the A1 (F(1,117) = 3.46, p = .035) and R (F(1,117) = 5.26, p = .006) ROIs, collapsed across hemispheres. Post hoc Bonferonni tests for multiple comparisons revealed a significant increase in the percentage of pRF activation for AP participants compared to controls within A1 ROIs (p < .05) and within R ROIs (p < .01), collapsed between hemispheres.

4.8 Discussion

This has been the first study to look at tonotopic and tuning width maps in AP musicians, non-AP musicians, and non-musician groups within A1, R, and RT subdivision of Heshl's Gyrus. We did not find significant differences in the center frequency or tuning width maps using our pRF model between groups suggesting that similar frequency selectivity mechanisms reside within these auditory cortical regions despite the level of musicianship. Furthermore, these results may indicate that other salient mechanisms are at play to account for the enhanced pitch categorization and auditory working memory abilities found in AP. Frequency selectivity or the sharpness of tuning reflects the gamut of frequencies neurons respond to. Previous studies that recorded these neurons in non-human primates found sharper (narrower) tuning within A1 core

regions as compared to broader tuning widths in neurons in belt regions (Rauschecker et al., 1995; Hackett et al., 1998; Rauschecker & Tian, 2004; Kajikawa et al., 2005; Kusmierek & Rauschecker, 2009). Tuning widths were also reported narrower in the human auditory core regions compared to non-human primates based on previous electrophysiological recordings (Bitterman et al., 2008).

It is often hard to compare frequency tuning widths in multiple auditory pathway areas using electrophysiology recordings due to the location (i.e., cortical, subcortical, brainstem) that neural responses are being recoded from (Barlett et al, 2011). The use of fMRI allows for full brain coverage and has the capability to probe both cortical and subcortical regions within each single subject and extract both tonotopic and tuning width maps (De Martino et al., 2013). De Martino et al. (2013) conducted an fMRI study using a 7T scanner and reported the selectivity of spectral tuning (i.e., tuning width) within the cortex and IC. Their results indicated narrow tuning within the center and broader tuning around the outer shell of the IC, and narrow tuning within a region along HG and broader tuning around belt regions of the auditory cortex. Furthermore, a number of IC voxels were more narrowly tuned up to 0.45 octaves (Q = 3.23) compared to broader tuning 0.6 octaves (Q = 0.45) within cortical regions. Our subcortical results of the IC are somewhat in line with DeMartino et al. (2013) in that sharper tuning was found more in the inferior central portion of the IC. Similarly, we also report narrower tuning within HG compared to broader tuning surrounding belt and parabelt regions where broader tuning was more pronounced on the posterior side of HG.

Tuning widths extracted from fMRI data take into account a population of thousands of neurons within a voxel. Comparing fMRI data to electrophysiology single neuron recordings may not be straightforward. De Martino et al. (2013) reported cortical tuning within a voxel spanned over a wide range of values and at their lower boundaries were roughly half (0.45) of an octave. These values differed from human (Bitterman et al., 2008) and monkey data (Barlett et al., 2011) from single neuron recordings that showed narrower tuning widths up to 1/12 octave. These disparities can be attributed to the lower spatial resolution of fMRI compared with electrophysiology studies. Moreover, broader tuning widths would then be designated to voxels that have a number of different best frequencies, further skewing the neuroimaging results to

more voxels that display broader tuning widths. In addition, noise can further skew the resulting tuning width maps since the voxel's response to the auditory stimulus may not represent all the varied receptive field responses neurons can have. Also, the pRF model that we used in our study compares to DeMartino's et al. (2013) model that measured sigma or tuning width as the width of the main center frequency or spectral peak within the voxel. As such, other spectral peaks within the voxel would not be included in our pRF fitting, so any correlation with tuning width and spectral complexity would not be warranted. Lastly, it has been shown that neural tuning width can be related to how loud the stimulus is such that tuning gets broader the louder the sound level. Therefore, direct comparisons to eletrophysiological research that normally use ~10 dB to measure tuning widths, may not be directly comparable to neuroimaging studies that normally use ~60 dB to deliver their stimulus (De Martino et al., 2013).

Both center frequency and tuning sharpness within all the ROIs were not significantly different and were generally distributed evenly within groups. Taken together, there were no significant differences in tuning sharpness when comparing AP musicians to non-AP musicians and non-musicians in our large sample size. Our results may indicate that AP subjects do not have sharper frequency selectivity that is linked to their performance in pitch acuity at the level of the population of neurons responding to the auditory stimulus.

Furthermore, a number of myeloarchitectonic studies in non-human primates (Hackett et al., 1998) and humans (Beck 1928; Hopf 1954; rev Nieuwenhuys, 2012) revealed heavy myelination due to increased staining for cortical myelin density on post-mortem tissue within the most caudally located A1 region of the primary auditory cortex, and less so in R and RT regions of HG, reflecting an increased density of thalamocortical connections with the MGN. These findings were corroborated with recent in vivo mapping of cortical myelin density non-invasively using MRI with quantitative T1 (Sigalovsky et al., 2006), or T2/T2* weighted contrasts (Glasser & Van Essen, 2011; De Martino et al., 2014) and had shown that HG was more densely myelinated compared to surrounding belt and parabelt regions. In addition, the human A1 (hA1) subdivision of HG was the most densely myelinated region (De Martino et al., 2014; rev Moerel et al., 2014). Of importance, it was described that the myelin-related contrast displayed individual variability among hemispheres and individuals (De Martino et al., 2014).

This may be in part due to differences in pitch processing abilities, which were not accounted for in either study. Since the MGN receives heavy reciprocal connections from the auditory cortex, this indicates that the cortex and MGN are grouped together as a functional unit. Taken together, our findings suggest that despite the level of musicianship and AP ability, the MGN may also not show differences in frequency selectivity—although future research in assessing differences in tuning width of the MGN in AP and non-AP musicians would still need to validate this assertion.

Furthermore, our results found consistent tonotopic maps of the cortex that did match previous studies which found: a high to low progression in A1, followed by a reversal gradient of low to high in R, followed by a gradient of high to low in RT, with extended gradients into neighbouring belt regions as found in neuroimaging studies in humans (Da Costa et al., 2011; Moerel et al., 2012; DeMartino et al., 2013, Moerel et al., 2014) and in micro-electrode studies non-human primates (Morel et al., 1993; rev Kaas & Hacket., 2000). The auditory cortical anatomical model in the monkey has been well defined predominantly based on neuro-electrical recordings (rev Kaas, 2011). However, there exist many differences in the human auditory cortex as compared to the monkey auditory cortex. Some differences include larger cortical surface areas, additional gyri, more inter-individual variability, and sharper frequency tuning in humans (Galaburda et al., 1978; Hackett et al., 2001, Bitterman et al., 2008). Therefore, it may not be as straightforward to apply the monkey model to the human brain for direct comparisons.

To our best knowledge, this has been the first study to extract the volume of auditory ROIs comprising Heschl's gyrus separately (A1, R and RT) in humans categorized by pitch perception attributes. Of most significance, A1 volumes were significantly larger in both hemispheres in AP musicians as compared to non-AP musicians and non-musician controls in this study. As well, our results are consistent with reported findings that A1 of the primary auditory cortex occupies approximately half of the HG volume (Rademacher et al., 2001). Furthermore, we report all left auditory ROIs comprising HG (A1, R and RT) were larger than those comprising the right HG in each group, however only the left A1 volumes in the non-AP musician and control groups were significantly larger than the right A1 volume.

A number of previous studies have reported the left HG was larger than the right using MRI (Penhune et al., 1996; McCarley et al., 2002; Sumich et al., 2002; Dorsaine-Pierre et al., 2006; Takahashi et al., 2006; Golestani et al., 2007; Salisbury et al., 2007) and post mortem (Chance et al., 2008; Smiley et al., 2013). Overall, the asymmetry differences described in these studies showed that the left HG on average was 10–30% larger than the right HG. We have found the similarity only in the A1 ROI, and taking together all ROIs comprising HG in summation, we did not find significant difference in the overall HG volume between hemispheres in all three groups. We had used boundary delineations of the recent working model of the human auditory cortex that is more stringent and only includes auditory regions comprising A1, R and RT to demark HG core in our analyses (Moerel et al., 2014). Our results are in line with other neuroimaging studies including those with large sample sizes that did not report hemispheric asymmetry of the HG (Kulynych et al., 1995; Franguo et al., 1997, Schneider et al., 2002; Knaus et al., 2006). Taken together these results in asymmetry discrepancies are likely due to various interpretations and methods of defining the borders of HG. It is frequently agreed that the auditory core comprises HG. There are a few studies that also include surrounding areas of the planum temporale and planum polare leading to considerable overestimation of the auditory core size and potential biases on asymmetry differences (Da Costa et al., 2011, Herdener et al., 2013; Langers, 2014).

As well, we report more significantly activated voxels in AP compared to control subjects when listening to the auditory task in A1 and R ROIs. Although non-AP musicians showed higher activations in these regions compared to controls, the results were not significant.

Chapter 5

Experiment 4: Central Basis for Absolute Pitch (structural MRI)

5.1 Abstract

The brains of musicians have been long studied. With the advent of neuroplasticity, questions pertaining to how musical practice affects learning, auditory processing, and motor skills have been described in a number of studies that looked at anatomical differences in musicians. Such findings include increased corpus callosum (Schlaug et al., 1995b; Gaser & Schlaug, 2003), cerebellum, and primary motor cortex volumes in musicians (Gaser & Schlaug, 2003; Hutchinson et al., 2003; rev Schlaug et al., 2001; Münte et al., 2006), increased gray matter density in Broca's area in male musicians (Sluming et al., 2002), increased volumes in premotor regions, parietal areas, Heschl's and inferior frontal gyri in expert musicians (Gaser & Schlaug, 2003) all compared to non-musician controls. There have not been many studies that looked at anatomical differences in AP, however a structure that has commonly been implicated in AP possessors is the planum temporale (PT). Based on structural neuroimaging, discrepancies within the PT volume in AP musicians, non-AP musicians, and controls with minimal to no musical experience have been reported. Some studies reported a leftward asymmetry in volume (Schlaug et al., 1995a; Chen et al., 2000; Keenan et al., 2001; Luders et al., 2004), while others do not (Zatorre et al., 1998; Bermudez & Zatorre 2005; Bermudez et al., 2009). Furthermore, inconsistencies have also been found using whole brain gray matter structural analyses and cortical thickness in AP. Some studies reported thinner cortex in AP (Bermudez et al., 2009), whereas other studies reported thicker cortex in AP (Dohn et al., 2013). The purpose of the following study was to compare cortical thickness and volume differences in a large sample size of AP musicians, non-AP musicians, and controls with minimal to no musical experience (N = 61), to see where our results diverge and compare with previous studies.

5.2 Methods: Participants

A high-resolution structural MRI scan was collected on 61 participants for the following experiment. Participant information is described in (Table 3.1).

5.3 Method: Data Acquisition, Processing, and Measurements

All images were acquired using a 3T Siemens Trio MRI scanner with a 32-channel head coil at York University. Each subject ($N = 61$) had a high-resolution T1 weighted three-dimensional MPRAGE scan of the entire collected on every with the following parameters: TR = 1.9 s, TE = 2.52 ms, 1 mm thick slices, 256 × 256 matrix (1 mm^3 isotropic voxel size).

Freesurfer 5.3.0 was used to automatically segment all ROI structures from subcortical and cortical parcellations based on the Destrieux 2009 atlas on AP, musician, and control subjects ($N = 60$). Visual inspection was performed to ensure quality assurance of all datasets. All ROIs were run through SPSS for statistical analysis. Results were obtained using post hoc pairwise comparisons (Bonferroni adjusted alphas = .025), $p < .05$ for all significant structures. Data for all tests were normally distributed as confirmed by the Shapiro-Wilk test ($p > .05$).

5.4 Results: Cortical Thickness and Volume

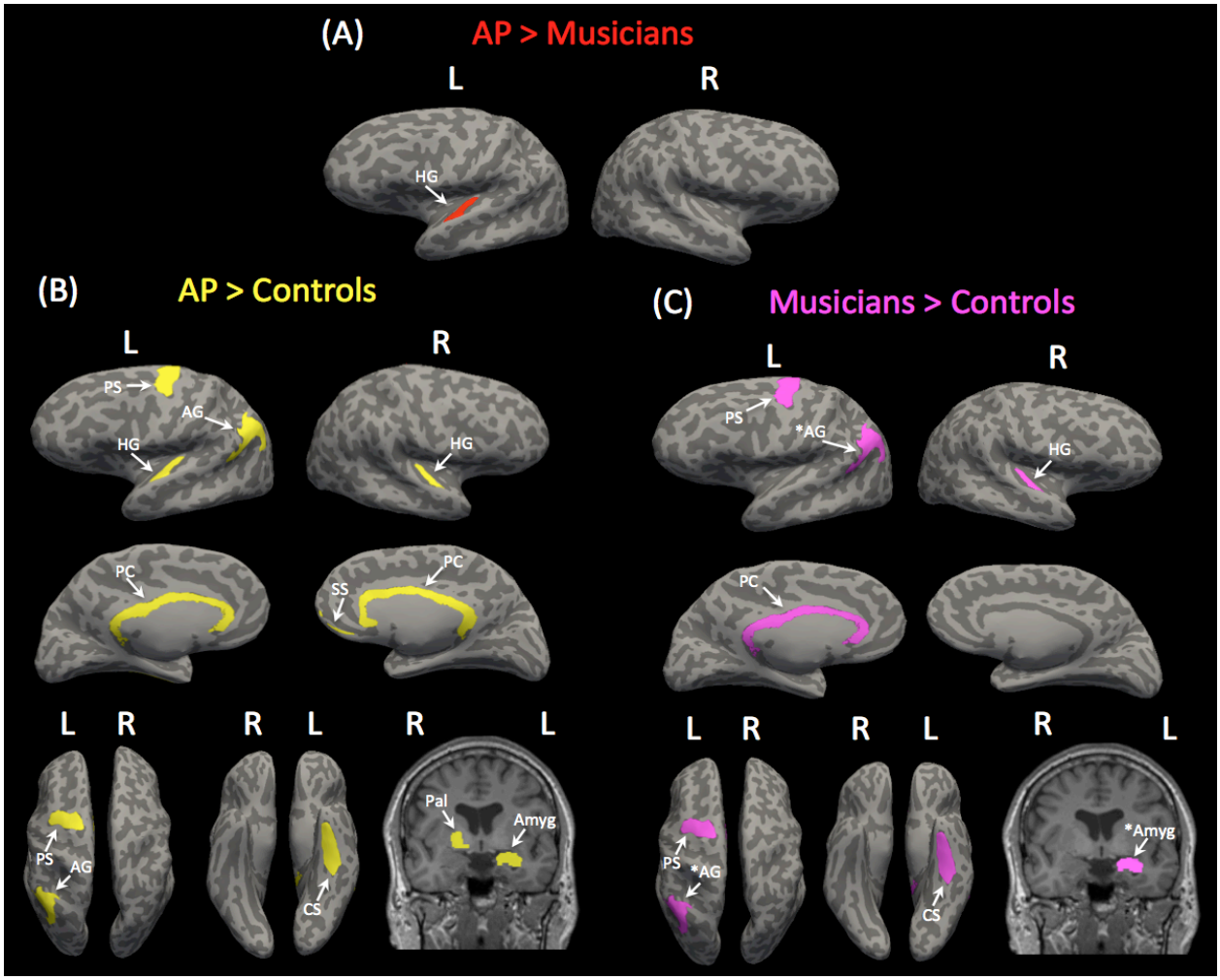

Figure 5.1 Cortical and subcortical areas showing significantly increased structures in thickness and volume in AP compared to musicians (red), AP compared to controls (yellow), and musicians compared to controls (pink). Results were displayed on an AP participant's semi-inflated cortical surface and whole brain volume as an example.

(A) Semi-inflated cortex, L and R lateral showing the region of interest (ROI) in red indicating a significant increase in cortical thickness of the in AP compared to musicians.

(B) Top row: L and R lateral, Second row: L and R medial, Third row: superior, inferior, and whole brain coronal views. Regions of interest (ROIs) in yellow indicate significant increases in cortical thickness (HG, PC) cortical volume (AG, CS, SS, PS), and subcortical volume (Amyg and Pal) in AP compared to controls. (C) Top row: L and R lateral, Second row: L and R medial, Third row: superior, inferior, and whole brain coronal views. Regions of interest (ROIs) in pink

indicate significant increases in cortical thickness (HG, PC), cortical volume (PS), and approaching significance as denoted with an asterisk in cortical (AG) and subcortical volume (Amyg) in musicians compared to controls. Results were obtained using post hoc pairwise comparisons (Bonferroni adjusted alphas = .025), $p < .05$ for all structures.

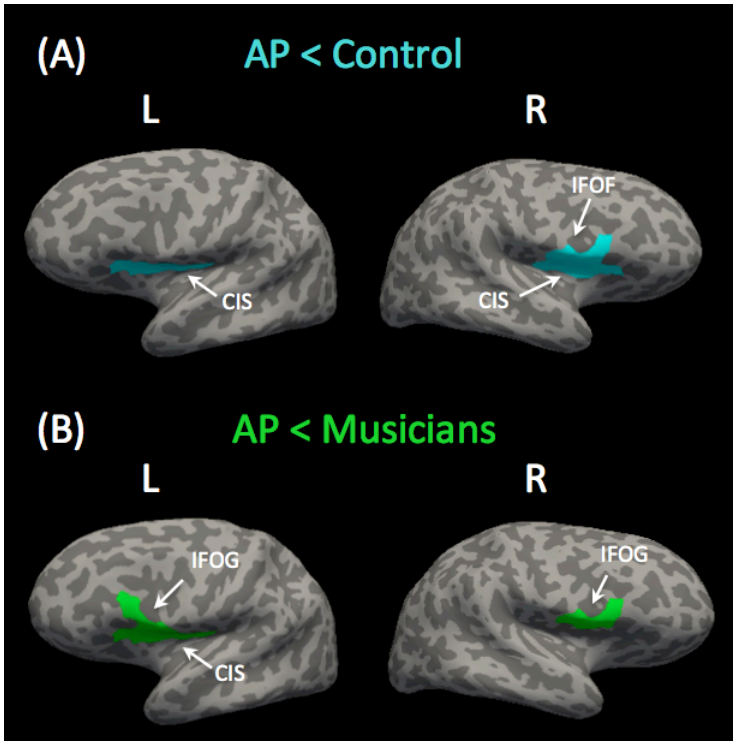

Figure 5.2 Cortical areas showing significantly decreased structures in thickness and volume in AP compared to controls (blue), and AP compared to musicians (green). Results were displayed on an AP participant's semi-inflated cortical surface. (A and B) Semi-inflated cortex: R and L lateral view. Blue ROIs indicate areas of significant decreased cortical thinning (IFO) and volume (CI) in AP compared to controls, and in AP compared to musicians (green). Results were obtained using Post hoc pairwise comparisons (Bonferroni adjusted alphas = .025), $p < .05$ for all structures.

Table 5.1
Cortical and Subcortical Thickness and Volume

Structure		*p*-values		
Thickness	***Side***	***AP > MUS***	***AP > CON***	***MUS > CON***
Heschl's gyrus (HG)	Left	.038	.001	
(Anterior transverse temporal gyrus of Heschl)	Right		.001	.036
Pericallosal sulcus (PC)	Left		.004	.026
(Pericallosal sulcus of corpus callosum)	Right		.012	
Volume				
Angular Gyrus (AG) (Parietal Inferior)	Left		.025	*.057
Amygdala (Amyg)	Left		.022	*.081
Pallidum (Pal) (Globus pallidus)	Right		.039	
Anterior transverse collateral sulcus (CS)	Left		.004	.005
Suboribital sulcus (SS)	Right		.025	
(sulcus rostrales, supraorbital sulcus)				
Precentral sulcus (PS) (superior part)	Left		.026	.018
Thickness		***AP < MUS***	***AP < CON***	
Inferior frontal opercular gyrus (IFOG)	Left	.045		
(Opercular part of the inferior frontal gyrus)	Right	.014	.037	
Volume				
Circular insular sulcus (CIS)	Left	.016	.001	
	Right		.028	

* *Marginally significant*

Heschl's gyrus: ***left and right Heschl's gyrus (HG) thickness***

The cortical thickness of Heschl's gyrus was analyzed with a 3 × 2 mixed model analysis of covariance (ANCOVA), with group (AP, MUS, and Control) as the between-groups variable and hemisphere as the within-group variable, using gender, brain volume, and age as covariates. There was no significant group by hemisphere interaction ($F(1,54) = 0.27$, $p = .77$) and no significant effect of hemisphere ($F(1,54) = 0.006$, $p = .94$). However, there was a significant main effect of group ($F(1,54) = 10.3$, $p < .001$). For all analyses, the covariates were never significant.

Post hoc pairwise comparisons (Bonferroni adjusted alphas = .025) reveal significantly increased left ($p = .038$) but not right ($p = .18$) HG thickness in AP participants compared to musicians, significantly increased left and right (ps = .001) HG thickness in AP participants compared to controls, and significantly increased right ($p = .036$) but not left ($p = .20$) HG thickness in musicians compared to controls.

There were no significant differences between the left and right HG thickness in AP ($p = .70$), musician ($p = .20$), or control ($p = .67$) groups.

In AP participants, the left HG thickness averaged 2.61 ± 0.23 mm (mean ± SD) and the right HG thickness averaged 2.64 ± 0.20 mm. In musicians, the left HG thickness averaged 2.45 ± 0.19 mm and the right HG thickness averaged 2.54 ± 0.19 mm. In controls the left HG thickness averaged 2.36 ± 0.28 mm and the right HG thickness averaged 2.38 ± 0.27 mm.

Pericallosal sulcus: ***left and right pericallosal sulcus (PC) thickness***

A 3 × 2 mixed model analysis of covariance (ANCOVA), with group (AP, MUS, and Control), as the between-groups variable and PC hemisphere as the within-group variable, using gender, brain volume, and age as covariates, revealed no significant group by hemisphere interaction ($F(1,54) = 0.59$, $p = .56$) and no significant effect of hemisphere ($F(1,54) = 2.68$, $p = .11$). However, there was a significant main effect of group ($F(1,54) = 7.09$, $p = .002$).

Post hoc pairwise comparisons (Bonferroni adjusted alphas = .025) reveal significantly increased left (p = .004) and right (p = .012) PC thickness in AP participants compared to CON, significantly increased left (p = .026) but not right (p = .29) PC thickness in musicians compared to controls, and no significant increases in the left (p = .46) or right (p = .14) PC thickness in AP compared to musicians.

There were significant differences between the left and right PC thickness in musicians (p = .15) and marginally significant in the AP group (p = .071) where the left PC thickness was larger. There were no significant differences between the left and right PC thickness (p = .34) in the control group.

In AP participants, the left PC thickness averaged (mean ± SD) 2.46 ± 0.32 mm and the right PC thickness averaged 2.31 ± 0.35 mm. In musicians, the left PC thickness averaged 2.39 ± 0.31 mm and the right PC thickness averaged 2.17 ± 0.22 mm. In controls the left PC thickness averaged 2.17 ± 0.28 mm and the right PC thickness averaged 2.11± 0.23 mm.

Amygdala: ***left amygdala volume***

A 3 × 2 mixed model analysis of covariance (ANCOVA), with group (AP, MUS, and CON) as the between-groups variable and amygdala hemisphere as the within-group variable, using gender, brain volume, and age as covariates, revealed no significant group by hemisphere interaction ($F(1,54) = 1.05$, p = .36) and no significant effect of hemisphere ($F(1,54) = 0.79$, p = .38), and no effect of group ($F(1,54) = 1.77$, p = .18).

Post hoc pairwise comparisons (Bonferroni adjusted alphas = .025) revealed only a significantly increased left (p = .022) but not right (p = .27) amygdala volume in AP participants compared to controls. The left amygdala in musicians approached significance (p = .081) compared to controls. There was no difference between the right amygdala in musicians compared to controls (p = .83), and no difference between the left (p = .56) and right (p = .35) amygdala volumes between AP and musicians. There were no significant differences between

the left and right amygdala volumes in AP (p = .57), musician (p = .83), and marginally significant within control (p = .076) groups.

In AP participants, the left amygdala volume averaged 1612 ± 126 mm^3 and the right amygdala volume averaged 1638± 231 mm^3. In musicians, the left amygdala volume averaged 1583 ± 218 mm^3 and the right amygdala volume averaged 1582 ± 187 mm^3. In controls the left amygdala volume averaged 1491 ± 178 mm^3 and the right amygdala volume averaged 1552 ± 244 mm^3**.**

Angular gyrus (parietal inferior): ***left parietal inferior angular gyrus (AG) volume***

A 3 × 2 mixed model analysis of covariance (ANCOVA), with group (AP, MUS, and CON) as the between-groups variable and AG hemisphere as the within-group variable, using gender, brain volume, and age as covariates, revealed no significant group by hemisphere interaction (F(1,54) = 1.20, p = .31) and no significant effect of hemisphere (F(1,54) = 2.72, p = .11) or group (F(1, 54) = 1.73, p = .19).

Post hoc pairwise comparisons (Bonferroni adjusted alphas = .025) revealed only a significantly increased left (p = .025) but not right (p = .62) AG volume in AP participants compared to controls. In musicians the left AG volume approached significance (p = .057) compared to controls. There was no significant difference between the right AG volume in musicians compared to controls (p = .87), and between the left (p = .73) or right (p = .74) AG volumes in AP participants compared to musicians.

There were significant differences between the left and right AG volume in all three groups (ps < .001), where the right AG volume was larger than the left.

In AP participants, the left AG volume averaged 6584± 1119 mm^3 and the right AG volume averaged 7847 ± 1118 mm^3. In musicians, the left AG volume averaged 6549 ± 921 mm^3 and the right AG volume averaged 7798 ± 1223 mm^3. In controls the left AG volume averaged 5804 ± 954 mm^3 and the right AG volume averaged 7641 ± 1079 mm^3.

Pallidum: ***right pallidum volume***

A 3 × 2 mixed model Analysis of Covariance (ANCOVA) with group (AP, MUS, and CON) as the between-groups variable and pallidum hemisphere as the within-group variables using gender, brain volume, and age as covariates revealed no significant group by hemisphere interaction, $F(1,54) = 2.68$, $p = .078$ and no significant effect of hemisphere (left vs. right), $F(1,54) = 0.84$, $p = .37$, and no effect of group, $F(1,54) = 1.45$, $p = .24$.

Post hoc pairwise comparisons (Bonferroni adjusted alphas = .025) revealed only a significantly increased right ($p = .039$) but not left ($p = .875$) pallidum volume in AP participants compared to controls. There were no significant differences between the left ($p = .16$) or right ($p = .18$) pallidum volumes in AP compared to musicians, and no differences in the left ($p = .22$) or right ($p = .45$) pallidum volumes in musicians compared to controls.

There was a significant difference between the left and right pallidum volumes in AP and musicians ($ps < .001$) where the right pallidum volume was larger, but not in the control group ($p = .25$).

In AP participants, the left pallidum volume averaged 1444 ± 327 mm^3 and the right pallidum volume averaged 1656 ± 283 mm^3. In musicians, the left pallidum volume averaged 1350 ± 227 mm^3 and the right pallidum volume averaged 1575 ± 363 mm^3. In controls, the left pallidum volume averaged 1398 ± 253 mm^3 and the right pallidum volume averaged 1445 ± 220 mm^3.

Anterior Transverse Collateral Sulcus: ***Left*** **Collateral Anterior Transverse Sulcus** ***(CS) Volume***

A 3 × 2 mixed model analysis of covariance (ANCOVA) with group (AP, MUS, and CON) as the between-groups variable and CS hemisphere as the within-group variables using gender, brain volume, and age as covariates revealed no significant group by hemisphere interaction ($F(1, 54) = 2.629$, $p = .081$) and no significant effect of hemisphere ($F(1, 54) = 1.28$, $p = .26$). However, there was an effect of group ($F(1, 54) = 4.22$, $p = .02$).

Post hoc pairwise comparisons (Bonferroni adjusted alphas = .025) revealed significantly increased left (p = .004) but not right (p = .084) CS volumes in AP participants compared to controls, and significantly increased left (p = .005) but not right (p = .30) CS volumes in musicians compared to controls. There was no significant difference between the left (p = .98) or the right (p = .48) CS volumes between AP and musician CS volume. There were significant differences between the left and right CS volumes in controls (p = .015) where the right CS volume was larger, whereas no difference was found between the left and right CS volumes in the AP (p = .78) or musician (p = .49) groups.

In AP participants, the left CS volume averaged 1976 ± 540 mm^3 and the right CS volume averaged 1993 ± 440 mm^3. In musicians, the left CS volume averaged 1998 ± 443 mm^3 and the right CS volume averaged 1933 ± 417 mm^3. In controls the left CS volume averaged 1526 ± 386 mm^3 and the right CS volume averaged 1739 ± 349 mm^3.

Suboribital Sulcus: ***Right Suboribital Sulcus (SS) Volume***

A 3 × 2 mixed model analysis of covariance (ANCOVA) with group (AP, MUS, and CON) as the between-groups variable and Suborbital Sulcus (SS) hemisphere as the within-group variables using gender, brain volume, and age as covariates revealed no significant group by hemisphere interaction ($F(1, 54) = 0.24$, p = .79) and no significant effect of hemisphere ($F(1, 54) = 0.17$, p = .68). However, there was an effect of group ($F(1, 54) = 4.47$, p = .042).

Post hoc pairwise comparisons (Bonferroni adjusted alphas = .025) revealed significantly increased right (p = .025) but not left (p = .16) SS volumes in AP participants compared to controls. There were no significant differences between the left (p = .36) or right (p = .26) SS volumes between AP and musicians, and the left (p = .61) or right (p = .25) SS volumes between musicians and controls. There were significant differences between the left and right SS volumes in AP, musicians, and controls (ps < .001), where the left SS volume was larger.

In AP participants, the left SS volume averaged 1100 ± 171 mm^3 and the right SS volume averaged 637 ± 250 mm^3. In musicians, the left SS volume averaged 1037 ± 211 mm^3 and the

right SS volume averaged 557 ± 204 mm^3. In controls the left SS volume averaged 1002 ± 246 mm^3 and the right SS volume averaged 479 ± 199 mm^3.

Precentral Sulcus (Superior Part): ***Left Precentral Sulcus (PS) Volume***

A 3 × 2 mixed model analysis of covariance (ANCOVA) with group (AP, MUS, and CON) as the between-groups variable and Precentral Sulcus (PS) superior part hemisphere as the within-group variables using gender, brain volume, and age as covariates revealed no significant group by hemisphere interaction ($F(1, 54) = 1.92$, $p = .16$) and no significant effect of hemisphere ($F(1, 54) = 1.11$, $p = .30$) or group ($F(1, 54) = 2.11$, $p = .13$).

Post hoc pairwise comparisons (Bonferroni adjusted alphas = .025) revealed significantly increased left ($p = .026$) but not right ($p = .63$) PS volumes in AP participants compared to controls, and significant left ($p = .018$) but not right ($p = .39$) PS volumes in musicians compared to controls. There was no significant difference between the left ($p = .88$) or right ($p = .18$) PS volumes between AP and musicians. Pairwise comparisons revealed no significant difference between the left and right PS volumes between in the AP group ($p = .66$), and in musicians ($p = .30$). There were significant differences between the left and right PS volumes in controls ($p = .024$), where the right PS volume was larger.

In AP participants, the left PS volume averaged 2327 ± 557 mm^3 and the right SS volume averaged 2258 ± 557 mm^3. In musicians, the left PS volume averaged 2375 ± 406 mm^3 and the right PS volume averaged 2518 ± 639 mm^3. In controls, the left PS volume averaged 1942 ± 475 mm^3 and the right PS volume averaged 2309 ± 589 mm^3.

Inferior Frontal Opercular Gyrus: ***Right and Left Inferior Frontal Opercular Gyrus (IFOG) Thickness***

A 3 × 2 mixed model analysis of covariance (ANCOVA) with group (AP, MUS, and CON) as the between-groups variable and IFOG hemisphere as the within-group variables using gender, brain volume, and age as covariates revealed no significant group by hemisphere interaction ($F(1, 54) = 0.70$, $p = .50$) and no significant effect of hemisphere ($F(1, 54) = 0.021$, $p = .89$), but a significant effect of group ($F(1, 54) = 4.07$, $p = .023$).

Post hoc pairwise comparisons (Bonferroni adjusted alphas = .025) revealed significantly increased right ($p = .037$) but not left ($p = .45$) IFOG thickness in controls compared to AP participants, and both significantly increased left ($p = .045$) and right ($p = .014$) IFOG thickness in musicians compared to AP participants. There were no differences between the left ($p = .22$) and right ($p = .74$) IFOG thickness in musicians compared to controls. There were no significant differences between the left and right IFOG thickness in AP ($p = .79$), musicians ($p = .43$), or controls ($p = .065$).

In AP participants, the left IFOG thickness averaged 2.91 ± 0.14 mm and the right IFO thickness averaged 2.92 ± 0.15 mm. In musicians, the left IFOG thickness averaged 3.00 ± 0.15 mm and the right IFOG thickness averaged 3.05 ± 0.13 mm. In controls, the left IFOG thickness averaged 2.95 ± 0.22 mm and the right IFOG thickness averaged 3.03 ± 0.20 mm.

Circular Insula Sulcus (Superior Part): Left and Right Circular Insular (CIS) Volume

A 3 × 2 mixed model analysis of covariance (ANCOVA) with group (AP, MUS, and CON) as the between-groups variable and the Circular Insula Sulcus (CIS) superior part hemisphere as the within-group variables using gender, brain volume, and age as covariates revealed no significant group by hemisphere interaction ($F(1,54) = 1.76$, $p = .18$) and an effect of hemisphere approaching significance ($F(1,54) = 3.21$, $p = .079$). There was a significant main effect of group ($F(1,54) = 6.79$, $p = .002$).

Post hoc pairwise comparisons (Bonferroni adjusted alphas = .025) revealed significantly increased left ($p = .001$) and right ($p = .028$) CIS volumes in controls compared to AP

participants, and only increased left (p = .016) but not right (p = .18) CIS volumes in musicians compared to AP participants. There were no differences between the left (p = .11) or right (p = .18) CIS volumes in musicians compared to controls. There were significant differences between the left and right PS volumes in all three groups (ps < .001), where the Left CIS volume was larger.

In AP participants, the left CIS volume averaged 2721 ± 383 mm^3 and the right CIS volume averaged 2272 ± 377 mm^3. In musicians, the left CIS volume averaged 2929 ± 381 mm^3 and the right CIS volume averaged 2365 ± 409 mm^3. In controls the left CI volume averaged 2968 ± 331 mm^3 and the right CIS volume averaged 2380 ± 256 mm^3.

Planum Temporale (PT) Volume

The same model was applied for probing the planum temporale (PT) volume. Post hoc pairwise comparisons (Bonferroni adjusted alphas = .025) revealed no significant difference between left (p = .48) and right (p = .74) PT volumes in AP and non-AP musicians, between left (p =.73) and right (p = .56) PT volumes in AP and controls, and between left (p = .72) and right (p = .37) PT volumes in non-AP musicians and controls. However, there were significant differences between the left and right PT volumes within AP (p = .44), non-AP musicians (p = .003), and approaching significance in the control (p = .078) group, where the left PT volume was lager. In AP participants, the left PT volume averaged 2047 ± 591 mm^3 and the right PT volume averaged 1771 ± 313 mm^3. In non-AP musicians, the left PT volume averaged 2177 ± 540 mm^3 and the right PT volume averaged 1748 ± 390 mm^3. In controls, the left PT volume averaged 2004 ± 494 mm^3 and the right PT volume averaged 1787 ± 584 mm^3.

5.5 Discussion

A predominant field of neuroscience studies how normal variation in brain anatomy relates to differences in brain function. The human auditory cortex is a good model to examine these relationships due to its known inter-hemispheric differences in both structure and function. Neural systems process both speech and music throughout the brain (Tervaniemi & Hugdahl, 2003; Hickok & Poeppel, 2007), however studies have shown a leftward laterization bias for language processing based on rapid acoustic changes, and rightward laterization bias for music processing based on complex frequency information (Zatorre et al., 2002). In our study, the only structure that was significantly increased in AP musicians compared to non-AP musicians was the left HG thickness within the auditory cortex. As well, bilateral HG thicknesses were significantly increased in the AP group compared with non-musician controls, and only the right HG thickness in non-AP musicians compared to non-musician controls.

We do not report any volume differences in HG from the automated Freesurfer parcellations, however we did find significant differences in A1 volumes (that make up approximately half of the HG volume) manually segmented in AP musicians, compared to non-AP musicians, and non-musicians bilaterally as reported in Chapter 4. Although no previous studies have reported increased thickness of the HG in AP and musician groups, our volumetric results are in line with previous studies that found enhancements in HG gray matter in musicians compared to non-musicians across hemispheres (Schneider et al., 2002; 2005). These studies reported that HG gray matter positively correlated with higher musical aptitude scores and enhanced early cortical responses to tonal stimuli. In Schneider et al. (2002), professional musicians generally had an increase in gray matter of HG bilaterally, suggesting that the HG within the auditory cortex played an important function in tonal perception and early evoked response even in musicians who do not have AP. Schneider et al. (2005) further reported that the relative left or right volumetric size of lateral HG gray matter predicted how participants perceived ambiguous tones; those focussing on fundamental frequency exhibited a leftward asymmetry, whereas those focussing on spectral cues exhibited a rightward asymmetry. Taken together, these studies relate the absolute size of HG gray matter volume to musical ability and the laterization of early cortical response preference mimicked the anatomical asymmetry. Furthermore, even though volumetric measurements and boundary delineations within the

auditory cortex have varied between studies, there still remains a consensus of how anatomical variations in HG affect how auditory spectral information is processed both at the fundamental acoustic processing level and in perception.

Recently, HG volumes were found to be increased in AP musicians compared to non-AP musicians predominantly in the right hemisphere suggesting an enhanced spectral sound perception property in AP musicians (Wengenroth, 2014). Our results were similar in that the right A1 volume was enlarged that comprised approximately 50% of HG. We also found substantial increases in the left A1 in our study that may indicate the AP possessors may also have enhancements in holistic perception to acoustic information. The slight discrepancies in our findings that show both A1 volumes larger within AP subjects instead of just the right HG volume as Wegenroth et al. (2014) described may be due to our increased sample size and inclusion of a control group. In addition, we incorporated more stringent inclusion criteria that also matched AP musicians, non-AP musicians, and non-musicians on the number and type (i.e., tonal vs. atonal) languages spoken.

We also report an increased thickness of the Pericallosal sulcus (or sulcus of the corpus callosum) bilaterally in AP musicians compared to non-musicians, and only in the left hemisphere in non-AP musicians compared to non-musicians. The callosal sulcus is located between the superiorly situated cingulate gyrus and the inferiorly situated corpus callosum deep within the medial longitudinal fissure bilaterally. Although no previous studies have reported differences in the callosal sulcus thickness, anatomically this sulcus separates the corpus callosum from the overlying cingulate gyrus and surrounds the corpus callosum by curving ventrolaterally to become the hippocampal sulcus (Bhatnagar, 2002). The corpus callosum is a well-known white matter structure comprised of the largest fiber pathway that connects both hemispheres together in the brain. The newer Freesurfer parcellations Destreux atlas had removed the corpus callosum segmentation, therefore future work by manual segmentation of the corpus callosum on this data set may reveal more similarities to previous published data. A number of studies have reported an increased corpus callosum volume in musicians (Schlaug et al., 1995b; Lee et al., 2001; Ozturk et al., 2002), however Gaser and Schlaug (2003) did not report differences in corpus callosum size in musicians. A possible explanation was suggested based on the methodology used in that voxel-based morphometry (VBM) may not have been

sensitive enough to pick up on white matter differences. Only one previous study reported increased cortical thickness of the left subcallosal cingulate gyrus (SCG) in AP, a region that lies ventrally to the corpus callosum. This structure is anatomically close to the corpus callosum sulcus where we report significant differences in AP musicians and non-AP musicians to non-musicians (Dohn et al., 2013). Although Dohn et al. (2013) did not report significant differences in the corpus callosum using diffusion tensor imaging (DTI), it would be interesting to test our data set compared with previous findings on this structure.

Furthermore, we also report an increased volume in the parietal inferior portion of the left angular gyrus in AP musicians compared to non-musicians, and approaching significance in non-AP musicians compared to non-musicians. The angular gyrus is located within the parietal lobe close to the superior edge of the temporal lobe, just posterior to the supramarginal gyrus. The parietal inferior portion of the AG where we report volumetric differences has been implicated in a number of functions spanning from language, number, semantic, spatial processing, memory, attention and theory of mind (rev. Seghier, 2013). Binder et al. (1996) reported that music, reading, and language processing have activated similar networks in the brain, one of which is the AG that responded both to musical tones and words. New research supports the idea that training-induced neuro-anatomic plasticity can occur in adulthood, resulting in noticeable structural changes that follow learning new skills (rev Draganski, 2008). We report only an increase in the left AG in AP musicians and non-AP musicians compared to non-musicians. Our findings coincide with studies that found increased gray matter density detected only in the left AG and bilateral mid-temporal regions after training on a new task e.g., juggling (Draganski et al., 2004), and bilateral AG cortical thickness in those who measured high on creative productivity scores across different skills, one of which included music (Jung et al., 2010). This has been the first study to find anatomical differences in the AG of AP musicians and non-AP musicians compared to non-musicians, and may support the idea that musical abilities may be influenced by enhanced language and memory processing, as well as with learning new skills that the AG has been implicated with.

Additionally, we report an increased volume of the left amygdala in AP musicians compared to non-musicians and marginally significant larger in non-AP musicians compared to

non-musicians. The amygdalae are two almond shaped nuclei that are part of the limbic system, and are located within the temporal lobes. They are involved in a number of functions that include memory processing, decision-making, emotional reactions, and play a role in learning the fear response to negative stimuli.

The medial portion of the MGN and posterior intralaminar nucleus both receive inputs from the IC. Also, they both have nearby anatomical links with the amygdala. A previous study in rabbits found that when an auditory stimulus was paired with a fear-inducing stimulus such as an electric shock to the foot, the input from the amygdala had modified the response of neurons located within the medial MGN (Duvel et al., 2001). Furthermore, a recent fMRI study found increased activation in the bilateral amygdala in AP compared to non-AP groups when subjects had to rate musical stimuli on emotional valence and arousal. This suggested that the AP group had increased integration for emotional memory and reward processing during music listening (Loui et al., 2012). Another study found that bilateral damage of the amygdala with the rest of the temporal lobe intact had impaired the recognition of sad and scary music, evidenced by a case study in subject S.M (Gosselin et al., 2007). As well, a large study that assessed 270 students with no musical background found larger gray matter volume of the bilateral amygdala that correlated with better interval judgments (Li et al., 2014). Taken together, our study has been the first to report significant differences in the amygdala volume within AP musicians compared to non-musicians. Our findings are in line with previous studies that suggest that the amygdala, a neural structure associated with emotional processing, is also involved in music perception and music processing.

The right globus pallidus (pallidum) was significantly increased in AP musicians compared to non-musicians. The pallidum is a sub-cortical motor nucleus of the thalamus that is located within the basal ganglia and has a number of functions that include regulation of controlled movements, behaviour and emotions. Previous neuroimaging studies found activation in the pallidum in the context of music imagery, specifically vividness in anticipatory imagery (Leaver et al., 2009). Similar to our findings, the right pallidum showed increased activation when control subjects moved to imagined music (Schaefer et al., 2014). As well, the right pallidum showed increased activation in musicians compared to non-musicians during tonal

working memory, suggesting that musicians may use a specialized and more complex neural system for memorizing pitches (Schulze et al., 2011)—although this wasn't tested in AP. Our findings suggest that this structure may also be implicated in AP ability.

We further report a significant increase in the left anterior transverse collateral sulcus volume in AP musicians and non-AP musicians compared to non-musicians. The collateral sulcus is located below and lateral to the calcarine sulcus from which it is separated by the lingual gyrus. It is a temporal sulcus that runs anteroposteriorly. A previous neuroimaging study found that reading words activated two foci within the collateral sulcus (Drury & Van Essen, 1997). As well, the left collateral sulcus has been implicated in having an increased number of tonality sensitive voxels within eight expert musicians, two of which reported having AP (Janata et al., 2003).

As well we report increased right suborbital sulcus volumes in AP musicians compared to non-musicians. The suboribital sulcus, also referred to as the sulcus rostrales or supraorbital sulcus is located parallel to the anterior part of the cingulate sulcus that lies towards the frontal pole (Destreux, 2010). Brodmann area 47 (BA47), also known as the orbital area 47 in humans surround the caudal portion of the orbital sulcus extending to the orbital part of the inferior frontal gyrus. BA47 has been associated with musical syntax and semantic language processing (Levitin & Menon, 2003).

Moreover, we found significantly increased left precentral sulci volumes in AP musicians and non-AP musicians compared to non-musicians. The precentral sulcus is located parallel to and in front of the central sulcus. The precentral gyrus (BA4) is bounded posteriorly and anteriorly by the precentral sulci, and the left precentral gyrus has been implicated in processing sad music with lyrics (Brattico et al., 2011), enhanced gray matter density within musicians (Gaser & Schlaug, 2003), and similar to our findings, increased intrasulcal length of the precentral gyrus in musicians (Bengtsson et al., 2005). More interestingly, hand finger movement representations have been associated with the precentral gyrus (Yousry et al., 1997; Herve et al., 2005). A gross anatomical structure known as the inverted omega sign, also referred to as a 'hand knob' within the precentral gyrus has been linked with the representation of finger movements that span from being barely visible in some individuals to highly prominent in others (Stewart, 2008). Previous studies reported that piano players exhibited an increased omega sign

gross anatomical feature on the left hemisphere, whereas violinists displayed the omega sign feature on the right hemisphere (Bangert & Schlauge, 2006). Taken together, the majority of our subjects in both AP and non-AP musician groups were piano players, and the increased volume in the left precentral sulcus (a region surrounding the left precentral gyrus) may be indicative of their piano aptitude.

In our study we report decreased cortical thickness in the inferior frontal opercular gyrus in the left and right hemispheres in AP musicians compared to non-AP musicians, and only the right opercular gyrus thickness in AP musicians compared to non-musicians. We also report reduced volumes of the left circular insular sulcus in AP musicians compared to non-AP musicians and non-musicians, and only the right circular insular sulcus volume in AP musicians compared to non-musicians. The circular sulcus is also referred to as the limiting sulcus that is located in the boundary between the cortex of the insula and of surrounding gyri of frontal, parietal and temporal lobes. Overall, the most significant results we discovered were reduced thickness in pars opercularis in AP musicians. The inferior frontal gyrus is also known as the pars opercularis (BA 44). It is located within the frontal cortex and corresponds to the opercular part of the inferior frontal gyrus. Interestingly enough, BA44 of the left hemispheres houses Broca's area involved in speech and semantic tasks. BA44 also has been implicated in music perception (Brown et al., 2006) and in hand movements (Rizzolatti et al., 2002).

To date, there have only been two previous studies that reported cortical thickness differences in AP. Our results replicate the findings in the first study that found significantly reduced cortex within the right pars opercularis in AP musicians compared to non-AP musicians (Bermudez et al., 2009). Bermudez et al. (2009) also reported other areas that had thinner cortex in AP including the right ventral premotor area, frontal, and parietal regions. Only the precalcarine cortex showed increased thickness with increased AP proficiency. As well, AP musicians exhibited an anatomical profile that was different than the non-AP musicians since none of the AP differences overlapped with the non-AP group. However, we do report a marginally significant difference between AP musicians and non-AP musicians in the left pars opercularis. The predominant difference we found was in the right hemisphere. This may be due to pruning of the right hemisphere in AP since the left hemisphere houses Broca's area that may be more involved in AP ability. This is still open to interpretation, since we do not report any

asymmetries between hemispheres within either group for the pars opercularis structure. Furthermore, Dohn et al. (2013) reported that AP subjects did not have thinner cortex compared to non-AP musicians, and instead only had increased cortical thickness in a number of regions including the bilateral STG, left inferior frontal gyrus, and right supramarginal gyrus (Dohn et al., 2013). These differences may be due to different methods being used within each study. In addition, our study had an increased sample size within each group, and we included more stringent matching criteria compared to both previous studies. Although our findings of reduced cortical thickness are not quite clear, it may be due to AP possessors incurring different pruning and training effects than non-AP musicians (Bermudez et al., 2009).

Lastly, we looked at the planum temporal (PT) volume in our data due to the inconsistences reported in AP. Structural neuroimaging data reveal discrepancies within the PT volume in AP musicians, non-AP musicians, and controls with minimal to no musical experience. We did not find a significant difference in volumes between AP, non-AP musician, and non-musician groups, however we found the left PT volume was significantly larger than the right PT volume within AP musicians, and non-AP musicians but only approached significance within the non-musician group. This leftward asymmetry has been well documented in normal populations (Geschwind & Levitsky, 1968; Steinmetz, 1996), and reported to be significantly increased in AP musicians compared to non-AP musicians (Schlaug et al., 1995a; Chen et al 2000; Luders et al., 2004) and in self-reported AP possessors (Keenan et al., 2001). It was thought that since the Wernicke's area involved in language comprehension is located within the PT, this leftward bias in AP might be indicative to the ability of verbal associations in pitch identifications. In contrast, our results are more in line with recent studies that did not find significant differences in PT volume in AP and non-AP subjects (Zatorre et al., 1998; Bermudez and Zatorre 2005; Bermudez et al., 2009). However, there was a difference in PT volume asymmetry based on musicianship (i.e., AP musicians and non-AP musicians had a larger PT volume asymmetry than non-musician controls) (Burmudez & Zatorre, 2005), suggesting that the PT volume asymmetry may be due to musical ability and not as an AP marker alone. However, Zatorre et al. (1998) reported that the right PT volume asymmetry was not evident, and that the right PT volume was larger in the AP group, although was not significant contrary to previous findings. Another study reported no differences in PT volume or left-right asymmetry in

musicians compared to non-musicians (Gaser & Schlaug, 2003). These discrepancies in PT asymmetry and volume have been suggested to be partly due to inconsistent and arbitrary delineations of PT boundaries, human error, and morphological variability with automated methods such as cortical thickness and voxel-based-morphometry VBM methods (Zatorre et al., 1998; Bermudez et al., 2009).

Chapter 6

Experiment 5: Central Basis for Absolute Pitch (diffusion MRI)

6.1 Abstract

Diffusion tensor imaging (DTI) is a well-established tool in neuroimaging that can reveal abnormalities in white matter fiber structure and integrity. It provides models of brain connectivity, and is used as a standard method in imaging for white matter disorders. The following study looked at the arcuate fascicles (AF) that connects Wernicke's areas for language comprehension (Wernicke, 1995) to Broca's area for language processing and music perception (Fadiga et al., 2009) using DTI. There have been inconsistencies pertaining to the AF in a number of studies. For example, the AF has been implicated in a number of studies that looked at musical disorders. In one study, the AF was reported significantly decreased in congenital amusia (tone-deafness) (Loui & Schlaug, 2009), whereas a more recent study found no differences between amusics and controls in AF size (Chen et al., 2015). For each hemisphere, we sought to look at the AF volume and white matter tract integrity as measured by fractional anisotropy (FA, a parameter in DTI that measures the diffusivity of water within biological tissue) and compare between groups of different pitch processing abilities.

6.2 Methods: Participants

A diffusion MRI scan was collected on 61 participants for the following experiment. Participant information is described in Table 3.1.

6.3 Method: Data Acquisition, Processing, and Analysis

All images were acquired on a 3T MRI scanner using a 32-channel head coil. For each participant ($N = 61$), a diffusion tensor weighted (DTI) scan was acquired with the following parameters: acquisition time 8 min 5 s, 64 diffusion directions, b-value of 1000 s/mm^2 (reference image with low b-value of 0 s/mm^2), 192 mm field of view, TR = 6900 ms, TE = 86 ms, 2 mm slice thickness, 128 × 128 matrix, field of view 192 mm, 1.5 × 1.5 mm in-plane resolution, 56

contiguous (no gap) slices with 2 mm thickness, 1 average, parallel imaging (iPat GRAPPA) with an acceleration factor of 3.

Previously reported, the detection of the AF depends on the tractography algorithm (Chen et al., 2015). Deterministic tracking methods model only one fiber orientation per voxel and are derived from the first eigenvector, or dominant orientation of the diffusion tensor. A number of studies using deterministic tractography were unable to track the AF in the majority of cases (Catani et al., 2007; Glasser & Rilling, 2008; Lebel & Beaulieu, 2009, Loui et al., 2009; Kaplan et al., 2010; Thiebaut de Schotten et al., 2011) which is why a more standard and appropriate probabilistic model was used for our analyses that has shown reliable AF reconstruction (Chen et al., 2015). In this study, probabilistic tractography was implemented that used a tracking algorithm to model crossing fibers. This method allowed for connectivity maps to be created that showed the probability of where a voxel occurred within a tract between two regions of interest (ROIs).

Pre- and post-processing of DTI scans were run through FSL (Eddy current correction and brain extractions followed by DTIFIT). BedpostX estimation of diffusion parameters (FSL) generated all files required for tractography. Both seed (BA22, which houses the Wernicke's area) and target ROI masks (BA44 which houses Broca's area) connecting the AF, were created in DSI Studio for each subject in diffusion space using the Brodmann Atlas for seed and target masks. The seed and target masks were both bilateral ROIs extracted for each subject in diffusion space. Therefore, in order to run tractography, both the left and right cerebral white matter masks were also created in diffusion space from the FreeSurfer Segmentation atlas for each subject that were used as regions of avoidance during probabilistic tractography. All masks were saved as Nifti files that were run in Probtrack within the FDT FSL software package for further analyses. For probabilistic tracking, ProbtrackX was run for each hemisphere separately with the following parameters: 5000 samples, 0.2 curvature, loopcheck applied, and modified Euler selected for computing probabilistic streamlines from advanced options for increased accuracy.

Broca's area (BA 44) has been reported to differ considerably in its size, location, and shape across different brains (Tomaiuolo et al., 1999). A number of researches brought up the

idea that given such variability in this structure, group analyses should be used with caution when bringing the data into common space since it may obscure the results. Instead, individual analyses were recommended as a more appropriate measure to conduct (Novick et al., 2010). As such, we performed tractography on each individual subject per hemisphere and group analyses was done afterwards. Probabilistic-based FA values were derived from ProbtrackX2 output fdt_paths files. The 3D tract density images that cover the AF were created when the fdt_path files were binarized using fslmaths, and multiplied by the FA map from dtifit using fslmaths. Mean FA values from each AF tract per hemisphere were extracted using fslmeants, and run through SPSS 23 for Mac for further analyses. Furthermore, FA maps of the AF were thresholded to 50% intensity to compare with the unthresholded FA maps.

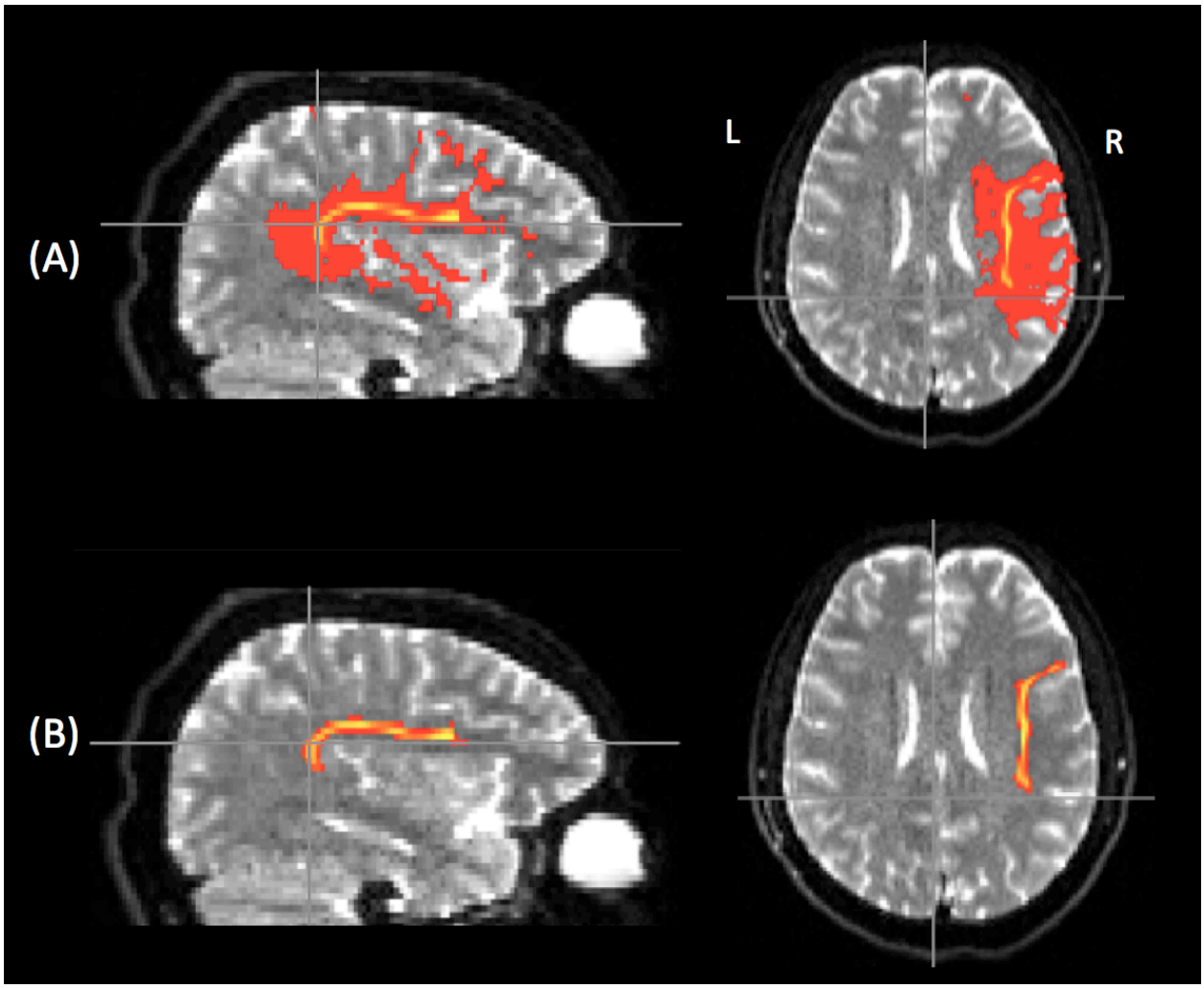

Figure 6.1 Example of the arcuate fasciculus (AF) tractography in a musician participant. Panel (A) shows sagittal and axial views of the right AF tract (not thresholded). Panel (B) shows the sagittal and axial views of the right AF (thresholded to 50 % intensity).

6.4 Results

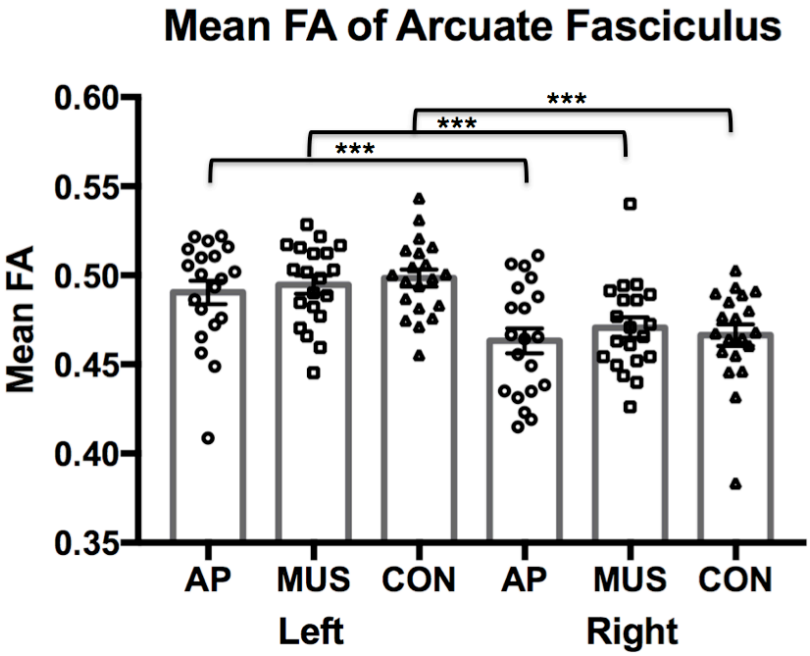

Figure 6.2 Thresholded mean FA (means ± SEM) of the AF in AP musicians (AP), non-AP musicians (MUS), and non-musicians (CON) for the left and right hemispheres. ***$p < .001$.

A 3 × 2 mixed model analysis of covariance (ANCOVA) was used to analyze the FA of the AF non-thresholded tracts, with group (AP, MUS, and CON) as the between-groups variable and hemisphere as the within-group variable, using gender, brain volume, and age as covariates revealed no significant group by hemisphere interaction ($F(1,54) = 0.41$, $p = .66$), or effect of hemisphere ($F(1,54) = 0.35$, $p = .56$) or group ($F(1,54) = 1.13$, $p = .33$). The same analyses were applied to the FA of the thresholded tracts that also revealed no significant group by hemisphere interaction ($F(1,54) = 0.26$, $p = .78$) or effect of hemisphere ($F(1,54) = 0.84$, $p = .37$) or group ($F(1,54) = 0.47$, $p = .63$). For all analyses, the covariates were never significant.

Post hoc pairwise comparisons (Bonferroni adjusted alphas = .025) revealed no significant differences in the unthresholded and thresholded FAs between groups, however there were significant differences between the left and right hemisphere for the unthresholded and thresholded FA within the AFs for all groups (ps < .001) that showed an increase in the left FA

of the AF tracts. The same trends were observed with the thresholded and unthresholded FA maps.

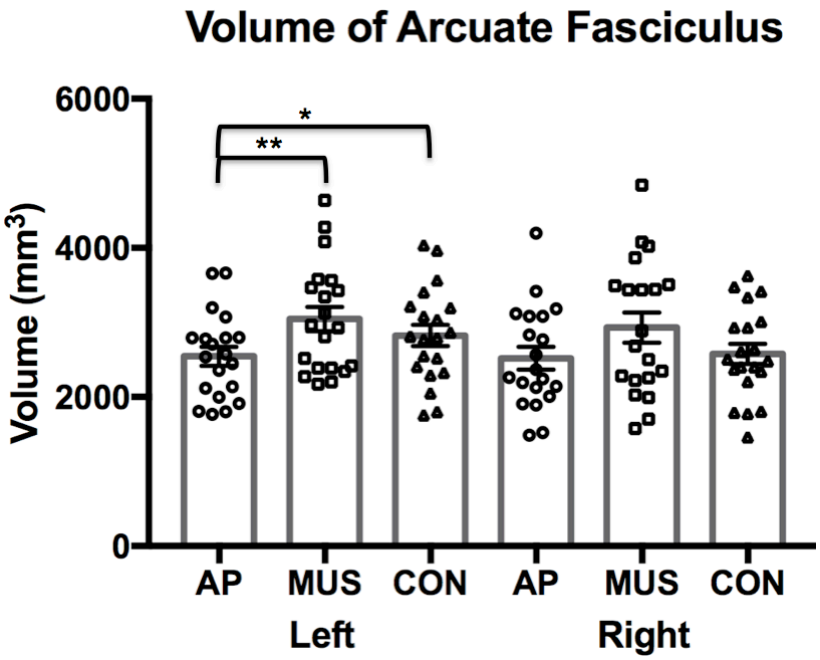

Figure 6.3 Thresholded volumes (means ± SEM) of the AF in AP musicians (AP), non-AP musicians (MUS), and non-musicians (CON) for the left and right hemispheres. $^{**}p < .01$, $^{*}p < .05$.

A 3 × 2 mixed model analysis of covariance (ANCOVA) was used to analyze the volume of the AF non-thresholded tracts, with group (AP, MUS, and CON) as the between-groups variable and hemisphere as the within-group variable, using gender, brain volume, and age as covariates. There was no significant group by hemisphere interaction ($F(1,54) = 1.62$, $p = .21$) or effect of hemisphere ($F(1,54) = 0.007$, $p = .93$), but there was a significant main effect of group ($F(1,54) = 5.07$, $p = .01$). The same analyses were applied to the FA of the thresholded volume tracts that also revealed no significant group by hemisphere interaction ($F(1,54) = 0.69$, $p = .50$) or effect of hemisphere ($F(1,54) = 0.21$, $p = .65$), and a significant main effect of group ($F(1,54) = 3.37$, $p = .042$).

Post hoc pairwise comparisons (Bonferroni adjusted alphas = .025) revealed significant differences in the left unthresholded AF tract volume between the AP musicians and non-AP

musicians ($p < .001$), and approaching significance between the left AF unthresholded volume between AP musicians and non-musicians ($p = .071$). Similarly, post hoc pairwise comparisons also revealed significant differences in the left thresholded AF tract volume between the AP musicians and non-AP musicians ($p = .008$), and AP musicians and non-musicians ($p = .02$).

As well, post hoc pairwise comparisons revealed significant differences between the left and right hemispheres for AF unthresholded volumes in AP musicians ($p = .033$), non-AP musicians ($p < .001$), and non-musicians ($p = .001$) where the left hemisphere was larger. With the thresholded volumes the left was larger than the right although it was not significant within each group.

6.5 Discussion

A common model in cognitive neuroscience focuses on structural differences in the brain linked to behaviour. Recent studies utilized different models that also looked at differences in brain connectivity within white matter tracts in order to explain brain networks that may function in abilities such as AP. Fractional anisotropy (FA), is a property in DTI analyses that measures the direction-dependent diffusivity of water molecules within tissues and is associated with white matter tract integrity. In our study, we report significantly increased FA in the left hemisphere compared to the right hemisphere in all groups, however, no significant differences in FA were found between AP musicians, non-AP musicians and non-musician groups. As well, we further report significantly smaller left AF tract volumes in AP musicians compared to non-AP musicians and non-musicians. Our results are similar and more in line with a previous DTI study that traced the superior longitudinal fasciculus (which includes the AF) in AP musicians, non-AP musicians, and non-musicians. AP subjects showed a leftward asymmetry in the superior longitudinal fasciculus and reduced FA within the white matter tracts compared to the other groups. The authors described a pioneering axon theory to explain their results of finding reduced FA in AP subjects. This theory suggests that the development of peripheral white matter differs from white matter in core regions and may be more susceptible to environmental factors such as musical training over a long period of time in postnatal life (Oechslin, 2010a).

However, if peripheral white matter development may be influenced by environmental factors, then white matter structures might be larger elsewhere in regions associated with auditory processing in musicians with more musical training. A previous DTI study was conducted on AP musicians compared to non-AP musicians where they hand-drew ROIs of the middle temporal gyrus (MTG) and the superior temporal gyrus (STG) in the temporal lobe. Performing deterministic tractography, they revealed increased structural connectivity and tract volume between these regions in the left hemisphere in AP compared to non-AP musicians (Loui et al., 2011).

Another DTI study on AP used the probabilistic tract-based spatial statistics (TBSS) and found one significant cluster within the path of the inferior fronto-occipital fasciculus and the inferior longitudinal fasciculus that was increased in FA in the right hemisphere in AP compared to non-AP musicians (Dohn et al., 2013). Using deterministic tractography, they found higher FA in AP musicians within the path of the inferior fronto-occipital fasciculus, the uncinate fasciculus, and the inferior longitudinal fasciculus. These regions are located close to the right STG and MTG. Taken together, the latter two studies that found significant FA values had differed in regions that may be due to the methodology used. Loui et al. (2011) hand drew ROIs in two regions and found enhanced connectivity and volume in the left peripheral tract connecting the STG and MTG within the temporal lobe. This differed from the whole brain comparison using an automated diffusion imaging algorithm that Dohn et al. (2013) used that found a significant cluster in the right hemisphere in regions close to the STG and MTG that were enhanced in FA in AP subjects. A possible explanation that Loui (2014) described was the TBSS algorithm that labeled significant regions of inferior longitudinal fasciculus and inferior frontal occipital fasciculus may have also included voxels that extended to other peripheral regions of the SLF that comprised the AF. Overall, our study was the only one that directly looked at the AF in AP, non-AP musicians, and non-musicians which reported similar results that Oechslin et al. (2010a) did when they performed tractography on the larger SLF structure that also included the AF.

Chapter 7: General Discussion

7.1 Summary and Conclusions

The ability of AP to name a note or collection of notes without a reference is generally considered to be extremely rare. The prevailing view describes its origins based on a combination of genetic/neural developmental cues and in some circumstances adheres to a critical period for its development on average. In our study we report that 20 % of our subjects in Experiments 2-5 that had AP only started musical training past the critical period, a feature that was hypothesized to be required in its manifestation from previous studies. In a noteworthy piece entitled 'The puzzle of absolute pitch', the author Diana Deutsch, who has AP, described that the puzzle surrounding AP is not why some people have it, but rather why it's so rare to begin with—much like our perception of the colour blue is direct, and not done so by comparing it to another colour and assessing the relationship between the two. One can reason that a lack of AP is akin to the rare syndrome of colour anomia, where patients can tell differences between different colours and can tell if two objects are of the same colour, but cannot label then.

Taken together, the nature versus nurture debate underlying AP development has been predominantly based on behavioural, genetic, cognitive neuroscience and cross-cultural experiments. Not many studies have been brought in from translational or diagnostic medicine simply because AP ability is thought of as a blessing (remarkable ability) rather than a curse (neurological/psychiatric disorder) (Loui, 2014). It has been suggested that models describing psychiatrics disorders may be useful in describing AP origins, one of which is known as the diathesis stress model (Zuckermann, 1999). In this model, a disorder can manifest itself when genetic and other dispositional vulnerabilities are brought on by a stressor. It may be that the origins of AP ability are caused by developmental influences which are most sensitive to a critical period, musical training, tonal language influence, as well as disposition (or vulnerability) that may be influenced by AP family history, ethnicity and neural correlates in genes coding for temporal lobe hemispheric differences (Loui, 2014). These pathways may then influence neural networks responsible for working memory and sound categorization as found to be enhanced in AP ability. For the neural requirements of AP to emerge, it may be that at least one developmental factor and at least one predisposition may be needed (Loui, 2014).

Although a plausible explanation, there are a number of gaps and inconsistencies in the literature on AP development and origins. We first tested if any differences could be detected initially within the cochlea in AP prior to further neural processing. We used OAEs as a means to probe for a peripheral basis for AP. Low-level OAEs are believed to arise primarily in the periphery and provide measures of both frequency sensitivity and selectivity. As such, they provide a possible means to objectively distinguish between peripheral versus central origins of AP. In short, we found no evidence that the periphery (i.e., cochlear responses) differ between AP and controls. Specifically, we report no obvious differences in SOAE activity or frequency tuning (as measured via pooled trends of SFOAE phase-gradient delays). A limitation in the peripheral study was not controlling for musicianship. Therefore, the slight differences between groups may be due to musical expertise, rather than an AP marker alone. Although unclear, these findings do suggest that the sharpness of tuning may become amplified as auditory information progresses towards the CNS. Taken together, these observations strengthen the notion that the primary mechanisms allowing for AP to arise lie centrally.

Based on our behavioural tests in this study, we report that AP musicians along with non-AP musicians had significantly smaller JND thresholds than their non-musical counterparts. Our findings are in line with previous studies that did not reveal differences in JND thresholds in AP and non-AP musicians (Fujisaki & Kashino, 2002), although musicians overall did significantly better than non-musician controls (Micheyl et al., 2006). Similarly, AP musicians along with non-AP musicians compared melodic mistuning excerpts better in working memory than non-musicians. Although musicianship did play a factor, we further report that the underlying AP marker may be more representative in central studies as we tested with functional, and structural MRI.

We used the pRF model to estimate the best frequency tonotopic maps and tuning bandwidth maps in cortical and subcortical auditory regions. We measured both center frequency and tuning width averages within A1, R, and RT ROIs comprising HG. In each region, both center frequency and tuning widths were not significantly different and were generally distributed evenly within groups. Our results may indicate that AP musicians do not have sharper frequency selectivity compared to their counterparts based on the population of neurons that

responded to the pure tone logarithmic sweeps. It would be interesting to test if natural sounds elicit the same response within the groups.

Areas outside of the auditory core including belt, parabelt, and regions beyond may play a more relevant role in pitch perception. For example, a previous fMRI study reported cortical activation in response to pitch height that extended past auditory core regions into the posterior planum temporale, whereas cortical activation in response to pitch chroma (i.e., pitch class, where a set of pitches are related to each other by octave) extended to the planum polare, a region just anterior to A1 (Warren et al., 2003). A hierarchical stream of pitch processing was proposed by Warren et al. (2003) to account for their findings that showed areas beyond the primary auditory cortex had specialized perceptual roles. More anterior regions to the core were responsive to object-independent auditory stimuli, whereas more posterior regions to the core including the planum temporale were more responsive to object identification. Future studies need to account for these extended regions that are involved in pitch processing, instead of focusing on single auditory cortical pitch centers to explain how cortical neurons encode pitch, frequency selectivity, and pitch judgments. Furthermore, it may be that differences in musicianship and specifically AP-ability are found in these extended regions.

In addition, we report significantly larger bilateral A1 volumes in AP musicians compared to non-AP musicians and non-musicians. Within A1, neurons have shown characteristic responses to harmonic spectral stimuli and periodic temporal modulations (Wang, 2013). Previously, a study in rats that had their bilateral A1 inactivated showed impairments in their response to pure tone frequency changes (Talwar et al., 2001). It seems that A1 does have some related function with auditory pitch discrimination. However, it is not certain if only a subset of A1 neurons take part in pitch encoding and other neurons function in analyzing temporal or spectral components of sound, or it may be the case that pitch is more preferentially encoded in secondary cortical fields that extend A1. Nonetheless, A1 still has been implicated in AP, suggesting that its enhanced volume may relate to AP ability in pitch categorization and perception. Furthermore, we report more significantly activated voxels in A1 and R ROIs for AP musicians compared to non-musicians when listening to the auditory task. Similarly, non-AP

musicians did show increased activations in these regions compared to non-musicians, although the results were not significant.

There are currently no existing models that predict functional or anatomical correlates to AP ability, and the only reasonable replication in a few studies describe the planum temporale volume as a marker, although this structure has shown inconsistencies from previous studies. This has been the first study to look at tonotopic and tuning width maps in these groups with different pitch processing abilities. Frequency selectivity at the level of cortex was not observed with respect to tuning revealing that other mechanisms in AP ability exist. We were also able to reliably extract tonotopic maps and tuning width maps of auditory subcortical structures of the IC and MGN in controls that are in line with previous neuroimaging and electrophysiological studies. Our functional results may further support Ross et al. (2005) explanation that musicians who have AP possess the Ability to Perceptually Encode (APE). This notion that AP musicians are biologically different in specific and discrete ways comes from the idea that they have better representation of frequency information in the form of a place code for pitch within the auditory system (Ross et al., 2005). Therefore, it may be that AP possessors have a better reference for internal pitch class representations that may be independent of sharper frequency selectivity as auditory information ascends the CNS.

We further investigated the neuro-anatomical correlates of musicianship and AP using structural MRI by investigating cortical thickness and volume differences among the three groups. Cortical thickness (CT) was significantly greater in the left HG in AP compared to non-AP musicians, a region known to function as a central hub for auditory processing. AP and non-AP musicians also had increased CT in the pericallosal sulcus of the corpus callosum compared to non-musicians. As well AP and non-AP musicians had larger angular gyrus, amygdala, anterior transverse collateral sulcus, and precentral sulcus volumes compared to non-musicians, and only AP musicians had larger pallidum and suborbital sulcus volumes compared to non-musicians. Interestingly enough, AP musicians had decreased CT in the inferior frontal opercular gyrus and decreased circular insular sulcus volumes compared to non-AP musicians and non-musicians. Previous studies also have reported significantly thinner cortex among AP possessors in a number of regions, including frontal cortices (Burmudez et al., 2009). Lastly, we further

report significantly smaller left AF volumes in AP compared to non-AP musicians and controls. A number of features can influence cortical thickness and white matter tract density such as the quantity of cells, cell size, myelination and packing density (Gittins & Harrison, 2004). Although we report reduced thickness and volume in frontal regions associated with AP, it may be that these regions were optimally reduced to form the most efficient network, which further supports the notion that AP possessors have stronger local but not global connectivity. Moreover, it may be that AP musicians are better able to bypass certain forms of processing done by most non-AP musicians (Klein et al., 1984; Wayman et al., 1992) that translates into neuroanatomical differences. For example, while AP is known as an enhancement in the ability of being able to label pitches without a reference, other skills like relative pitch judgments were reported worse in AP musicians compared to non-AP musicians (Miyazaki, 1993, 1995; 2004). This in turn may influence the gross anatomy in regions processing these abilities that require different training effects in AP compared with non-AP possessors (Burmudez et al., 2008).

Based on both structural findings in our study we found significantly reduced cortical thickness in the pars opercularis part of the inferior frontal gyrus (BA44) of the frontal cortex in AP as well as reduced volumes in the left AF that connects BA22 to BA44 together. These results were in line with Burmudez et al. (2009) that also found reduced CT in BA44 within AP musicians compared with non-AP musicians.

A different and more speculative view has been proposed to account for the reduction in CT found in AP. A previous study revealed abnormal cortical folding in the pars opercularis region (BA44) within autistics, further supported by findings that showed inversely correlated mirror neuron activity in BA44 in response to emotional expression and imitation with the degree of autistic symptoms (Dapretto et al., 2006). These were the same regions that were implicated in our findings that showed thinner cortex and also included an area that showed reduced volume in white matter tract integrity. Brown et al. 2003 softly implies that AP musicians may have mild cognitive, social, perceptual predispositions that are linked with autistic spectrum behaviours. It is also noteworthy to point out that there was no overlap between the differences found in AP compared with non-AP musicians and non-musicians in

decreased CT and volume, suggesting that the anatomical profile in AP stands alone compared with their non-AP counterparts.

7.2 Future Directions

There are a number of prospective lines of experimentation that could further increase the body of knowledge on AP ability and normal auditory development following the synthesis of our results. Future studies would include testing the pRF model in the subcortex (MGN and IC) in AP and non-AP musicians, and non-musicians, as well as in regions that extend the auditory core regions. Since sharper frequency selectivity was not observed at the level of the cortex within the auditory core region, it would be interesting to see if surrounding belt, parabelt, planum polare and planum temporale regions are implicated.

Moreover, this has been the first study that delineated A1, R and RT ROIs of the auditory cortex in a large sample size that can be further used in generating automated atlases for these regions. Future work on this data set would also include looking at structural differences in the corpus callosum since the automatic Freesurfer parcellation algorithm did not extract this region in the analyses. Although AP is thought to be more or less of a circumscribed trait, future research needs to address the degree to which this unique ability may transfer towards other skills and extra musical domains. As well, further research needs to be conducted on characterizing why decreases in cortical thickness and volume regions in AP are commonly found. Furthermore, future studies need to address to what degree memory is associated with AP ability, both at the structural and functional level.

7.3 Concluding Remarks

There still remains a debate over the origins of AP although evidence suggests that the clearest form of AP will develop when an innate predisposing biology is combined with experiential factors, such as musical training that uses a stable tuning system all during a normal developmental stage in childhood. These factors may give rise to the enhancements in AP that enable automatic and working memory independent categorization ability. AP ability also shares certain commonalities with other special populations, and is described to both include increased

and decreased neural networks as evidenced by cortical thickness, grey matter volume, and white matter connectivity, as well as higher efficiency in local but not global functional connectivity.

Overall, our findings suggest that sharpening of auditory tuning information as it originates at the peripheral level and traverses centrally is not evident in AP. It seems that there are no difference in how frequency information is encoded despite the level of musicianship. The underlying AP marker based on the JND is not found when comparing AP to non-AP musicians, although JND differences are found when comparing musicians to non-musicians despite AP ability. This tells us that musical aptitude does allow one to perceive frequency thresholds better, however does not improve with AP ability. Two regions have been implicated in AP, increased volume and thickness in HG (a hub for auditory processing), and decreased cortical thickness and tract volume in pars opercularis of the frontal lobe (known for its involvement in language processing). These two regions seem to compliment each other in that they support the idea that AP ability has structural differences in enhanced local connectivity (surrounding auditory processing regions), and reduced global connectivity, indicative of feed forward connections to the frontal lobe. These structures may be optimally enhanced and reduced to form the most efficient network for AP to emerge. Furthermore, it seems that memory associated regions for pitch categorization are evident in AP as the most probable candidate in conjunction with neuroanatomical differences mentioned as a marker for AP.

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