



Structural and Functional Changes in the Brain Caused by Short-term Pitch Discrimination Training

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قُلْ إِنَّمَا الْحَيَاةُ لِلْأَنْجَانِ
وَالْمَوْتُ لِلْمَوْتِ
فَمَا أَنْتُ مَعَنِّي بِهِمْ

Abstract

Background

Pitch discrimination learning has been shown to enhance psychoacoustic performance, which is hypothesised to be supported by structural and functional changes in the brain. Several investigations have shown that long-term auditory training positively impact on brain function and morphology; for instance, proficient musicians show neuroplastic alterations of the brain. However, only a few studies have investigated the effects of short-term auditory training on neuroplasticity.

Method:

The first study investigated the effects on neural plasticity in auditory areas that were associated with short-term training in pitch discrimination over three consecutive days across musical novices ($n=26$), and the second study compared these effects with those caused by long-term experiences among proficient musicians ($n=11$). Another target of the current study was to explore the effect of pitch discrimination learning on hemispheric lateralisation of functional activity by presenting different acoustic stimuli. These study targets were achieved through use of a combination of functional (task-based fMRI) and structural (T₁w and DTI)imaging as psychoacoustic performance was monitored. A battery of quantitative image analysis methods was employed.

Result:

One of this project's main findings is that short-term auditory training causes significant functional and structural changes in the auditory areas. These changes are most prominent in the superior temporal gyrus and the right white-matter pathways, including the corticospinal tract and corona radiata. The changes were noticed to occur in parallel with progress in psychoacoustic performance. Project's findings are in line with differences that have been observed in proficient musicians compared with novices. The results also reveal hemispheric lateralisation in functional activity within auditory regions affected by musical practice levels.

Discussion:

The project outcome makes a significant contribution to knowledge regarding short-term pitch discrimination learning, which will help to expand the understanding of changes in brain plasticity with learning.

Declaration

No portion of this work has been submitted in support of any other application for a degree or qualification at this or any other university or institute of learning.

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The cortical thickness of the superior and transverse temporal gyrus can predict the auditory learning outcomes.

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Abbreviations

- AC: Auditory Cortex
AD: Axial Diffusivity
ADC: Apparent Diffusion Coefficient
AFC: Alternative Forced Choice
 B_0 : External Magnetic Field
BOLD: Blood Oxygenation Level Dependent
CC: Corpus Callosum
CDF: Cumulative normal Distribution Function
CR: Corona Radiata
CSF: Cerebrospinal Fluid
CST: Corticospinal Tract
DARTEL: Diffeomorphic Anatomical Registration Through Exponentiated Lie algebra
dB: Decibels
Df: Test Tone Frequency
DKI: Diffusion Kurtosis Imaging
DLF: Difference Limen for Frequency
 D_n : D1: First Day, D2: Second Day, D3: Third Day
DT: Discrimination Threshold
DTI: Diffusion Tensor Imaging
DWI: Diffusion Weighted Imaging
EEG: Electroencephalogram
EPI: Echo Planar Imaging
 F_0 : Fundamental/ Reference Tone Frequency
FA: Fractional Anisotropy
FDT: Frequency Discrimination Threshold
fMRI: Functional Magnetic Resonance Imaging
FMRIB: Functional Magnetic Resonance Imaging of the Brain
FOV: Field of View
FSL: Oxford Centre for FMRIB Software Library
FWE: Family Wise Error
FWHM: Full Width Half Maximum
GLM: General Linear Model

GM: Grey Matter
HG: Heschl's Gyrus
Hz: Hertz (frequency unit)
IFC: Interval Forced Choice
IFOF: Inferior Fronto-Occipital Fasciculus
ILF: Inferior Longitudinal Fasciculus
JNDs: Just Noticeable Differences
LI: Lateralisation Index
MD: Mean Diffusivity
MEG: Magnetoencephalography
MNI: Montreal Neurological Institute
MPRAGE: Magnetisation Prepared Rapid Acquisition Gradient Echo
MR: Magnetic Resonance
MRI: Magnetic Resonance Imaging
MS: Multiple Sclerosis
 M_{XY} : Transverse Magnetisation
 M_z : Longitudinal Magnetisation
NMR: Nuclear Magnetic Resonance
NMV/ M_0 : Net Magnetisation Vector
PAC: Primary Auditory Cortex
PET: Positron Emission Tomography
PP: Planum Polare
PT: Planum Temporale
RD: Radial Diffusivity
RF: Electromagnetic Radio Frequency
ROI: Region of Interest
SE: Spin Echo Sequence
SEM: Standard Error of The Mean
SLF: Superior Longitudinal Fasciculi
SON: Superior Olivary Nucleus
SPM: Statistical Parametric Maps
STG: Superior Temporal gyrus
 T_1 : Longitudinal Relaxation Time
 T_2 : Transverse Relaxation Time
TBSS: Tract-Based Spatial Statistics

TE: Echo Time

TFCE: Threshold-Free Cluster Enhancement

TI: Inversion time

TIV/ICV: Total Intracranial Volume/Intracranial Volume

TR: Repetition Time

TTG: Transverse Temporal Gyrus

UF: Uncinate Fasciculus

VBM: Voxel-based morphometry

WM: White Matter

γ : Gyromagnetic ratio

ϵ : Eigenvectors

λ : Eigenvalues

μ : Magnetic Dipole Vector

$\omega\theta$: Angular Frequency of Protons

Chapter 1. Introduction to Training-induced Neuroplasticity

“Practice makes perfect” (William James, 1890)

1.1 Introduction

One of the most essential features of the auditory system is its ability to detect the difference in sound frequency between two successive tones; this is known as ‘pitch discrimination’ (Roth et al., 2004; Lopez-Poveda, 2014). Training on pitch discrimination employs repetitive acoustic stimulation in such a way that the behaviour and the neural base of auditory and related systems are positively altered (Chermak & Musiek, 2013). These positive changes in brain function and structures underlie learning. They are known as neural plasticity (Herholz & Zatorre, 2012). These changes have become a commonly researched topic over the previous two decades.

Overall, several studies have revealed the induction of structural and functional plasticity by long-term auditory training (Pantev et al., 1998; Schneider et al., 2002, 2005; Bermudez et al., 2009; Hyde et al., 2009; Foster & Zatorre, 2010; Bianchi et al., 2017). Bianchi et al. (2017) found distinct neural functional activity in musicians’ cortical and subcortical auditory regions compared with non-musicians. This functional alteration corresponded to structural changes that were observed within auditory regions in musicians (Schlaug et al., 1995; Zatorre et al., 1998; Limb, 2006). In contrast, there is very little evidence of rapid neural changes that are associated with short-term auditory training (Lappe et al., 2008; Carcagno & Plack, 2011), although this has recently been demonstrated in many other domains. For example, a reduction in functional activation within auditory cortices was found to result after a short period (over one week) of auditory training (Jäncke et al., 2001). Moreover, short-term (two hours) of spatial learning was found to cause significant microstructural changes that involved effects on the brain diffusivity within training-related regions, such as the hippocampus (Sagi et al., 2012; Hofstetter et al., 2013).

These studies confirmed that short-term plasticity manifested as long-term changes when groups that had received extensive perceptual training were compared with controls. However, the research’s limitation was its comparison of one group of highly trained people with controls. People who become musicians are interested in the subject as they can feel the music and they can discriminate the pitch differences in melodies quite easily, whereas other people who cannot hear the pitch differences will never be musicians. There may be a feature in the structure of musicians’ brains that predisposes them to be able to perform the pitch

discrimination task; this would not be linked to training as the differences would have been predeveloped in utero. According to Seashore (1938) and Wyatt (1945), the ability to discriminate pitch does not change with age or training, but instead depends on each individual's inherited morphological properties. Another study that supported these statements was performed by Golestani and co-workers (2011). The researchers suggested that brain structure predetermined people's profession choices after they found that phoneticians exhibited anatomical differences in their auditory cortices compared with non-expert controls and they surmised that these morphological alterations had been established in utero (Golestani et al., 2011). This raises the question of whether short-term auditory training for novices would result in functional and structural changes similar to the changes caused by long-term learning in proficient musicians.

One way to test this is through perceptual learning, which is a type of learning that leads to a stronger use of sensory input and which results in enhancement of the perceptual task performance (Fahle, 2001; Dosher and Lu, 2005). Perceptual learning has been used in many learning-based research projects (Fiorentini et al., 1981; Karni and Sagi, 1991; Karmarkar and Buonomano, 2003; Watanabe and Sasaki, 2015). It provides very well-defined stimulus sets and it enables a researcher to conduct effective training (Fahle 2001; Dosher and Lu, 2005).

To achieve its aim, this study involved two groups. The first was a group of novices who learned a new task through application of pitch discrimination training over a short period. The second group was made up of proficient musicians who had already learnt to discriminate subtle pitch differences during their musical practice. To investigate the learning effects on both groups, a combination of functional and structural imaging techniques were used while psychoacoustic performance was monitored, and several quantitative image analysis methods were employed.

It was hypothesised in the current study that an enhancement in the functions, structure and psychoacoustic measures of auditory regions would result from short-term acoustic training in novices. Moreover, these short-term neuroplastic changes would match the neuroplastic alterations that would be seen in the musicians' group as well as alterations that had been reported previously in many studies that involved musicians; however, it was hypothesised that these improvements would be more obvious in proficient musicians.

1.2 Research Questions

To fill a knowledge gap that was found in previously published literature, the primary purpose of the current study was to apply advanced magnetic resonance imaging (MRI) techniques along with acoustic training to answer the following questions:

- 1- Will short-term pitch discrimination training reduce the pitch discrimination threshold in novices?
- 2- How does short-term pitch discrimination training influence the anatomy and the function of auditory regions and other involved structures, such as the corpus callosum?
- 3- What is the effect of hemispheric lateralisation in pitch discrimination? This is examined from two perspectives:
 - a- Musical practice (training) - is there right hemispheric advantage in pitch processing across proficient musicians and novices, in terms of psychoacoustic measures, auditory cortex structures and functions?
 - b- Acoustic stimulation - how do the auditory cortices in proficient musicians and novices respond to different acoustic stimuli, such as those that are supplied binaurally or monaurally? Is there hemispheric lateralisation across groups?
- 4- How do auditory areas vary structurally and functionally in proficient musicians compared with novices?
- 5- Does short-term plasticity reflect long-term differences that are seen between musicians and non-musicians?

By seeking to answer these questions, the study will increase the understanding of the neuroplasticity mechanisms induced by auditory learning, which will help in the development of knowledge regarding the achievement of the best neuroplasticity applications in clinical fields, as well as skill perfection.

1.3 Study Overview

This research explored the neural plasticity in auditory areas that were associated with pitch discrimination learning and it involves two studies. The first study investigated the effects on neural plasticity in auditory areas across group of novices who learned a new task through application of pitch discrimination training over a short period. The second study compared

these short-term training effects with those caused by long-term experiences among proficient musicians.

Chapter One: The introduction chapter explains the design of the current research, and the relevance and significance of the study. Additionally, the research questions are outlined in this chapter.

Chapter Two: As the main purpose of the current research was to explore the structural and functional plasticity changes that underlay short-term pitch discrimination training, this chapter provides a short introduction to the basics of pitch perception, and the effects of learning on brain function and structure.

Chapter Three: As MRI was used as a research tool in this study, it is essential to have a brief overview of MRI physical principles, the physics behind the MR sequences that were used, and an overview of the analysis software.

Chapter Four: The methodology of the research is explained in this chapter, which describes the experimental design overview, recruitment of participants, MRI scanning protocols, and analysis programs that were employed.

Chapter Five: The work that is described in this chapter was designed to explore the effect of short-term training on pitch discrimination through the assessment of psychoacoustic performance. Another target of the experiment was to investigate the superiority of the right auditory cortex in pitch discrimination tasks.

Chapter Six: The aim of the work that is described in this chapter was to investigate the functional changes that were caused by short-term training in pitch discrimination. This was achieved through use of functional magnetic resonance images (fMRI). Another target of the experiment was the investigation of lateralisation of functional activity in the auditory cortices in terms of presentation of acoustic stimuli and pitch processing.

Chapter Seven: The work that is explained in this chapter was planned to investigate any structural changes with respect to the volume of grey matter (GM) and cortical thickness that were caused by short-term training in pitch discrimination across trainees compared with the experienced controls.

Chapter Eight: The work explained here was designed to investigate the changes of structural integrity of white matter (WM) that were caused by short-term auditory training. The changes

were observed through use of magnetic resonance (MR) diffusion tensor imaging (DTI) across the trainees compared with the controls.

Chapter Nine: In this chapter, the project that is described was designed to explore the auditory areas, as well as variations from both functional and structural perspectives between musicians and novices. Another target of the experiment was to investigate the hemispheric laterality in functional responses that were associated with different acoustic stimuli in musicians compared with novices.

Chapter Ten: An overall conclusion is offered of the main findings from the current research, the research limitations and future work recommendations.

Chapter 2. Background on the Basics of Pitch Perception and the Effect of Learning on Neuroplasticity

2.1 Introduction

This chapter provides a general overview in regard to the basics of pitch perception and the effects of learning on brain function and structure.

2.2 What is Pitch?

Oxenham (2013) defined pitch as an initial auditory sensation that connects the perception directly with the repetition rate or the periodicity of sound waveforms (Oxenham, 2013). The American National Standards Institute (ANSI, 1994) has also defined pitch; it states: “Pitch is that attribute of auditory sensation in terms of which sounds may be ordered on a scale extending from low to high.” In general, the most common way by which the pitch of a tested sound is measured is through the utilisation of a pitch-match process. This involves assessment of the frequency of comparative sounds, which can include sinusoidal tones or a sequence of clicks. The sounds are supplied at varying frequency in order for the listener to judge the pitch in sound stimulus to compare with the pitch in the test stimulus (Yost, 2009).

Pitch is normally understood in regard to music and as the base for musical scales and intervals. Accordingly, pitch sequences demonstrate melody, while pitch combinations produce harmony. Pitch, nevertheless, functions in many ways; it is vital in everyday speech, as the highs and lows of speech help in language rhythm and improve the transmission of speech to other people (Miller et al., 2010). In spoken languages, pitch helps to transmit prosodic information, which includes semantic connotations that written language does not produce (Bolinger, 1978). Languages that are based on tone (e.g. Mandarin) function through the use of pitch, which is used to distinguish lexical content and particular contextual grammar. Darwin (2005) states that complex acoustic environments produce differences in pitch, which can assist listeners to separate and understand different and conflicting sounds.

There are two pitch types: the first is a pure tone, which is considered mathematically as the simplest sound with a single frequency, and is produced through sinusoidal motion. The second type is a complex-toned harmony that is made up of sinusoids that are based at the fundamental frequency (F_0) and combine with integer multiples of the F_0 ; these are referred to as ‘harmonics’ (Oxenham, 2013). These complex harmonics are the most commonly ascertained sound form that produces pitch, and they produce the common sounds that are heard in normal

life, including speech and music (Yost, 2009). These components are represented in the auditory system in which sound processing, which involves pitch extraction, occurs.

2.3 Overview of Auditory System Pathways and Pitch Perception Centres in the Brain

2.3.1 Physiology of the Auditory Pathways

Generally, the auditory system transforms the mechanical energy in sound waves into neuro-electrical signals, which can be interpreted and analysed by the brain. The ear is made up of three main components: the inner, middle, and outer ear (see Figure 2.1). When the auditory signals are received by the outer ear (pinna and external auditory meatus) as a mechanical sound wave, they pass through the tympanic membrane in the ear drum (which is part of the middle ear) and they vibrate the middle ear ossicles. Then the sound wave is transmitted into the inner-ear fluid inside the cochlea, which is a coiled tube that is filled with fluid. The cochlea is tonotopically organised, as its base is stimulated by high frequency, whereas its apex is stimulated by low frequency. Motion across the cochlear fluid causes the hair cells on the top of the basilar membrane to release neurochemicals. These neurochemicals travel through the auditory nerve fibres to the cochlear nuclei in the respective hemispheres. The cochlear nuclei are tonotopically organised; they are divided into groups according to their particular frequency response features. The ventral, rostral and lateral parts of the cochlear nuclei act on low-frequency sound waves, whereas the dorsal, caudal and medial parts respond to high-frequency sound waves. This spatial tonotopic arrangement is preserved by the auditory nerve fibres, which branch as they enter the brainstem into anterior and posterior branches.

The anterior branches project into the ventral part of the cochlear nuclei, whereas the posterior branches project into the dorsal part of the cochlear nuclei. The auditory nerve fibres then transfer the auditory signals from the ipsilateral and contralateral cochlear nucleus to the superior olivary nucleus (SON), which is also located in the brainstem. The SON has a crucial role in the temporal coding of auditory signals, as the medial part of the SON acts on the time differences in the sound wave, while phase differences of the sound waves are processed by the lateral part of the SON. From the SON, sound information ascends in an auditory spatial map through the lateral lemniscus tract to the inferior colliculus, and then to the medial geniculate body of the thalamus in both hemispheres. Finally, from the medial geniculate body, sound signals are transmitted to the auditory cortex, where the sound processing occurs (see Figure 2.2) (Pickles, 2015; Peterson et al., 2018).

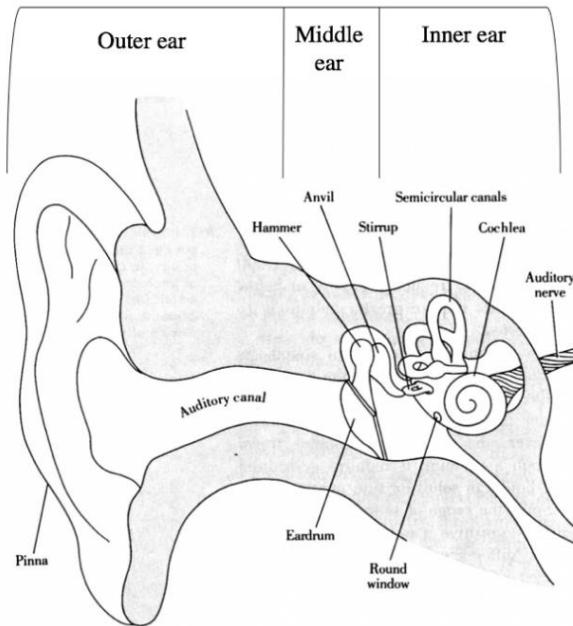


Figure 2.1. The diagram illustrates the peripheral auditory system and the outer, middle and inner divisions of the ear (Human ear anatomy, 2020).

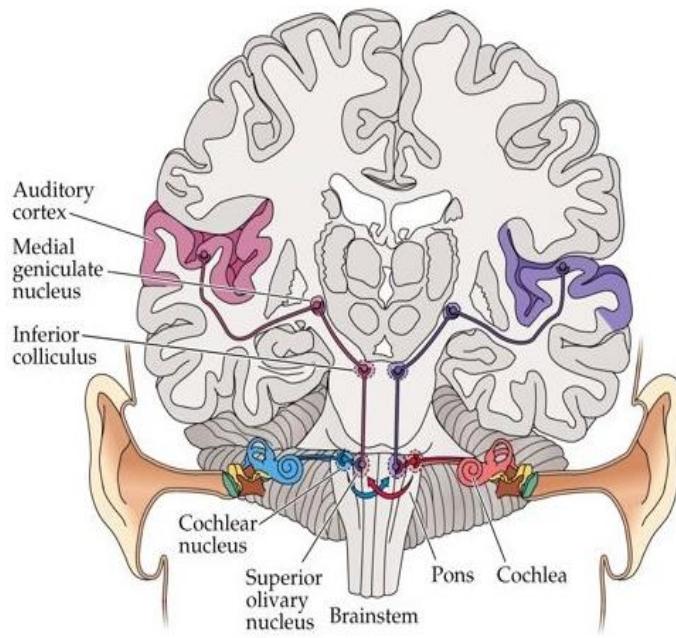


Figure 2.2. The central auditory system pathways; the nerve impulses travel from the cochlear nuclei to reach both auditory cortices (Perception Lecture Notes: Auditory Pathways and Sound Localization, 2001).

2.3.2 Pitch Perception Centre

The upper medial surface of the superior temporal gyrus (STG) in the temporal lobe occupies the primary auditory cortex (PAC), which involves Heschl's gyrus (HG) (matches to Brodmann areas 41 and 42) (see Figure 2.3). The lateral aspect of the STG (posterior to the PAC) occupies the secondary auditory cortex, which is also called the auditory association area, and matches to the Brodmann area 22 (also called Wernicke's area) (Purves et al., 2001). The PAC, and specifically the HG, is known as 'the human pitch perception centre', as revealed by many neuroimaging studies (Griffiths et al., 2001; Patterson et al., 2002; Warren & Griffiths, 2003; Bianchi et al., 2017). The secondary auditory cortex has a significant role in the interpretation of sounds, which is also performed through the combination of the information from the auditory and other sensory mechanisms (Snell, 2010; Kiernan, 2012).

There is intra- and inter-individual variability in PAC locations and sizes, and in their situations in the left and right hemispheres, as the PAC in the right hemisphere is found to be located more anteriorly than the PAC in the left hemisphere (Morosan et al., 2001; Rademacher et al., 2001; Patterson et al., 2002). The auditory cortical areas in each hemisphere are connected together through the corpus callosum.

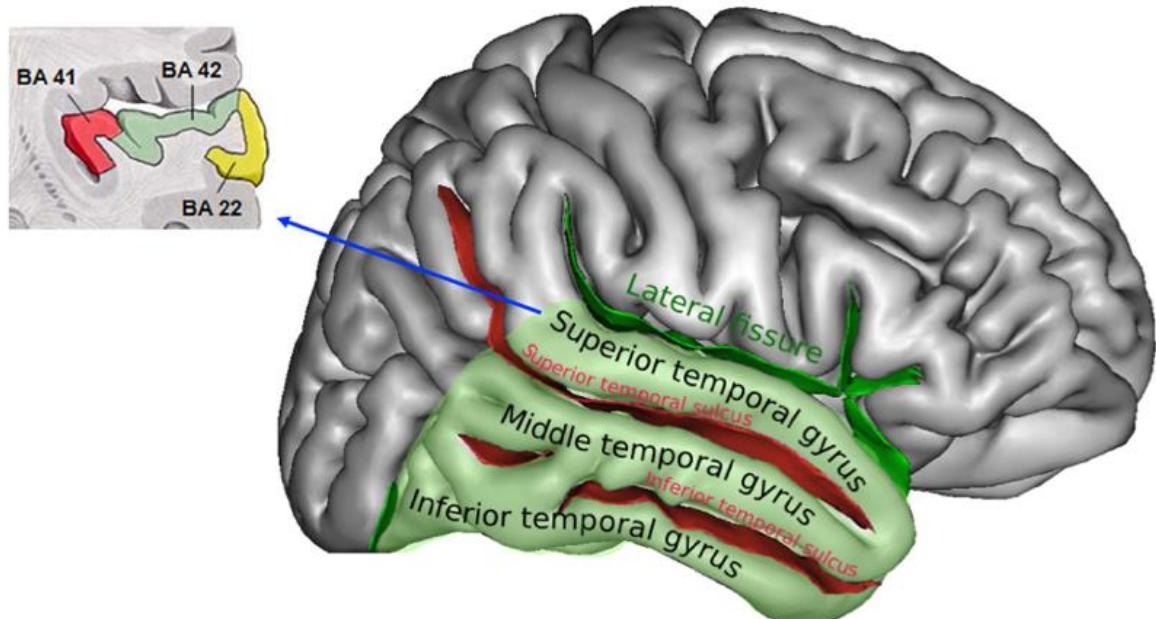


Figure 2.3. An illustration of the lateral aspects of the temporal lobe, which consists of: superior, middle and inferior temporal gyri. The cross-sectional image (arrowed) shows the primary auditory cortex (which involves the Heschl's gyrus, BA 41 and 42), and the lateral-posterior aspect of the superior temporal gyrus (STG), which consists of the secondary auditory cortex (which involves the Wernicke's area, BA 22). BA: Brodmann areas. (The lateral image is republished from Sebastian (2011) and the arrowed image is republished from Talbot et al. (2011)).

2.4 Pitch Perception Theories

The sound frequency, magnitude and time/phase are the physical characteristics that are usually used to describe a sound. However, these aspects of sound are not the only basis on which pitch is based, since as sound passes through the auditory system it is changed significantly. The auditory system processes the sound through auditory mechanisms that change the sound representation, particularly in peripheral structures; thus, these mechanisms change how spectra and time-pressure waveforms function and how pitch is perceived. Currently, pitch perception theories stem from potential neural sound representations at the auditory periphery, and are not based on physical sound properties (Yost, 2009).

One of the major scientific interests in this field is to understand the mechanism that occurs in the central auditory system to code the tonal frequency, and to apply this approach in clinical applications (Oxenham, 2008). Despite the ambiguity of knowledge regarding the information that is used by the brain for pitch perception, the most popular method by which researchers understand how pitch perception is coded in the brain involves the integration of ‘spectral’, or ‘place’, and ‘temporal’ mechanisms (McClaskey, 2016).

2.4.1 Place Theory

In terms of place theory, tonal pitch is determined based on the location of the vibration along the basilar membrane in the cochlea of the inner ear. For instance, the basal end of the basilar membrane is found to be most excited by high frequencies, whereas the apical end responds more to low frequencies. Hence, the parts of the basilar membrane respond to distinct frequencies at different strength levels. This frequency-to-place organisation is known as ‘tonotopic mapping’, and is sustained along the auditory pathways through to the PAC. This system provides the tonal pitch with a potential neural code (Oxenham, 2013; Pickles, 2015) (see Figure 2.4).

With regard to pure tones, the travelling wave has its peak at one particular frequency, with a location that represents the audible pitch (Plack & Oxenham, 2005; Popper & Fay, 2005). Additionally, excitation patterns commonly show pitch perception in complex tones that are comprised of various frequencies (Plack & Oxenham, 2005; Oxenham, 2013). As a result, this mechanism is called ‘place coding’, or ‘rate-place coding’, and the indications that produce this information are referred to as ‘energy indications’ or ‘excitation-pattern indications’ (McClaskey, 2016). Rate-place coding is processed quickly and does not need a long duration of temporal integration (Moore, 2012; Pickles, 2013). These energy indication forms occur

throughout the complete basilar membrane length, and occur for all the frequencies that humans can hear (a range of 20-20,000Hz) (McClaskey, 2016). In addition, there is a variety of important sections of the spectral pitch theory that originate from particular properties of the basilar membrane.

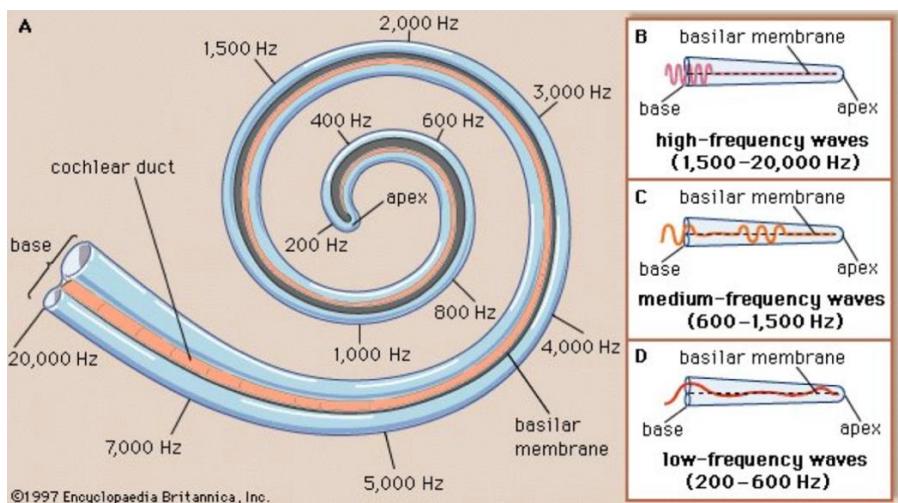


Figure 2.4. The tonotopic mapping in the basilar membrane of the cochlea, where sound is analysed based on its frequencies. (A) The basilar membrane starts with a narrow width in the apex of the cochlea and then becomes gradually wider in the cochlear base. (B) High-frequency sound waves stimulate the basilar membrane base. (C) Medium-frequency sound waves stimulate the central part of the basilar membrane. (D) Low-frequency sound waves vibrate the apex of the basilar membrane (Encyclopaedia Britannica & Inner ear anatomy, 1997).

In relation to pitch perception, there is a large amount of evidence to support the theory of rate-place coding, which is believed to be the central mechanism in pitch extraction of pure tones and complex tones with undetermined harmonics (i.e. at high-frequency levels) (Moore, 1973; Plack & Oxenham, 2005; Gockel et al., 2007; Moore, 2012; Marmel et al., 2015). Nevertheless, there are various pitch phenomena that cannot be determined through application of spectral theories. For instance, even with a lack of energy, stimuli can extract pitch at frequency levels that correspond to the audible perception of pitch, which occurs with the missing fundamental ‘residue pitch’ (Schouten, 1940). These phenomena have been explained through expanded rate-place theories and through pitch temporal theory, which is a second type of pitch theory.

2.4.2 Temporal Theory

According to the temporal theory of pitch, the brain relies on spikes that are created in the auditory nerve, which normally occur during specific phases within a sinusoid period – referred

to as a ‘phase-lock’. From this, the brain potentially is able to represent pure-tone frequencies through time intervals between continuous rises, when set in the auditory nerve (Griffiths et al., 2001; Oxenham, 2013); an evaluation of these is provided using auto-correlation or a full inclusive interval rise (i.e. spike) histogram (Schouten et al., 1962; Cariani & Delgutte, 1996; Oxenham, 2013).

One important feature of temporal pitch theory is that temporal pitch can be very precise, as the non-random discharge patterns of the auditory nerve fibres can present precise peak timings in the waveforms at quality low-waveform rates of repetition (Siebert, 1970; Moore, 1973; Heinz, Colburn & Carney, 2001). Additionally, temporal coding can determine low-frequency discrimination points and raise levels in frequency different limens (FDLs) with elevated stimuli frequencies that cannot be determined through use of spectral theories. What is more, use of temporal theories can lead to explanations of other pitch forms, such as missing fundamentals and periodicity pitches (Cariani & Delgutte, 1996), because attention is paid to waveform periodicity instead of spectral energy.

However, this theory has certain limitations that occur in general during application to the phase-locking process, as it is only able to represent periodicities of adequately slow rates, which require long integration windows. Hence, under this theory, the system does not have sufficient time to ascertain the rates of repetition when the stimulus is too short or there are not enough repetitions. Consequently, shorter periods of stimuli can be better explained by temporal pitch in comparison with rate-place mechanisms (McClaskey, 2016). Indeed, temporal pitch theory can reasonably code frequencies that fall below approximately 4 kHz, while more elevated frequencies at >5 kHz are normally coded by spectral pitch, due to the absence of the phase-lock process at this level of tone vibration (Sek & Moore, 1995; Moore & Sek, 1996; Plack & Oxenham, 2005; Oxenham, 2012; Pickles, 2013).

2.5 Hierarchical Pitch Processing

Auditory scene analysis is vital in the separation of sounds from background noises that can disturb the focus. As a result, this must be analysed and processed through a fine spectral and temporal scale in order to exploit features of the sound, such as the differences in pitch between the target sound and those that compete with it, and the minimal differences in the elements’ onset times that comprise the auditory setting. Consequently, the analysis must be undertaken with a high-resolution representation (Meyer et al., 2006).

Griffiths et al. (1998) and Patterson et al. (2002) provide further insights regarding pitch processing. They suggest that the definition of the pitch value or pitch strength is a quick process that is executed in the HG, whereas long processes, such as pitch contour estimation (pitch changes through time), occur in the posterior STG (BA 22) and the planum polare (PP), which is part of the STG and is located in the lateral aspect of the transverse temporal gyrus (TTG). According to Patterson et al. (2002), pitch processing involves two steps: firstly, it derives the time-interval information from the firing of the neurons across auditory nerve fibres, which occurs in the brainstem; and secondly, the resultant time information is used by the HG to assign the pitch value. An additional step is required for melody processing, which involves the tracking of pitch change across the melody. This occurs in the STG and the PP. Therefore, studies suggest that there is a hierarchy in the pitch process in humans, which begins in the brainstem and is finalised through the lateral HG (Griffiths et al., 2001; Patterson et al., 2002; Warren & Griffiths, 2003).

2.6 Hemispheric Asymmetries in Tonal Processing

Hemispheric asymmetries in acoustic processing have been revealed in many experiments (e.g. Zatorre and Samson, 1991; Patterson et al., 2002; Schönwiesner et al., 2005; Oechslin et al., 2018). These studies propose several possible explanations for the observed hemispheric asymmetries. One possible explanation lies in the acoustic stimulus characteristics: the left auditory cortex has superiority in temporal modulation (speech), whereas spectral modulation (melody) is predominantly represented in the right auditory cortex (Zatorre and Samson, 1991; Patterson et al., 2002; Schönwiesner et al., 2005). Another possible explanation for hemispheric lateralisation is the influence of practice, as musicians show right auditory cortex advantage in tonal processing (Mazziotta et al., 1982; Zatorre, 1998; Tervaniemi et al., 2000; Bianchi et al., 2017; Oechslin et al., 2018). For example, Oechslin et al. (2018) found evidence of lateralised plasticity that was related to training; they observed an improvement in acoustic information transfer across the right hemisphere in musicians. Their result reflects the idea that musical practice could be a reason for the lateralisation of tonal processing across the auditory pathway in the right hemisphere.

In addition, the method by which the auditory stimulus is presented may be a cause of hemispheric lateralisation. Woldorff et al. (1999) and Schönwiesner et al. (2007) used the fMRI technique to investigate whether the hemispheric lateralisation was dependent on the ear stimulation by application of binaural and monaural acoustic stimulus. Their results show that monaural sound stimuli cause contralaterality in functional activation within auditory regions,

whereas this lateralisation is not seen with binaural sounds. Goldstein (1973) argued that there was a central pitch processor in the auditory system that functioned irrespective of the presentation form of the pitch stimuli (monaurally or binaurally). These explanations could each be correct in particular cases (Zatorre et al., 2007); however, there are inconsistencies in the effects that have been reported to differ according to the form of presentation of the auditory stimuli.

2.7 Pitch Discrimination

Pitch discrimination refers to the detection of differences in pitch dimensions, such as frequency, tone duration, and the pitch direction as it ‘rises or falls’ (Long, 2014). The minimum discriminable change in pitch dimension is defined as the discrimination threshold. Humans are sensitive to frequency alterations through pure tones. In the pure tones the mid-frequencies of which range from 500 to 2,000 Hz at levels above 30dB, the just-noticeable differences (JNDs), which are also called difference limens, can reach 0.2% for well-trained listeners and approximately 0.5% for untrained listeners (Oxenham, 2013; Long, 2014). In the cases of complex tones, the highest level at which a subject can determine changes in frequency within the tone has been reported to be <1 kHz (Zeitlin, 1964).

Forced choice is a common procedure that is used in pitch discrimination tests (Levitt, 1971). This may involve a two-interval forced choice (2IFC), in which the listener is required to judge the higher pitch frequency of two tones or the direction of the rising or falling pitch; or a three-interval forced choice (3IFC), in which the listener is required to assign the ‘odd’ pitch of three tones (Sergeant, 1973). Subsequently, the pitch discrimination threshold can be obtained through ‘adaptive’ or ‘non-adaptive’ methods. In adaptive methods, such as the ‘staircase’, the stimulus intensity level is shown to the subjects based on their reaction to the previous stimulus (Wetherill & Levitt, 1965; Levitt, 1971; Bode & Carhart, 1973). However, in non-adaptive methods, such as constant stimuli, the intensities are decided beforehand and function independently of the responses provided (King-Smith et al., 1994). The adaptive methods are usually found to be more efficient than the non-adaptive, as the level samples are adaptively clustered around the psychometric threshold (Dixon & Mood, 1948; Watson & Fitzhugh, 1990).

After a run of trials through the pitch discrimination test, the threshold can be estimated in numerous ways. The most common method involves the researchers ending a sequence after a set number of directional reversals (García-Pérez, 1998).

The threshold estimate is then determined as an average intensity level of stimulus from the last few trials in which reversal had occurred. A different way to ascertain threshold estimation is to fit the experimental data into relevant psychometric functions, in which threshold differences are set as the number of correct responses that attain certain criteria (e.g. 75%) (Prins, 2016).

2.7.1 Learning through Pitch Discrimination

Various research studies have demonstrated that people's ability to detect differences in frequency levels between sequence tones can be noticeably improved through a set duration (i.e. days or weeks) of auditory training (Wyatt, 1945; Demany, 1985; Delhommeau et al., 2002). In Demany's study, the focus was on the effects of training at different frequencies: 200, 360, 2500 and 6000 Hz. These frequencies were set at individual frequency discrimination thresholds (FDTs). Two training sessions were conducted, each of 75 minutes duration and with a two-day minimum rest period in-between. The participants' FDTs were measured using the staircase method. The results showed that the FDTs improved with training at 200, 360 or 2500 Hz; however, a lower level of improvement was observed at 6000 Hz. These findings concurred with the concept that different processes occur at frequencies of >5000 Hz and <5000 Hz, which affect both frequency discrimination and perception of pitch.

Another study conducted by Delhommeau et al. (2002) investigated whether frequency discrimination transfer could be altered through stimulus duration and between the ears. In that study, a total of six sessions over a period of three weeks were used to measure the participants' FDTs, with each session lasting for two hours. These sessions included the use of 3IFC and two-alternative forced-choice (2AFC) procedures. In the 2AFC method, participants are offered two stimuli and are asked to choose one based on a set criterion. These 2AFC tests each lasted for 200ms. The right ear received a fixed 1kHz tone, while the FDT test was set for both ears, which received 1kHz tone pips through durations of 40, 100, and 200 ms. The researchers observed that the participants' FDTs decreased by an average of 68%; after the training, there was no marked difference between the results for the right and left ears compared with the results that were obtained before the training, although during the trained 200ms duration there was a significantly smaller difference in the right (trained) ear. Hence, it can be determined that frequency-discrimination learning produces improvements across durations of stimuli and between ears, although these are particular to the duration ranges and to the ear that undergoes training.

Other researchers have studied the effect of training intensity on pitch discrimination ability. In particular, many studies have focused on the comparison of the discrimination threshold between musicians and non-musicians, as musicians normally demonstrate enhanced abilities to discriminate pitch (Kishon-Rabin et al., 2001; Tervaniemi et al., 2005; Bianchi et al., 2016). In the study by Kishon-Rabin, the difference limens for frequency (DLFs) of musicians were measured in comparison to those of non-musicians. These were studied for pure tones from the frequencies 0.25, 1 and 1.5 kHz. The DLFs were ascertained through the use of a 3IFC adaptive procedure, with the 2IFC procedure for 1kHz. The findings showed that the average DLF for musicians was around 50% of what was found for non-musicians. The study that was performed by Tervaniemi provided a comparison between the accuracy of pitch processing in musicians who could play many instruments against that of non-musicians. This research process included spectrally complex tones through deviant sounds (0.8, 2, or 4% higher in frequency), and the 2AFC method was used to estimate the FDT. Their findings highlight that musicians are able to determine changes in pitch at a quicker rate and more precisely than non-musicians.

Bianchi investigated the perceptual enhancement for complex tones of resolved/low frequency (300–1500 Hz) and unresolved/high frequency (1500–3500 Hz) with fundamental frequencies (F_0 s) of 100-500 Hz. This study was conducted in order to determine the level of musicians' enhanced performance in pitch discrimination and whether it could be credited to higher peripheral frequency selection, and/or to contrasting levels of effort in the procedure of a task. A 3AFC method was utilised with a weighted 'up-down' method (Kaernbach, 1991) that measured the achievement of 75% of the psychometric function. The performance levels of pitch discrimination in musicians increased similarly for both resolved and unresolved complex procedures.

Since these study results indicate that musicians show superior pitch discrimination abilities compared with non-musicians, it is necessary to evaluate how pitch processing differs amongst musicians.

2.7.2 Pitch Discrimination in Musicians

In 1919 Seashore noted that pitch discrimination was a fundamental skill that was observed in musicians, since musical appreciation and expression relied on this skill. Indeed, high-calibre musicians require high-quality pitch in order to determine the intricate differences in tones, which the acts of playing and singing are able to draw out.

Research has confirmed that musicians have superior pitch discrimination ability due to their musical practice (Spiegel & Watson, 1984; Kishon-Rabin et al., 2001; Micheyl et al., 2006). These studies show that musicians have smaller FDTs that are associated with advanced performance levels in comparison with non-musicians. Specifically, Spiegel and Watson (1984) found that musicians' thresholds covered a range of 0.001 to 0.0045, while the comparison figures for non-musicians were considerably higher at 0.005-0.017. Similarly, Kishon-Rabin et al. (2001) determined that musicians' mean DLFs were approximately 50% of those for non-musicians.

The enhancement of musicians' ability in auditory sensations led to research into psychology and neuroimaging (Kishon-Rabin et al., 2001; Zatorre et al., 2007; Bianchi et al., 2016; 2017). Studies have also attempted to find out why musicians show superiority in pitch discrimination ability. A possible answer is that fine pitch discrimination is required by proficient musicians as they must adjust musical instruments to be in tune, often during a concert (Alghamdi, 2012). Frequency discrimination of melodies requires higher level processes that involve segregation of the tones in melody, pitch contours and harmonies. These higher level processes are presented in the human auditory cortex as a hierarchical approach pattern (as described previously). According to Zatorre et al. (2007), both pitch interval production and timing must be controlled precisely in order to achieve activities that are involved in musical performance. Correspondingly, Brattico et al. (2001) used electroencephalography (EEG) to investigate the brain's response to music. They determined that changing tonal pitch caused a rapid neural response in musicians compared with novices. Therefore, the musical context has an effect on neural response that is represented by higher level processes which are associated with pitch perception.

2.8 The Effects of an Enriched Environment on Neuroplasticity

Scientists have found that the brain is a flexible organ that can undertake structural and functional remodelling through time- and activity-dependent events; this process has been named 'neuroplasticity' (Konorski, 1948; Vital Durand & Jeannerod, 1975; Herholz & Zatorre, 2012). Neuroplasticity underlies the processes of maturation and skill development, and may underlie neural changes that are required for a person to adapt to changes to the environment (Kolb, 1999; Fields, 2008; Feldman, 2009; Abdulkareem, 2012; Filley et al., 2016), and/or due to pathology (Zilles, 1992; Nudo et al., 1996; Lledo et al., 2006). An enriched environment is the most commonly utilised experimental paradigm during studies of training-induced plasticity.

Research has found that environmental improvement at the microscopic level produces various morphological changes, which include: cellular proliferation, angiogenesis, and conversion of silent to active synapses, which leads to production of myelinating glia (Markham & Greenough, 2004; Fields, 2008; Butz et al., 2009). In addition, functional plasticity occurs, an example of which is the functional reorganisation of neurons and synapses (Feldman, 2009). According to Lynch and Eilers (1991), children with musical experience demonstrate improved auditory perceptual skills in comparison with children who have no musical experience. In their study, they observed that 10-13 year-olds with musical training were able to detect subtle frequency deviances (~25 cents, or an eighth of a tone) in single notes within both major and minor scales. However, neurons degenerate if they do not participate actively in neural activity for long periods of time. Hubel and Wiesel (1965) were the first to focus on this concept, as they analysed the change in kittens' eyes with a reduction of light. This change resulted in a reduction in the number of neurons in the visual cortex.

The results of several research studies into training-induced plasticity have generated great levels of interest in vivo-neuroimaging techniques that have helped to determine how environmental enrichment affects the human brain (Maguire et al., 1997; Mechelli et al., 2004; Park et al., 2009). There is an evident substantial environmental influence upon an adult brain's structure and function. For example, the correlation between adult environmental enrichment and localised brain volume differences were analysed in taxi drivers who worked within the London area, where the drivers faced distinct spatial navigation demands (Maguire et al., 2000). In comparison with a control group, the structural scans of the drivers' brains that were obtained through magnetic resonance imaging (MRI) presented enlarged posterior hippocampal volumes, together with smaller anterior hippocampal volumes. It is vital to note that a region-specific correlation was found between the hippocampal volume and the drivers' levels of experience; the number of years of experience was positively correlated with the posterior and negatively with the anterior hippocampal volume.

2.8.1 Musicians as a Model of Neuroplasticity

Skilled musicians have been used as an ideal model in the analysis of brain plasticity due to their sensitivity to dynamic stimuli and their exposure to complex stimuli in music (Schlaug, 2001; Münte et al., 2002). Indeed, professional performances of music are widely seen to exhibit some of the most profound human achievements, as auditory-motor interaction is increasingly involved in the musical processing of information, such as rhythm and pitch, along with other cognitive processes, for example attention and memory (Haueisen & Knösche, 2001;

Zatorre et al., 2007; Chen et al., 2008; Alho et al., 2014). Hence, extensive musical practice over long periods that is performed by musicians can induce neuroplastic changes that impact upon brain function and structure. The different forms of neuroplasticity that have been studied in musicians' brains are explained in the next subsections.

2.8.1.1 Structural Plasticity

MRI morphometry techniques have revealed anatomical variances between the auditory processing and motor areas of the brains of musicians and non-musicians. The motor areas are affected due to their role in the control of music. Sluming et al. (2002) and Gaser and Schlaug (2003) used the voxel-based morphometry (VBM) technique to examine GM density, and they found higher GM volumes in music-correlated regions across musicians. Certain brain regions show differences in size and function between musicians and non-musicians, and these are: the planum temporale (PT), Heschl's gyrus (HG), the corpus callosum and motor areas (Münte et al., 2002; Schneider et al., 2002; Sluming et al., 2002). The structural differences that are found in musicians may reflect interplay between genetic factors and the amount of practice that musicians perform during their lives (Gaser and Schlaug, 2003; Bangert and Schlaug, 2006; Golestani et al., 2011). Wyatt (1945) claimed that the pitch discrimination ability did not change with age or training; however, there was a fixed 'physiological limit' that controlled the individual's ability in pitch discrimination. This idea was suggested by Seashore (1938), who defined the physiological limit as an individual's limit in pitch discrimination ability that depended on the inherited morphological properties of the auditory sensor, which were not susceptible to change by environmental effects. In a supportive study by Golestani et al. (2011), the researchers showed that their group of highly trained phoneticians had different brain structures that had developed early in utero compared with the controls. They deduced this conclusion from their finding in the phoneticians' brains only of multiple transverse gyri in the left auditory cortex, which is known to play a dominant role in speech perception. They suggested that brain structure predetermined the professions that people would select. Although their study was carried out across phoneticians, it seems likely that this finding is transferable to musicians.

2.8.1.2 Plasticity in terms of Water Diffusivity

Use of diffusion-weighted imaging (DWI) provides detailed maps regarding the metrics of microstructural characteristics of water diffusion (see Chapter Three , section 3.4.4 for further detail). Studies that have used DWI have shown that there is a significant microstructural

change in the representative areas of the brain that create the base for musicians' specific skills (Steele et al., 2013; Engel et al., 2014; Moore et al., 2017). For instance, Engel et al. (2014) found that musical- and motor-learning tasks, such as learning piano melodies, could produce a neuroplastic alteration of WM tracts. Their results showed that the level of fractional anisotropy (FA) was increased within the corticospinal tract (CST), which is the tract that connects the auditory regions to the motor regions. In agreement with a study that was performed by Moore et al. (2017), they found that music-cued motor trainees showed a significant increase in their FA with a reduction in radial diffusivity in the arcuate fasciculus. They attributed this increase to the trainees' style of learning.

2.8.1.3 Functional Plasticity

Musicians' brains process auditory and motor signals differently to the brains of non-musicians. This has been shown by multiple studies that have used neuroimaging techniques, which include: functional MRI (fMRI) (Gaab et al., 2005; Bianchi et al., 2017); magnetoencephalography (MEG) (Maess et al., 2001); EEG (Altenmüller et al., 2000; Koelsch et al., 2000; Bangert and Altenmüller, 2003); and positron emission tomography (PET) (Satoh et al., 2001). Gaab et al. (2005) and Bianchi et al. (2017) used fMRI to measure brain activity during the performance of pitch discrimination tasks. The results of the Gaab study show that auditory stimulus processing is rapid across the auditory cortices of musicians compared with non-musicians. Bianchi found that both cortical and subcortical auditory regions exhibited greater neural responses to complex tones in musicians compared with controls. Altenmüller et al. (2000) used EEG to record event-related brain potentials (ERPs) that were produced by the brains of the participants during a melodic pitch discrimination task. They found that the brain activity was limited to the right temporal lobe in non-musicians, whereas the brain activity involved bilateral temporal lobes as well as the frontal lobe in the musicians. They suggested that the differences in brain region activation were due to the use of different cognitive strategies by the two groups.

Some studies have linked structural and functional changes that are induced by musical training, such as those by Schneider et al. (2002) and Benner et al. (2017). Schneider et al. (2002) used structural MR images and MEG. They observed greater neural activity and GM volume in the HG of proficient musicians. Benner et al. (2017) investigated the difference in the structure–function relationship between proficient and amateur musicians by combining the use of structural MRI and functional imaging modalities (fMRI and MEG).

Their results indicated that proficient musicians had larger HG than amateur musicians. They found that there were inter-individual and inter-hemispheric morphological differences in the HG within groups and that this anatomical variation was consistent with functional activation, which reflected HG size multiplications.

Generally, these results support the concept of improvement through utilisation, since in these studies, extended training was shown to improve specific brain function, and thus, enhance overall function (Kleim and Jones, 2008). This may also emphasise how a skill that is acquired through perpetual practice over a long period can lead to many cortical plastic changes. However, little is known about the plastic changes that are associated with short-term training effects.

2.8.2 Neuroplasticity with Short-term Training

The previous section described many investigations that have revealed the effect of training over long periods on neuroplasticity. However, the effects of short-term learning have only been investigated in a few studies. For instance, Sagi et al. (2012) and Hofstetter et al. (2013) used diffusion tensor imaging (DTI) to investigate short-term (two hours) effects of spatial learning on the diffusivity of the brain. Their results revealed that WM underwent plasticity in the human brain, and this correlated with the behavioural performance of the study subjects. They found significant microstructural changes, which caused reductions in the mean diffusivity (MD) and elevation in the levels of FA in the hippocampus, parahippocampus and fornix areas. In another recent study, Hofstetter et al. (2017) used DTI to study cortical plasticity that resulted from the application of short-term (one hour) training to language tasks. It was shown that notable differences occurred in diffusivity within the cortical regions and WM tracts, which includes areas that are used in language and reading: the inferior frontal gyrus, the middle temporal gyrus, the inferior parietal lobule and the superior longitudinal fasciculus (SLF). These changes in cortical diffusivity were found to be correlated with the participants' learning rates. Thus, these studies confirmed that short-term training in tasks that demanded high levels of cognition could induce neuroplasticity within the task-related brain regions.

Sagi et al. (2012) have investigated further the biological relevance of this microstructural neural plasticity that occurs in the DTI. They hypothesised that the cellular mechanism that was associated with learning caused changes in the MRI measurements (a MD reduction resulted in FA elevation). As this cellular mechanism could not be seen in a human study, they

performed a further study by training rats on spatial tasks for two hours, and they used a similar DTI protocol followed by histological analysis to discover the effect on the rat brains. They found that the DTI results were similar to those of their first study, which was conducted on humans, as MD was reduced across the hippocampus area. Their histological analysis showed that there was a change in immunoreactivity levels, which meant that there had been a synaptic adaptation caused by learning. Moreover, they claimed that this synaptic adaptation was the biological reason for their DTI results. For example, learning can induce a synaptic adaptation that results in changes in extracellular space, which is followed by a decrease in MD.

In contrast, Field (2008, 2015) argued that myelinating glia were the starting point for neuroplastic alterations that were induced by learning. Field's argument relies on the close interrelationship that exists between myelinating glia and neurons that provide them with a base to function in order to change the structure of WM and the connections that are imperative in the process of passing on information. Hence, myelin plasticity can potentially provide cellular mechanisms for learning that improve established synaptic plasticity functions. Therefore, it can be seen that both Field (2008, 2015) and Sagi et al. (2012) have attempted to investigate the impact of learning on brain plasticity by linking cellular structural modifications that occur in the neural tissue with the alterations in MRI measurements, specifically diffusion metrics. However, the exact starting point of cellular structural modifications remains unclear. Thus, the biological processes that trigger learning-induced plasticity of WM, as well as their correlation with diffusion metrics, require further investigation (Hofstetter et al., 2013).

In sum, the previous section introduced the basics of pitch perception, physiology of the auditory pathway, and pitch processing in human brains. Also, it showed how perpetual practice can cause many morphological and functional changes, such as neuroplastic alteration found in musicians. MRI is a neuroimaging modality that has been used frequently to investigate the functional and structural neural alterations that are induced by learning. Thus, the following chapter focuses on the physical principles of MRI, the MR sequences that were used in the study that was performed as part of the work of this thesis, and an overview of the analysis software.

Chapter 3. The Basics of Magnetic Resonance Imaging Technology

3.1 Aim of the Chapter

This chapter provides a general overview of basic MRI physics, and covers the MRI sequences that were used in this project.

3.2 Introduction

Detailed images, as well as an extensive description of brain functions and structures, can be provided by advanced magnetic resonance imaging (MRI) technology. MRI has numerous properties that make it the most desirable system in neuroimaging, including: good spatial resolution images, broad availability, non-invasiveness, it involves use of no radiation and it enables study repetition. MRI can be used to perform complete brain examinations of the GM and WM regions; this is now the preferred technique for the detection of structural and functional evidence of neuroplasticity. A vast amount of research into cross-sectional imaging has demonstrated that structural (Sluming et al., 2002; Gaser & Schlaug, 2003a; Sagi et al., 2012; Steele et al., 2013; Engel et al., 2014); and functional (Callan et al., 2003; Tillmann et al., 2006; Stojanovic, 2010; Bianchi et al., 2017) parts connect to learning and experiences in various cognitive areas within healthy adult human brains, due to plasticity. However, MRI has several drawbacks: long scan time, frightening and noisy environment, metallic artefacts, poor temporal resolution and high cost (Oldendorf, 1988). The following section considers the technological aspects of MRI.

3.3 Basic MRI Physics Principles

Nuclear magnetic resonance (NMR) is a feature of MRI that enables images to be taken of the internal body structure based on the signals released by hydrogen atoms, which are the main components of most biological tissues, such as fat and water. The nucleus of the hydrogen atom consists of a positively charged proton, which usually spins around by itself; it produces randomly distributed small magnetic fields (see Figure 3.1, A and B). When protons are exposed to an external magnetic field (B_0), they align in parallel with or anti-parallel to B_0 (see Figure 3.1, C). Most of the spinning protons align parallel to the applied external magnetic field, and this alignment with the applied field creates the total magnetic field, which is referred to as the net magnetisation vector (NMV/M_0). The strength of the magnetic field is directly proportional to the precession of the protons that spin around the external field axis with an

angular frequency, as expressed in the Larmor equation (3.1) (Chavhan, 2013; McRobbie et al., 2017).

$$\omega\theta = \gamma B_0 \quad (3.1)$$

In which:

$\omega\theta$ = Angular frequency of protons in Hertz;

γ = Gyromagnetic ratio, which is specific to certain nuclei; γ for hydrogen protons at 1 Tesla is 42.6 MHz;

B_0 = External magnetic field in Tesla.

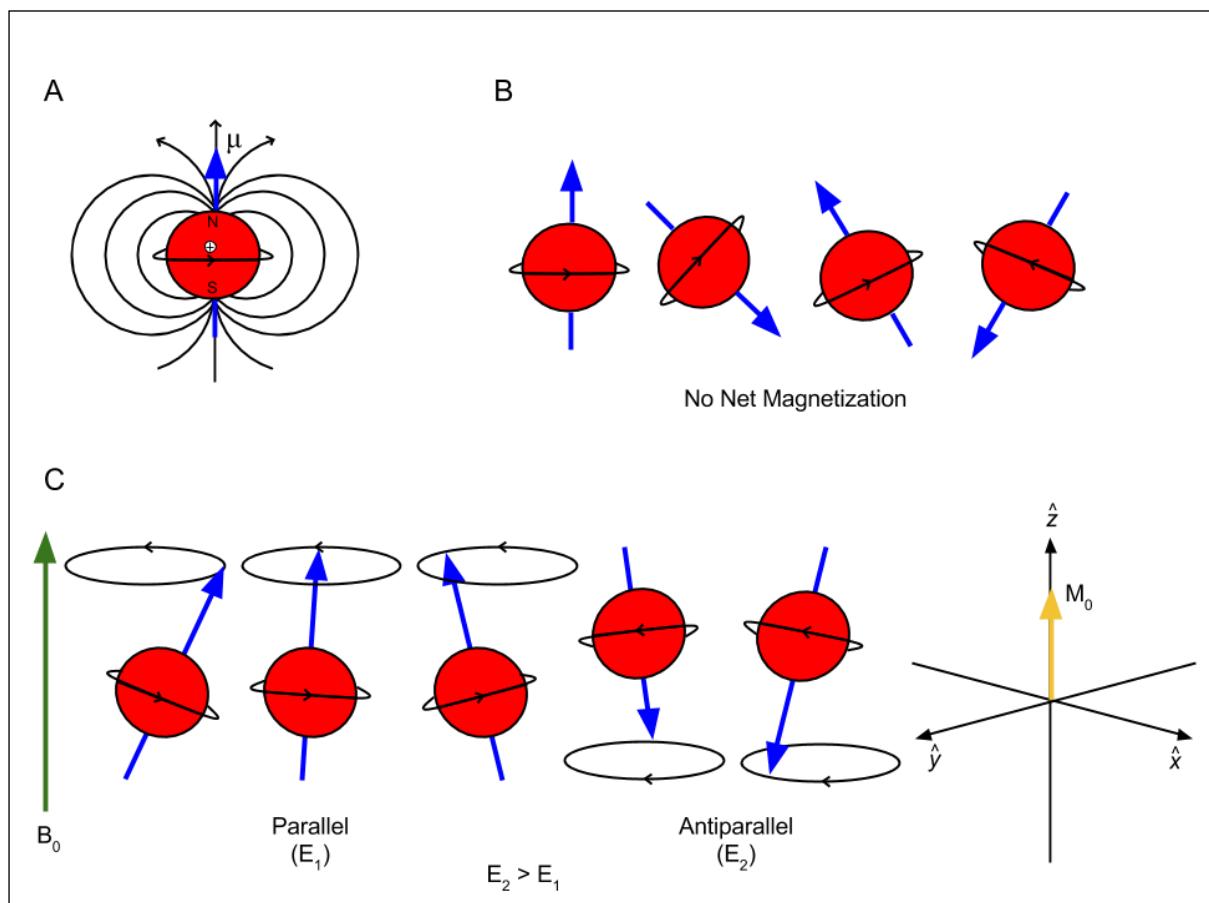


Figure 3.1. The effect of the magnetic field on spinning protons. A) Spinning proton μ is referred to as the magnetic dipole vector. B) Protons spinning randomly with no net magnetisation. C) The magnetic field B_0 is presented, which makes spinning protons align parallel or antiparallel to B_0 (Bushberg et al., 2003).

3.3.1 MRI Image Creation

To produce MRI images, the subject is placed inside a large magnet, and electromagnetic radio frequency (RF) is sent to the subject via gradient coils. The RF pulses are absorbed by the body, which causes the spinning protons to flip from low- to high-energy levels. When the RF pulses are turned off, the absorbed energy is released. This emitted energy is absorbed by NMV protons, which resonate and produce a voltage that is detected by the gradient coil. These MRI signals, which are received in the RF coil, then transfer to the computer, which creates the MR image (see Figure 3.2) (Chavhan, 2013; McRobbie et al., 2017).

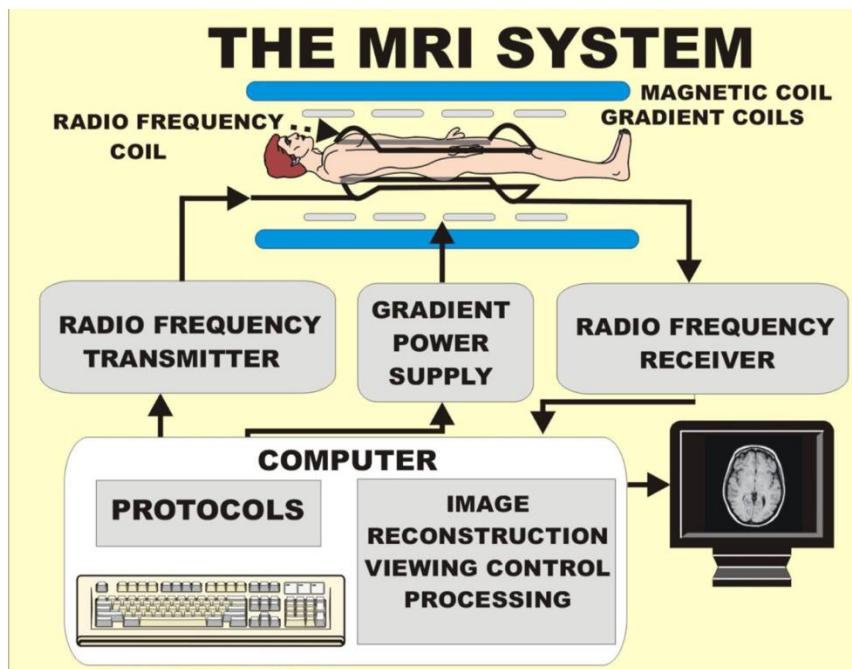


Figure 3.2. An illustration of the MRI system's major components (Sprawls, 2000).

3.3.2 Relaxation Times

When RF pulses are applied, the transverse relaxation time (T_2) is the time constant that is required by the excited protons to move (decay) into the transverse axis. In this configuration, T_2 is related to transverse magnetisation, which involves the X and Y components (M_{XY}). In contrast, when the RF is turned off, the excited protons return to their normal status (recover) and release their energy into the surrounding environment; the time constant of this process is known as longitudinal relaxation time (T_1). In this case, the longitudinal magnetisation, which is a Z component (M_z), is related to T_1 and is equal to M_0 (see Figure 3.3). Both T_1 and T_2 are

found to vary across different tissue types, due to variations in fat and water ratios, which result in different tissue contrasts in MR images (Chavhan, 2013; McRobbie et al., 2017).

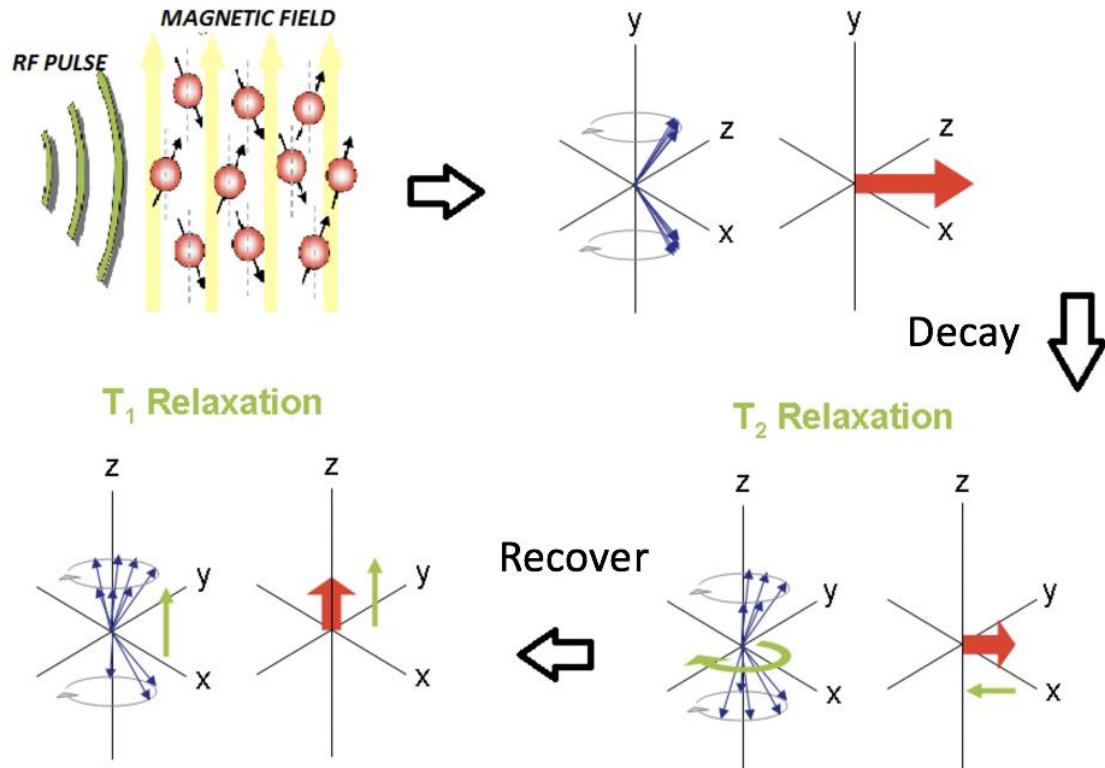


Figure 3.3. An illustration of the way in which radiofrequency pulses (RF) cause protons to decay into transverse vectors (T_2 relaxation), after which protons recover into the longitudinal vector (T_1 relaxation) (George et al., 1998).

3.3.3 Spin Echo Sequence

The spin echo sequence (SE) is considered to be the basis of many MRI sequences. SE involves 90° and 180° pulses. The application of a 90° pulse moves the M_0 from the Z-axis into the transverse plane (X-Y) and this results in the dephasing of protons. To flip the protons back to the phase, a 180° rephasing pulse is applied to form a signal (the spin-echo). The spin-echo process is repeated several times during the study in order to produce signals that form MR images. The time to echo (TE) is the time that passes between the middle of the excitation pulse and data acquisition (echo), and time to repeat (TR) is the defined time between two excitation pulses (see Figure 3.4) (Chavhan, 2013; McRobbie et al., 2017).

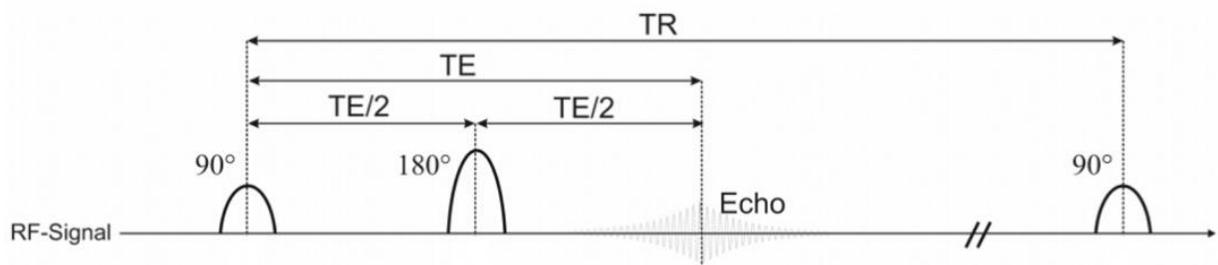


Figure 3.4. Simplified diagram of the spin-echo sequence in which RF pulses (90° and 180°) create an echo. Both the time to repeat (TR) and time to echo (TE) are represented in the timeline (Jung & Weigel, 2013).

3.3.4 MR Image Contrasts

Two main factors cause tissues to show up differently in the images and therefore to create the MR image contrast. The internal factors include the T_1 and T_2 values, which are based on tissue characteristics and the density of the protons within the tissue. The external factors depend on the operator's selection of settings; these include the TE and TR. The MRI operator can manipulate the TE and TR in order to achieve the required contrast, which is a feature of MR imaging that makes it a sensitive modality to enable visualisation of multiple anatomical tissues, as well as pathological conditions (Hashemi et al., 2012; McRobbie et al., 2017).

3.4 MRI Sequences used in Current Project

3.4.1 T_1 -weighted Images

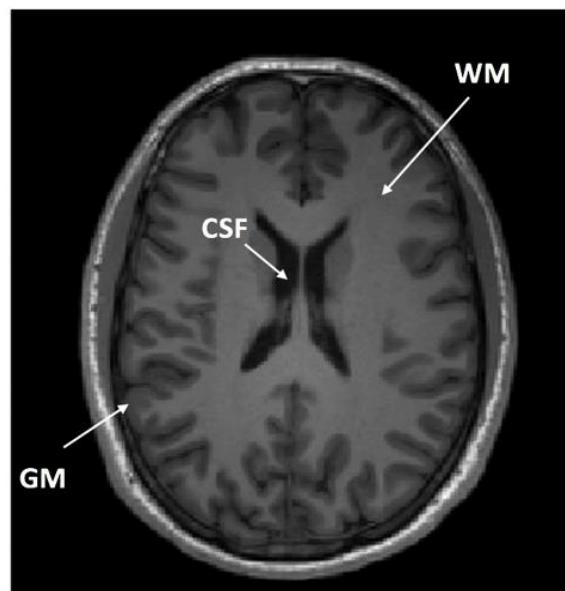


Figure 3.5. A T_1 -weighted image shows white matter (WM) brighter than grey matter (GM) and cerebrospinal fluid (CSF) as black.

T_1 -weighted images, also known as ‘anatomical images’ because they provide a strong contrast that clearly reveals tissue boundaries, cause fatty tissues to appear very brightly, while watery tissues are mid-grey and fluids are very dark; this contrast is mainly based on T_1 variances across the tissues (see Figure 3.5). To achieve these images both TR and TE must be short, because use of a short TR will prevent the full return to equilibrium of the proton spins in both water and fat. In addition, use of a short TE will reduce the T_2 -weighting appearance (McRobbie et al., 2017).

3.4.2 T_2 -weighted Images

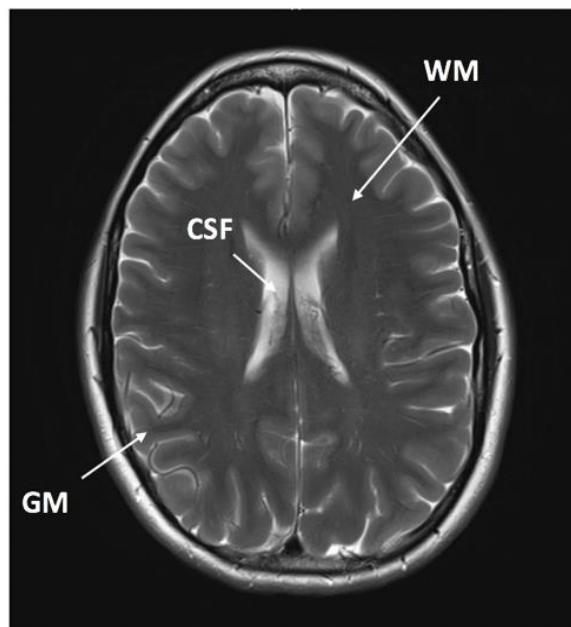


Figure 3.6. A T_2 -weighted image shows grey matter (GM) brighter than white matter (WM) and cerebrospinal fluid (CSF) as white.

In T_2 -weighted images, watery and fatty tissues tend to show as mid-grey, while fluids seem very bright, which is due to T_2 variances across the tissues. Therefore T_2 -weighted images are known as ‘pathology images’, since they show abnormal fluid collections that are brighter than the surrounding normal tissues that appear darker (see Figure 3.6). To achieve T_2 -weighted images, both TR and TE should be long in order to enable the recovery of the signals and to reduce the T_1 -weighting appearance (McRobbie et al., 2017).

3.4.3 Functional MRI and Blood Oxygenation Level Dependent (BOLD) Imaging

Brain function information can be revealed by the MR imaging method, which is blood-oxygen-level dependent (BOLD). MR images can be adapted to increase their sensitivity to detect changes in the oxygenation of blood haemoglobin (Ogawa et al., 1990). Blood has magnetic properties: when blood is highly oxygenated it is known as oxyhaemoglobin, which acts as a diamagnetic substance; when blood has a low oxygen level it is called deoxyhaemoglobin and behaves as a paramagnetic substance. The BOLD image shows up those areas that have a higher oxyhaemoglobin level than the surrounding areas, because they give a strong signal and therefore appear as bright regions (Amaro & Barker, 2006). Therefore, BOLD images are considered as natural contrast agents that have been used to reflect haemodynamic changes that are associated with brain activities (Ogawa et al., 1990).

BOLD images can be created in real time to demonstrate in-vivo neuronal activity during task execution, as well as during rest status (Amaro & Barker, 2006). When stimuli excite a specific brain area, neurons within this area consume more oxygen, which causes an elevation in blood flow to feed the excited neurons. Consequently, the ratio of oxyhaemoglobin to deoxyhaemoglobin in venous blood and capillaries is increased. Subsequently, the tissue oxyhaemoglobin content decreases again due to the high consumption that is caused by metabolic demand during the neural activity (see Figure 3.7). As a result, higher signal intensity (bright area) is seen in the oxyhaemoglobin-rich areas of BOLD images, which represent the location of brain function.

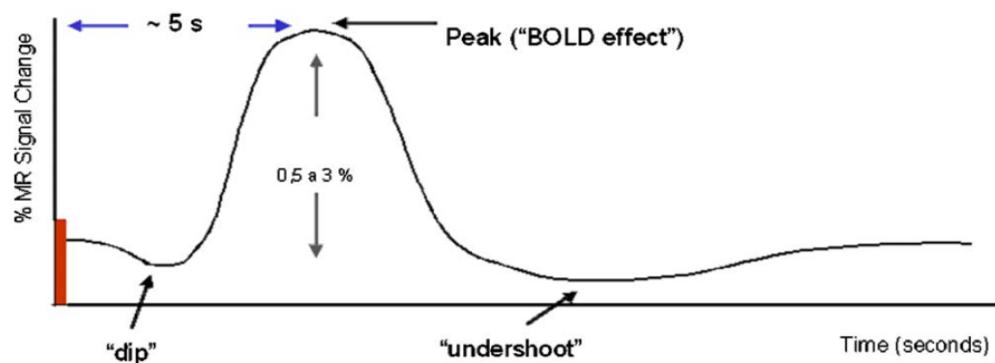


Figure 3.7. Haemodynamic response function. The initial dip results from a temporary rise in deoxyhaemoglobin levels when a particular brain area is excited by stimulus. After 3s of presented stimulus, the BOLD effect peak is created. Removal of the stimulus results in return of the MR signal to the baseline via the 'undershoot' effect (Buxton et al., 1998; Yacoub et al., 2001) (Figure reprinted from Amaro & Barker, 2006).

3.4.3.1 Limitations of fMRI in Auditory Experiments

A major drawback in the use of fMRI to study application of auditory stimuli arises from interference with the auditory stimulation that is caused by the acoustic noise from the scanner, which results from gradient switching (Müller et al., 2003). A systematic study of this issue was conducted by Hall et al. (2001), who provided evidence that activation of the auditory cortex (AC) was reduced when there was interference between the experimental auditory stimuli and scanner noise. It should be noted that scanner noise masks the stimulus presentation and can activate the AC through its repetitive nature, which is assessed in terms of TR (Bandettini et al., 1998; Hall et al., 2000). A solution for this interference problem is the development of sparse fMRI, which is used for research on primary AC function (Belin et al., 1999; Hall et al., 1999). For instance, researchers have used sparse imaging to investigate tonotopic maps (Humphries et al., 2010; Langers and van Dijk, 2011; Langers, 2014).

In sparse-imaging experiments, auditory stimuli are presented in the absence of gradient switching noise, while a single set of fMRI data is acquired with a delay that is suitable for the capture of the haemodynamic response to the stimuli of interest (Tanaka et al., 2000; Di Salle et al., 2001). After stimulus onset, the primary AC response has been shown to peak after four to five seconds and then decay after another five to eight seconds (Hall et al., 1999; 2000). A study was conducted by Baumann et al. (2010) in which the researchers examined the characterisation of the BOLD response. They stated that the BOLD response could be seen to begin two seconds after the onset of stimuli and peaked after approximately four seconds. The duration of data acquisition should therefore typically not go beyond approximately two seconds, while the inter-scan interval must be of the order of 20 seconds in order to render negligible the effect of scanner noise (Talavage et al., 1999; Olulade et al., 2011). However, in the Baumann study, this resulted in a significantly low data acquisition rate. As a result, the cluster method was introduced to provide multiple image acquisitions (Schmithorst and Holland, 2004; Langers et al., 2007; Zaehle et al., 2007).

3.4.4 Diffusion-weighted Imaging

Diffusion-weighted imaging (DWI) is an MRI sequence that is based on signals caused by motion of water molecules (diffusion). DWI has a useful imaging feature as it indicates the organisation of WM inside the brain and it can also be used to evaluate the GM. Therefore, DWI is an imaging sequence that is widely used clinically, such as in early stroke diagnosis, as well as in research (McRobbie, 2017; Jenkinson & Chappell, 2018).

Water molecules inside the brain usually diffuse randomly (by Brownian motion) and this motion may be restricted by biological barriers, such as axon bundles, or non-restricted in extracellular space. Normally, as water molecules diffuse through tissue, axons are oriented in axial or perpendicular (radial) directions, whereas diffusion of water molecules in extracellular areas, where they are less tightly packed, occurs in a more free and therefore random fashion (Jenkinson & Chappell, 2018) (see Figure 3.8).

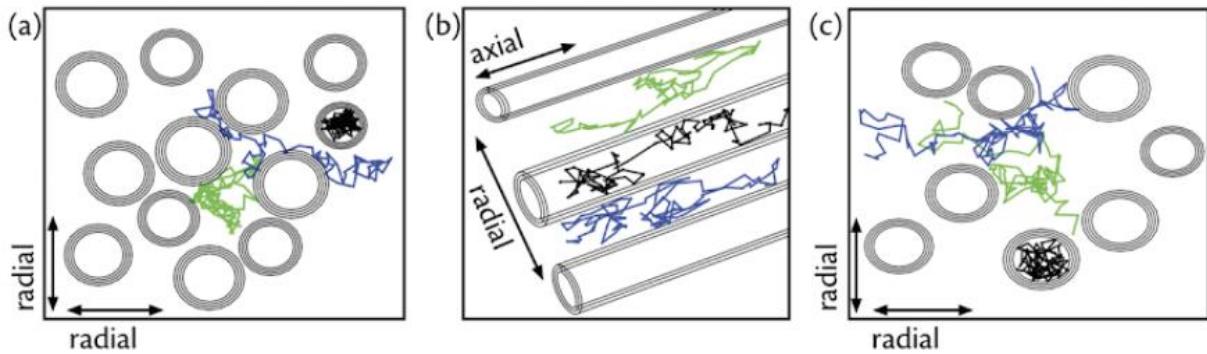


Figure 3.8. Diffusion motion of water molecules (a) axons are packed together, so the water diffusion in intra- and extra-cellular space becomes restricted in the radial direction compared with axial; (b), (c) water molecules in extracellular areas diffuse more freely (Jenkinson & Chappell, 2018).

When a strong magnetic field and additional gradient fields are applied, water molecules move in multiple directions (Jellison et al., 2004). However, it has been shown that the direction of highest diffusivity is aligned with the direction of the WM fibre tract due to the presence of axonal membranes and myelin-sheath barriers (Moseley et al., 1990). Therefore, water diffusion within WM fibres is considered to be anisotropic (directionally dependent) (Jellison et al., 2004).

To determine the orientation of the dominant diffusion direction inside a voxel accurately, diffusion along thousands of axes must be calculated. However, this is impractical. Therefore, Basser and colleagues introduced the ‘diffusion tensor’ model, which can be used to measure anisotropic direction and degree correctly (Basser et al., 1994a). Diffusion-tensor imaging (DTI) is a mathematical model of diffusion in a 3D pattern. It is represented as a 3×3 matrix and it involves eigenvalues (λ_1 , λ_2 , and λ_3) and eigenvectors (ϵ_1 , ϵ_2 , and ϵ_3) that are derived from diffusion measurements along six spatial directions (see Figure 3.9). This tensor model can be used to quantify the degree of diffusivity as well as the dominant direction of diffusion across each imaging voxel (Jellison et al., 2004).

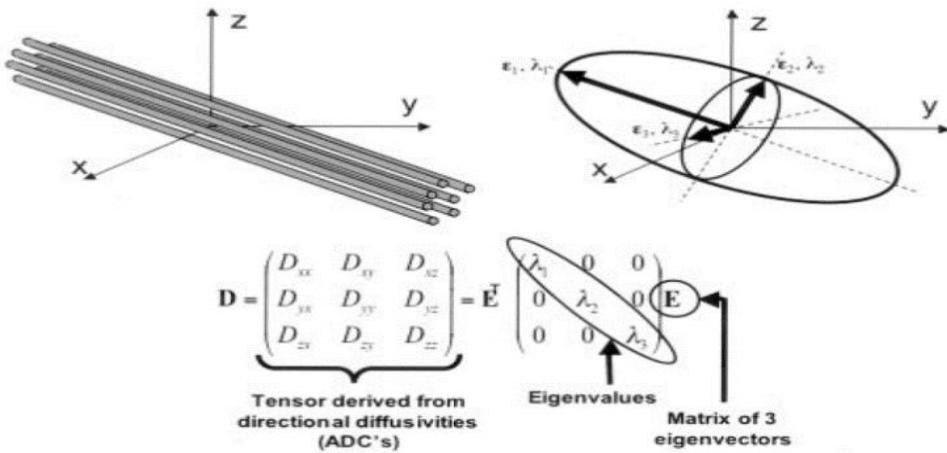


Figure 3.9. Diffusion-tensor imaging. Top left, diagram shows fibre tracts in an arbitrary alignment with respect to scanner geometry (x , y , z axes) and placed in a direction dependent on diffusion measurements (anisotropy). Top right, the three-dimensional diffusivity is represented as an ellipsoid, which is characterised by three eigenvectors (e_1 , e_2 , and e_3) and three eigenvalues (λ_1 , λ_2 , λ_3). Bottom, diffusion tensor matrix is derived that involves six non-collinear diffusion measurements. The eigenvectors represent the maximum diffusivity direction and the eigenvalues reflect diffusivity along three axes (Jellison et al., 2004).

DTI can illustrate tissue microstructure, and thus it is largely used to provide various physical quantities that include mean diffusivity (MD) and fractional anisotropy (FA). MD is a physical quantity that is derived from DTI, also known as ‘apparent diffusion coefficient’ – (ADC); MD represents the average diffusivity across voxels (equation 3.2, Figure 3.10). MD is based on axial diffusivity (AD) and radial diffusivity (RD). AD quantifies diffusion that occurs along the main direction (longitudinal) (equation 3.3, Figure 3.10), and RD measures diffusion that occurs in the transverse direction (equation 3.4, Figure 3.10) which is perpendicular to AD. FA describes the direction of water diffusivity across voxels and it can be obtained from the equation 3.5 (Koerte & Muehlmann, 2014). Hence, low FA, such as the scalar value of 0, means diffusion is relatively similar in all directions (isotropic). However, high FA indicates that there is a dominant diffusion direction (anisotropic), which has a scalar value of 1 (Figure 3.10, a and b).

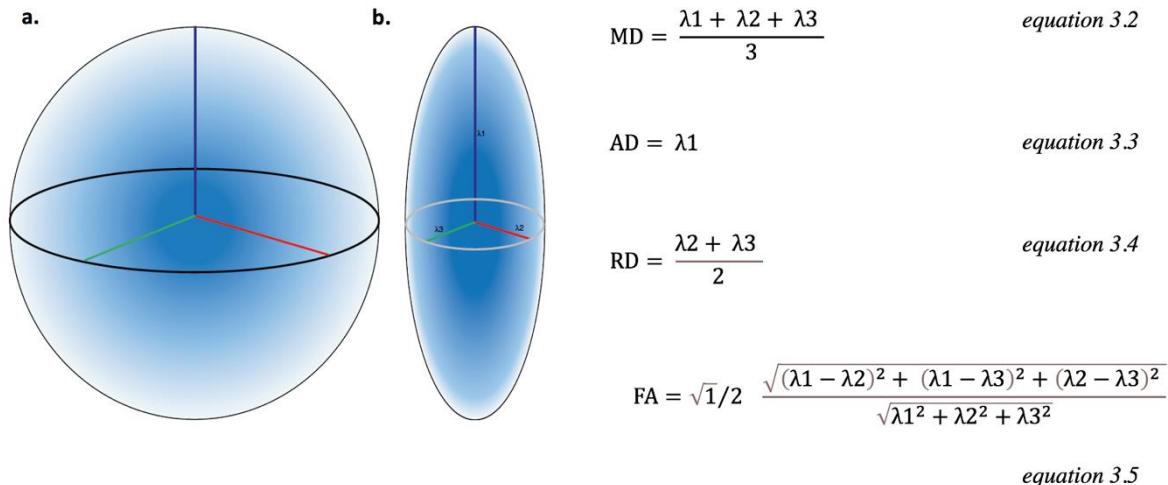


Figure 3.10. Water diffusivity tensor shapes and measures. (a) represents the shape of isotropic diffusion, in which eigenvalues are generally equal across main vectors. (b) represents the shape of anisotropic diffusion, in which diffusion is primarily in one direction. Equations are shown on the right for each diffusivity measure: mean diffusivity (MD), the axonal direction (AD), radial diffusivity (RD), and fractional anisotropy (FA) (equations 3.2, 3.3, 3.4 and 3.5 respectively) (Koerte & Muehlmann, 2014).

In order to extract these physical measures, we need to conduct appropriate DTI fitting analysis by providing two sets of diffusion-encoded images: one set with no diffusion ($b=0$), which acts as a baseline for DTI model fitting; and the other set with a b -value that varies between 700 and 1300 s/mm² (1000 s/mm² is the most commonly used in research studies) (Alexander et al., 2007; Jenkinson & Chappell, 2018).

As water molecules diffuse differently through brain tissue depending on the tissue type, this results in different voxel intensity when shown in DTI. Therefore, CSF appears dark, as the water is freely and equally diffused in all directions, while water within GM is weakly restricted in diffusion motion, and therefore, GM voxels have a higher intensity than CSF. Comparatively, WM is represented by the brightest voxels, as the water diffusion is restricted by the direction of the axonal fibre bundle (see Figure 3.11) (McRobbie, 2017; Jenkinson & Chappell, 2018).

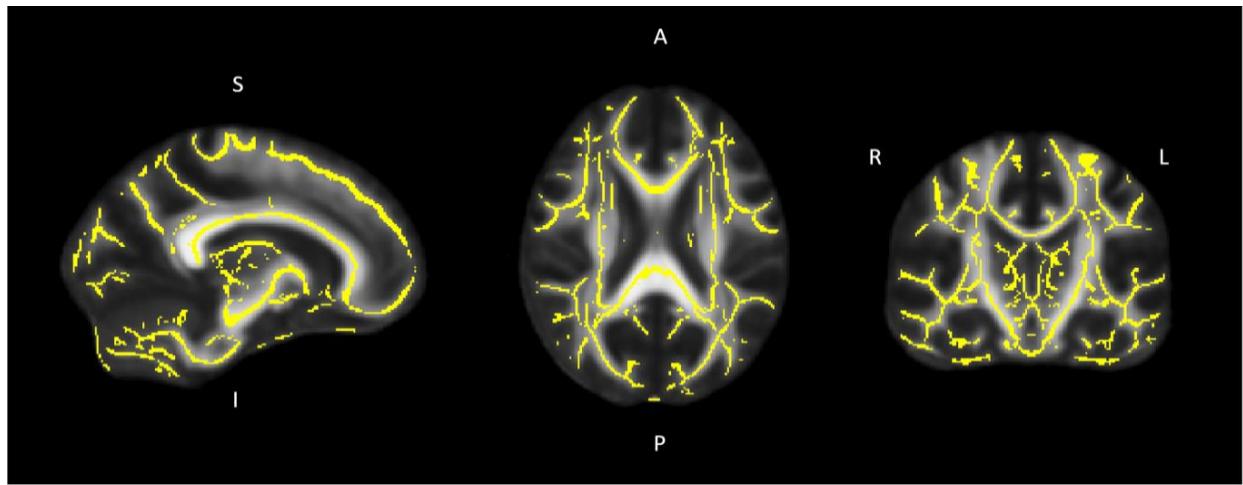


Figure 3.11. DTI-weighted images. White area represents the WM skeleton and the yellow highlight is the fractional anisotropy skeleton (FA map). R: right; L: left; A: anterior; P: posterior; S: superior; I: inferior.

Although DTI is useful to image WM organisation in the brain, it is inadequate for GM, as diffusion there is mostly isotropic (Lopes et al., 2015). Another limitation of DTI relates to the crossing of fibres, which can negatively affect DTI information quality (Jenkinson & Chappell, 2018).

To summarise, the basic principles of MRI technology have been covered in this section. The following section focuses on the general methodology that was used in the present study.

Chapter 4. General Methodology

4.1 Aim

In this chapter, the methodology of the research is explained. The chapter describes the experimental design overview, recruitment of participants, MRI protocol and analysis programs that were employed in the project.

4.2 Overview of Experimental Design

4.2.1 Pitch Discrimination Training

The acoustic training that was used in the study was based on application of a pair of tones of two different frequencies. The participant in the study was asked to decide whether the first or second tone had a higher pitch. This acoustic training was used over a short period to achieve the study target through the exploration of its effects on psychoacoustic measures and on alterations in the structural and functional plasticity of the auditory regions. These alterations were compared with those that were seen in experienced musicians.

Another auditory training approach involved the investigation of the lateralisation in pitch processing across different groups and different presentations of acoustic stimuli.

4.2.2 Study One

A longitudinal study was conducted over four consecutive days. It comprised daily MRI scanning along with three daily auditory training sessions. This experiment was undertaken on healthy trainees ($n=26$). A separate control group ($n=15$) did not receive any auditory training. To control for potential lateralisation differences that have been reported previously for pitch discrimination tasks (Zatorre, 1988; Johnsrude et al., 2000; Zatorre and Belin, 2001; Hyde et al., 2008) trainees were separated into two groups (13 in each group):

1. Right ear group: subjects were trained on the right side only; a pair of tones was presented to the right ear only.
2. Left ear group: subjects were trained on the left side only; the pair of tones was presented to the left ear only.

The scanning protocol for the training group involved two functional scans and four structural scans. However, the control group was scanned twice, once on the first day and once on the fourth day (Table 4.1).

4.2.3 Study Two

A cross-sectional study was conducted across the musicians' group ($n=11$) during one day without any auditory training. In this study, the scanning protocol and sequences that had been performed in a single day of the first study were used. The main target of this study was to compare the findings from study one with those that were obtained from a well-trained population (musicians) (Table 4.1).

Group	Day 1	Day 2	Day 3	Day 4
Trainees	**Scanning + Training	*Scanning + Training	*Scanning + Training	**Scanning
Musicians	**Scanning			
Controls	*Scanning		*Scanning	

Table 4.1. Experimental design and timeline for three groups. *Scanning: structural scan, **Scanning: functional and structural scans.

4.3 Ethical Approval

This study was conducted after it was granted ethical approval by the Ethics Committee of the University of Liverpool on 10 March, 2017; reference number: 1550.

4.4 Recruitment

An advertisement for the study was placed on the University of Liverpool website. An informative email was sent to all individuals who expressed interest. The email contained: the study aim, a detailed explanation of what would happen in the experiment, including the images that would be collected, and the researcher's contact details (all information documents that were sent to participants are provided in Appendix B, section 1).

Before recruitment for any research study, specific research standards must be considered. In this study, these were:

Inclusion criteria:

1. Adults aged 18 or above.
2. Able to undertake MRI scans.

3. Healthy participants without any history of neurological or hearing impairment, who were either:

- a) Non musicians with no musical background.
- b) Proficient musicians who were active players and had been awarded high grades by a music examination board.

Exclusion criteria:

1. Minors (under 18 years old).
2. Inability to undertake MRI scans, because of:
 - a) Presence of any neurological conditions.
 - b) Pregnancy.
 - c) Presence of any metal implants.
 - d) Claustrophobic.

4.4.1 Justification for Recruitment

Given that this research was performed in a high magnetic field area, pregnant volunteers and patients with metal implants were excluded due to safety concerns. The study considered only healthy volunteers who had no previous neural or hearing disorders because these conditions could change the brain structure and lead to inconsistent data analysis and unreliable conclusions.

4.5 Pre-scanning Procedure

Prior to any MRI scan, the research objectives and MRI procedures were explained to the participants. Then qualified clinical radiographers assessed the participants' suitability for MRI scanning according to the standard screening protocols. Also, each participant was required to fill in and sign a consent form (Liverpool Magnetic Resonance Imaging Centre (LiMRIC) safety screening questionnaire). To ensure that each participant had a normal hearing level, a pure tone audiometry test was conducted for each subject.

All participants including the musicians were given a clear description of the experiment. A pre-scanning test for the pitch discrimination task was conducted to ensure that each participant understood the task and could hear the sound clearly while they were inside the scanner. Then basic MRI scanning was conducted as participants underwent a MRI scan. For all MRI scans, participants were instructed to lie supine within the scanner bore. To eliminate the acoustic noise of the scanner, earplugs were provided to participants.

4.5.1 Pure Tone Audiometry

Pure-tone audiometry is a hearing assessment test that was used at the beginning of the project to ensure that each individual enjoyed normal hearing. It measured hearing threshold levels. Different frequency ranges were displayed at different intensity levels and the individual responses were plotted on a graph known as an audiogram (Figure 4.1). The resultant audiogram showed the hearing sensitivity of each listener (Sliwinska-kowalska, 2015). For example, a range of values in the audiogram that is less than or equal to 20 decibels (dB) reflects normal hearing, whereas a shift up to 50 dB in the range of values indicates hearing impairment (Gorga et al., 1993). The audiometry tests were carried out in a quiet room and were performed for each ear separately.

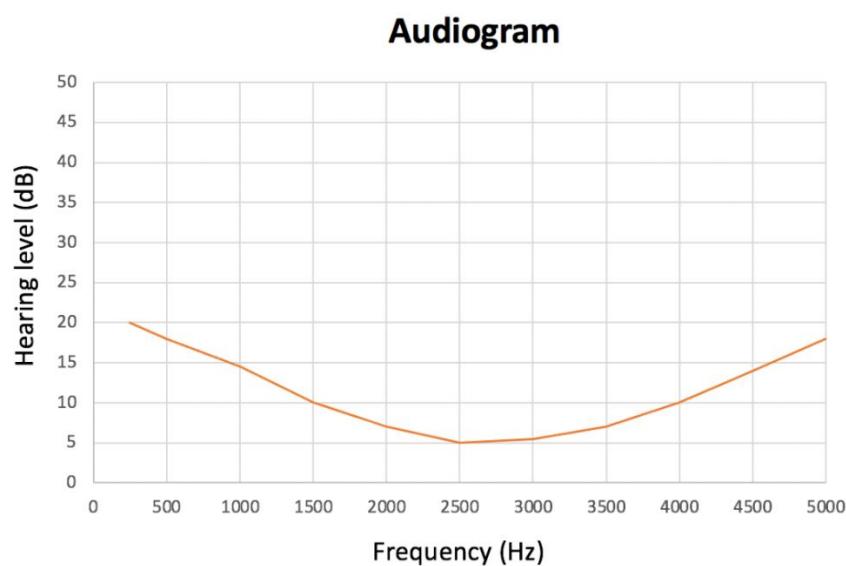


Figure 4.1. A pure-tone audiogram representing a normal hearing level, as the range of values does not exceed 20 dB. dB: decibels (sound intensity units), Hz: Hertz (frequency unit).

4.5.2 Questionnaires

4.5.2.1 LiMRIC Safety Screening Questionnaire

The LiMRIC safety screening questionnaire was given to each participant. This is mandatory for all subjects before they undergo MRI to confirm that they are able to undertake the procedure and are safe in a magnetic field area. This safety form was monitored and signed off by a LiMRIC research radiographer (screening form is provided in Appendix B, section 2). This screening step is conducted routinely to ensure the health of the centre's subjects and guests.

4.5.2.2 Edinburgh Handedness Inventory Questionnaire

The Edinburgh handedness questionnaire is the most widely used measure of hand preference in scientific research. Hand preference was investigated in this study because in previous studies, it may have contributed to the functional and structural variances that were reported (Levine et al., 1983; Hugdahl & Andersson, 1984). The results of these studies revealed that auditory ascending pathways between the cochlea and auditory cortices showed a functional left-right asymmetry that was correlated with the handedness. Khalfa et al. (1998) found that right-handers had a more effective medial auditory efferent system in the right ear compared with the left ear. Another investigation performed by Cuzzocreo et al. (2009) used a verbal memory task to examine the effect of handedness on brain function and structure. The researchers found significant increases of functional activation in the left hippocampus and amygdala across left-handed participants only. Taking all the above into consideration, the Edinburgh handedness questionnaire was used in this project to reduce bias and to ensure an overall conformity between participants. A brief handedness questionnaire that had been adapted from the Edinburgh handedness questionnaire (Oldfield et al., 1971) (handedness form is provided in Appendix B, section 3) was given to each participant to discover their preferred hand. Ten activity items were included in the questionnaire. If the participant showed a strong preference for one hand, ‘++’ was recorded, whereas ‘+’ was expressed if the participant showed equivalent preference for each hand. Then the sum of left-hand points was subtracted from the sum for the right and this figure was divided by the total of both. The result was multiplied by 100 to produce a percentage. A positive percentage meant that the participant showed right-handed preference, but a negative percentage indicated left-handed preference; the higher the figure, the stronger the preference.

4.6 Participant Demographics

This study recruited 52 participants who were placed in three groups: 26 trainees, 11 musicians and 15 controls. Participants' demographic information is listed in Tables 4.2 and 4.3. All subjects had normal hearing as had been evaluated through pure-tone audiometry. Normal hearing was defined as showing hearing thresholds of 20 dB hearing level or better at frequencies between 250Hz and 5000 Hz. None of the trainees was a musician or had received any musical training (except for compulsory music classes at school). Since the controls were needed for comparison with the trainees to ensure that any neural change that occurred was caused by auditory training only. The data that were collected for the controls followed those that were collected in another study that focused on visual training, but the controls data that

were used for the current study were taken before any training was conducted. Moreover, the controls data matched those of the study design as they were taken over the same time gap (two days) between two data sets. In terms of the musicians' group, the planned sample size was 26, but due to the COVID-19 pandemic the recruitment for the study was stopped prematurely and therefore only 11 musicians participated in this study. The musicians' group involved professionals who had achieved grade 7 in a music examination board such as the Associated Board of the Royal Schools of Music.

Group	Trainees	Controls
Sample number	26	15
Age range (mean± SD)	19-35 years (25.9 ± 4.1)	22-61 years (36.8 ± 12.7)
Gender	12 males and 14 females	8 males and 7 females
Handedness	26 right-handed	15 right-handed

Table 4.2. Demographic data for trainee and control groups for study one.

Group	Musicians
Sample number	11
Age range (mean± SD)	19-40 years (23.5 ± 5.9)
Gender	3 males and 8 females
Handedness	11 right-handed
String/ Non-string trained	7 string-trained (violin, guitar), 4 non-string trained (piano, clarinet, flute)
Number of hours practising music range (mean± SD)	1800-9700 (4481.8 ± 2304.3)

Table 4.3. Demographic data for the musicians group for study two.

In terms of group differences, statistical tests were conducted to investigate the age variance across study groups using GraphPad Prism 8. The ages of the trainee and control groups were compared through use of unpaired t-tests and the result showed a significant difference ($p<0.0003$, $t=4.03$, $df=39$). However, there was no significant difference between the trainee ages and those of the musicians, as revealed by unpaired t-tests ($p<0.15$, $t=1.49$, $df=35$). Another group variance was handedness, as the previous studies indicated functional and structural variances due to handedness. As explained in section 4.5.2, a brief handedness questionnaire had been completed by each subject before the scan to reduce bias and ensure overall conformity between participants.

4.7 MRI Scanning Protocol

4.7.1 Location and Scanner

This study was performed in the University of Liverpool, at the LiMRIC. All experiments were performed using a 3T MRI scanner *MAGNETOM Prisma* (Siemens, Germany) with a 32-channel phased-array head coil. The scans that were performed on the first and last days of the study took approximately 50 minutes, but the scans that were performed on the second and third days lasted for 30 minutes.

4.7.2 MRI Scan Sequences

This study utilised a number of scan sequences: T₁-weighted (T₁), T₂-weighted (T₂), diffusion tensor imaging (DTI) and functional magnetic resonance imaging (fMRI).

- 3D T₁-weighted magnetisation prepared rapid acquisition gradient echo (MPRAGE)

This MRI sequence was developed by LiMRIC. The sequence is: repetition time (TR): 2000ms; echo time (TE): 2.26 ms; inversion time (TI): 900ms; field of view (FOV): 256 mm; flip angle: 8°; voxel size: 1.0×1.0×1.0 mm; and slice thickness: 1mm. This is an anatomical image that is used in clinical evaluation as well as for research in spatial normalisation, tissue segmentation and quantitative morphometric brain analyses. I used this sequence twice: at the beginning of the study (before any auditory training had taken place) and at the final stage (after performance of the auditory training sessions).

- 2D T2-weighted image

This is also a LiMRIC-developed MRI sequence, the settings of which are: TR: 5770 ms; TE: 100 ms; FOV: 220 mm; flip angle: 150°; voxel size: 0.4×0.4×0.4 mm; slice number: 33; and slice thickness: 4 mm. This is a clinical sequence that is used mainly for detection of lesions

and abnormalities. I used this sequence once (at the beginning) only to ensure that the candidate was fit and well for my study with no underlying neurological conditions.

- Functional MRI (EPI_bold_multi_slice).

The functional imaging protocol was adapted from Langers et al. (2014) to set up the scanning parameters in a cluster acquisition method. I applied a cluster imaging technique for the auditory task-based fMRI. The method involved an ON-period (when imaging volume was acquired using echo-planar imaging (EPI)) and an OFF-period (which produced a silent gap when the sound stimuli were displayed) with duration of 2200ms in each period.

The sequence was: TR: 4400 ms; TE: 30 ms; FOV: 192 mm; flip angle: 90°; slice number: 48; slice thickness: 2.7 mm; voxel size: $3.0 \times 3.0 \times 2.7$ mm. A multiple-slice acceleration was applied, which acquired two slices per volume acquisition. This was done to increase the volume of imaging data that was captured and to offer more powerful statistical analysis. Further details regarding the auditory task that was employed during the fMRI scan are provided in the functional chapter, Chapter Six. The fMRI sequence was used twice: at the beginning (before any auditory training) and at the final stage (after performance of auditory training sessions) to assess the change in neural functional activation that had resulted from auditory training.

- Diffusion Kurtosis Imaging (DKI_BIPOLAR_2.5mm_64dir_50 slices)

This is an optimised DKI/DTI scan that was developed by Glenn et al. (2015) to reduce the compaction requirements for analysis and to improve the reproducibility and sensitivity of DKI for the detection of crossing fibres. Parameter settings were: TR: 3200ms; TE: 90ms; FOV: 220mm; diffusion directions: 64; slice number: 50; slice thickness: 2.5mm; and voxel size: $2.5 \times 2.5 \times 2.5$ mm. It is a research scan to analyse the brain's structural integrity and pathways, especially in the WM.

In order to investigate any structural changes that resulted from auditory training, I used this sequence four times: at the beginning (before any auditory training had taken place), during training and at the final stage (after performance of auditory training).

4.8 Software Programs for Analysis

When the scans had been acquired, standard image analysis software was used on scan output data to process and analyse the information obtained. The advanced structural and functional MRI data were analysed quantitatively through use of a battery of image and statistical analysis

software, which included: FreeSurfer (<http://freesurfer.net>) (v 6.0); Oxford Centre for fMRI of the Brain (FMRIB) Software Library (FSL) (<http://fsl.fmrib.ox.ac.uk/fsl/fslwiki>) (v 6.0) (Jenkinson et al., 2012); statistical parametric mapping (SPM 12) (version: 6906) (<http://www.fil.ion.ucl.ac.uk/spm>) (Penny et al., 2011); and various packages that had been developed for use in the context of MATLAB software (version: R2016b) (<https://uk.mathworks.com/products/matlab.html>). These software packages were used primarily for automated brain structure and function analysis, with a specific interest in structural and functional connectivity. Statistical analysis programs were used in GraphPad version 8 for MAC, La Jolla, California, USA (www.graphpad.com).

4.8.1 Analysis Methods

At the beginning, all MRI scan output (in DICOM format) was converted into a NIfTI format (nii.gz) to be used in the analysis software. For this purpose, two programs were used: MRI convert version 2.1.0 (<https://lcni.uoregon.edu/downloads/mriconvert>) and DICOM to NIfTI as evolved by Chris Rorden (dcm2nii, 6 June, 2013). Each analysis method for MRI images is described in detail in the next designated chapters.

4.9 Conclusion

In short, the current study used different advanced MRI sequences to explore the structural and functional plasticity changes that occurred in non-musicians who were given short-term training on pitch discrimination tasks. These changes were compared with those that were seen in the auditory regions of musicians with long-term experience. Also, the impact of short-term acoustic training on the behavioural measure across non-musicians was compared with these measures among a group of musicians. A second aim of the study was to investigate the lateralisation in pitch processing across different groups and with different acoustic stimuli presentations. Therefore, three groups of participants were used in the current study: the first group of subjects who were trained for a short period, the second group of controls who did not receive any acoustic training and the third group of trained musicians.

Chapter 5. Psychoacoustic Training

5.1 Aim

The work described in this chapter was designed to explore the effect of short-term training on pitch discrimination through assessment of psychoacoustic performance. Another target of the experiment was to investigate whether auditory learning was lateralised or generalised.

5.2 Introduction

Training in pitch discrimination leads to neurophysiological improvements that can be assessed by discovery of the discrimination threshold (DT) (Menning et al., 2000). Staircase is a research tool that is used routinely to evaluate the threshold of frequency differences (Kollmeier et al., 1988). Through use of the staircase method, the trials are distributed adaptively across the psychometric threshold and the threshold estimate becomes more efficient (Dixon and Mood, 1948). One example of the staircase method is query using extended search techniques (QUEST), which is an adaptive procedure that changes the intensity of stimuli according to the participant responses (Watson and Pelli, 1983). QUEST is based on pre-existing knowledge and assumptions regarding the relative probability of the occurrence of the threshold parameter across populations (Prins, 2016). QUEST was used in a study that investigated attention resources during visual and auditory interactions. The results showed an efficient estimation of the DT for an auditory task (pitch) as well as a visual task (contrast) (Alais et al., 2006). Another study performed by Micheyl et al. (2006) used psychoacoustic training to evaluate differences in pitch discrimination across musicians and non-musicians. The researchers found that musicians exhibited lower (better) DTs than did non-musicians.

Adaptive auditory training has been used widely in research. Most of these studies have confirmed the positive influence of the training on perception as well as cognitive skills. This is because an enhancement in perceptual discrimination results from progress in stimulus encoding through multiple sensory processing levels (Ahissar and Hochstein, 2004). The improvement in perceptual discrimination is not limited to the trained senses, but also involves other perceptions that can be included in the discrimination task (Goldstone, 1998; Amitay, 2009). Indeed, training in frequency discrimination plays a crucial role in the improvement of cognitive skills such as attention, and this result has a positive impact on people who suffer from tinnitus. For example, in a study by Hoare et al. (2012), the researchers tested the hypothesis that auditory training across a range of hearing loss frequencies could reduce the

tinnitus that was generated by hearing loss. They suggested that long-term training at any frequency (not particularly hearing-loss frequencies) resulted in greater alleviation of tinnitus. Ferguson et al. (2014) explored the effect of adaptive auditory discrimination training on elderly subjects who were aged between 50 and 74 years, suffered from mild sensorineural hearing loss and did not use hearing aids. After the test subjects underwent training periods of 360 min across four weeks; their results showed significant improvements in hearing threshold, attention and working memory.

A right-hemisphere superiority in pitch perception has been shown by many researchers (Tervaniemi et al., 2000, Zatorre et al., 2002; Hyde et al., 2008; Hoch & Tillmann, 2010). These research studies compared speech with music perception. Another supportive study confirmed that the right AC played a significant role in pitch discrimination (Johnsrude et al., 2000). They used a pitch discrimination task that involved a pure-tone pair and asked the subjects to define the direction of pitch change from the first tone to the second (i.e., whether the pitch rose or fell). They measured the mean of DTs. They found that patients whose temporal lobe in the right hemisphere had been removed exhibited significantly higher thresholds (worse performance) than the controls.

However, other researchers argue that hemispheric lateralisation in tonal processing is caused by training (Micchely et al., 2006; Bianchi et al., 2017). Micchely et al. (2006) claimed that the right-hemisphere advantage in pitch perception was found in musicians only when they applied pitch discrimination tasks that used pure tone contralateral on-frequency noise. Another supportive study that was performed by Bianchi et al. (2017) found that a right hemispheric superiority in terms of DTs was found in musicians who performed pitch discrimination tasks for complex tones relative to noise. These studies were conducted among musicians who had been trained for long periods of time. However, it is unclear whether this hemispheric lateralisation in terms of DT can be observed after a short period of acoustic training.

The work that is described in this chapter aimed to explore whether short-term pitch discrimination training could improve the psychoacoustic threshold of non-musicians, and whether left-ear trainees would show similar levels of or more behavioural improvements compared with those who were trained in the right ear. I hypothesised that trainees would exhibit an enhancement in their psychoacoustic performance as a result of short-term auditory training.

5.3 Effect of Short-term Pitch discrimination Training on the Psychoacoustic Threshold

5.3.1 Participants

This experiment was undertaken by a group of healthy trainees ($n= 26$) with normal hearing. All participants' demographics are described in the methodology chapter (Chapter Four).

Trainees were separated into two groups, each of 13 members (Figure 5.1):

1. Right trainees: subjects who were trained on the right ear only. Thus, the pair of tones was presented monaurally to the right ear only.
2. Left trainees: subjects who were trained on the left side only. Thus, the pair of tones was presented monaurally to the left ear only.

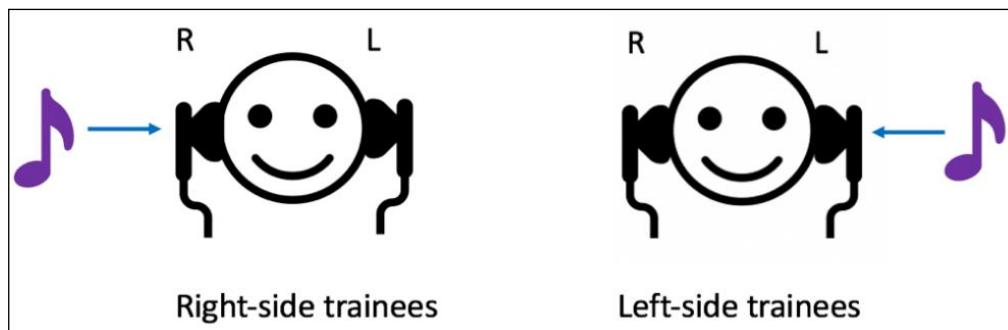


Figure 5.1. Right- and left-ear trainees undergoing a pitch discrimination task. Right-ear trainees received tones through the right ear only; left-ear trainees received tones through the left ear only. R: right; L: left.

5.3.2 Experimental Design

The study experiment was designed to determine whether short-term pitch discrimination training could improve participants' hearing thresholds. To achieve this target, an adaptive psychophysical staircase QUEST (Watson and Pelli, 1983) was used for the auditory training with a two interval-forced choice (2IFC) paradigm (Prins, 2016). Then the pitch discrimination task results were used to estimate the psychoacoustic threshold. This method was adapted from that of Alais et al. (2006). Moreover, a varying (roving) frequency range (above and below the reference frequency) was used. Amitay et al. (2005) investigated the effect of a roving frequency range on frequency-discrimination learning among untrained listeners. Their results indicated that good listeners who had been trained on slightly roving tones showed greater frequency discrimination compared with other groups who were trained on fixed and widely varying frequencies.

The auditory training was conducted over three consecutive days. This period was selected based on previous auditory-training studies. Menning et al. (2000) trained participants over a period of three weeks; however, they found that only the first week of training showed a fast enhancement in their discriminate performance. In another study (Gaab et al., 2006), subjects were trained in a pitch memory task over five days and the results indicated progress in their behavioural scores.

5.3.3 Pre-training Test

A pre-training test was conducted to ensure that all listeners understood the task clearly before training commenced. In this test, a large step between frequencies was supplied (between 1020 Hz and 1070 Hz) to provide a clear example of the auditory stimulus, as suggested by Green et al. (1989).

5.3.4 Procedure

The training was supplied through the running of customised code that involved QUEST algorithms in MATLAB R2016b (The Mathworks Inc., Natick, MA, USA) (code is provided in Appendix C, section 1). This code involved the sounding of a pair of tones: one of them was the reference (F_0) and had a frequency of 1000 Hz, while the other was the test tone (D_f). This tone was of a frequency above or below F_0 . It was adaptively assigned based on the participant's previous response. The participant had to decide whether the first or second tone was of the higher pitch (2IFC). Participants gave their answers by pressing keyboard buttons (i.e. button number 1 if the first tone had the higher pitch, or button number 2 if the second tone had the higher pitch). The feedback was displayed on the computer screen after each trial. Each tone was of duration 250 ms. The sampling rate was 44100 Hz and a silent interval of 250 ms was presented between the tones. The stimuli were delivered monaurally to the right or left ear through noise-cancelling headphones and the study was carried out in a soundproof room. Each training session consisted of 300 trials and lasted for approximately 30-40 min, based on participant responses, without rest breaks in between. Finally, the FDT value was estimated using the mean of stimulus intensity at the final eight reversal points (García-Pérez, 1998; Prins, 2016). A reversal is a changing point, at which the stimulus level is reduced and then increased afterwards (Prins, 2016). Participants were informed about their threshold progress rates and they were paid upon completion of their study.

5.3.4.1 Statistical Analysis

The statistical testing analysis was performed through use of GraphPad Prism version 8 for MAC (GraphPad Software, La Jolla, California, USA, www.graphpad.com).

5.4 Results

5.4.1 Effect of Pitch discrimination Training on Psychoacoustic Performance

A paired t test, which compared pre- and post-training thresholds, revealed a significant decrease in threshold across all trainees ($t(25) = 4.86, p < 0.0001$), which meant that psychoacoustic performance had improved (Figure 5.2).

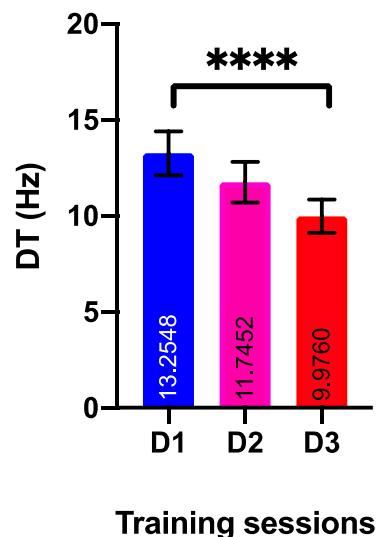


Figure 5.2. Illustrates a gradual decrease in discrimination threshold which reflects progress in performance over three days of pitch discrimination training. Descriptive statistics of the threshold mean and standard error are provided. Significant difference at *** $p < 0.0001$. D1: first day; D2: second day; D3: third day; DT: discrimination threshold in Hertz.

5.4.2 Differences between Effects of Training on the Right and Left Ears

A study of paired t tests revealed that the psychoacoustic threshold was significantly decreased across both right-ear trainees after training ($t(12) = 2.942, p < 0.012$), and across left-ear trainees after training ($t(12) = 3.923, p < 0.002$). A two-sample t-test analysis was conducted to evaluate the differences in DTs between right- and left-ear trainee groups. No significant group effect was found ($t(24) = 0.21, p < 0.84$) in the DT difference (post- minus pre-training). Therefore, the psychoacoustic thresholds were found to improve significantly after a short period of auditory training in both groups without significant differences in their performance (Figure 5.3).

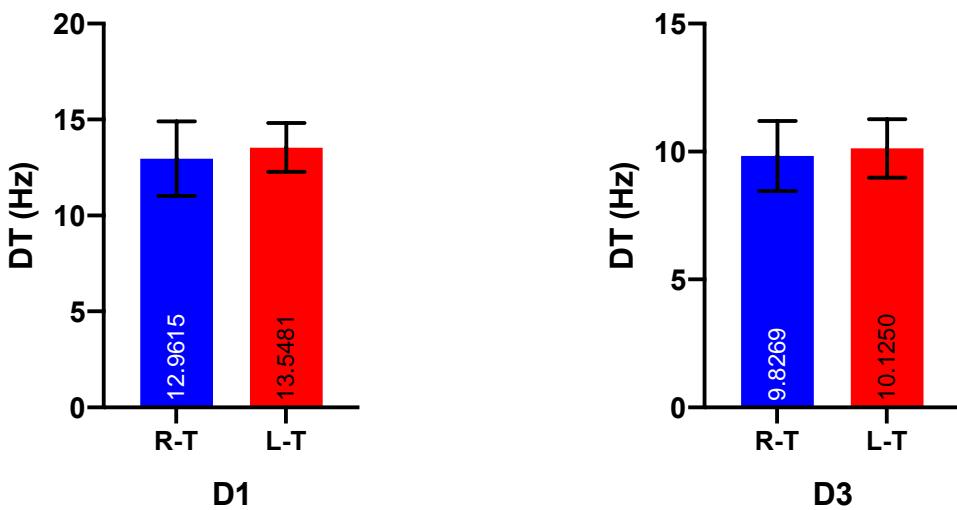


Figure 5.3. Mean and standard error of DTs pre- and post-training across right- and left-ear trainees show no significant groups differences. R-T: right ear trainees, L-T: left ear trainees, D1: day 1 (pre-training); D3: day 3 (post-training); DT: discrimination threshold in Hertz.

5.5 Discussion

Auditory training has been shown to improve FDTs across listeners (Baker et al., 1954; Delhommeau et al., 2002; Demany, 1985; Amitay et al., 2005). The current study results revealed that short-term training in pitch discrimination produced a limited but substantial improvement in hearing efficiency. This result was in parallel with a study performed by Carcagno et al. (2011), who investigated the changes of a behavioural measurement that was related to training in pitch discrimination. They found that short-term training in pitch discrimination produced minor but significant progress in a behavioural measure. According to Zhang et al. (2016), the improvement that resulted from pitch discrimination training was not limited to enhancement of frequency discrimination performance, but also improved the working memory. This was because of the involvement of working memory during the listener's attempts to distinguish little differences between tone frequencies. Therefore, the perceptual training led to an increase in cognitive and sensory interaction.

The current study also tested whether auditory learning was lateralised or generalised through examination of the difference in DTs between right- and left-ear trainees. The results showed that there was no significant difference between the groups and both groups exhibited similar improvement in their psychoacoustic thresholds. Thus auditory learning was generalised across the ears. This result agreed with those of a previous study done by Roth et al. (2004), who

tested the generalisation of learning across ears, by comparing the DTs of subjects who were trained in the right ear against those trained in the left ear after one hour of training on a frequency-discrimination task. The researchers did not find variance in the FDTs between left- and right-ear trainees.

However, the current study result was inconsistent with those of other previous studies (Micheyl et al., 2006; Bianchi et al., 2017). These researchers found left-ear advantage in pitch processing. A possible explanation for this result could lie in the amount of training and practice that was undertaken by study subjects. For example, both Micheyl et al. (2006) and Bianchi et al. (2017) found a right AC advantage in tonal processing across highly trained subjects (musicians). According to Bianchi et al. (2017), their findings also linked the functional activation in the right AC with musical practice, as they found superiority of activation of the right AC during performance of pitch discrimination tasks in musicians. Thus, the hemispheric lateralisation may be more obvious in functional activity during performance of pitch discrimination tasks than the psychoacoustic threshold. Therefore, the studies that are described in the next chapters were designed to test short-term auditory training effects as well as the lateralisation in pitch processing in terms of the functional activity and structure of auditory areas as well as in terms of the amount of musical practice that had been undertaken.

5.6 Conclusion

Pitch discrimination training that was based on an adaptive psychophysical staircase method was used to estimate the change in discrimination thresholds over a short period of training. The results of this study suggest that short-term pitch discrimination learning leads to a significant behavioural performance improvement, which is reflected by changes in the discrimination threshold. Another purpose of the study was to investigate whether auditory learning was lateralised or generalised across the ears. The result revealed that auditory learning was generalised across the ears, as there was no significant difference in the psychoacoustic thresholds between right- and left-ear trainees.

Chapter 6. Functional Neuroplasticity Related to Pitch discrimination Training

6.1 Study Aim

This part of the study used task-based fMRI to investigate the impact of short-term pitch discrimination training on brain functional activity and laterality of functional signals, along with psychoacoustic performance. Another aim of the study was the exploration of the lateralisation of learning (whether such an impact of learning is limited to the trained side of the brain).

6.2 Introduction

Functional MRI is one form of technology that uses BOLD activation signals to evaluate brain behaviour during the performance of tasks (further details of the fMRI technique are provided in Chapter Three). Numerous studies have employed fMRI in auditory processing for different research purposes. Researchers have used fMRI to compare the functional activations that occur in the AC during the performance of pitch discrimination tasks that involve different forms of stimulation, such as noise bursts that have a fixed pitch against noise bursts with varying pitch (Müller et al., 2001; Patterson et al., 2002; Warren & Griffiths, 2003). Another study compared the functional response in the AC that was elicited by pitch direction (rising versus falling) against the responses that were elicited by pitch duration (short versus long) (Brechmann & Scheich, 2005).

Further investigations that were conducted by Hall et al. (2009) used fMRI to localise the site of pitch perception in the AC, and identified the lateral HG and planum temporale as areas that were activated selectively during pitch processing. The AC showed a significant response to multiple pitch-evoking stimuli that involved pure and complex tones that comprised different resolvable harmonics. The involvement of the HG and superior temporal gyrus (STG) in pitch processing have also been confirmed by other studies (Müller et al., 2001; Zatorre, 2002; Schneider et al., 2005; Hall et al., 2006; Bianchi et al., 2017). The fMRI technique has been used to investigate the distribution of frequency-related activations (tonotopic mapping) within the auditory region (Yetkin et al., 2004; Norman-Haignere et al., 2013; Langers et al., 2014). These studies also indicate that the major sites of pitch-related processing are the HG, the STG, the planum temporale (PT), and the planum polare (PP) (see Figure 6.1).

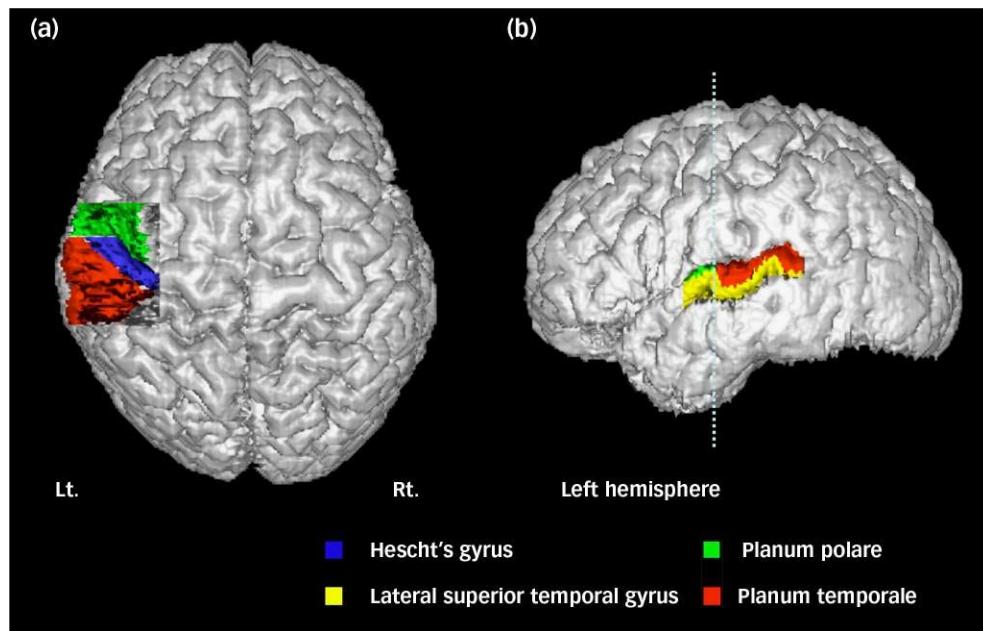


Figure 6.1. Pitch perception sites in the superior temporal subregions. (a) Top-down view illustrates the site of the planum polare, Heschl's gyrus and the planum temporale. (b) Lateral view shows the superior temporal gyrus, planum temporale and planum polare (Takahashi et al., 2010).

Further studies have used the asymmetry of functional activity that is observed across auditory cortices as evidence of hemispheric lateralisation in sound processing. For example, Specht & Reul (2003) suggested that functional activity patterns (strength and lateralisation) could be used to determine the auditory stimulus type, as their results indicated that different bilateral activation patterns in the primary and secondary auditory cortices represented different types of stimuli: verbal and non-verbal (tones and sound of animals and musical instruments). Tones and sounds produced an increase of fMRI activation in the right AC, whereas verbal stimuli produced strong fMRI signals in the left AC.

Other studies, such as those by Brechmann and Scheich (2005) and Hyde et al. (2008), have claimed that the lateralisation in tonal processing is controlled by pitch categorisation. When Brechmann and Scheich (2005) asked participants in their study to classify the direction of pitch change (rising versus falling), the results showed enhanced fMRI activation in the right posterior AC, whereas when participants were asked to classify note duration (short versus long), the left posterior AC was reported to be dominant. Hyde et al. (2008) investigated the functional activation that was associated with pure-tone stimuli and differences in pitch distance. Fine changes in pitch caused a strong BOLD signal in the right lateral AC (the planum temporale), while the left AC responded more to the largest pitch change. These investigations

suggest that acoustic sound features control the extent of the lateralisation of AC involvement in sound processing.

In comparison, Schönwiesner et al. (2007) argued that not only the feature of the acoustic sound determined the hemisphere that was involved, but also the sound context. For example, their studies demonstrated that monaural auditory stimulation caused auditory structures on both sides to respond to contralateral stimulation. However, when monaural acoustic stimuli were followed by binaural acoustic stimuli, the left-side auditory structures revealed a predominant functional activity with the right-ear stimulation, whereas the right-side auditory structures showed no significant differences in functional response with monaural stimuli to either ear. With binaural stimuli, no predominant functional activation was seen in the auditory structures of either side. Their results confirmed earlier investigations by Woldorff et al. (1999), who also noticed that contra-laterality in fMRI signals was elicited by monaural stimulus, and that this functional asymmetry disappeared with binaural stimulus. Both studies used the magnitude of brain activation in the auditory regions to calculate the lateralisation indices (LIs), which determine the hemispheric lateralisation level in sound processing.

Other research has examined the generalisation of auditory learning. For instance, it has been noted that when a subject undergoes training in frequency discrimination in one ear only, the other untrained ear shows improvement in this ability. This finding suggests cross-ear generalisation (Delhommeau et al., 2002, 2005; Roth et al., 2004). In contrast, the generalisation of learning has not been found with other perceptual learning, such as in visual training, in which training has been found to specifically affect only the trained areas and does not lead to enhancements in other sites (or for different stimulus parameters). For instance, one study showed that there were no improvements among individuals who were prepared in the discrimination of a texture region's orientation in one visual hemifield when perpendicular stimuli were used to test the trained orientation's location or stimuli in the opposite visual hemifield (Karni & Sagi, 1991).

Several experimental paradigms have been used to gain an enhanced understanding of the neural substrates that are involved in auditory training and to obtain results that are applicable clinically. It has been found that there is a neural plasticity in brain regions that are involved in acoustic training. For instance, Callan et al. (2003) observed that, because speech related acoustic features were complex, the enhancement in functional activity involved those brain areas that were involved in speech processing and acquisition, such as auditory-motor

mapping areas, as well as those that were specialised in phonetic processing. Furthermore, the superiority of musicians in pitch extraction and manipulation was found to be related to enhancement in functional connectivity between the right temporal and frontal cortices (Zatorre et al., 1994; Koelsch et al., 2005; Schulze et al., 2011; Bianchi et al., 2017).

Some supportive research has suggested that long-term music practice induces structural plasticity in the right AC, particularly in the HG, which has been correlated with its functional specialisation in pitch processing (Zatorre, 2002; Schneider et al., 2005; Oechslin et al., 2018). In contrast, other investigations have argued that the left PT shows a stronger functional activation across musicians during musical perception tasks compared with controls (Ohnishi et al., 2001; Schlaug, 2001). Functional MRIs have also been used to examine the impact of frequency-discrimination training over a short time (one week) on BOLD responses within the AC. They found a bilateral reduction in functional activation within the HG and STG that involved the PT as a result of fast learning (Jäncke et al., 2001).

In summary: although many studies have investigated functional activation patterns that are seen during pitch perception and differences between highly trained individuals (musicians) and controls, relatively little is known about the short-term effect of auditory training on AC functional activity. Therefore, the present study was designed to examine whether short-term auditory training had an impact on the AC, and whether such an impact was limited to the trained side of the brain (i.e. whether learning was lateralised or generalised across the AC). Based on previous findings in psychoacoustic training (see Chapter Five), it was expected that no laterality of learning would be seen in trainees across their behavioural performance (acoustic threshold). Therefore, it could be hypothesised that, based on previous research (Jäncke et al., 2001), short-term pitch discrimination training would show a reduction in functional activation across both auditory cortices that might be correlated with the DT. Further, the study was performed by comparing the neural activity and laterality, along with the DTs that were measured across participants' pre- and post-pitch discrimination training.

6.3 Study Design Considerations of fMRI

6.3.1 MRI Scanner Noise

The loud noise that results from the switching of the MRI gradient makes the collection of fMRI data of the auditory system a challenge (more details about scanner noise are provided in Chapter Three, section 3.4.3.1). The scanner noise can be decreased by use of suitable image acquisition protocols and the determination of the best protocol based on the examination of

goals and experiment design. Langers et al. (2014), for example, measured frequency organisation in the brain (tonotopic mapping) by assessing the response signals that were evoked by sound. They compared tonotopic mapping across three acquisition protocols: sparse, clustered and continuous imaging protocols that were characterised by inter-scan intervals of 8800ms, 2200ms, and 0ms, respectively. The researchers observed similar sensitivities regarding sound-evoked activation in the sparse and clustered protocols, and both showed greater activation than the continuous method. Further, small amounts of data were collected per unit of time under the continuous and sparse protocols, and this situation produced poor imaging quality compared with the clustered (multi-slices) protocol. However, in order to identify tonotopic mapping, the sparse sequence proved to be the optimum protocol, as it provided long periods of silence (8800ms), which were necessary to ensure that the previous scan responses had generally decayed back to baseline.

The present study was designed to compare functional activation changes in the AC that were associated with pitch discrimination training across different presentations of acoustic stimuli. Taking all the above into consideration, a clustered protocol was implemented to investigate the AC without the interference of scanner noise. Another advantage of this method was that it would provide many images over a short scanning time. The imaging protocol was adapted from that of Langers et al. (2014) to set up scanning parameters in a cluster acquisition method. In terms of the presentation of auditory stimuli, an event-related fMRI design was used to delineate the BOLD signal change that was evoked during a pitch discrimination task across different acoustic stimuli presentations (Di Salle et al., 2001; Bianchi et al., 2017). This work enabled an evaluation of individual responses to trials and offered the means to assess the neural correlates of the behavioural responses (Amaro et al., 2006).

6.3.2 Pilot Study

The aim of the pilot study was to develop an efficient experimental design in terms of defining significant levels of fMRI BOLD activation and the determination of the optimum scanning duration. A review of the published literature indicated the superiority of fMRI cluster imaging for auditory tasks, as this technique solved the issue of acoustic noise that resulted from the MRI scanner (Belin et al., 1999; Hall et al., 2001; Bianchi et al., 2017). Therefore, a pilot study was undertaken that used the fMRI cluster technique to monitor three healthy volunteers who would then undertake pitch discrimination tasks. This method was successful and resulted in optimised BOLD signals within the auditory cortices.

6.3.3 Auditory Stimuli

The auditory stimulus consisted of a pair of tones, one of which was set at a reference frequency (F_0) of 1000Hz and the other was set at a test frequency that was above or below the reference frequency. These test frequencies were: 1040Hz, 1020Hz, 1010Hz, 1005Hz, 995Hz, 990Hz, 980Hz and 960Hz. The experiment encompassed the following four acoustic stimuli-driven conditions: both tones delivered to the left ear (LL); both tones delivered to the right ear (RR); the reference tone delivered to the left ear and the other to the right ear (LR); and the reference tone delivered to the right ear and the other to the left ear (RL).

6.3.4 Task Design

To highlight the signal change that occurred with a pitch discrimination task, an event-related fMRI design was used (Amaro et al., 2006). Auditory events were synchronised with fMRI volume acquisitions by use of customised code in MATLAB R2016b (The Mathworks Inc., Natick, MA, USA) (see Appendix C, section 2). This code worked by presenting auditory stimuli randomly in pre-assigned sets during the silent part of the image acquisition. The participant task was based on 2IFC paradigms, in which the test subject was required to press one button (A, if the first tone was higher) or the other button (B, if the second tone was higher) in a response grip. All responses were recorded; the stimuli were delivered through MRI-safe headphones. A monitor screen displayed the instruction ‘Rest’ or ‘Listen’ to the participant, while the participant lay inside the scanner.

Two volumes of fMRI data were acquired within one repetition time (TR). Each TR lasted for 4.4s, as the scanner was on for 2.2s and off for 2.2s, during which period the auditory stimuli were presented as pairs of tones (each tone was of 0.4s duration, and two silent intervals: one lasted for 0.4s and was presented between the tones, and the other lasted for 1s before the next volume). Each fMRI lasted for 7.14 minutes and comprised 95 trials. Four fMRI runs were carried out per participant (two runs before and two runs after the behavioural acoustic training). The timeline of three sample trials is illustrated in Figure 6.2.

Before the start of the test, each participant in the trials performed a pre-test that involved large differences in frequencies between the two tones that were monitored: 20Hz and 70Hz. This was performed in order to ensure that the participants understood the task and could hear the sounds clearly.

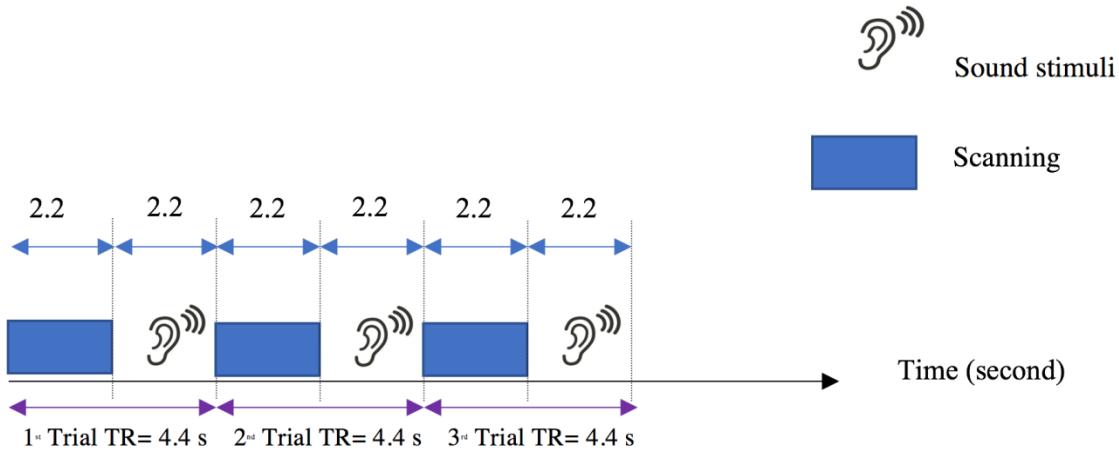


Figure 6.2. Timeline of three sample trials. Each scan acquisition lasted 2.2s, each trial lasted 2.2s, and the TR was 4.4s.

6.3.5 Assessment of the Psychoacoustic Performance

To correlate the functional activity with participants' behavioural performances, the acoustic thresholds for each participant were evaluated while they were being scanned. Lower threshold values indicated better pitch discrimination performance as the participants could detect small differences between the display tones (Prins, 2016). The responses that were recorded during the fMRI tasks were used to evaluate the thresholds before and after auditory training. The thresholds were estimated by use of cumulative normal distribution function (CDF). The CDF used the standard normal distribution for correct responses, which falls between 0 and 1, and computed the probability that the threshold value was the frequency at which the correct response proportion reached 0.75 (75%) (see Figure 6.3) (Kanabus et al., 2002; Prins, 2016).

The CDF analysis was performed in MATLAB.

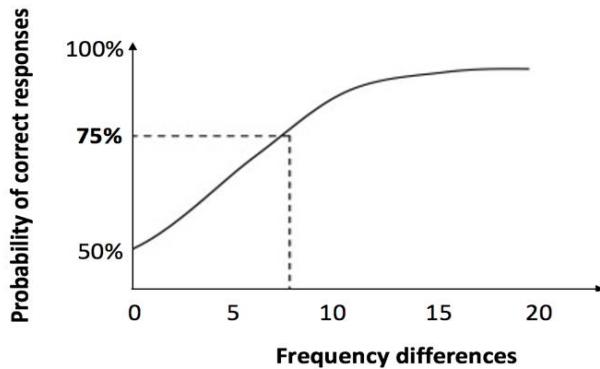


Figure 6.3. Cumulative normal distribution function that was used to estimate discrimination threshold during fMRI task.

6.4 Functional Neuroimaging Analysis

Data analysis was performed using statistical parametric mapping software SPM12 (The Wellcome Department of Imaging Neuroscience, University College London, UK) running on MATLAB_R2016b (The Mathworks, Inc., Natick, MA, USA). Functional data analysis involves three main steps: pre-processing, first level analysis (individual level), and second level analysis (group-wise level).

6.4.1 Pre-processing

Initially, the individual data were pre-processed to remove the artefacts and to prepare the data for the statistical analysis. This involved five steps:

- 1- Slice timing correction: the exact time acquisition was computed for each EPI slice and corrected for acquisition delays.
- 2- Realignment: This step aimed to eliminate the motion artefact in the fMRI time series by realigning all EPI scans with respect to the reference slice, which was the middle slice of the temporal sequence. In addition, this would create the mean functional image, which would be used for the next step (coregistration).
- 3- Coregistration: The raw anatomical images (T_1) were first reoriented to the anterior commissure and then registered to the mean functional image.
- 4- Segmentation and normalisation: the coregistered images were segmented into WM, GM and CSF, and were corrected for bias. Subsequently, the resultant scans were spatially normalised according to the Montreal Neurological Institute (MNI) standard space.
- 5-Smoothing: The output functional data were then smoothed with an 8-mm Gaussian kernel at full-width half-maximum (FWHM).

6.4.2 First-level Analysis

This analysis was performed at the single-subject level; a general linear model (GLM) approach was used for the analysis of the data. In the GLM approach, design matrices model the onsets and durations of the sound stimulus of every trial for all functional runs as per particular experimental demands; two models of interest in this case were developed.

The first was the ‘task-related’ model, which examined and compared the global activation patterns that resulted from the modelling of the pitch discrimination tasks in which all four acoustic stimuli conditions were combined together against the rest period. Such a model was

developed to localise the region of interest (ROI) and to analyse the observed activations, as well as to determine possible task-related impacts. The second model (the ‘condition-related model’) was created to evaluate activation patterns that were associated with each acoustic stimulus condition. Therefore, each condition was modelled separately; hence, LL, RR, LR and RL against the rest period. This model was created to evaluate how auditory cortices respond to binaural and monaural presentation of acoustic stimuli.

6.4.3 Second-level Analysis

The second-level analysis was conducted at group level to interrogate questions that were based on group statistics. There are multiple statistical models that have been used for different study purposes. The statistical testing analysis was performed by use of the GLM model in SPM12 and GraphPad Prism (version 8) for MAC (GraphPad Software, La Jolla, California, USA, www.graphpad.com). REX (<http://web.mit.edu/swg/rex>); and the SPM toolbox were used to extract numerical data from ROIs for use in statistical analysis.

6.4.3.1 Assignment of ROIs

The task-based fMRI paradigms were used to assign the locations of neural-activated regions as ROIs during the performance of the pitch discrimination tasks. To increase the accuracy of this method by avoiding the variety of fMRI activations across subjects, one sample t-test was used to provide an ‘activation map’ that could be used to locate the ROIs (Bullmore et al., 2003; Geissler et al., 2005; Liu et al., 2011). The t-test resulted in clusters that were located bilaterally in auditory cortices, and these were saved as cluster masks. The locations of activated clusters were determined by use of the SPM-Anatomy toolbox v.1.7, which used the MNI coordinate system to define the anatomic labelling based on probabilistic maps of the human brain.

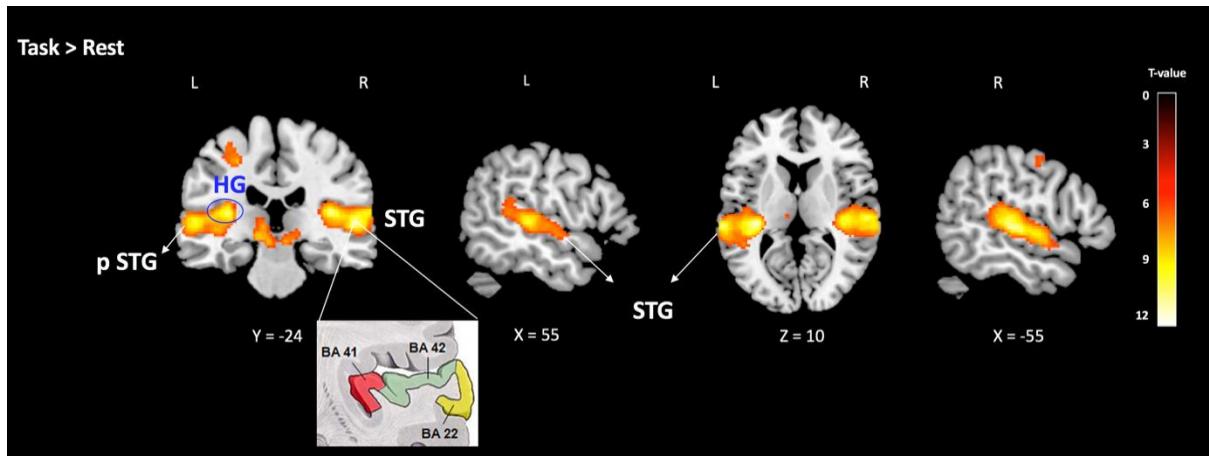


Figure 6.4. Average activation maps show the contrast of Task > Rest (for all acoustic stimuli) for the 26 listeners. Map threshold is set at $t > 6.28$ (FWE corrected, $p < 0.05$). The cross-sectional image shows the primary auditory cortex, which involves the Heschl's gyrus (BAs 41 and 42) and the posterior portion of the superior temporal gyrus that consists of Wernicke's area (BA 22), this image is republished from Talbot et al. (2011). R: right; L: left; STG: superior temporal gyrus; p STG: posterior superior temporal gyrus; HG: Heschl's gyrus; BA: Brodmann areas with numbers.

Figure 6.4 above shows the average activations of the bilateral AC that were related to pitch discrimination tasks for all acoustic stimuli for all participants (both L and R training groups) before any acoustic training had been undertaken. The strongest BOLD signals were found in the superior temporal gyri that occupied the posterior part (right STG: $x, y, z = 62, -18, 1$; $t = 11.60$; left STG: $-59, -32, 7$; $t = 12.39$) and the Heschl's gyri (right HG: $x, y, z = 42, -27, 10$; $t = 10.48$; left HG: $-34, -32, 13$; $t = 11.75$), which are known as the dominant brain regions in pitch discrimination. Further details regarding all BOLD responses that were observed during the pitch discrimination tests in a set of cortical and subcortical areas (all peak-level coordinates and t-values) are listed in the fMRI result table in Appendix A (section 1).

To produce a more specific ROI analysis, each cluster mask was divided into the right and left STG, as well as the right and left HG, as they showed the highest activation in t-test resulted clusters, which are known to be superior in pitch processing (Schneider et al., 2002; Bermudez et al., 2008; Alho et al., 2014). This was conducted by use of the ImageCalc option in SPM to re-slice and multiply cluster masks with the anatomical masks (for the same ROIs) that were extracted from the Bspmview toolbox (v.20170411). The numerical data were extracted from the ROIs through use of REX to be used in statistical tests, for instance to calculate the BOLD signal change within the ROIs.

6.4.3.2 The Lateralisation of Learning

To investigate whether there was a dominant hemisphere for each trainee group (13 right- and 13 left-ear trainees), the laterality of functional signals, as well as the psychoacoustic performance, were investigated through statistical analysis. The lateralisation of functional signals was estimated through use of the laterality index (LI), which can be obtained from the following equation (6.1):

$$LI = \frac{L-R}{L+R} \quad \text{equation 6.1}$$

L and R represent the numbers of activated voxels in the left and right hemispheric ROIs at a fixed threshold level. The LI is a number between -1 and +1; a negative LI means right-hemisphere dominance, while a positive LI refers to a left-hemisphere dominance and LI at approximately zero is considered to show bilateral evenness (Jansen et al., 2006).

Laterality of functional signals in right- and left-ear groups

To investigate the effect of auditory training on the functional laterality across the trainee groups, two-way analysis of variance (ANOVA) was computed for any laterality index change (post-pre) in the ROIs. The factors that were taken into account were: the group (right- or left-ear trainees), and the stimulus presentation (LL or RR). ANOVA analysis was performed through use of a GraphPad Prism.

Laterality of psychoacoustic performance in right and left groups

To model the effect of auditory training on the psychoacoustic performances of the right- and left-ear groups separately, the two-way ANOVA was used. The design matrix included the threshold change (post-pre) as measures with the factors to be accounted for: group (right- and left-ear trainees), and stimulus presentation (LL and RR). ANOVA analysis was performed through use of the GraphPad Prism.

6.4.3.3 Pitch discrimination Training Effects

To clarify the effect of short-term pitch discrimination training on the AC of all 26 trainees, multiple statistical tests were conducted. The effect of auditory training was examined in terms of brain functional activity and the laterality of functional signals, along with psychoacoustic performance.

Brain functional activity

To evaluate the impact of learning on the brains' functional signals in all the trainees' ROIs, a two-way repeated measures ANOVA that was implemented as a second level analysis in SPM

was used. Functional signal intensity was employed as a measure, and the factors of training (pre and post) and type of stimulus presentation (LL, RR, LR, RL) were considered. The repeated factor was ‘participant’. The model was employed to evaluate the impact of learning on the pattern of activations, and therefore the corresponding contrast images from the condition-related model for all acoustic stimuli were used. Correction for multiple comparisons was applied at the voxel level using the family-wise error (FWE) with $p < 0.05$, as implemented in SPM12. Additional post-hoc paired t-tests were undertaken for significant changes in the BOLD response.

Laterality of functional signals

To evaluate the impact of learning on the laterality of the presentations of the functional signals in all the trainee ROIs, two separate repeated measures ANOVAs were implemented as a second-level analysis in SPM. LI was used as a measure for two ROIs (HG and STG) and the factors training (pre and post) and stimulus presentation (LL, RR, LR, and RL) were examined. Post-hoc paired t-tests were used to test for significant changes in the laterality of the functional signals.

Psychoacoustic performance

To evaluate the effect of auditory training on the psychoacoustic performance of all trainees, a two way-repeated measures ANOVA was used. This used the participants’ acoustic thresholds as the repeated measure with the factors being training (pre and post) and stimulus presentation (LL, RR, LR, RL). Post-hoc paired t-tests were used to test for significant changes in acoustic thresholds between selected conditions.

6.4.3.4 Correlation between Functional Activity and Psychoacoustic Performance

Correlations were computed between the significant changes in functional activations that could be observed from the ANOVA analysis and the changes in individual acoustic thresholds. The correlations analysis was conducted via the GraphPad Prism.

6.5 Results

6.5.1 The Lateralisation of Learning

To investigate whether there was a dominant hemisphere in each trained group (right- and left-ear trainees), the laterality of the functional signals in the ROIs of each trained group and their psychoacoustic performance were compared through two separate ANOVA analyses. ANOVA that was computed for the functional laterality indicated no significant effects of the interaction between the groups and the stimulus presentation on the laterality index change in STG,

$F(1,48) = 1.30, p = 0.26$. Similarly for the HG, no significant interaction was found between the effects on the groups and the stimulus presentation on the laterality index change in HG, $F(1,48) = 0.01, p = 0.93$. Additionally, the second ANOVA that was run for the psychoacoustic performance revealed no significant interaction between the effects in the groups and stimulus presentation on the acoustic threshold change, $F(1,48) = 0.04, p = 0.85$. Therefore, the overall result showed that both the left- and right-ear trainees presented no significant differences in their behavioural performances or in their functional responses, which means that auditory learning was not lateralised across the AC. Therefore, in the studies that were conducted after this test, these two groups were considered as one trainee group. Further details regarding descriptive statistics of the laterality of the BOLD signal and the behavioural performances for each group are provided in Tables 6.1 and 6.2.

Acoustic stimulus	RT trainees Mean ($\pm SD$)	Paired t- test (df= 12)	LT trainees Mean ($\pm SD$)	Paired t- test (df= 12)
a. LI in STG				
LL, pre	-0.10(0.06)		-0.10(0.06)	
LL, post	-0.04(0.10)	p= 0.03, t=2.42	-0.07(0.06)	p=0.15, t= 1.55
b. LI in HG				
RR, pre	-0.06(0.09)		-0.10(0.05)	
RR, post	0.75(0.05)	***p< 0.0001, t=22.98	0.75(0.04)	***p< 0.0001, t=39
LL, pre	-0.04(0.07)		-0.03(0.16)	
LL, post	-0.06(0.06)	p=0.53, t=0.65	-0.08(0.08)	p=0.30, t=1.08
RR, pre	-0.03(0.12)		-0.02(0.14)	
RR, post	-0.07(0.06)	p=0.34, t=0.99	-0.08(0.09)	p=0.13, t=1.65

Table 6.1. Comparison of the mean, SD and paired t-test results for the laterality index (LI) before and after auditory training for the functional signal that was associated with different acoustic stimulus presentations. LI was evaluated in (a) STG and (b) HG across the right- and left-side trainees. A negative LI means right-hemisphere dominance, while a positive LI means left-hemisphere dominance, and an LI around zero is considered to show bilateral evenness effect. LL: both tones to the left ear; RR: both tones to the right ear; LR: first tone to the left ear and second tone to the right ear; RL: first tone to the right ear and second tone to the left ear; HG: Heschl's gyrus; STG: superior temporal gyrus. Significant difference at ***p < 0.001.

Acoustic stimulus	RT trainees		LT trainees	
	Mean (\pm SD)	Paired t-test (df= 12)	Mean (\pm SD)	Paired t-test (df= 12)
LL, pre	11.11 (7.95)		10.70 (6.98)	
LL, post	6.79 (4.56)	p=0.05, t=2.17	6.10 (3.55)	p=0.04, t= 2.25
RR, pre	11.89 (8.61)		9.43 (6.43)	
RR, post	10.08 (4.60)	p=0.36, t=0.96	6.63 (3.37)	p=0.12, t=1.68

Table 6.2. Comparison of the mean, SD and paired t-test results for the acoustic threshold in the right- and left-ear trainees before and after auditory training. Both groups showed reduction (improvement) in their discrimination threshold after training. LL: both tones to the left ear; RR: both tones to the right ear; LR: first tone to the left ear and second tone to the right ear; RL: first tone to the right ear and second tone to the left ear.

6.5.2 The Effects of Short-term Pitch discrimination Training

6.5.2.1 Brain Functional Activity

The aim of this part of the study was to evaluate the impact of learning on the brain functional signals that were observed in all trainees. A two-way repeated measures ANOVA was performed; the factors were training and stimulus presentation. The ANOVA results highlighted the main effect of training through observation of clusters that were produced through contrast (*pre-> post-training*) and were located in the posterior division of the right STG (x, y, z = 57, -22, -3), $F(1,50) = 37.45$, $p < 0.05$ (FWE) and the left STG with involvement of part of the middle temporal gyrus (x, y, z = -59, -22, -5), $F(1,50) = 42.10$; $p < 0.05$ (FWE) (see Figure 6.5). Additional post-hoc paired t-tests demonstrated no significant changes in BOLD activation in the overall AC after training. At the subregion level, a significant reduction in BOLD activation was found bilaterally in the STG after training, although not in the HG (see Table 6.3). In terms of the acoustic stimulus factor, no significant effect of stimulus presentation on brain functional response was found.

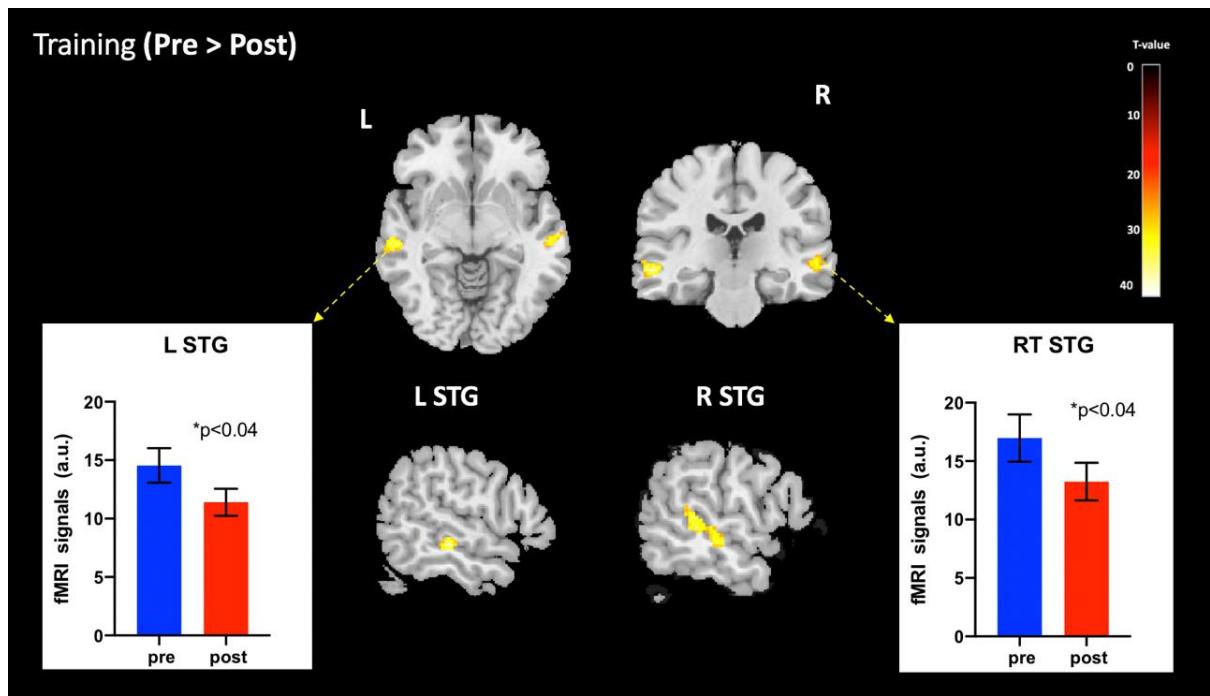


Figure 6.5. fMRI image reflects significant reduction of BOLD signals in the posterior division of right and left STG with involvement of part of the left middle temporal gyrus after pitch discrimination training across learners. The bar charts represent the BOLD signals in the STG before and after pitch discrimination training; error bars represent the standard error of the mean. *Significant difference at $p<0.05$. STG: superior temporal gyrus; R: right; L: left.

ROI	BOLD activation (Z-score)		
	Pre-training: M (\pm SD)		Paired t- test (df= 25)
	Post-training: M (\pm SD)		
R AC	16.90 (8.14) 16.36 (5.83)		p=0.68, t=0.42
L AC	15.75 (7.52) 15.06 (5.19)		p=0.63, t=0.49
R p-STG	16.97 (10.31) 13.25 (8.21)		*p=0.04, t=2.22
L p-STG	14.53 (7.53) 11.40 (5.93)		*p=0.04, t=2.18
R HG	18.52 (9.96) 19.54 (8.33)		p=0.59, t=0.55
L HG	19.31 (8.97) 19.06 (9.86)		p=0.89, t=0.14

Table 6.3. Comparison of fMRI BOLD signals before and after pitch discrimination training at the ROIs level. Only the posterior portion of the STG reflects a significant reduction in BOLD activity. *Significant difference at $p<0.05$. AC: auditory cortex; HG: Heschl's gyrus; pSTG: posterior superior temporal gyrus; R: right; L: left.

6.5.2.2 Laterality of Functional Signals

In the current study, different acoustic stimulations were supplied to the ears that involved binaural and monaural conditions, which caused bilateral neural activation within auditory cortices with *all* stimulus conditions. To test whether laterality was caused in these functional activations within the ROIs (HG and STG) by auditory learning, the LI measures were used in two separate, repeat-measure ANOVAs in which the factors were training and stimulus presentation. The ANOVA results revealed that there was a significant main effect of training on lateralisation in the functional signals within HG, although with no significant effects of stimulus presentation on signal lateralisation. Moreover, the post-hoc paired t-test illustrated that there were no significant effects of learning on the laterality of the functional signals with different stimuli presentations within HG (see Table 6.4).

Factor	ANOVA	Post-hoc two-tailed paired t-test		
		Stimulus presentation	Pre: M (\pm SD) Post: M (\pm SD)	Pre vs. Post (df= 25)
Training factor	F (1, 100) = 5.38, $*p=0.02$	LL	-0.03 (0.12) -0.07 (0.07)	t = 1.27, p = 0.22
Stimulus presentation factor	F (3, 100) = 0.25, $p=0.86$	RR	-0.03 (0.13) -0.07 (0.08)	t = 1.88, p = 0.07
Interaction (Training vs. stimulus presentation)	F (3, 100) = 0.18, $p=0.91$	LR	-0.05 (0.24) -0.09 (0.11)	t = 0.92, p = 0.37
		RL	-0.05 (0.07) -0.07 (0.06)	t = 1.29, p = 0.21

Table 6.4. Statistical summary of the main training effects and stimulus presentation on the laterality of functional signals within HG, as shown by ANOVA. Post-hoc t-tests compare lateralisation indices of different stimuli presentations both before and after training. The auditory training had a significant impact on functional laterality, as revealed by ANOVA. Post-hoc tests show no significant effects of learning on functional signal laterality with different stimuli presentations within HG. Negative LI means right-hemisphere dominance, whereas positive LI means left-hemisphere dominance, and an LI around zero is considered to show bilateral evenness effect. *Significant difference at $p<0.05$.

In terms of STG, the ANOVA results indicated that both training and stimulus presentation factors had significant influences upon the lateralisation of functional signals. The results of post-hoc paired t-tests showed that there was significant lateralisation of the functional signal toward the left STG following the training with RR, LR and RL stimuli. However, no functional lateralisation either before or after training was found in the STG for the LL stimulus, although the LI changed significantly with training. The left laterality of the signals indicates low functional activity (more learning) in the right STG (Table 6.5 and Figure 6.6).

Factor	ANOVA	Post-hoc two-tailed paired t-test		
		Stimulus presentation	Pre: M (\pm SD) Post: M (\pm SD)	Pre vs. Post (df= 25)
Training factor	F (1, 100) = 1487 ***p <0.0001	LL	-0.10 (0.06) -0.06 (0.08)	t = 2.87, **p = 0.008
Stimulus presentation factor	F (3, 100) =159.1 ***p <0.0001	RR	-0.08 (0.08) 0.75 (0.05)	t = 40.25, ***p <0.0001
Interaction (Training vs. stimulus presentation)	F (3, 100) =144.2 ***p <0.0001	LR	-0.05 (0.29) 0.75 (0.06)	t = 13.54, ***p <0.0001
		RL	-0.09 (0.06) 0.76 (0.04)	t = 66.81, ***p <0.0001

Table 6.5. Statistical summary of the main training effects and stimulus presentation on the laterality of functional signals within STG, as shown by ANOVA. Post-hoc t-tests compare lateralisation indices of different stimuli presentations both before and after training. The auditory training had a significant impact on functional laterality, as revealed by the ANOVA and post-hoc tests. Post-hoc tests show that functional activity became left lateralised after the training in RR, LR and RL stimuli, but not after LL stimulus. Negative LI demonstrates right-hemisphere dominance, whereas positive LI means left-hemisphere dominance, and an LI around zero is considered to show bilateral evenness effect. Significant difference at ***p < 0.001, **0.001 < p < 0.01.

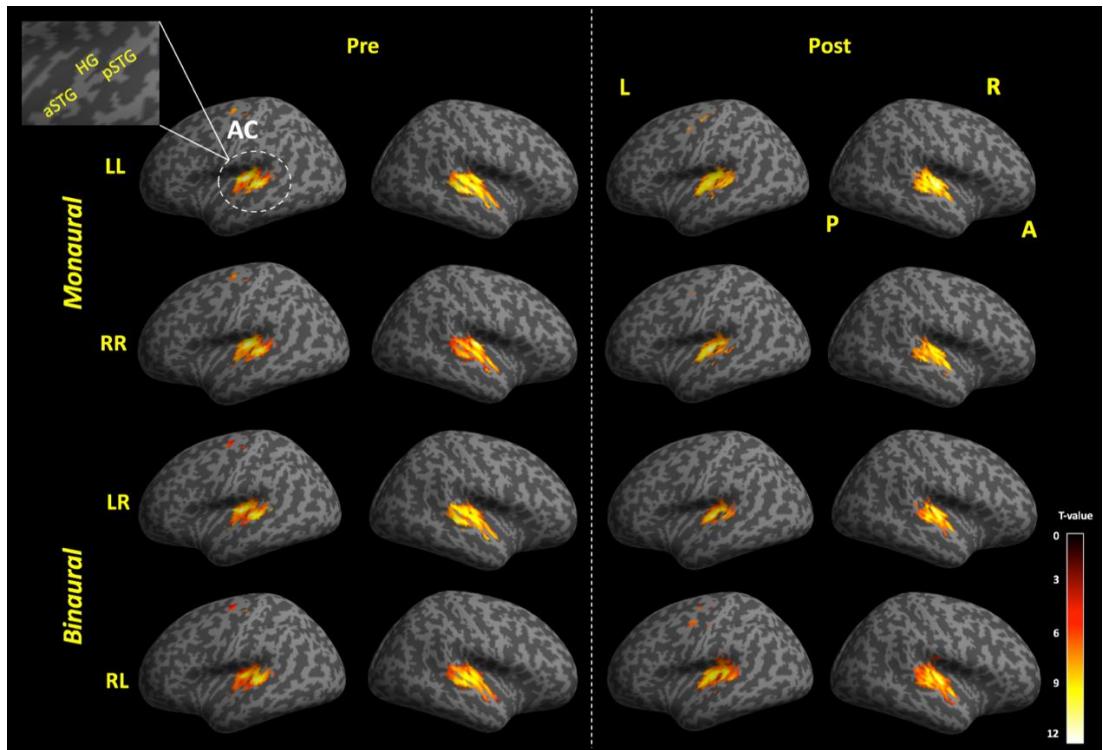


Figure 6.6. fMRI reflects BOLD signals across auditory cortices both before and after pitch discrimination training across monaural (both tones delivered to one ear) and binaural (two tones delivered to both ears) acoustic stimuli. Further detailed bar charts comparison is provided in Appendix A (section 1). LL: both tones to left ear; RR: both tones to right ear; LR: first tone to the left ear and second tone to the right ear; RL: first tone to the right ear and second tone to the left ear. R: right; L: left; A: anterior; P: posterior; AC: auditory cortex; HG: Heschl's gyrus; aSTG: anterior superior temporal gyrus; pSTG: posterior superior temporal gyrus.

6.5.2.3 Psychoacoustic Performance

In this test, a two-way repeat-measure ANOVA was used to evaluate the effects of pitch discrimination training on trainees' psychoacoustic performance. The discrimination threshold was used as the repeated measure, while the factors were training and stimulus presentation. The ANOVA result revealed that there was a significant main effect of auditory training on the acoustic threshold, whereas no significant impact was found with the stimulus presentations factor. Post-hoc, paired t-tests showed that the acoustic threshold was reduced (improved) after training across all acoustic stimuli presentations; however, this reduction was significant only for the LL stimulus, although not for other stimuli (RR, LR and RL) (see Table 6.6 and Figure 6.7).

Factor	ANOVA	Post-hoc two-tailed paired t-test	
		Stimulus presentation	Pre vs. Post (df= 25)
Training factor	F (1,100) = 21.65 ***p <0.0001	LL	t = 3.07, **p = 0.005
Stimulus presentation factor	F (3,100) =1.76 p = 0.16	RR	t = 1.87, p = 0.07
Interaction (Training vs. stimulus presentation)	F (3,100) =0.35 p = 0.79	LR	t = 2.02, p = 0.05
		RL	t = 2.42, p = 0.05

Table 6.6. A statistical summary of the main training effects and stimulus presentation on the acoustic threshold, as shown by ANOVA. Post-hoc t-tests compare the acoustic threshold of separated stimuli presentations both before and after training. Auditory training had a significant impact on the discrimination threshold, as revealed by ANOVA and post-hoc tests. Post-hoc tests show significant improvements in acoustic threshold with LL stimulus, although not with other stimuli (RR, LR and RL). Significant difference at ***p < 0.001, **p < 0.01.

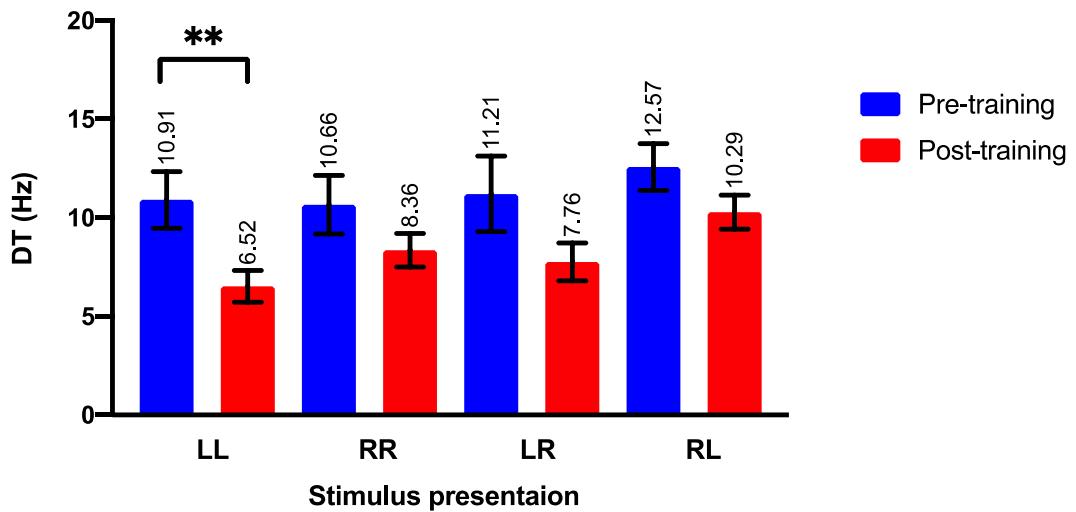


Figure 6.7. Descriptive statistics of the acoustic threshold measure both before and after training. Post-hoc paired t-tests indicated that the acoustic threshold was improved (reduction) significantly after auditory training in the LL stimulus only. Error bars represent the standard error of the mean. Significant difference at **p < 0.01.

Correlation between Functional Activity and Psychoacoustic Performance

Pearson's correlation was used to investigate whether the change in individual psychoacoustic performance was related to the change in functional activity. No significant correlation was found between the enhancement in acoustic threshold and the reduction in functional activity within the posterior STG (pSTG) bilaterally (R STG; $r=0.36$, $p=0.07$; L STG; $r=0.32$, $p=0.11$).

6.6 Discussion

6.6.1 The Lateralisation of Learning

One of the present study's aims was to investigate whether auditory learning was lateralised or generalised throughout the auditory cortices. The results (see section 6.5.1) revealed that both left- and right-ear trainees showed no significant differences in their psychoacoustic performances. This was also indicated in terms of the laterality of the BOLD responses to different acoustic stimuli presentations. This result concurred with previous findings in psychoacoustic training (see Chapter Five), which had shown no laterality of learning in trainees across their acoustic thresholds. Therefore, this study showed that there was no lateralisation in auditory learning, and thus, there was a generalisation of learning across ears; hence, both groups could be considered as a single trainee group.

The current result is in accordance with those of previous studies, which have shown that there is a cross-ear generalisation of auditory learning (Roth et al., 2003; Delhommeau et al., 2005; Micheyl et al., 2006; Wright & Zhang, 2009). Specifically, according to Wright and Zhang (2009), tonal discrimination learning seems to shift from the trained to the untrained ear. Their suggestion is based on previous research observations that show how training in frequency discrimination can be transferred from trained to untrained stimuli, such as frequencies in which the trainee is untrained (Delhommeau et al., 2005) or noise conditions that have not been experienced previously (Micheyl et al., 2006). Added to that, the generalisation of auditory learning is not limited to the stimulus, as it can be transferred from a trained ear to an untrained ear. Roth et al. (2003), for example, showed that listeners who were trained in frequency discrimination in the left ear enjoyed similar performance improvements to those that were experienced by listeners who were trained in the right ear after 24 hours of training. That study was focused on the behavioural aspect only, whereas the present study aimed to explore the generalisation of auditory training from different aspects, including behavioural performance and functional brain activity.

6.6.2 The Effects of Short-term Pitch discrimination Training on:

6.6.2.1 Brain Functional Activity

The findings that are explained in the results section (see section 6.5.2.1) showed a significant reduction in functional activation after pitch discrimination training. This reduction was found in the STG bilaterally, but not HG. This finding was in agreement with those of previous investigations (Jäncke et al., 2001; Bergerbest et al., 2004). In particular, the study that was conducted by Jäncke et al. (2001) involved the scanning of the subjects twice in fMRI: first before and then towards the end of their auditory training. It was noted that there was less BOLD response from the bilateral AC, particularly in the STG, after training, and that this reduction was only seen in subjects who displayed a high-performance level during training. Hence, brain activation was noted to be negatively correlated with individual performance. In contrast, this activation was not observed in the control group. This result suggested that the posterior part of the STG (planum temporale) was the core region that was responsible for pitch discrimination as it showed more learning effects than HG. This was plausible, as the planum temporale includes neural networks that are considered to be actively engaged in pitch processes.

According to Ohl & Scheich (2005), AC plasticity can be represented as an increase or a decrease in functional activation, which varies according to the demands of the task and the mechanisms involved. For example, the reduction in functional activity that was caused by auditory training was explained as the restriction of the activation to small neuron ensembles that exhibited expert properties concerning identification of category (Ohl & Scheich, 2005).

Reduction in BOLD response may also result from the rapid identification of repeated auditory stimuli; this confirms the findings of a study by Bergerbest et al. (2004), which noted that decreased activation of the auditory cortices was related to enhancement in recognition performance. However, the complexity of an acoustic stimulus will result in an increase in functional activity. For instance, Callan et al. (2003) used extensive perceptual training on the English /r-l/ phonetic among Japanese speakers (which is considered to be a difficult task) and they observed an enhancement in functional activity in auditory-motor areas that were involved in speech processing and acquisition.

6.6.2.2 Laterality of Functional Signals

The results that are described in section 6.5.2.2 show that use of different acoustic stimulations that involve binaural and monaural conditions result in bilateral neural activation within auditory cortices under *all* stimulus conditions. This is consistent with previous investigations, which reported that both auditory cortices worked together at a central level, and that this cooperation resulted in an inter-hemispheric interaction (Beerends & Houtsma, 1989; Suzuki et al., 2002; Sinai & Pratt, 2003). The current study also investigated the effect of learning on the laterality of the functional signal within ROIs. There was no lateralisation in functional signal across HG, as revealed by the laterality measure that was performed both before and after training.

However, the STG showed significant changes in the functional signal presentation after training. The BOLD response was lateralised toward the left hemisphere during the supply of most auditory stimuli. As a result, the right STG exhibited low functional activity after training, and this shows that more learning occurred in it. The reduction of functional activity with learning may be caused by the rapid identification of repeated auditory stimuli (Bergerbest et al., 2004), and the restriction of activation to small, expert neuron ensembles (Ohl & Scheich, 2005).

Both results that are described in sections 6.5.2.1 and 6.5.2.2 reveal that the effect of pitch discrimination training was more prominent in the STG compared with HG. This may be due to more active engagement of the STG in the pitch process, as has been suggested by Jäncke et al. (2001). Another possible reason is the size of the STG, as it occupies a large part of the AC that involves secondary auditory regions (BA 22); further anatomical details are provided in Chapter Two.

6.6.2.3 Psychoacoustic Performance

Auditory training has been shown to improve FDTs across listeners (Baker et al., 1954; Demany, 1985; Delhommeau et al., 2002; Amitay et al., 2005; Carcagno et al., 2011). In the present study, the results that are described in section 6.5.2.3 reveal that participants' acoustic thresholds were significantly improved, which may be attributed to auditory training. This result was in parallel with the results that were found for psychoacoustic training (acoustic threshold assessment outside the scanner) and which are described in Chapter Five, as these showed an improvement in DT after the training.

In terms of the presentation of the auditory stimuli, previous neuroimaging studies have found that the monaural sound stimulus creates a greater response in the contralateral hemisphere than in the ipsilateral hemisphere (Scheffler et al., 1998; Suzuki et al., 2002; Schönwiesner et al., 2007). In the present study (previous section 6.6.2.2), the auditory cortices were activated bilaterally before training, but after training, a shift was observed in the BOLD response toward the left hemisphere (right STG exhibited low activation). Moreover, in the results that are described in section 6.5.2.3, the DT in all acoustic conditions was reduced post-training; however, this reduction was significant only when the LL stimulus was supplied. A possible reason for this finding could be the functional superiority of the right hemisphere in pitch discrimination. This right-hemisphere advantage in pitch perception has been observed previously by many researchers (Zatorre, 2002; Schneider et al., 2005; Hyde et al., 2008; Bianchi et al., 2017); their results illustrate that melody and pitch perception tend to be processed in the right STG, particularly in musicians. The absence in the results of this study of any significant correlation between psychoacoustic performance and neural functional response could be due to the short training period and an insufficient amount of training to produce a significant correlation.

6.7 Conclusion

Task-based fMRI was used to explore the impacts of short-term pitch discrimination training on the lateralisation of learning and functional activity, and on the laterality of the BOLD signal, with presentation of different acoustic stimuli. The results indicated that no laterality of auditory learning was seen in the BOLD responses of trainees (right-and left-ear trainee groups), or in their acoustic thresholds (matched with the previous finding in psychoacoustic training - Chapter Five), and thus, the groups could be combined as one trainee group. This result means that auditory training can be transferred to the untrained ear.

In terms of functional activity, a significant reduction in functional activation was observed in the STG bilaterally after pitch discrimination training. Moreover, a BOLD response was lateralised toward the left STG in most of the auditory stimuli after the training, and thus, the right STG exhibited low functional activity (more learning). This was consistent with the findings for psychoacoustic performance, as the DT improved after the training in all acoustic stimuli; however, this improvement was significant only in the LL stimulus.

Therefore, the effect of pitch discrimination training was more prominent in the STG (especially the right STG) compared with HG.

Generally, the results of the current study suggest that improvements in the encoding of the acoustic stimuli at the functional level make a significant contribution to short-term pitch discrimination learning. The next chapter will investigate the effects of pitch discrimination training on brain structures.

Chapter 7. Association between Grey Matter Volume Differences and Pitch Discrimination Training

7.1 Aim and Objectives

The aim of the study that is described in this chapter was to investigate the morphological changes that were caused by training in pitch discrimination through use of anatomical T₁-weighted magnetic resonance (MR) images. Therefore, the work that is described in this chapter was designed to provide insights into structural changes of the brain by investigating whether short-term auditory training could cause differences across trainees compared with controls, with respect to (1) volume of GM and (2) cortical thickness.

7.2 Introduction

The human brain has an outstanding capacity to reorganise neural pathways and to change cortical structures according to the nature of the surrounding world. For example, brain development is markedly altered by thorough and vigorous musical training at a young age (Shahin et al., 2004), and this change in development can lead to modifications in the number of neurons that participate in processing, synchronisation timing and the number and robustness of excitatory and inhibitory synaptic links (Schneider et al., 2002; Jones et al., 2010). These brain changes, which are defined as neural plasticity, need to be comprehensively evaluated to be relevant to clinical application as well as to perceptual learning. One way to assess neural plasticity is through the use of MR anatomical images (T₁-weighted), which enable identification of post-training morphological alterations as they facilitate the quantitative assessment of white-matter (WM) and grey-matter (GM) characteristics. Voxel-based morphometry (VBM) is the method that is most widely employed to measure longitudinal structural alterations (Ashburner and Friston, 2000). The automatic VBM method involves the entire brain and makes it possible to compare groups statistically. Such comparison groups may be learners and controls, or the same group at different time-points during training. VBM performs a voxel-wise analysis on brains that have been transformed into a standard space to enable inference regarding the volume or density of local GM. The standard VBM processing stream employs T₁-weighted structural images of the brain as input (Ashburner and Friston, 2000), through use of statistical parametric maps (SPM), to create output that reflects variances in brain-tissue density or volume.

As highlighted by Fischl and Dale (2000), the T₁-weighted images that serve as input for VBM can facilitate the production of cortical thickness maps as well. This can also be done by use

of FreeSurfer, which is a surface-based analytical software tool that is used for subcortical segmentations to generate useful information about cortical measures, such as cortical thickness, surface, and mean curvature. The key difference between the two approaches is that automatic segmentation (FreeSurfer) provides average morphological statistics for predefined anatomical areas in native space for each participant, while VBM approaches provide data for statistical inference at the level of each voxel without the need for anatomical segmentation. However, there is the constraint that images must be transformed into a common space, which is either a standard space, such as the MNI152 template, or an average of all acquired scans in a study.

Both approaches have been used in many research studies that have investigated the impact of musical training on neuroplasticity (Schneider et al., 2002; Gaser et al., 2003). Their results show that musicians display enlarged GM volumes in the motor cortex and auditory regions (STG and HG) compared with non-musicians. Another related study was performed by Bailey et al. (2014), who investigated GM volume and cortical thickness to explore the impact of musical training in the early-life stage. Their results revealed that early musical practice led to increased cortical surface area in the ventral pre-motor cortex.

Neural structural changes that are induced by long cognitive training periods have been widely investigated. However, little attention has been paid to the structural changes that occur when the training period is short. Most research into short-term auditory training has focused on behavioural changes and neural response patterns , such as auditory-evoked potentials measured by electroencephalogram (EEG) (Lappe et al., 2008; Carcagno and Plack, 2011; Moreno et al., 2011), and the factors that may contribute to structural changes in the brain, such as gender (Hutchinson et al., 2003) and handedness (Khalfa et al., 1998; Mišić et al., 2018), rather than structural changes that are induced by short training periods.

Therefore, the work that is described in this chapter aimed to cover the gaps that have been discovered in previous literature through the examination of the structural effects of short-term training. This study was performed by exploring the impact of short-term training in pitch discrimination on the neuroanatomical structures. Two approaches (VBM and FreeSurfer) were used to investigate the plasticity of different cortical features, including GM density and the cortical volume and thickness of brain regions that are involved in the pitch discrimination task. My hypothesis was that a short period of training might produce a small change in GM volume and cortical measures within auditory processing and associated regions.

7.3 Method

7.3.1 Participants

Study participants were 26 trainees and eight controls only of the original group of 15 (this was because the T₁ data with a two-day gap in between was not available for all controls). Participants' demographics are described in the study methodology (Chapter Four).

7.3.2 VBM Method

Data analysis was performed via VBM (Ashburner and Friston, 2000) in statistical parametric mapping software SPM12 (v6906) (The Wellcome Department of Imaging Neuroscience, University College London, UK) running on MATLAB (vR2016b) (The Mathworks, Inc., Natick, MA, USA). VBM is an automatic technique for whole-brain analysis, which is mainly used for investigation of changes in GM (Thomas and Baker, 2013).

All data processing steps were implemented as described in detail by Ashburner and Friston, 2015 (VBM manual). Firstly, the data were pre-processed. This involved reorientation, segmentation, template creation and normalisation. All T₁-weighted images were reoriented manually to the centre of the image, which showed the anterior commissure. Then the reoriented images were linearly registered and transformed to the Montreal Neurological Institute standard space (MNI 152). The standardised images were segmented into three tissue types: WM, GM and cerebrospinal fluid (CSF). This segmentation step involved the warping of GM images to MNI space to generate 'imported images' that would be aligned together with their averages to estimate deformations. This estimation step was performed by creating local-group templates using the diffeomorphic anatomical registration through exponentiated lie (DARTEL) algebraic tool, which proved to be more sensitive for inter-subject brain image registration than the standard VBM method (Klein et al., 2009). The DARTEL tool works by aligning images of GM and WM simultaneously. This is accomplished by producing increasingly crisp average template data to which the data are matched iteratively. The average template that resulted in this study was spatially normalised to MNI space with a preserved number of signals in each region separately to achieve 'modulation' to compare tissue volumes. Finally, images were smoothed through convolution with an 8-mm Gaussian kernel, as recommended in the manual (Ashburner and Friston, 2015). The smoothed and normalised tissue images that were produced in this manner were obtained for group statistics to discover the differences in the GM volume of participants' whole brains before and after the training period.

7.3.3 FreeSurfer Method

FreeSurfer is a piece of neuroimaging analysis software that performs surface-based inter-subject registration. FreeSurfer (v 6.0, 2017) was used for segmentation and estimation of cortical and subcortical volume and thickness (Fischl, 2012). FreeSurfer utilises vertex (triangular) and edge scales rather than voxel-based analysis to achieve accurate measurements of volume and thickness (Fischl, 2004).

FreeSurfer is mainly based on ‘Recon-all’ commands, which are used to reconstruct the cortical surface automatically (ReconAllDevTable - FreeSurfer Wiki, 2020). Therefore, the program requires T₁-weighted images that show good contrast in order to distinguish easily between GM and WM. For this study, the workflow began with conversion of T₁ images into a specific format (.mgz) through use of a FreeSurfer command (mri_convert). Then the Recon-all command was activated to begin the automatic transformation of the converted T₁ images to Talairach space with corrections for scan intensity variations. After that, the images of the non-brain tissue, such as skull, were removed and then other brain tissue was segmented into cortical structures, WM, and subcortical structures. The WM and GM (Pial) boundaries were identified based on a probability map that used the greatest variation in tissue intensity to assign the tissue border. As a result, the cortical or GM thickness could be calculated (Fischl et al., 2002, 2004) (Figure 7.1). The resultant segmented images were inflated to form the shape of a sphere and registered into a template that was located in the FSL directory, which comprised the average of 40 brain subjects. This surface-based method created more accurate registration of the major gyri and sulci in two dimensions (axial and radial). Then the cortical parcellation of the template sphere, which was identified based on the FreeSurfer atlas, was mapped back to individual subject parcellations, and adjusted for small variations in individual anatomies (Fischl et al., 2004). These cortical parcellations were identified based on the FreeSurfer atlases: the Desikan-Killiany and the Destrieux atlases.

Finally, the complete cortical models resulted in multiple output files that consisted of numerical values that were related to the cortical thickness, tissue volumes, surfaces, and curvature. A quality control test was performed for these output data and it was visually checked for segmentation errors and then the statistical analysis for regions of interest (ROIs) was carried out.

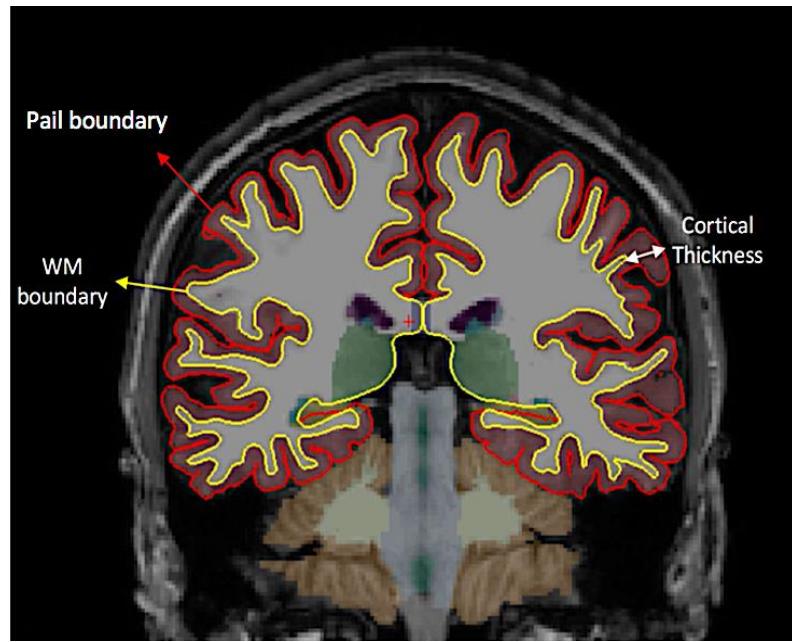


Figure 7.1. FreeSurfer output clearly indicates surfaces of WM and Pial (GM). The cortical thickness is represented by the distance between the WM and Pial surfaces (white arrow).

7.4 Statistical Analysis

7.4.1 VBM

Paired t-tests were conducted on previously smoothed GM images through analysis of the whole-brain voxels using the general linear model (GLM) part of SPM12 (v7487). T-tests were run twice: once to compare the pre- and post-training data for the trainees to correlate the specific effects of the pitch discrimination training, mainly in GM volume. The other paired t-test was performed for the controls, who had been scanned twice with a two-day gap between the scans that matched the timing of the auditory-training period. Two contrasts were assigned to assess the probability that GM volume had increased in the trainees ($\text{post} > \text{pre}$) or decreased ($\text{pre} > \text{post}$). The same contrasts were used for the controls. To reduce the effect of brain-size variation between individuals on the calculations, global brain-tissue volumes were used to scale the original voxel values (Whitwell et al., 2001). This was performed through the use of the total intra-cranial volume (TIV); it involved the sum of GM, WM and CSF volumes that were calculated during the first-level analysis. A family-wise error (FWE) that used a corrected p-value of 0.05 was applied.

7.4.2 FreeSurfer

The FreeSurfer analysis was based on ROIs that were assigned across areas that were involved in auditory processing, as discovered according to functional changes (see Chapter Six). These included the temporal gyri (superior (STG) and transverse (TTG)), the inferior frontal gyrus (IFG) (Brodmann area 44) and the corpus callosum (CC).

The extracted values for ROI cortical volumes were normalised manually by dividing them by the TIV (Region/TIV*100), which gives a percentage of the region volume proportional to the brain volume, to reduce inter-subject head size variability (Sargolzaei et al., 2015). Next, the extracted ROI values for cortical volume (normalised) and thickness were exported to GraphPad Prism software (version 8 for MAC, GraphPad Software, La Jolla, California, USA, www.graphpad.com) to be used for statistical analysis. Paired t-tests were used to analyse the findings for the trainee group to explore the changes in the cortical thickness and volume values of ROIs before and after the training period. Another paired t test was performed for the controls as explained in section 7.4.1.

7.4.2.1 Correlation of Cortical Thickness with Behavioural Performance

The correlation between psychoacoustic performance data (threshold) and the cortical thickness of the ROIs was tested via GraphPad Prism version 8 for MAC (GraphPad Software, La Jolla, California, USA, www.graphpad.com).

The correlation analysis was based on comparison between the change that occurred in cortical thickness of the ROIs and the change that occurred in psychoacoustic performance over the training period. A further correlation was made to investigate whether pre-training cortical thickness in ROIs could be used to predict a corresponding acoustic learning performance. This was performed by comparing pre-training ROI cortical thicknesses with pre-training psychoacoustic performance across trainees.

7.5 Results

7.5.1 Volume of Whole-brain GM measured by VBM

Paired t-tests were conducted for each group separately (trainees and controls) to evaluate the changes in GM volumes from before to after the training period. The results revealed that no significant GM volume differences were observed in either contrast (pre < post-training or pre > post-training) in either group.

7.5.2 Influence of Pitch discrimination Training on Volume and Cortical Thickness of ROIs as measured by FreeSurfer

Paired t-tests were computed for each group separately (trainees and controls) across the cortical volumes and thicknesses in the ROIs (auditory processing areas) to find out whether any differences could be observed between the data that were taken before and after the auditory training period. The t tests revealed that no significant changes could be detected in cortical volume (Table 7.1) or in cortical thickness; however, there was borderline significance ($p=0.06$) in the change in right STG thickness across the trainees compared with the controls (Table 7.2).

ROIs	Trainees		Controls	
	Pre: M (\pm SD)	Paired t test (df= 25)	Pre: M (\pm SD)	Paired t test (df=7)
	Post: M (\pm SD)		Post: M (\pm SD)	
R STG	0.81 (\pm 0.08) 0.81 (\pm 0.08)	t=1.40, p=0.18	0.88 (\pm 0.07) 0.88 (\pm 0.06)	t=0.82, p=0.44
L STG	0.89 (\pm 0.09) 0.88 (\pm 0.10)	t=0.37, p=0.72	0.08 (\pm 0.01) 0.07 (\pm 0.03)	t=0.54, p=0.61
R TTG	0.07 (\pm 0.01) 0.06 (\pm 0.01)	t=0.32, p=0.75	0.07 (\pm 0.01) 0.07 (\pm 0.01)	t=0.09, p=0.94
L TTG	0.08 (\pm 0.01) 0.08 (\pm 0.01)	t=1.35, p=0.19	0.09 (\pm 0.01) 0.09 (\pm 0.02)	t=0.69, p=0.51
R IFG	0.16 (\pm 0.03) 0.16 (\pm 0.03)	t=0.31, p=0.76	0.15 (\pm 0.03) 0.15 (\pm 0.02)	t=0.39, p=0.71
L IFG	0.19 (\pm 0.04) 0.19 (\pm 0.04)	t=0.28, p=0.78	0.21 (\pm 0.05) 0.21 (\pm 0.06)	t=0.08, p=0.94
Anterior CC	0.06 (\pm 0.01) 0.06 (\pm 0.01)	t=0.79, p=0.44	0.06 (\pm 0.01) 0.06 (\pm 0.01)	t=1.09, p=0.31
Central CC	0.05 (\pm 0.01) 0.05 (\pm 0.01)	t=0.39, p=0.70	0.05 (\pm 0.01) 0.05 (\pm 0.01)	t=0.68, p=0.52
Posterior CC	0.07 (\pm 0.01) 0.07 (\pm 0.01)	t=0.90, p=0.38	0.06 (\pm 0.01) 0.06 (\pm 0.01)	t=1.181, p=0.28

Table 7.1. Comparison of paired t-test results for the ROI cortical volumes (normalised proportion of the region volume in the brain), which were extracted by FreeSurfer analysis, before and after auditory training in trainee and control groups. R: right; L: left; STG: superior temporal gyrus; TTG: transverse temporal gyrus; IFG: inferior frontal gyrus; CC: corpus callosum.

ROIs	Trainees		Controls	
	Pre: M (\pm SD)	Paired t test (df= 25)	Pre: M (\pm SD)	Paired t test (df=7)
R STG	2.95 (\pm 0.09) 2.99 (\pm 0.12)	t=2.27, p=0.06	2.89 (\pm 0.15) 2.90 (\pm 0.16)	t=0.95, p=0.35
L STG	2.91 (\pm 0.17) 2.91 (\pm 0.19)	t=0.48, p=0.64	2.90 (\pm 0.12) 2.91 (\pm 0.12)	t=0.34, p=0.75
R TTG	2.59 (\pm 0.25) 2.58 (\pm 0.24)	t=0.48, p=0.64	2.65 (\pm 0.26) 2.64 (\pm 0.33)	t=0.06, p=0.96
L TTG	2.59 (\pm 0.25) 2.58 (\pm 0.24)	t=0.42, p=0.68	2.44 (\pm 0.25) 2.44 (\pm 0.22)	t=0.06, p=0.96
R IFG	2.70 (\pm 0.15) 2.73 (\pm 0.15)	t=1.81, p=0.08	2.70 (\pm 0.21) 2.69 (\pm 0.15)	t=0.15, p=0.89
L IFG	2.75 (\pm 0.18) 2.74 (\pm 0.18)	t=0.59, p=0.56	2.80 (\pm 0.19) 2.80 (\pm 0.18)	t=0.02, p=0.98

Table 7.2. Comparison of paired t-test results for the ROI cortical thicknesses (mm), which were extracted by FreeSurfer analysis, before and after auditory training in trainee and control groups. R: right; L: left; STG: superior temporal gyrus; TTG: transverse temporal gyrus; IFG: inferior frontal gyrus.

7.5.3 Correlation of Cortical Thickness with Behavioural Performance

Correlation analysis was performed to examine whether changes in cortical thicknesses of the ROIs were correlated with the changes (post-pre) in psychoacoustic performance. Using Pearson's correlation, there was no significant correlation between the change in cortical thickness across ROIs and acoustic threshold (Table 7.3).

Another correlation analysis was carried out to discover whether the cortical thicknesses of the ROIs could be used as indicators of individual performance in psychoacoustic learning. Negative correlations, which meant that a thicker cortex was associated with better performance (lower threshold), were found between bilateral STG thickness and acoustic threshold. Other negative correlations were found between bilateral TTG thickness and acoustic threshold (Figure 7.2, Table 7.4).

ROIs	Pearson r	p value
R STG	0.10	0.63
L STG	0.17	0.40
R TTG	-0.08	0.67
L TTG	-0.24	0.24
R IFG	-0.16	0.43
L IFG	0.19	0.36

Table 7.3. Correlation between the change (post-pre) in psychoacoustic performance and the change in cortical thickness (mm) across ROIs. R: right; L: left; STG: superior temporal gyrus; TTG: transverse temporal gyrus; IFG: inferior frontal gyrus.

ROIs	Pearson r	p value
R STG	-0.56	**0.003
L STG	-0.64	***0.0004
R TTG	-0.70	****0.0001
L TTG	-0.49	*0.01
R IFG	-0.34	0.09
L IFG	-0.37	0.06

Table 7.4. Correlation between pre-training psychoacoustic performance and pre-training cortical thickness (mm) across ROIs. R: right; L: left; STG: superior temporal gyrus; TTG: transverse temporal gyrus; IFG: inferior frontal gyrus. Significant difference at ****p < 0.0001, ***p < 0.001, **p < 0.01, *p < 0.05.

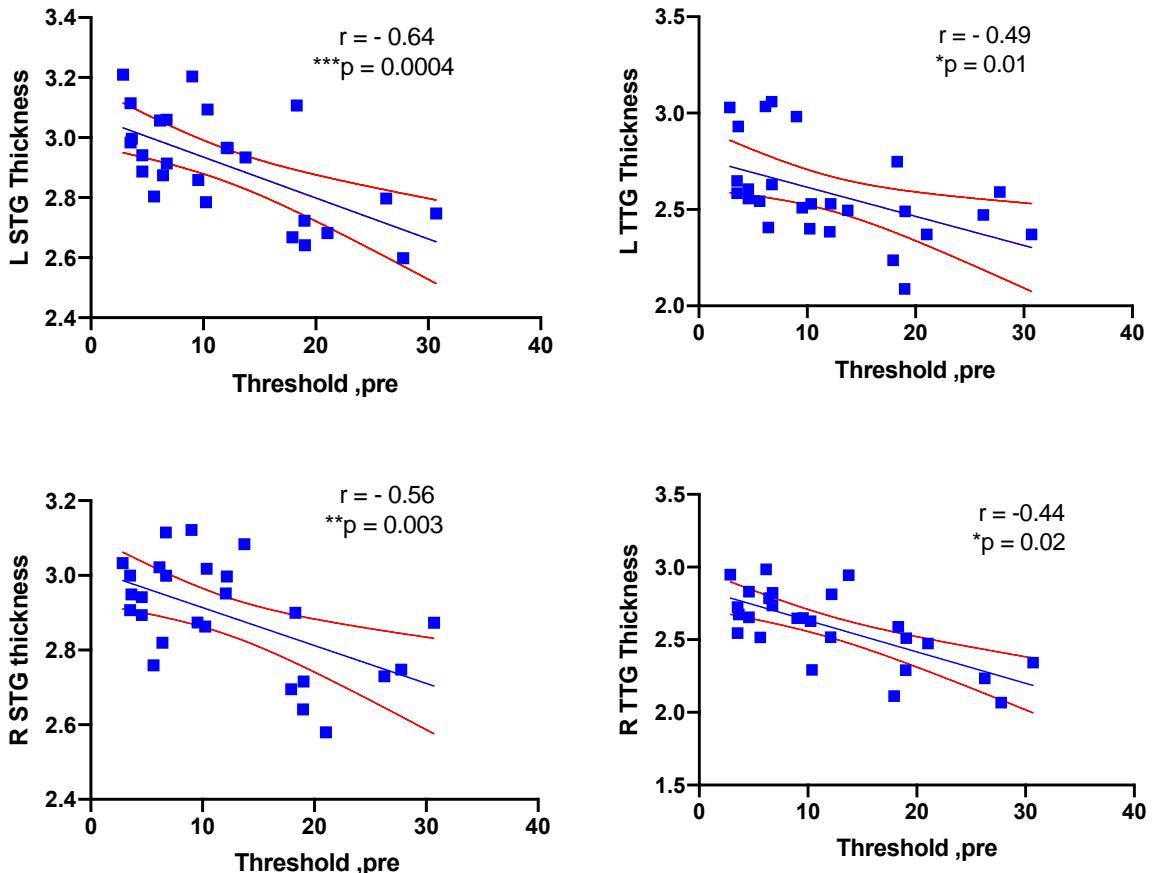


Figure 7.2. Graphs illustrate the correlation between pre-training psychoacoustic performance and pre-training cortical thickness (mm) across the transverse temporal gyrus (TTG) and superior temporal gyrus (STG). R: Right, L: Left. Significant difference at $***p < 0.001$, $**p < 0.01$, $*p < 0.05$.

7.6 Discussion

Since not much is known regarding changes that are caused to the GM within the auditory cortices by short-term auditory training, I decided to investigate structural changes that might be associated with pitch discrimination training. In the work described in this chapter, VBM was used to assess the volume of GM and FreeSurfer was used to measure the cortical volumes and thicknesses within ROIs. As the regions that were studied were the temporal gyri (superior and transverse), the inferior frontal gyrus (Brodmann area 44) and the corpus callosum, which previously had been shown to exhibit changes as a result of short-term auditory training.

The VBM results revealed no significant changes ($p < 0.05$) in GM volume in trainees that could be attributed to short-term pitch discrimination training. In terms of cortical measures, FreeSurfer results revealed no significant changes in cortical thickness or volume within the

ROIs. However, there was a trend towards a significant change ($p=0.06$) in the thickness of the right STG across the trainees compared with the controls. The right STG is known to play a dominant role in pitch discrimination tasks, as revealed by previous studies (Bermudez et al., 2009; Foster & Zatorre, 2010; Alho et al., 2014). Therefore, this result with borderline significance could indicate an early stage of structural change, which is known to develop over longer periods than functional changes (Lampit et al., 2015).

The reason for the results of the current study could be the short duration of training, and this is consistent with findings of previous studies (Schneider et al., 2005; Bermudez et al., 2009; Foster & Zatorre, 2010) that correlated pitch perception among musicians with structural neural changes. The results of these previous studies showed that greater GM concentration in the right Heschl's gyrus and greater cortical thickness in the superior temporal cortex and inferior frontal gyrus could be distinguished in musicians compared with non-musicians. Another study of similar design found that long-term music practice resulted in increased GM density and cortical volume in areas that are associated with auditory-motor connection networks: the right postcentral gyrus and the left inferior parietal lobe. Change was also discerned in the shape of the right hippocampus (Algamdi, 2012). These studies were performed among highly trained musicians who had been practising their skill with musical instruments for many years.

No correlation was found between the changes of cortical thickness in ROIs and the behavioural performance change. However, a significant correlation was found in pre-training data, as the cortical thickness of bilateral STG and TTG, which were recorded before the training took place, were correlated negatively with behavioural performance. This negative correlation reflects the association of a thicker cortex with better psychoacoustic performance. This correlation can be used as an indicator of behavioural performance gains and structural change at the end of training. This result was in parallel with that of a previous study, which found that the left fusiform cortex thickness before training was negatively correlated with the face discrimination learning index (Bi et al., 2014). Moreover, Frank et al. (2016) showed that individuals who had a thicker visual cortex (motion-sensitive area) before training learned more quickly than those with a thinner visual cortex. Therefore, the findings suggest that the effect of behavioural learning on subjects can be predicted based on cortical thickness.

7.7 Conclusion

In the work described in this chapter, GM volume and cortical measures were investigated among listeners who were trained in pitch discrimination for a short period, and the results were compared with those obtained from controls who had not undertaken similar training. The VBM result that was obtained in this study revealed no significant changes in the GM volume within auditory regions. Use of FreeSurfer to investigate the cortical thickness showed a borderline of significance in the thickness of the right STG, which can be an indicator of an early stage of structural change. No significant correlation was found between the changes of cortical thickness in ROIs and the behavioural performance change. However, the pre-training psychoacoustic performance and cortical thickness were correlated in some ROIs (bilateral STG and TTG) and this correlation could be used as an indicator of behavioural performance gains and structural change at the end of training.

As this chapter investigated the plasticity of GM with pitch discrimination training, the next chapter explores the changes in WM tract.

Chapter 8. Investigation of the Effect of Pitch discrimination Training on WM tract

8.1 Aim and Objectives

The aim of the study described in this chapter was to use MR diffusion tensor imaging (DTI) to investigate the changes in white matter (WM) tract that were caused by auditory training. Therefore, the work that is explained in this chapter was designed to provide additional insights into brain structural changes through the exploration of the differences that might be caused by short-term auditory training between a group of trainees and a group of controls with respect to (1) white-matter integrity, as measured by fractional anisotropy (FA), and (2) mean diffusivity (MD).

8.2 Introduction

The diffusivity of water molecules can be measured in vivo through the non-invasive MR method of DTI. This form of imaging supplies several quantitative measures, including the three major diffusivities (the eigenvalues of the diffusion tensors $\lambda_1, \lambda_2, \lambda_3$), the resulting MD and the FA. Therefore, it is understood that DTI measurements indirectly reflect alterations in the microstructure of WM (Basser et al., 1994a). Such measurements indicate the level of integral macroscopic cohesion of WM fibre tracts (Pierpaoli and Basser, 1996) (more details are provided in Chapter Three).

Since its discovery, DTI has become the preferred approach for the examination of the microstructural characteristics of WM and biological traits (e.g. axonal dimensions, density, cohesiveness and myelination level). These microstructural characteristics affect diffusivity because they control the movement of the water molecules (Moseley et al., 1990; Basser et al., 1994a). Detection of disease-related brain alterations based on utilisation of diffusion images in voxel-wise statistical analyses is an increasingly common research approach. DTI offers advantages over other methods of data collection and is therefore the routine protocol that is adopted by numerous clinical centres. Multiple sclerosis (MS) and other neurodegenerative conditions (Filippi et al., 2001), as well as stroke, brain trauma and psychiatric disorders (Schaefer et al., 2000; Sundgren et al., 2004) can be distinguished successfully via use of DTI. Moreover, DTI may also provide insights into WM changes that are related to ageing and pathological conditions that are associated with the auditory system, including hearing impairment (Husain et al., 2011) and tinnitus (Cripa et al., 2010).

The DTI technique is not limited to clinical uses; it has also been used to study learning-related changes in diffusivity (Fields, 2015). Many structural brain-imaging studies have shown that musical training induces enhancement in brain plasticity. For example, it has been found that, compared with non-musicians, professional musicians display a larger CC, which is a dense bundle of WM fibres that is involved in communication between the two brain hemispheres and connects between motor regions of the brain (Schlaug et al., 1995).

Abdul-Kareem et al. (2011) performed a study across different cohorts of musicians in which they used diffusion and morphometric imaging techniques to investigate brain regions that were thought to be essential to enable advanced musical performance, such as Broca's area, the CC and the cerebellum. Their results showed that musicians had increased volumes of WM in the right cerebellar hemisphere. Further related investigation found that increased levels of FA, which resulted from music training, were concentrated in the auditory-motor projection fibres and in the CC (Bengtsson et al., 2005; Han et al., 2009; Steele et al., 2013). Recently, Engel et al. (2014) and Moore et al. (2017) investigated the microstructural neuroplasticity effects of musical- and motor-learning tasks through use of DTI. Engel et al. (2014) reported that learning of piano melodies was associated with higher FA values that were observed in the bilateral corticospinal tracts and the right superior longitudinal fasciculus. Their finding was consistent with those of Moore et al. (2017), who found that FA increased significantly in the arcuate fasciculus, with a trend towards reduction in radial diffusivity (RD) and elevation in axial diffusivity (AD), across the music-cued motor trainees. These studies indicate that training can induce plastic alteration of WM tracts and that these alterations are regionally specific.

The length of the training period is an important factor that greatly affects structural plasticity. Structural neural adaptation is the expected outcome of the permanent retention of newly attained cognitive skills over a lengthy interval of time of weeks or months (Scholz et al., 2009; Blumenfeld-Katzir et al., 2011). In contrast, Sagi et al. (2012) argue that short-term training can induce structural changes. Their results showed significant microstructural changes in the hippocampus and parahippocampus that could be detected by DTI indices after only two hours of training on spatial learning and memory tasks. Another supportive study by Hofstetter et al. (2013) suggested that short-term spatial learning could cause WM plasticity in the human brain. Their results revealed that two hours of training on a computer car-racing game could change diffusion indices in the fornix and hippocampus areas. Generally, however, knowledge is

limited regarding the impact of short-term auditory learning (minutes or hours) on the extent of such alterations.

This present study considers the importance of training periods in auditory training, to investigate whether short training terms can induce microstructural changes in WM. I hypothesised that the trainee group would present small changes in the WM tracts, which link areas of the brain that are involved in auditory processing and attention. Based on several preceding neuroimaging studies (Giacosa et al., 2016; Moore et al., 2017), my hypothesis was that positive learning outcomes would involve increases in levels of FA and reductions in diffusivity measures (MD, RD, AD) in the auditory-region pathways and the CC in trainees. We expected no change in the control group.

8.3 Method

Sequences of diffusion tensor images were collected to evaluate the auditory training effect on WM structures. For this study I used a bipolar DTI sequence, which involved two acquisitions of the phase-encode with opposing polarities. This was required for image distortion correction before DTI analysis (Embleton et al., 2010). The DTI sequences involved 64 diffusion directions and two b values (0 and 1000); other acquisition parameters are described in the general methodology chapter (Chapter Four). I conducted four diffusion-imaging scans: before, during (two scans) and after auditory training, in order to investigate the structural changes that may have resulted from the training.

8.3.1 Participants

The study involved 26 trainee and 15 control participants (the controls undertook two DTI scans that were separated by a three-day gap). Participants' demographics are described in the general methodology section (Chapter Four, section 4.6).

8.3.2 Diffusion Imaging Analysis

An ideal image analysis is required to provide reliable data that reflect water diffusivity changes caused by auditory training. There are three basic stages of diffusion analysis: artefact correction, model fitting, and statistical tests. Correction of artefacts is a crucial step in image analysis to provide reliable imaging data that reflect intensity changes with diffusion. The next stage requires the fitting of a diffusion tensor model to provide information regarding the directions of bundles of WM fibres as well as connectivity in the brain. Finally, the statistical analysis is performed at voxel level to evaluate changes in diffusivity measures. It is conducted across the whole brain as well as in specific regions.

8.3.2.1 Artefact Correction and Model fitting (Top-up, Eddy and DTIFIT)

DTI imaging data were analysed using the FMRIB software library (FSL, version 5.0.9) following a standard procedure (Smith et al., 2006) that included top-up and eddy current corrections, brain data extraction and use of the DTIFIT tool. The first pre-processing step was the correction of the diffusion data to allow for image distortions, which are commonly associated with echo planar imaging (EPI). The image distortions could be caused by susceptibility (that results from the subject's head) and eddy currents (that are caused by the fast switching of diffusion gradients). This geometric distortion was corrected by use of top-up and eddy current correction (FDT program 2.0), which depended on the recruitment of two images with opposing phase-encoding directions. The resulting pairs of images were merged into single corrected images according to the method proposed by Andersson et al. (2003) as applied in FSL (Smith et al., 2004). The next step was the use of the program BET 2.1 to extract brain data by removing data for non-brain tissue and skull (Jenkinson et al., 2005). Then DTIFIT was used to fit a diffusion tensor, which is a mathematical model assigned for each diffusion direction. This model deals with each voxel separately to calculate many important physical attributes, such as maps of FA, MD, AD and RD, which can be used for diffusion-based brain analysis.

8.3.2.2 Tract-Based Spatial Statistics (TBSS)

The pre-processed data were statistically analysed at voxel level by the use of the TBSS part of FSL (Smith et al., 2006). Non-linear registration was used to align all the FA data of the subjects to the target template, which was the FMRIB58_FA standard space image, through use of FMRIB's non-linear image registration tool (FNIRT). Then, the target image was linearly aligned into a $1 \times 1 \times 1$ mm Montreal Neurological Institute standard space (MNI 152). The aligned FA data for all subjects were merged into one compressed 4D image file, which was used to extract mean FAs (FA maps). Then the FA maps were thinned to produce a skeletonised mean FA image, which showed all FA tract centres that were commonly found across the group. Finally, the non-FA voxels were removed from the mean-FA skeleton by use of a 0.2 threshold value in order to include the major tracts only.

A similar technique was implemented for the other diffusion measures, namely RD, AD and MD. For each diffusivity measure, nonlinear registration to the common space and the skeletonisation procedure were applied based on the steps that had been accomplished for FA. The resulting diffusion measure map for every subject was then aligned onto the mean FA skeleton. The resulting data were used for statistical testing across subjects at voxel level.

8.3.2.3 Statistical Analysis

To evaluate the effects of pitch discrimination training on the WM tracts of the brain, statistical analysis was performed at a global level (whole brain) and at a specific level (ROIs).

8.3.2.4 Whole Brain Voxel-wise Analysis

To identify diffusion changes in the brain that were related to auditory training, further statistical analyses were required. The skeletonised data that resulted from use of TBSS were used for statistical testing across subjects at voxel level. Regression voxel-based analysis was used to measure gradual diffusion changes in each subject during the training period (Ostertagová, 2012). This technique is sensitive to detection of diffusion changes as it computes voxel-by-voxel correlation over time.

Regression voxel-based analysis has been used previously in research that investigated the relationship between defined factors and brain diffusivity metrics. For example, Hsu et al. (2010) used polynomial regression modelling to explore age-related changes in WM diffusion metrics, and the same technique was used to study microstructural alterations in the CC that were related to age (Pietrasik et al., 2020). Another study used regression analysis to measure pre-lesional DTI changes in MS across multiple time points, and the results indicated that the regression model provided an informative view of the pathological changes that resulted in MS lesions (Ontaneda et al., 2014).

Therefore, in the present study, regression analysis was used to detect gradual changes in diffusion that were caused by auditory training. The regression analysis was performed via a customised MATLAB (R2016b) script for all skeletonised diffusion variables (FA, MD, AD and RD). The MATLAB script worked by reading the diffusion imaging data that had been collected over four scans and then fitting these data into a regression model (Figure 8.1). The resulting regression model then represented the correlation between scans across each voxel set. The regression analysis output data were smoothed using a 5-mm kernel to increase the signal-to-noise ratio and then they were used for statistical analysis.

The standard FSL randomisation tool was used with the threshold-free cluster enhancement (TFCE) option. This has been implemented in most related studies (Nichols and Holmes, 2002; Smith and Nichols, 2009). Randomisation was performed across 5000 permutations and one sample t-test was used to investigate the diffusion metric differences during auditory training. Finally, the p-value was set to 0.05 with correction for multiple comparisons via FWE, to show a statistically significant difference in the resulting diffusion data.

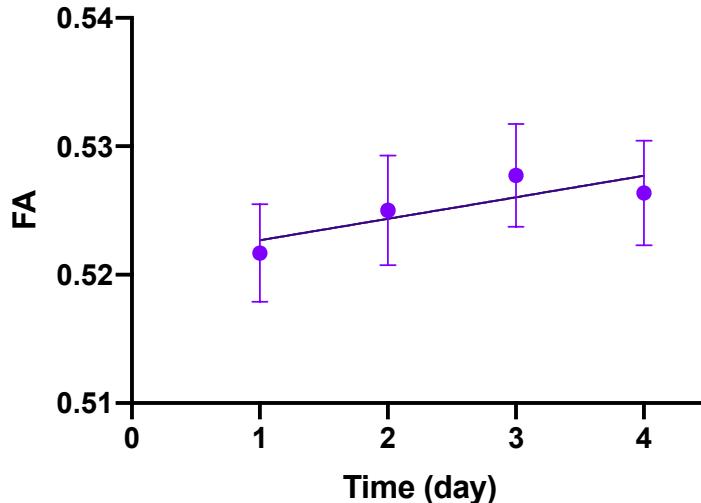


Figure 8.1. Illustration of the use of regression analysis to measure the gradual change in FA (across the whole brain) that was caused by acoustic training. Error bars represent the standard error of the mean.

8.3.2.5 Regions of Interest Analysis

ROI analysis was performed to investigate the effect of pitch discrimination training on specific WM tracts. Exploration of these ROIs involved the production of cluster and anatomical masks. Detailed methodology is explained in the next section.

ROIs cluster masks

Clusters that were produced by regression analysis of four diffusion scans of the whole brain were used to produce a ROI mask. These significant clusters were right lateralised and located in the superior longitudinal fasciculi (SLF), the corona radiata (CR) and the corticospinal tracts (CST).

Pre- and post-training skeletonised data (TBSS results for all DTI scalar metrics, which involved the FA, MD, RD and AD) were compared across the ROIs cluster masks through use of a GLM in FSL. Pairwise tests were used to compare the baseline values (pre-training) and follow-up values (post-training) for each group (trainees and controls) separately. Two contrasts were used (post> pre and pre> post). Permutation-based statistics were conducted through 5000 permutations using a FSL randomisation tool with the TFCE option (Smith and Nichols, 2009). Correction for multiple comparisons was made by setting the p-value to the significant threshold level (0.05). To confirm the validity of the cluster mask results, the anatomical mask analysis was used.

Anatomical masks for ROIs

Most previous investigations have identified the ROI mask based on anatomical region (Lou et al., 2009; Steele et al., 2013; Engel et al., 2014; Moore et al., 2017). These previous studies showed that the WM tracts that were involved in pitch discrimination tasks were: the SLF, right and left, the CR, right and left, the CC (genu, body and splenium), and the CST, right and left. The anatomical masks for these tracts were extracted from the Johns Hopkins University (JHU) ICBM 1-mm white-matter label atlas (Mori et al., 2006), except for the CST mask, which was created using the Juelich histological 1-mm atlas (Eickhoff et al., 2006), as it was unavailable in the JHU atlas. All ROIs anatomical masks were binarised and then skeletonised (multiplying by the mean FA skeleton mask using FSL commands). Masks were generated using the atlas toolbox of FSL (<https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLeyes>).

After this, statistical analysis was performed using the anatomical masks as ROIs. This procedure involved the multiplication of the anatomical masks by skeletonised data (TBSS results) across all DTI scalar metrics (FA, MD, RD and AD). The resulting numerical data were used in paired t-tests to compare the baseline values (pre-training) with the follow-up values (post-training) for each group (trainees and controls) separately.

8.3.2.6 Correlation with Behavioural Performance

The correlation between psychoacoustic performance data (threshold) and DTI scalar metrics were tested via GraphPad Prism version 8 for MAC (GraphPad Software, La Jolla, California, USA, www.graphpad.com).

The correlation analysis was based on comparison between the change (post-pre) in diffusion scalar metrics and the change (post-pre) in psychoacoustic performance. A further correlation was made to investigate whether pre-training diffusion measurements in ROIs could be used to predict a corresponding acoustic learning performance. This was performed by comparing pre-training diffusion scalar metrics with pre-training psychoacoustic performance across trainees.

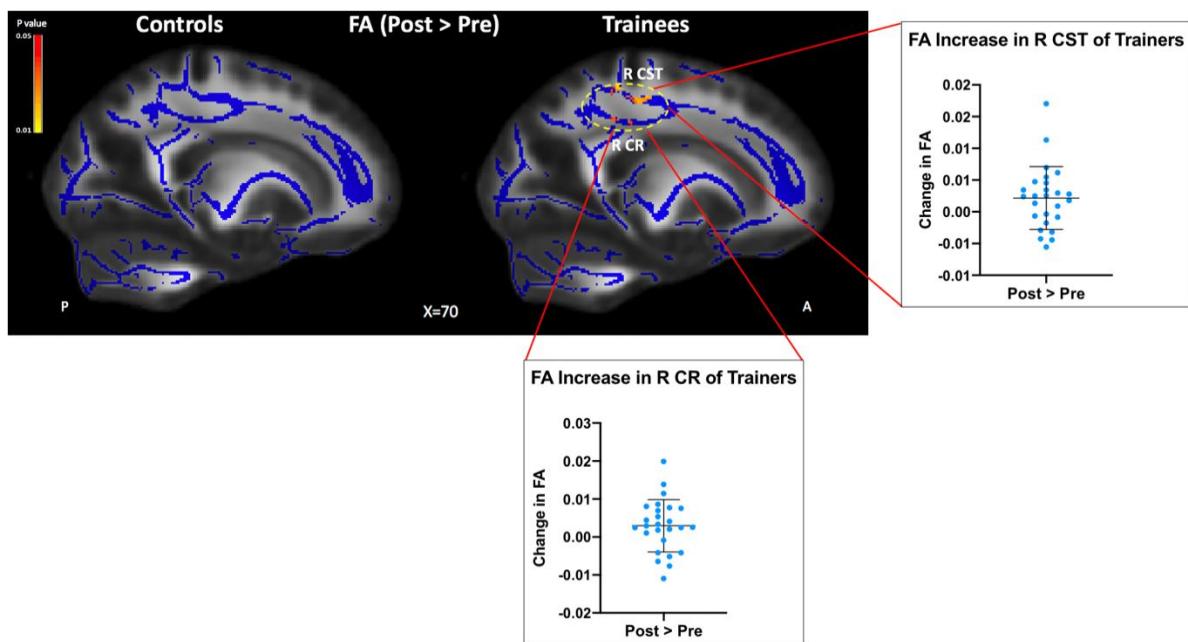
8.4 Results

8.4.1 The Effect of Pitch discrimination Training on WM Tracts

8.4.1.1 ROI Analysis Based on Cluster Masks

To discover the impact of auditory training on the WM tracts, paired t-tests were conducted across the cluster masks. The test revealed that, in the trainee group, there was a significant FA increase ($\text{post} > \text{pre}$) in the right CST, right posterior CR and right SLF after the training (Figures 8.2 and 8.3). A significant reduction in diffusivity (both RD and MD maps) ($\text{pre} > \text{post}$) was observed within the right anterior CR (Figure 8.4). All significant clusters in trainees are reported in Table 8.1. There were no significant findings in the AD map.

Another paired t-test was performed for the control group to compare diffusion scalar metrics that were taken before and after the training period. The t-test revealed no significant change in any diffusion scalar metric for either contrast ($\text{pre} > \text{post}$ and $\text{post} > \text{pre}$) (Figures 8.2, 8.3 and 8.4).



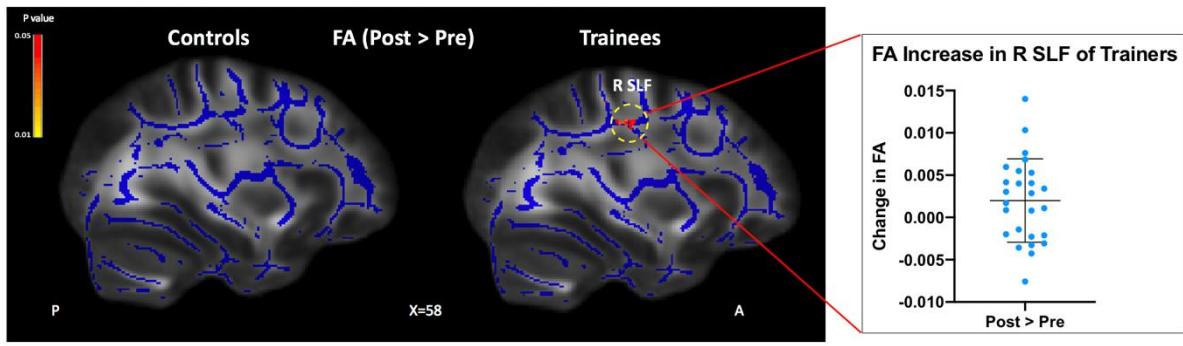


Figure 8.3. Significant increase in FA (circled clusters) across the right SLF in trainees after auditory training. No FA change was seen in controls. The mean FA skeleton is shown in blue. Graphs on the right represent the mean and SD of the FA increase in the right SLF across trainees. SLF: superior longitudinal fasciculi; R: right; A: anterior; P: posterior

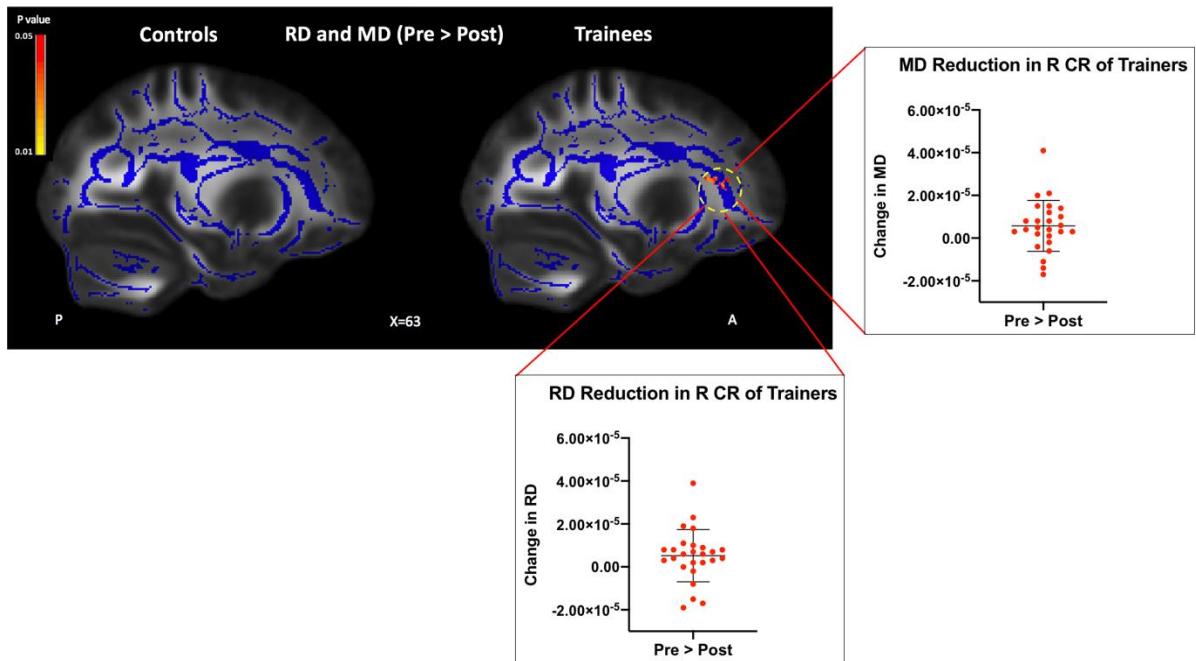


Figure 8.4. Diffusion map (MD and RD) illustrates a significant decrease in diffusivity (circled clusters) across the right posterior CR in trainees only, whereas no diffusion change was observed in controls. The mean FA skeleton is in blue. Graphs on the right represent mean and SD of MD and RD reductions in the right posterior CR across trainees. CR: corona radiata; R: right; A: anterior; P: posterior.

Cluster Size (voxels)	p-value	MNI space coordination (mm)		
<u>FA</u>				
213	0.02	20	-27	49
10	0.03	20	-37	39
16	0.05	32	-20	39
		R Corticospinal Tract		
		R posterior Corona Radiata		
		R Superior Longitudinal Fasciculus		
<u>MD</u>				
28	0.05	27	30	10
		R Anterior Corona Radiata		
<u>RD</u>				
6	0.03	27	30	10
		R Anterior Corona Radiata		

Table 8.1. Cluster sizes, peak coordination and significant p value (FWE-corrected) of FA increase and MD and RD decrease after pitch discrimination training across trainees only.

8.4.1.2 ROI Analysis Based on Anatomical Masks

To confirm the validity of the cluster-mask results, the anatomical-mask analysis was used in paired t-tests to evaluate the impact of auditory training. For trainees, the t-test result revealed that there was a significant FA increase in the right CR and right CST after the training (Table 8.2). The test result also indicated a significant reduction in diffusivity within the right CR, whereas there were no similar significant findings across the SLF and CC mask regions (Tables 8.3 and 8.4). The changes that were detected in the CR and right CST matched those that were found in the cluster-mask analysis. For the control group, no significant changes in FA or other diffusion metrics were found by application of paired t-tests (results tables are provided in Appendix A, section 2).

ROI	Pre-training Mean (SD)	Post-training Mean (SD)	Trainees Paired t test (df= 25)
<u>FA (Post > Pre)</u>			
R CR	0.52 (0.03)	0.53 (0.03)	t=2.20, p=*.03
L CR	0.51 (0.03)	0.51 (0.03)	t=1.17, p=0.25
R CST	0.54 (0.01)	0.55 (0.01)	t=2.23, p=*.03
L CST	0.55 (0.01)	0.55 (0.01)	t=1.41, p=0.17
R SLF	0.54 (0.02)	0.55 (0.02)	t=2.01, p=0.06
L SLF	0.54 (0.02)	0.54 (0.02)	t=0.65, p=0.52
BCC	0.72 (0.02)	0.72 (0.02)	t=1.11, p=0.28
GCC	0.76 (0.01)	0.76 (0.01)	t=1.03, p=0.31
SCC	0.80 (0.02)	0.80 (0.02)	t=0.65, p=0.52

Table 8.2. Comparison of FA measurements for trainees before and after auditory training across anatomical masks of ROIs. Significant FA increases were found across right hemispheres only. *Significant difference at $p<0.05$. CST: corticospinal tract; CR: anterior corona radiata; SLF: superior longitudinal fasciculi; BCC: body of corpus callosum; GCC: genu of corpus callosum; SCC: splenium of corpus callosum; R: right; L: left.

ROI	Pre-training Mean (SD)	Post-training Mean (SD)	Trainees Paired t test (df= 25)
<u>MD (Pre>Post)</u>			
R CR	0.79 (0.03)	0.79 (0.03)	t=2.46, p=*.02
L CR	0.78 (0.03)	0.78 (0.03)	t=1.61, p=0.12
R CST	0.73 (0.02)	0.73 (0.02)	t=1.83, p=0.08
L CST	0.73 (0.01)	0.72 (0.02)	t=1.30, p=0.21
R SLF	0.73 (0.02)	0.73 (0.02)	t=0.49, p=0.63
L SLF	0.72 (0.02)	0.72 (0.02)	t=0.04, p=0.97
BCC	0.82 (0.03)	0.81 (0.03)	t=1.72, p=0.10
GCC	0.77 (0.03)	0.77 (0.03)	t=1.00, p=0.33
SCC	0.74 (0.02)	0.74 (0.02)	t=1.14, p=0.27

Table 8.3. Comparison of MD measurements for trainees before and after the auditory training across anatomical masks of ROIs. The significant diffusivity change was found across the right hemisphere only. MD Mean (in 10^{-3}) and SD (in 10^{-3}) mm 2 /s. *Significant difference at $p<0.05$ (FWE corrected).

ROI	Pre-training Mean (SD)	Post-training Mean (SD)	Trainees Paired t test (df= 25)
<u>RD (Pre>Post)</u>			
R CR	0.54 (0.02)	0.53 (0.03)	t=2.20, p=*.04
L CR	0.54 (0.03)	0.54 (0.03)	t=1.61, p=0.12
R CST	0.48 (0.02)	0.47 (0.02)	t=2.04, p=*.05
L CST	0.47 (0.01)	0.47 (0.02)	t=1.50, p=0.15
R SLF	0.48 (0.02)	0.48 (0.02)	t=0.51, p=0.61
L SLF	0.48 (0.02)	0.48 (0.02)	t=0.22, p=0.83
BCC	0.39 (0.03)	0.39 (0.04)	t=1.66, p=0.11
GCC	0.33 (0.02)	0.33 (0.03)	t=0.91, p=0.37
SCC	0.28 (0.02)	0.28 (0.03)	t=0.93, p=0.36
<u>AD (Pre>Post)</u>			
R CR	1.30 (0.05)	1.29 (0.05)	t=2.40, p=*.03
L CR	1.26 (0.05)	1.26 (0.05)	t=1.03, p=0.31
R CST	1.22 (0.03)	1.22 (0.03)	t=1.26, p=0.22
L CST	1.22 (0.02)	1.21 (0.03)	t=0.95, p=0.35
R SLF	1.23 (0.05)	1.21(0.04)	t=0.38, p=0.71
L SLF	1.21 (0.05)	1.22 (0.04)	t=0.32, p=0.75
BCC	1.67 (0.05)	1.67 (0.05)	t=1.27, p=0.22
GCC	1.65 (0.06)	1.64 (0.06)	t=0.93, p=0.36
SCC	1.65 (0.05)	1.65 (0.05)	t=1.21, p=0.24

Table 8.4. Comparison of diffusion scalar matrices (RD and AD) for trainees before and after the auditory training across anatomical masks of ROIs. The significant diffusivity change was found across the right hemisphere only. MD Mean (in 10^3) and SD (in 10^{-3}) mm 2 /s. *Significant difference at $p<0.05$ (FWE corrected).

8.4.1.3 Correlation with Psychoacoustic Performance

Correlation between the change in psychoacoustic performance and the change in diffusion measurements

Correlation analysis was performed to examine whether changes in diffusion scalar metrics in ROIs were correlated with the changes in psychoacoustic performance. Using Pearson's correlation, no significant correlation was found between the change in DTI metrics and the change in psychoacoustic performance in trainees (see the results table in Appendix A, section 3).

Correlation between pre-training psychoacoustic performance and pre-training diffusion measurements

Pearson's correlation analysis was carried out to find out whether the diffusion scalar metrics in ROIs could be used as indicators of individual performance in the auditory learning. Positive correlations were found between the pre-training RD value in the right SLF, $r(26) = 0.47$, $p < 0.02$, the CC body $r(26) = 0.41$, $p < 0.04$, and the pre-training acoustic threshold (Figure 8.5). A significant negative correlation was found between the pre-training FA value in the right SLF and the pre-training acoustic threshold, $r(26) = -0.49$, $p < 0.01$, (Figure 8.5). However, no significant correlation was seen between acoustic threshold and the other ROIs, which were the left SLF, the CR (bilateral), the CST (bilateral), and the CC genu and splenium (Table 8.5).

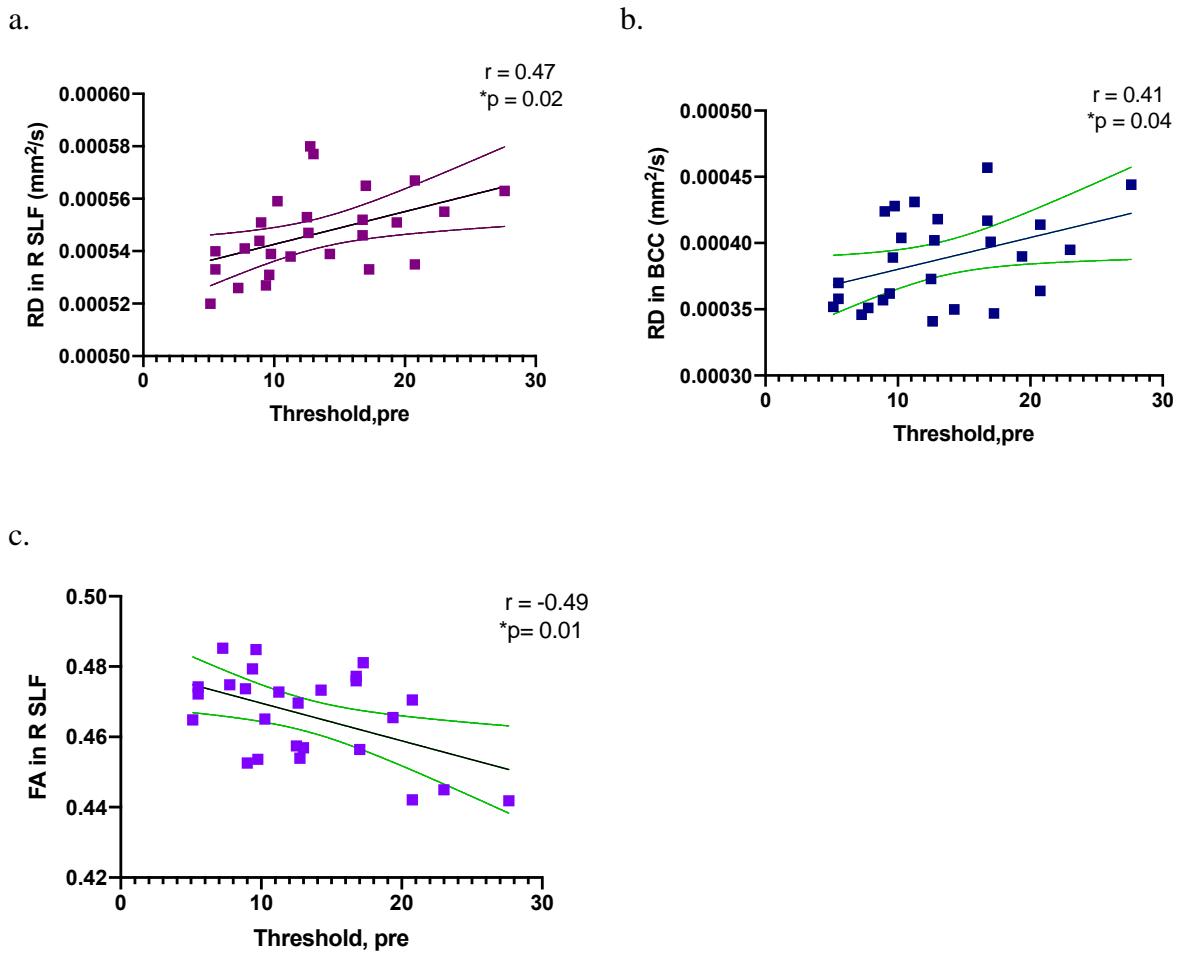


Figure 8.5. Correlation between pre-training psychoacoustic performance and pre-training diffusion measures. (a) a positive correlation between pre-training RD diffusivity and the right SLF. (b) a positive correlation between pre-training RD diffusivity and the body of CC. (c) a negative correlation between pre-training FA and the right SLF. *Significant difference at $p < 0.05$.

ROI	Pearson r	p value						
BCC	-0.37	0.06	0.38	0.06	0.41	*0.04	0.18	0.37
GCC	-0.33	0.09	0.21	0.30	0.36	0.07	-0.02	0.93
SCC	-0.29	0.15	0.38	0.06	0.34	0.09	0.13	0.54
R SLF	-0.49	*0.02	0.30	0.14	0.47	*0.02	0.17	0.41
L SLF	FA	-0.14	0.48	MD	0.35	0.09	RD	0.33
R CR	-0.30	0.14	0.32	0.11	0.38	0.06	AD	0.18
L CR	-0.35	0.08	0.35	0.08	0.39	0.07	0.08	0.72
R CST	-0.32	0.14	0.23	0.26	0.36	0.07	0.01	0.98
L CST	-0.30	0.14	0.24	0.25	0.30	0.14	0.02	0.91

Table 8.5. Correlation between pre-training psychoacoustic performance and pre-training diffusion measures. *Significant difference at $p < 0.05$.

8.5 Discussion

This part of the study was designed to investigate through the use of diffusion imaging whether short-term pitch discrimination training could influence brain connectivity. TBSS results of whole brain analysis (clusters) and ROIs analysis (anatomical masks) revealed that auditory training caused significant changes that presented as clusters located in the right hemisphere only. They occupied a small region in the CR and CST with FA elevation. The RD and MD also showed reduction across a small part of the right CR.

The CST is a projection of fibres that connect the cerebral cortex with the brainstem. They descend through the CR and internal capsule (Crossman & Neary, 2018). The CR is a projection of fibres that make a connection point between the CC and the cerebral cortex via radiating WM tracts (Catani et al., 2002; Stave et al., 2017).

The FA increases as WM matures (Eluvathingal et al., 2007) but diminishes with normal ageing (Barrick et al., 2010) and in the case of neurodegenerative (Sundgren et al., 2004) and demyelinating conditions (Filippi et al., 2001). For these reasons, FA is thought to be a WM integrity marker (Alexander et al., 2007b; Fields, 2008).

Moreover, the FA value indicates the directionality and cohesiveness of fibre tracts (Basser and Pierpaoli, 1996). Molecular displacement is more pronounced in a parallel than in a perpendicular direction to the axonal orientation, because membranes and myelin sheaths that have a parallel orientation to the axonal long axis limit most of the diffusion. Therefore, diffusion in a voxel is considered to be directional (anisotropic) if the axons in that voxel display strong alignment (Figure 8.6). Hence, trainees who exhibit higher FA in the CST and CR pathways may have axons that are orientated in parallel in this area.

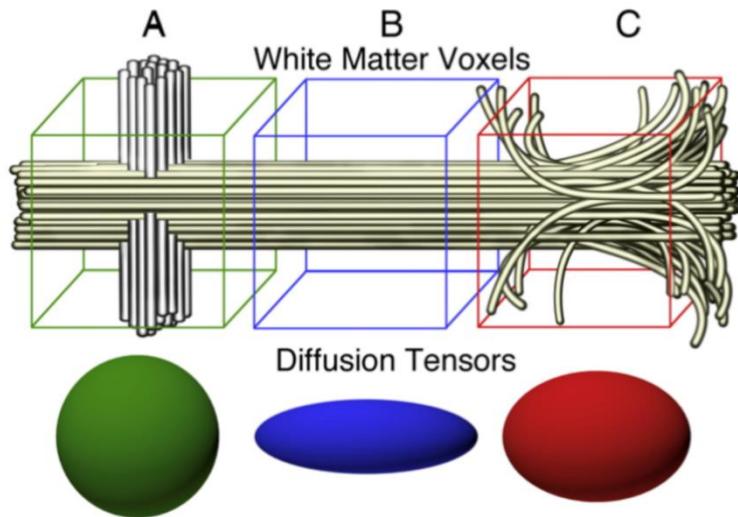


Figure 8.6. Environmental contributions to the anisotropy of the tract. Voxel A comprises the tract of interest (yellow) as well as the cross-tract (grey) leading to low anisotropic measurements at this point. Voxel B comprises only a tract of interest and displays high anisotropy. Inside voxel C, axons of adjacent grey matter, which joins the tract and some axons, split off towards grey matter targets. The result is a decrease in anisotropic measurements at this point (Johnson et al., 2013).

Nevertheless, definition of tissue alterations may require more than just FA measurement. For instance, a reduction in radial (perpendicular) diffusivity may elevate FA values, so the mechanism of diffusion tensor modifications may be derived from MD measurements. The results of the present study show that trainees exhibit a trend towards lower MD values in the CR tract than controls. Greater reduction of diffusion by surrounding cellular constituents, especially the axonal membranes and myelin sheaths, may be indicated by lower MD values (Beaulieu, 2002). In the case of the participant pitch discrimination trainees, this may have translated into development of more numerous axons and/or greater thickness of the myelin sheath, as reflected by the presence of more membrane and more myelin, respectively. Evidence that supports the latter premise may be provided by my observations that the CR and CST pathways displayed increases in volume. Thus, higher levels of WM cohesiveness, fibre density and myelin thickness in the CR pathways of the trainee group may be shown by higher FA values alongside lower MD values.

A range of research studies has revealed that the plasticity that is observed in WM tracts is regionally specific. For example, in one study, musicians who had absolute pitch, which is the ability to identify the pitch of a note without a reference, were found to have a leftward hemisphere asymmetry in the SLF, which was due to the tract that connected the temporal gyri to the parietal lobe (Oechslin et al., 2010). In contrast with this result, Dohn et al. (2015)

discovered a rightward asymmetry in the ILF, the uncinate fasciculus (UF) and the inferior fronto-occipital fasciculus (IFOF) across musicians who exhibited absolute pitch. Similarly, in the current study, the significant changes were right lateralised across the subjects who were trained in the pitch discrimination task.

There are two explanations for right lateralisation of the results. Firstly, there is functional asymmetry, as the right hemisphere is known to be superior in pitch perception (Zatorre, 1988; Bianchi et al., 2017). Secondly, the anatomical and topological differences of the right AC result in improved integration and communication with other brain regions, as revealed by Mišić et al. (2018).

The absence of change in auditory areas such as the STG could be due to the duration of training. The auditory training that was applied in this study is considered short (175 min) and therefore it may not have been sufficient to alter the microstructure of the WM in the STG and the middle temporal gyrus. However, the changes that were produced in the CST and CR tracts were possibly due to the complexity of the pitch discrimination task. This task not only involved auditory processing but also other cognitive processing, such as attention, working memory and somatosensory processing. These results are in parallel with those of previous research, in which microstructural changes in the hippocampus and parahippocampus have been reported after a short period of training (2 hours) in spatial- and memory-learning tasks (Sagi et al., 2012; Hofstetter et al., 2013). Therefore, the change in CR that was detected in this study may have been due to the attention that was induced by the pitch discrimination training. For example, Stave et al. (2017) found that an alteration of microstructural WM in the CR was correlated with attention-based tasks. Another study found that increased myelination was discovered within the CR and the body of the CC after the undertaking of auditory working-memory tasks (Chung et al., 2018).

In terms of correlation, none was found between the changes that were observed in the WM and those that were observed in behavioural performances. The lack of correlation may be associated not with the level of skill attained but with training specificity, which implies that connections among various perceptions may be promoted by pitch discrimination training. This may aid rehabilitation in cases in which, for example, the outcome aim is improvement of frontal and parietal-temporal connections (Moore et al., 2017). A significant correlation was found in pre-training data, as the FA and RD measures in the right SLF that were recorded before training were correlated with psychoacoustic performance. The right SLF showed

structural changes after the training. Thus, this correlation could be used as an indicator of behavioural performance gains and structural change at the end of training (this result matched with the previous finding in Chapter Seven, section 7.5.3). According to Frank et al. (2016), anatomical variations across subjects could possibly be used to predict learning outcomes, as their results showed that individuals who had a thicker visual cortex (motion-sensitive area) before training was undertaken learned more quickly than did those with thinner visual cortices.

8.6 Technical Limitations of The Study Analysis

TBSS is an established methodology, which is widely used for voxel-based analysis of whole-brain WM diffusion measures. However, the major limitation of TBSS is that it depends on skeleton projection, which impedes the accuracy of the registration algorithm.

Computation of a WM ‘skeleton’ is based on morphological thinning of the mean FA between subjects, followed by projection of every FA voxel to the closest site on the skeleton (Schwarz et al., 2014). This method therefore shows reduced sensitivity in detection of true group differences (Bergamino et al., 2017). Despite its shortcomings, TBSS presents a number of advantages (e.g. reduced user dependence, diminished reliance on data smoothing due to its basis in skeletonisation, attenuation of residual image misalignment, and improvement of statistical power through decrease of dimensionality) that make it an ideal methodological approach (Bach et al., 2014; Chung et al., 2018). Furthermore, unlike other analysis methods such as tractography, which is limited to specific ROIs, TBSS enables comprehensive FA analysis that encompasses the entire brain. In this TBSS analysis, use of correction of several whole-brain comparisons resulted in restriction to regions with significant FA differences (Dohn et al., 2015).

8.7 Conclusion

This study used DTI metrics and TBSS to investigate the plasticity of WM microstructure that was associated with pitch discrimination training across a group of trainees compared with controls who did not undergo training. The observed results indicate that short auditory training periods alone cannot induce WM structural plasticity across auditory regions. However, short auditory training can cause changes in the right-side WM pathways, including the CST and CR tracts that connect between the temporal, parietal and occipital lobes. Therefore, auditory training has a positive impact on WM pathways, which play a role in pitch discrimination ability.

No significant correlation was found between the observed WM changes and the changes that were found in the behavioural performance. However, the pre-training psychoacoustic performance and diffusion measures were correlated in some ROIs and this correlation could be used as an indicator of behavioural performance gains and structural change at the end of training.

Since changes in WM tracts were found with short auditory learning periods, neural plasticity that is related to long-term musical practice is investigated in the next chapter.

Chapter 9. A comparison of the neural plasticity of auditory regions in musicians and non-musicians

9.1 Aim of This Study

This part of the study was designed to explore the variations in the auditory areas of the brains of musicians and non-musicians from both functional and structural perspectives.

9.2 Introduction

Clinical studies help in the analysis of information regarding the structure of the brain, as well as its function and plasticity. Nevertheless, the most beneficial source of information may stem from those studies that focus on ‘advanced’ brains, particularly in relation to a specific domain’s high-level abilities. Proficient musicians have been considered as an ideal model in the exploration of brain plasticity, due to their exposure to complex stimuli in music (Schlaug, 2001; Münte et al., 2002). Indeed, professional music performances are commonly noted to exhibit some of the most in-depth human accomplishments, as auditory-motor interaction is involved in relation to the processing of information, such as the musical rhythm, pitch, tone, etc. (Zatorre et al., 2007; Chen et al., 2008) (see Figure 9.1). A pianist, for example, has to coordinate bimanually the production of up to 1,800 notes per minute, which involves both auditory and visual stimuli (to manage the music sheet and piano keys).

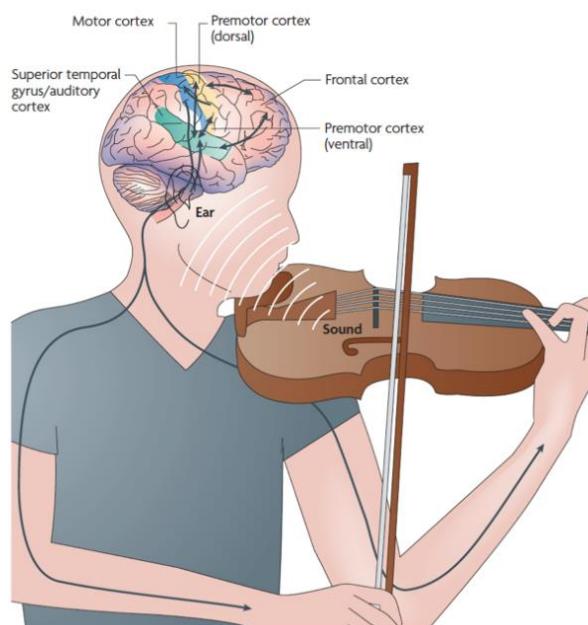


Figure 9.1. Illustration of the auditory–motor interactions during a music performance (Zatorre et al., 2007).

Moreover, the emotion that is connected with a particular musical piece should be considered. Therefore, a complex array of connections within the brain is involved in a pianist's performance. Therefore, there is a recognition of clear cortical plastic distinctions between musicians and non-musicians, especially in the auditory domains, which are detailed in this chapter.

9.2.1 Structural and Functional Changes that are Induced by Music

The long-term training leads to the acquisition of skills that are exhibited by musicians and are reflected in neural plastic changes that impact upon brain function while the musicians perform auditory processing. These changes lead to neuronal population reorganisation that can result in an increase or decrease in the volume of GM. Bangert and Schlaug (2006) and Gaser and Schlaug (2003) found that the structural changes that occurred in musicians' brains reflected debatable interplay between genetic factors and the amount of practice that they performed. Certain prominent brain areas show differences in their sizes and structures between musicians and non-musicians. These areas are: the planum temporale (PT), HG, the CC and motor areas (Muente et al., 2002). For instance, the PT is an auditory association cortex structure, which supports the processing of pitch intervals and sound sequences (Koelsch & Siebel, 2005); it has been shown to be activated asymmetrically during pitch-perception tasks in musicians compared with non-musicians, and this corresponds with structural enlargement of the PT in musicians (Schlaug et al., 1995; Zatorre et al., 1998; Limb, 2006). Separately, HG is correlated with musical skill and pitch processing; Schneider et al. (2002) found an increase in neural activity and in GM volume in HG of proficient musicians.

Another structure that is found to differ between musicians and non-musicians is the CC, which is an interhemispheric fibre tract that links the two hemispheres. The structural difference of the CC in musicians is explained by the need for close communication between the two hemispheres, since such communication is a prerequisite for the close coordinated movement of the left and right hands during musical performances. Therefore, a great concentration of GM volume in the anterior part of the CC was found to relate to musical training at an early age (Schlaug et al., 1995a).

In addition, the structural shifts between musicians and non-musicians result in differences of functional activation patterns. Bianchi et al. (2017) used fMRI to measure brain activity during pitch discrimination tasks. Their results showed that greater neural responses for complex tones in the cortical and subcortical auditory regions were observed in musicians compared

with non-musicians. Moreover, an fMRI study that was conducted by Gaab et al. (2005) noted an enhancement in auditory stimulus processing (rapid spectro-temporal processing) in professional musicians compared with controls. Furthermore Benner et al. (2017) performed a study that found a link between structural and functional changes that were induced by musical training. They used structural MRI (T_1 -weighted MR images) and functional imaging that involved fMRI and magnetoencephalography (MEG) to study the structure-function relationships in professional musicians compared with amateur musicians. They found inter-individual and inter-hemispheric morphological differences in HG across groups and reported that the functional activations reflected HG size multiplications. In summary, proficient musicians have larger Heschl's gyri than amateur musicians.

These structural and functional differences make musicians more sensitive to certain acoustic features that are critical in music processing, such as pitch discrimination. The superior ability of musicians to discriminate between fine-pitch changes has been reported in numerous behavioural investigations, as musicians have better frequency discrimination ability than non-musicians (Spiegel & Watson, 1984; Micheyl et al., 2006; Bianchi et al., 2017). Added to that, Wengenroth et al. (2014) found that musicians who possessed absolute pitch, which refers to the ability to recognise a tone without a reference tone (Marin & Perry, 1999), show a correlation between their GM volume in the right HG and their behavioural performance. This results in the formation of intrinsic functional networks between auditory and somatosensory regions.

9.2.2 Lateralisation of the Brain in Acoustic Processing

There is debate regarding the determination of hemispheric lateralisation in pitch perception; that is, whether the right or left AC is dominant in pitch discrimination. Many neuroimaging and lesion studies have claimed that the left hemisphere of the brain is adapted for analytical organisation, which is required for tasks such as speech activity (Bever, 1975; Alho et al., 1998; Hickok and Poeppel, 2007; Friederici, 2011); whereas the right hemisphere is specialised for holistic and synthetic analysis (Mazziotta et al., 1982; Zatorre, 1991, 1994, 1998; Johnsrude et al., 2000; Tervaniemi et al., 2000). Researchers have argued that melody and pitch perception tend to be processed in the right STG, particularly in the HG, across musicians (Zatorre, 2002; Schneider et al., 2005; Bianchi et al., 2017). A study that was conducted by Oechslin et al. (2018) suggested that the lateralisation phenomena that were seen across musicians referred to the plasticity of pathways that were related to musical practice, which facilitated transfer of auditory signals through the right hemisphere. What is more, Micheyl et al. (2006) reported

that musicians showed superiority in acoustic thresholds in the right hemisphere over non-musicians during performance of pitch discrimination tasks; their finding was valid when they used pure-tone contralateral on-frequency noise. Similar results of right hemispheric advantage (better acoustic thresholds and more functional activation) were observed in musicians who performed pitch discrimination tasks for complex tones relative to noise (Bianchi et al., 2017).

In contrast, some studies argued that melody could be processed by the left hemisphere. Ohnishi et al. (2001) also determined that the left planum temporale (PT/BA22) showed stronger functional activation across musicians during musical perception tasks compared with controls. They correlated their functional results with the anatomical variation in musicians who were found to possess large PT cortical volumes, which corresponded to previous findings (Schlaug et al., 1995; Zatorre et al., 1998).

According to Schlaug (2001), the left-sided asymmetry of the functional activation of the PT is found only in musicians who possess absolute pitch. Bever and Chiarello (1974) proposed that experienced musicians listened to the melodies in an analytical way, which resulted in the transfer of the superiority of melody processing from the right to left hemisphere. Their results were consistent with those of Mazziotta et al. (1982), who used a tonal memory task and used PET imaging to test hemispheric lateralisation. Their results indicated that listeners who used analytical approaches showed left-dominant temporo-parietal activation, whereas subjects who used visual imagery tended to show greater activation in the right auditory areas. Another factor that affects hemispheric lateralisation is the acoustic context, as shown by Schönwiesner et al., (2007), who reported that the sound context had a strong effect on the functional asymmetry in human auditory parts of the brain.

From the aforementioned points, it seems that lateralisation in sound processing can be affected by multiple factors and that the most dominant factor is musicianship. In the work that is described in this chapter, hemispheric laterality was investigated through the performance of pitch discrimination tasks across different acoustic stimuli (binaural and monaural) in musicians and non-musicians under fMRI guidance. This study combined psychoacoustic measures and functional and structural MRI to observe differences in the auditory areas of musicians compared with non-musicians. I hypothesised that, based on my previous findings in study one, as well as previous research, professional musicians would show evidence of superior pitch discrimination thresholds (lower) than non-musicians. In addition, distinct functional activation patterns, which would involve decreases in activity levels, and a structural

plastic variation (increased GM volume and cortical thickness) would be seen in the auditory regions of musicians.

9.3 Method

In this cross-sectional study, the MRI sequences that were involved were: T₁, T₂, and fMRI with DTI (see General Methodology, Chapter Four). In terms of imaging data analysis, the same pre-processing steps that were described previously were used for all imaging sequences. However, in order to evaluate the differences in the auditory regions of musicians and non-musicians, the ROI analysis and statistical testing were different for each imaging modality.

9.3.1 Participants

This study involved 37 participants: 11 musicians and 26 non-musicians. All non-musicians were participated in pitch discrimination training, but only baseline measures were used in this study. The demographic characteristics of both groups are described in Chapter Four.

9.3.2 Statistical Analysis

Multiple statistical models were used for different study purposes. The statistical testing analysis was performed by the GLM model in SPM12 and GraphPad Prism (version 8) for MAC (GraphPad Software, La Jolla, California, USA,

9.3.3 fMRI

A GLM methodology was used to evaluate the data at the single subject level (first-level-analysis). In the GLM method, design matrices model the onsets as well as the durations of each trial's sound stimulation according to different experimental demands for all practical runs. Two models of interest were developed for this case. The task-based and condition-based models were compared with the silent condition. The task-based model represented the total activity associated with all acoustic stimuli, whereas the condition-based model investigated the activity of each acoustic stimulus separately, which included: two monaural (LL, RR) and two binaural (LR, RL) stimuli (further details of each model are provided in Chapter Six, section 6.4.2). Then the second-level analysis was performed on the basis of group statistics to answer the research questions. The corresponding contrast images from the task-related model were used in one sample t-test in musicians as well as non-musicians to investigate the differences in the functional activation patterns. The same process was repeated for the condition-based model.

Because this experiment was designed to investigate the variations between auditory areas of musicians and non-musicians, a ROI analysis was required. Thus, the result of the task-based single-sample t-test was used to extract ROIs that were located in the STG and HG bilaterally (details of ROI locations are provided in Table 9.1).

For all the analyses, the locations of activated clusters were determined using the MNI coordinates system. To calculate the BOLD signal intensity (Z-score) within the ROIs for each subject, numerical data were extracted using REX. Two-sample t-tests were also used to investigate the variation in BOLD responses between groups.

In terms of lateralisation of functional activation, the lateralisation index (LI) was used to assess the hemispheric dominance in each acoustic stimulus across both the groups of musicians and non-musicians. The LI was assigned according to the activation in the HG and STG, due to the consistent activation of those regions in musical studies, which was seen in the experimental data from this study (Chapter Six) as well as in other pitch discrimination studies (Johnsrude et al., 2000; Schneider et al., 2002; Mathys et al., 2010; Bianchi et al., 2017). The LI was computed based on the numbers of activated voxels that were observed in the left and right hemispheric ROIs at a fixed threshold level. Further details about data extraction for the LIs of ROIs and the LI calculation are provided in Chapter Six sections 6.4.3.1 and 6.4.3.2 respectively.

9.3.4 Pitch Discrimination Threshold

The pitch discrimination thresholds for the musicians and non-musicians were computed based on the participants' responses during the fMRI task. DTs for each participant were estimated through use of the cumulative distribution function (further details of the threshold calculation method are provided in Chapter Six, section 6.3.5). The difference in pitch discrimination thresholds between musicians and non-musicians was evaluated using two sample t-tests.

9.3.5 VBM

Two sample t-tests were conducted through VBM analysis of the ROIs using the GLM part of SPM12 (v7487), in order to compare musicians against non-musicians. Two contrasts were assigned to assess the probability that GM volume was higher in musicians (musicians > non-musicians) or lower (musicians < non-musicians) in the bilateral auditory cortices. To reduce the effect of brain size variation between individuals, global brain-tissue volumes, which are called total intracranial volume (TIV), were used to scale the original voxel values (Whitwell et al., 2001). This was performed through the use of the tissue volumes that were calculated

during the first-level analysis, which involved the sum of GM, WM, and CSF volumes, in the second-level statistical analysis. Another two-sample t-tests were conducted to investigate the TIV differences between musicians and non-musicians. Overall, the results were corrected for multiple comparisons ($p < 0.05$).

9.3.6 FreeSurfer

Two-sample t-tests were computed using GraphPad Prism (version 8) for group comparisons (musicians against non-musicians) across the cortical thicknesses and volumes in the ROIs. These were the auditory processing areas and pathways, which involved the auditory cortices, CC and hippocampus. The tests were performed to obtain data that would show any differences between the two groups. ROIs cortical measures were also correlated with the behavioural performance threshold. Only p values of < 0.05 after Bonferroni correction were considered to be statistically significant.

9.3.7 DTI Method

The pre-processed DTI data were analysed through use of the TBSS method, which was explained in Chapter Eight, section 8.3.2. Group comparisons were performed on the skeletonised DTI data to compare musicians and non-musicians. This statistical testing was performed at the level of the anatomical tract-based analysis. A t-test was performed by application of GraphPad Prism (version 8); this test was conducted on the skeletonised DTI data within ROIs only (details about the data extraction method were explained previously in Chapter Eight section 8.3.2.5). The same anatomical masks that were produced for the study that was described in Chapter Eight were used for the ROIs in this project. These were: the SLF, right and left, the CR, right and left, the CC (genu, body, and splenium) and the CST, right and left.

9.4 Results

9.4.1 Functional MRI

9.4.1.1 Do the Functional Responses of Musicians' Brains vary from Those of Non-musicians During Performance of Pitch Discrimination?

One sample t-test of the task-based model, which represents the total activity associated with all acoustic stimuli, was compared with the silent condition that resulted in different BOLD activation maps in musicians and non-musicians (see Figure 9.2). Both groups of listeners exhibited task-related activations in the auditory cortices bilaterally, with stronger BOLD signals, especially in the HG and the posterior aspect of the STG.

The functional activation intensities (Z score) across ROIs in musicians were compared with those of non-musicians using two sample t-tests. Subsequently, the t-tests revealed that functional activation was reduced in musicians, particularly in HG, compared with non-musicians (see Table 9.1).

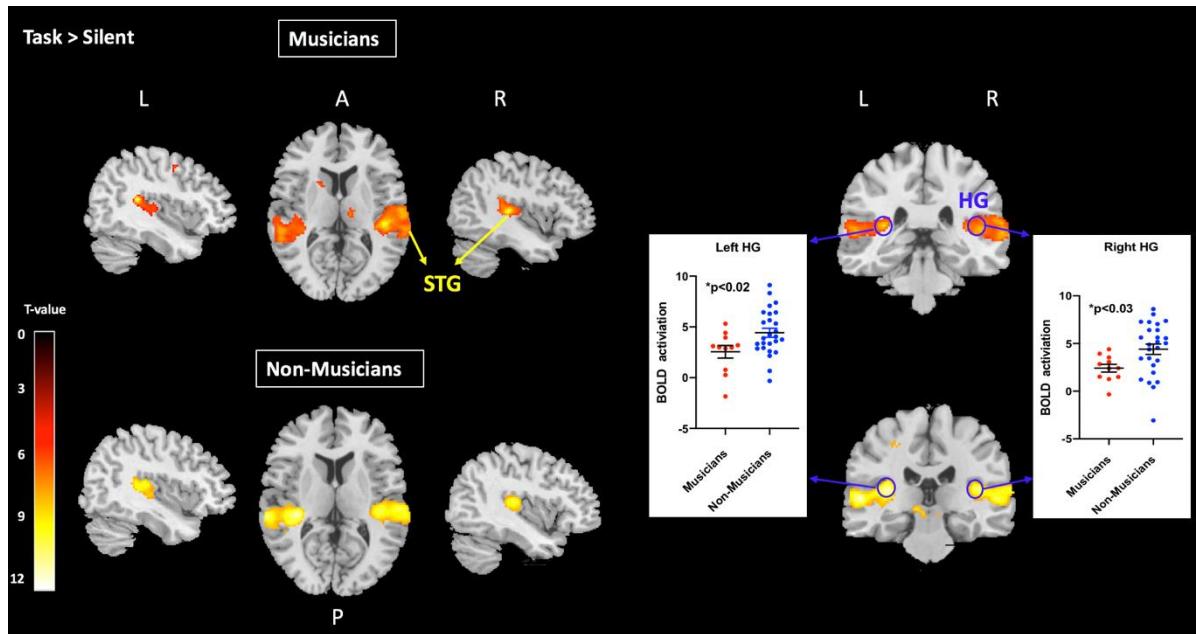


Figure 9.2. Different functional activation maps for musicians and non-musicians (FWE corrected, $p < 0.05$). Musicians have lower intensity of BOLD signals compared with non-musicians across ROIs. Error bars represent the standard error of the mean. *Significant difference at $p < 0.05$. R: right; L: left; A: anterior; P: posterior; STG: superior temporal gyrus; HG: Heschl's gyrus.

ROI	Coordination			Musicians	Non-Musicians	Two sample t test (df=35)
	X	Y	Z			
R HG	42	-27	10	2.41 ± 0.41	4.40 ± 0.55	$t = 2.24, *p < 0.03$
R p STG	62	-18	1	3.91 ± 0.43	4.24 ± 0.51	$t = 0.40, p < 0.69$
L HG	-34	-32	13	2.55 ± 0.62	4.43 ± 0.44	$t = 2.38, *p < 0.02$
L p STG	-59	-32	7	3.31 ± 0.53	3.63 ± 0.37	$t = 0.48, p < 0.63$

Table 9.1. Results of the group-level analysis (two-sample t test). Peak-level coordinates (mm), mean and standard deviation (SD) values of local activation. R: right; L: left; p: posterior; STG: superior temporal gyrus; HG: Heschl's gyrus. *Significant difference at $p < 0.05$ (FWE corrected).

9.4.1.2 How Do Musicians' Brains Respond to Monaural and Binaural Acoustic Stimulation Compared with Those of Non-musicians? Is There Lateralisation of their Neural Responses?

One sample t-test was applied to musicians and non-musicians to model the activation pattern for monaural (LL, RR) and binaural (LR, RL) acoustic stimuli (Figure 9.3). Additionally, the LI was used to assess lateralisation in each acoustic stimulus, which compared both groups by application of two sample t-tests (Table 9.2). The LI result showed that the LL stimulus indicated contralateral fMRI activation in the right HG, particularly in the musicians compared with the non-musicians. In terms of STG, there was a right lateralisation in fMRI activation that was associated with LL stimuli in the STG across musicians, but this right lateralisation was not significantly different from that observed in non-musicians as revealed by t-test. However, the contralateral BOLD signal disappeared with other acoustic stimuli (RR, LR, RL), which means that both auditory cortices were activated to approximately the same level in musicians, as well as non-musicians. Hence, the hemispheric lateralisation in this study was affected by musical practice.

Stimulus	Musicians Mean (\pmSD)	Non-musicians Mean (\pmSD)	Two sample t test (df=35)
a. LI in STG			
LL	-0.18 (0.19)	-0.10 (0.06)	t=1.93, p=0.06
RR	-0.14 (0.15)	-0.08 (0.08)	t=1.67, p=0.11
LR	-0.12 (0.04)	-0.05 (0.29)	t=0.80, p=0.43
RL	-0.13(0.09)	-0.09 (0.06)	t=1.85, p=0.07
b. LI in HG			
LL	-0.19 (0.29)	-0.03 (0.12)	t= 2.38, *p=0.02
RR	-0.14 (0.29)	-0.03 (0.13)	t= 1.57, p=0.13
LR	-0.07 (0.06)	-0.05 (0.24)	t= 0.23, p=0.82
RL	-0.08 (0.07)	-0.05 (0.07)	t= 0.86, p=0.40

Table 9.2. Laterality index (LI) mean and SD in musicians and non-musicians across different acoustic stimuli presentations. LI was evaluated in (a) STG and (b) HG across both groups. A negative LI means right-hemisphere dominance, while a positive LI means left-hemisphere dominance and a LI around zero is considered as bilateral evenness. HG in musicians shows right lateralisation with LL stimulus compared with non-musicians. *Significant difference $p<0.05$. LL: both tones to left ear; RR: both tones to right ear; LR: first tone to the left ear and second tone to the right ear; RL: first tone to the right ear and second tone to the left ear; HG: Heschl's gyrus; STG: superior temporal gyrus.

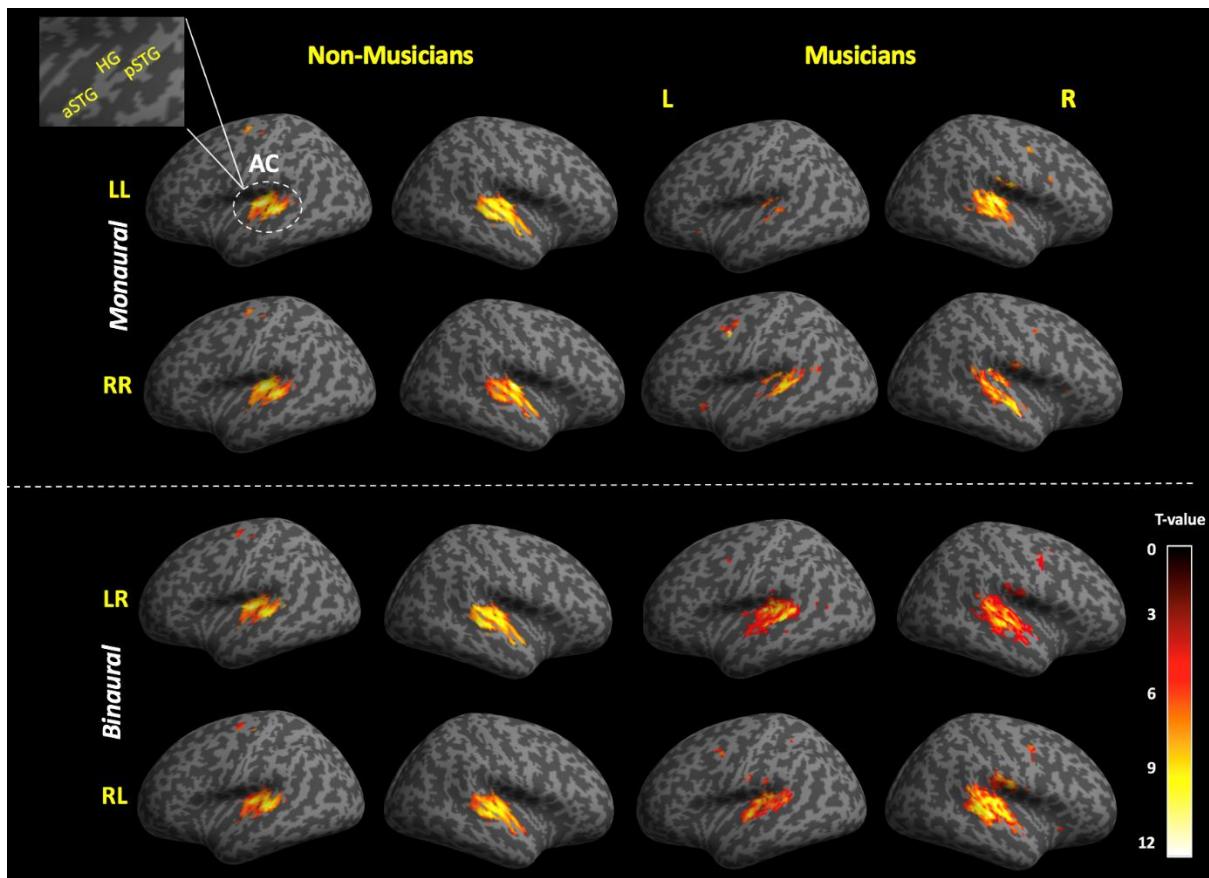


Figure 9.3. Maps of functional activation within auditory cortices of musicians and non-musicians across monaural (both tones delivered to one ear only) and binaural (two tones delivered to both ears) acoustic stimuli. The notable difference between musicians and non-musicians that was seen in monaural (LL) condition in musicians had a strong contralateral functional activation toward the right AC. LL: both tones to left ear; RR: both tones to right ear; LR: first tone to the left ear and second tone to the right ear; RL: first tone to the right ear and second tone to the left ear; R: right; L: left; AC: auditory cortex; HG: Heschl's gyrus; aSTG: anterior superior temporal gyrus; pSTG: posterior superior temporal gyrus.

9.4.1.3 How Does Musical Skill impact on the Pitch discrimination Threshold?

Pitch discrimination thresholds of musicians were compared with those of non-musicians using two sample t-tests. The result indicated that the pitch discrimination threshold in musicians was significantly lower ($mean=5.97$, $SD=1.90$) than that in non-musicians ($mean =11.98$, $SD=8.12$), $t(35)= 2.41$, $p < 0.02$ (see Figure 9.4). Therefore, musicians were found to have a better pitch discrimination ability than non-musicians.

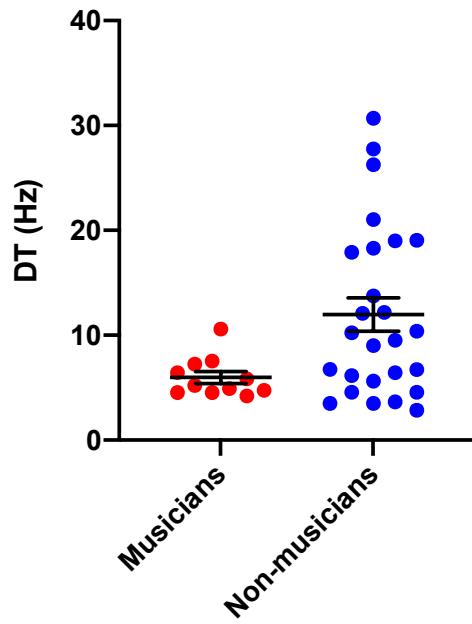


Figure 9.4. Comparison of the pitch discrimination threshold by mean and standard error (SEM) shows a lower musicians threshold (better performance) compared with non-musicians. DT: discrimination threshold in Hertz.

9.4.2 VBM

Two sample t-tests were conducted for group comparison (musicians against non-musicians) to discover whether the volume of GM in the whole brain was different in musicians compared with non-musicians. Additionally, t-test measurement with the FWE correction ($p < 0.05$) of the ROI analysis did not reveal any significant GM changes in the bilateral auditory cortices between the groups for either contrast (musicians $>$ non-musicians and musicians $<$ non-musicians). Moreover, there were no differences in the overall brain volumes between musicians and non-musicians.

9.4.3 FreeSurfer

9.4.3.1 The Influence of Music on Cortical Volume and Thickness in ROIs

Two sample t-tests were computed to compare the groups across the cortical thicknesses and volumes in the ROIs, which were organs in the auditory processing areas and pathways. The two sample t-tests revealed that a significant change was detected in the volume of the central part of the CC; this was significantly lower in the musicians' group, even with the Bonferroni correction (corrected $p = 0.005$) (Table 9.3 and Figure 9.5). Moreover, the right STG was thicker in the musicians compared with the non-musicians; however, this finding did not survive after the application of the Bonferroni correction (corrected $p = 0.007$) (Table 9.4, Figure 9.6).

In terms of correlation, the behavioural performance threshold was found to correlate negatively with the thickness of the right STG across the musicians' group, but this correlation unexpectedly appears as a positive correlation due to one participant (outlier) (Figure 9.6). Hence, the better performance in pitch discrimination ability (lower threshold) was associated with a thicker right STG. In contrast, no significant correlation was found between the behavioural performance threshold and the thickness of the right STG of non-musicians.

ROIs	Non-musicians	Musicians	Non-musicians vs. Musicians (df= 35)
	Mean (\pm SD)	Mean (\pm SD)	
R STG	0.81 (\pm 0.08)	0.86 (\pm 0.12)	t = 1.56, p = 0.13
L STG	0.89 (\pm 0.09)	0.90 (\pm 0.09)	t = 0.32, p = 0.75
R TTG	0.07(\pm 0.01)	0.06 (\pm 0.01)	t = 0.76, p = 0.45
L TTG	0.08 (\pm 0.01)	0.09 (\pm 0.01)	t = 1.19, p = 0.24
R hippocampus	0.29 (\pm 0.03)	0.28 (\pm 0.02)	t = 0.46, p = 0.65,
L hippocampus	0.28 (\pm 0.03)	0.27 (\pm 0.02)	t = 1.00, p = 0.32
Anterior CC	0.06 (\pm 0.01)	0.06 (\pm 0.01)	t = 0.35, p = 0.73
Central CC	0.05 (\pm 0.01)	0.04 (\pm 0.004)	t = 3.06, **p<0.004
Posterior CC	0.07 (\pm 0.01)	0.07 (\pm 0.01)	t = 0.57, p = 0.57

Table 9.3. Two sample t-tests of ROI cortical volumes (normalised proportion of the region volume in the brain) produced through FreeSurfer analysis. The table reveals a significant difference between musicians and non-musicians was only found in the volume of the central part of the corpus callosum. R: right; L: left; STG: superior temporal gyrus; TTG: transverse temporal gyrus; CC: corpus callosum. Significant at **p<0.01.

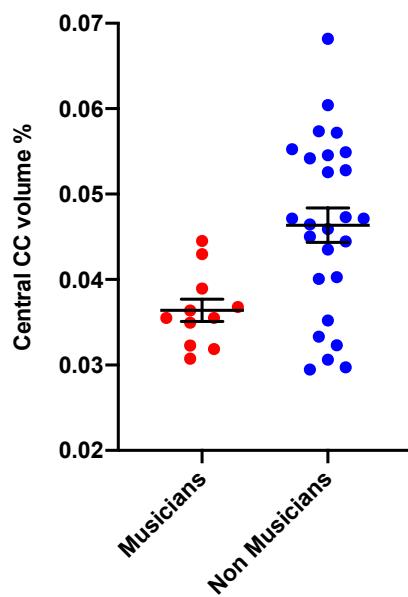


Figure 9.5. The central corpus callosum showed a reduced cortical volume (normalised proportion of the region volume in the brain) in musicians compared with non-musicians. CC: Corpus Callosum. Error bars represent the standard error of the mean.

ROI	Non-musicians Mean (\pm SD)	Musicians Mean (\pm SD)	Non-musicians vs Musicians (df= 35)
R STG	2.89 (\pm 0.15)	3.01 (\pm 0.17)	t=2.13, *p<0.04
L STG	2.91 (\pm 0.17)	2.94 (\pm 0.15)	t= 0.55, p<0.59
R TTG	2.59 (\pm 0.25)	2.66 (\pm 0.23)	t= 0.75, p<0.46
L TTG	2.59 (\pm 0.25)	2.51 (\pm 0.25)	t= 0.85, p<0.40
R parahippocampal	2.77 (\pm 0.23)	2.88 (\pm 0.29)	t=1.19, p<0.24
L parahippocampal	2.84 (\pm 0.30)	2.77 (\pm 0.29)	t= 0.64, p<0.53

Table 9.4. Two sample t-tests of ROIs cortical thicknesses (mm) through FreeSurfer analysis. The table shows a significant difference between musicians and non-musicians in the right superior temporal gyrus only. R: right; L: left; STG: superior temporal gyrus; TTG, transverse temporal gyrus. *Significant at $p<0.05$.

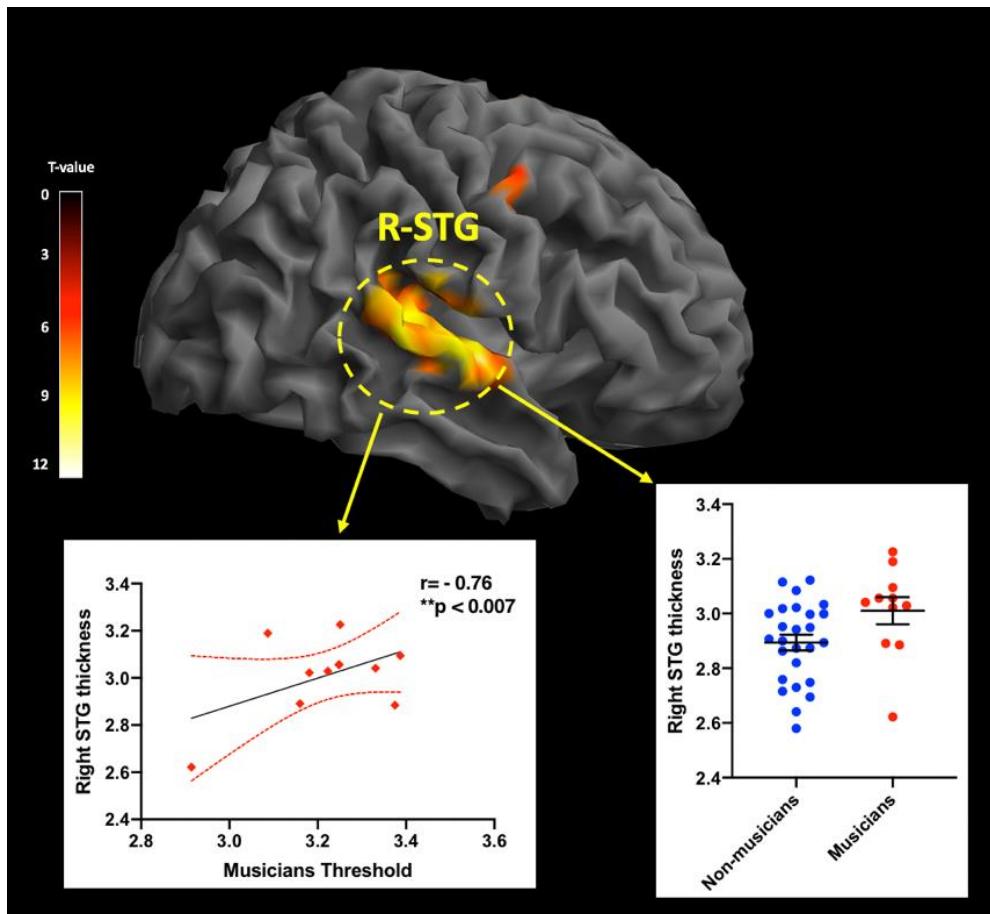


Figure 9.6. Graph shows the right superior temporal gyrus thickness (mm) in musicians. The right superior temporal gyrus was thicker in musicians than in non-musicians. A negative correlation was found between the thickness of the right STG in musicians and their discrimination threshold. This means that the thicker right STG was associated with better hearing performance. Error bars represent the standard error of the mean. Significant at $**p<0.01$. STG: superior temporal gyrus; R: right.

9.4.4 DTI – Is the White Matter Tract in Musicians Different from that Found in Non-musicians?

The musician and non-musician groups were compared to discover whether there was any change in the WM tract. The unpaired t-test of ROI analysis revealed no significant changes in the DTI metrics of the musicians, compared with those of the non-musicians (see Table 9.5).

ROI	Non-musicians	Musicians	Musicians vs. non-musicians (df=35)
	Mean (\pm SD)	Mean (\pm SD)	
<u>FA</u>			
R CR	0.52 (\pm 0.03)	0.53 (\pm 0.03)	t = 0.72, p = 0.48
L CR	0.51 (\pm 0.03)	0.52 (\pm 0.03)	t = 0.32, p = 0.75
R CST	0.54 (\pm 0.01)	0.55 (\pm 0.02)	t = 1.00, p = 0.32
L CST	0.55 (\pm 0.01)	0.56 (\pm 0.02)	t = 1.38, p = 0.18
R SLF	0.54 (\pm 0.02)	0.54 (\pm 0.02)	t = 1.06, p = 0.30
L SLF	0.54 (\pm 0.02)	0.55 (\pm 0.02)	t = 0.67, p = 0.51
BCC	0.72 (\pm 0.02)	0.71 (\pm 0.03)	t = 1.21, p = 0.23
GCC	0.76 (\pm 0.02)	0.76 (\pm 0.03)	t = 0.17, p = 0.86
SCC	0.80 (\pm 0.02)	0.81 (\pm 0.01)	t = 0.76, p = 0.46
<u>MD</u>			
R CR	0.79 (\pm 0.03)	0.79 (\pm 0.03)	t = 0.36, p = 0.72
L CR	0.78 (\pm 0.03)	0.78 (\pm 0.04)	t = 0.39, p = 0.70
R CST	0.73 (\pm 0.02)	0.74 (\pm 0.02)	t = 1.23, p = 0.23
L CST	0.72 (\pm 0.01)	0.73 (\pm 0.02)	t = 1.48, p = 0.15
R SLF	0.73 (\pm 0.02)	0.74 (\pm 0.02)	t = 0.83, p = 0.41
L SLF	0.72 (\pm 0.02)	0.72 (\pm 0.02)	t = 0.49, p = 0.63
BCC	0.82 (\pm 0.03)	0.82 (\pm 0.04)	t = 0.49, p = 0.63
GCC	0.77 (\pm 0.03)	0.77 (\pm 0.03)	t = 0.05, p = 0.96
SCC	0.74 (\pm 0.02)	0.74 (\pm 0.03)	t = 0.18, p = 0.86

Table 9.5. DTI measures (FA and MD) that resulted from comparison of two sample t tests between musician and non-musician groups across anatomical masks of ROIs. MD Mean (in 10^3) and SD (in 10^{-3}) mm 2 /s. CR: corona radiata; CST: corticospinal tract; SLF: superior longitudinal fasciculi; CC: corpus callosum.

9.5 Discussion

This research project investigated the contrasts between musicians and non-musicians, which has demonstrated the neural plasticity effect as a musical practice consequence. The research examined the functional activation patterns that were caused in response to an auditory task and the structural differences that were observed across musicians and non-musicians. The result showed that bilateral superior temporal gyri were activated during performance of the auditory task due to their auditory properties; for example, auditory attention would be displayed when the subjects concentrated on the presented pitch discrimination task. Specifically, in previous studies the STG has been found to be activated in response to the processing of melodies (Schmithorst & Holland, 2003), and in connection with musical training (Koelsch et al., 2005). The results of this study indicated that functional activation of auditory regions was stronger in non-musicians in comparison with musicians, particularly in HG. This finding is consistent with the fMRI experimental results (see Chapter Six), which showed a decrease in BOLD signals after pitch discrimination training across trainees. Furthermore, since previous studies suggested that the reduction in functional activity reflected the plasticity of stimuli processing in specific regions, it was surmised that only small ensembles of expert neurons were activated (Bergerbest et al., 2004; Ohl & Scheich, 2005).

A prior study had been performed by Schönwiesner et al. (2007) to consider cortical response lateralisation among non-musicians. The researchers used a train of noise bursts as an acoustic stimulus. Their results showed that there was a clear contralateral stimulus preference that was exhibited by auditory structures in the left hemisphere by monaural stimulus, whereas no contralateral stimulus preference was found in the right auditory structures as they reacted at similar levels to both left- and right-ear stimulation. When binaural stimulus was applied, no predominant functional activation was seen in the auditory structures of either side. This finding concurred with those of previous studies (Woldorff et al., 1999; Hashimoto et al., 2000). These researchers argued that the sound context had a strong effect on the functional activity of the AC, as their results showed that contra-laterality in fMRI signals was elicited by monaural stimulus and that this functional asymmetry disappeared with binaural stimulus. They suggested that the differences in functional activation patterns were a result of the attention-related factor. For example, in the binaural condition, when a target was presented, the listener needed to direct focus to one ear, and subsequently, when the target was shifted to the other side, the attention switched to the other ear. Hence this process caused activation in both auditory cortices.

In contrast, other investigations reported that the auditory cortices worked together at a central level, and that this cooperation resulted in an inter-hemispheric interaction (Beerends & Houtsma, 1989; Suzuki et al., 2002; Sinai & Pratt, 2003). This was consistent with the results of the current study, as in this study, it was found that both auditory cortices were activated at the approximate same level in musicians and non-musicians in most auditory stimulation that involved RR, LR, and RL supply of the stimulus. However, the LL stimulus produced strong contralateral activity within the right HG in musicians compared with non-musicians. Therefore, the current study showed that the lateralisation of functional activation was influenced by musical practice.

In real life, we usually listen to binaural sound; listening to monaural sound is uncommon. However, study of monaural sound processing is important, since a better understanding of the mechanism that occurs in the auditory cortices during sound processing could help with hearing impairment diagnoses and treatment, such as to improve the design of cochlear implants (Oxenham, 2008).

In terms of behavioural performance, the musicians' threshold was lower (by about 50%) than that of non-musicians, which reflects the more advanced pitch discrimination ability in musicians. This result was in parallel with those of previous research, such as a study by Kishon-Rabin et al. (2001), who found that musicians' frequency discrimination thresholds in pure tone were better (half the value) than those of non-musicians. Another supportive study that was conducted by Micheyl et al. (2006) revealed that non-musicians' frequency discrimination thresholds were greater than those of musicians.

Another result in the present study related to cortical measures. FreeSurfer analysis revealed that the volume of the central part of the CC was significantly lower in musicians than in non-musicians. This unexpected result could be due to the sharpening of pathway architecture (reduction in tract volume), which has been suggested by Oechslin et al. (2018) to be a key consequence of musical proficiency and to affect the ventral stream morphology. They found that smaller tract volume in the middle temporal gyrus and pars opercularis pathway was associated with musical expertise. In contrast, Schlaug et al. (1995a) claimed that the mid-area of the CC was larger in musicians who had started musical training at an early age in comparison with those who had begun their musical training later in life. They suggested that the increase in CC volume was due to the presence of more fibres, and that this resulted in faster interhemispheric interaction.

Moreover, Abdulkareem (2012) found that the anterior and mid-posterior parts of the CC volume were larger in proficient musicians compared with controls and that this change was a representation of the structural plasticity that was caused by musical training, rather than a genetic tendency for being a musician.

Another observation that was detected by FreeSurfer analysis was in the right STG, which was found to be thicker in musicians than in non-musicians. Moreover, the absolute thickness of the right STG in musicians was correlated with their pitch discrimination ability. This finding confirmed that the structural differences in the right AC were induced by musical proficiency. Similarly, Foster and Zatorre (2010) produced results that showed an increase in cortical thickness of the right AC, as well as of the bilateral anterior interparietal sulcus, and this finding was correlated with the subjects' accuracy in pitch perception performance. Additionally, according to Bermudez et al. (2008), musical skills could change the neural anatomy, as their results indicated that greater cortical thickness in auditory areas and high GM concentration was found in the HG of musicians. Another supportive investigation suggested that the musicians' status was highly correlated with structural differences, as they found increased GM volume in the HG of musicians relative to non-musicians (Schneider et al., 2002; Gaser & Schlaug, 2003). Therefore, the result that was expected from the VBM analysis was that musicians would show a greater GM volume in the AC than non-musicians. The present study's VBM result, however, did not reveal significant differences in GM volume across the auditory regions of musicians and non-musicians. Moreover, there was no difference in the overall brain volume of musicians and non-musicians.

Many studies have suggested that musical training can cause WM plasticity. For instance, FA increases were reported in the CST of musicians, due to the development of fine motor skills during use of musical instruments (Dohn et al., 2013; Rüber et al., 2013; Engel et al., 2014). However, the results from the present study did not reveal significant differences in the WM tract between the groups. The possible cause was the small sample size, as Moore et al. (2014) suggested that MRI analysis techniques, such as TBSS analysis, were only effective with relatively large sample sizes.

9.6 Conclusion

The present study was designed to explore the structural and functional variations of brain areas between musicians and non-musicians. The results indicate a reduction in functional activation of the auditory regions of musicians, and this reflects the plasticity of auditory processing in those regions. Regarding hemispheric asymmetry, only left-ear stimuli showed a contralateral response in the right AC across the musicians' group only, with no contralateral response found with the presentation of right-ear or binural stimuli. This result means that both auditory cortices were activated at approximately the same level in both groups. Therefore, it can be proposed that musical training plays a significant role in the lateralisation of functional activation.

In terms of structural changes, the present study did not reveal significant differences in the WM tract between the groups. However, the volume of the central part of the CC in musicians was smaller than that in non-musicians. There were no significant differences in GM volume across the auditory regions between musicians and non-musicians. However, the right STG was thicker in musicians, and this change was correlated with their behavioural performance (discrimination threshold). Added to that, psychoacoustic tests indicated that musicians had better pitch discrimination thresholds than non-musicians. Therefore, the current study extends the level of prior knowledge as it demonstrates that structural and functional neural plasticity is a consequence of musical practice.

Chapter 10. General Conclusion

10.1 Overview

This thesis investigates the alterations to auditory regions caused by short-term training in pitch discrimination and compared these changes with those caused by long-term experiences (proficient musicians). The alterations to the auditory regions were investigated by integrating functional and structural imaging to expand our understanding of how learning affects brain plasticity and fill the knowledge gap found between previously published research works in short-term auditory training effects.

10.2 Key Findings:

10.2.1 Effects of Short-term Training on Pitch Discrimination:

10.2.1.1 Psychophysics Measure (Discrimination Threshold)

Pitch discrimination training that was based on an adaptive psychophysical staircase method was used to estimate the change of discrimination threshold over a short period of training. Results revealed that short-term training in a pitch discrimination task produced a significant improvement (reduction) in discrimination threshold. This result was consistent with those of a previous study that had been performed by Carcagno et al. (2011), who found that short-term training in pitch discrimination produced little but significant progress in a behavioural measurement. Another aim of the current study was to explore the lateralisation in auditory learning by examination of whether there was a difference in discrimination thresholds between right- and left-ear trainees. Both right- and left-ear trainees showed an improvement in discrimination thresholds at approximately the same level with no significant difference. This result agreed with a previous study performed by Roth et al. (2004), who proved the generalisation of auditory learning across ears as they did not find variation in the discrimination thresholds between left- and right-ear trainees after an hour of training on a frequency discrimination task.

10.2.1.2 The Brain Function

- a. The fMRI result revealed that there was no lateralisation in BOLD responses throughout the auditory cortices of both groups (right- and left-ear trainees). Besides, no significant differences were seen in the groups' psychoacoustic performances, which reflected the findings in the participants' discrimination thresholds that were assessed during fMRI scanning. This fMRI result was consistent with the psychoacoustic

training result. Therefore, no lateralisation was found in auditory learning and both groups could be considered as a single trainee group. The current study result, as per previous studies, proved that there was a generalisation of auditory learning across ears (Roth et al., 2003; Delhommeau et al., 2005; Micheyl et al., 2006; Wright & Zhang, 2009).

- b. Auditory learning resulted in a significant reduction in functional activation across auditory regions, and this reduction was more prominent in the STG (precisely, the right STG) compared with the HG. This fMRI result was parallel with previous investigations performed by Jäncke et al. (2001) and Bergerbest et al. (2004). They observed a reduction in BOLD responses from the bilateral AC, particularly in the STG, after acoustic training, which reflected the rapid identification of auditory stimuli in the AC.

10.2.1.3 The Brain Structure (GM)

- a. The VBM analysis revealed that pitch discrimination training led to no significant changes in the GM volume within auditory regions. Interestingly, a borderline of significance in a change in the right STG thickness was revealed by FreeSurfer analysis. This result with borderline significance could be considered an indicator of the early stage of structural change, especially in the right STG, which is known to carry the pitch discrimination centre. Greater cortical thickness in the STG has been found in previous research to be distinguished in musicians compared with non-musicians and this structural neural change was correlated with musicians' performance of pitch-perception activities (Bermudez et al., 2009; Foster & Zatorre, 2010).
- b. Negative correlations were found in pre-training data between the thickness of the bilateral superior as well as the transverse temporal gyrus and the acoustic threshold, which means that a thicker cortex is associated with a lower threshold (better performance).

10.2.1.4 Water Diffusivity (WM)

- a. The results of DTI metric and TBSS analyses indicated that short auditory training periods could not induce WM structural plasticity across auditory regions by themselves. However, auditory training had a positive impact on the right WM pathways, including the CST and CR tracts, which play a crucial role in pitch

discrimination. DTI analysis results revealed that the FA value was elevated in both the CR and the CST, but the RD and MD showed reduction across a small part of the right CR. In previous research, these WM structural plastic alterations (elevation of FA values and reduction in diffusivity) have been considered consequences of musical training (Engel et al., 2014; Moore et al., 2017). Moreover, in the current study the significant changes were found to be right lateralised and this finding complemented one that had been performed by Dohn et al. (2015), who discovered a rightward asymmetry in the WM tracts across musicians who showed absolute pitch.

- b. The significant correlation was found in pre-training data between the psychoacoustic performance and some ROIs' diffusion metrics. For instance, the FA and RD measures in right SLF recorded before training were correlated with pre-training psychoacoustic performance and after the training the right SLF showed structural changes.

10.2.1.5 Correlation between Psychoacoustic Performance and Neuroplastic Changes

No significant correlation was found between the observed functional, structural neuroplastic changes and the psychoacoustic performance. However, the pre-training psychoacoustic performance was correlated with cortical thickness and diffusion measures in some ROIs, and this correlation could be used as an indicator of behavioural performance gains and structural change after the training. This correlation was formerly confirmed by Bi et al. (2014) and Frank et al. (2016), who found that anatomical variations between individuals could be used to predict their learning outcomes.

10.2.2 A Comparison of the Alterations in Neural Plasticity in the Musicians Resulted from their Long-term Experience when Compared with the Auditory Regions in Non-musicians

10.2.2.1 Psychoacoustic performance

Superior discrimination thresholds (lower by about 50%) were observed in musicians compared with non-musicians. This result was in parallel with those of prior research, such as that by Kishon-Rabin et al. (2001) and Micheyl et al. (2006), who found that the musicians' frequency discrimination threshold was lower (half the value in Kishon-Rabin study) than that of non-musicians.

10.2.2.2 Functional alterations

- a. A reduction in functional activation was seen in musicians' auditory regions compared with those of non-musicians. This was in line with previous studies' findings, which suggested that the reduction in functional activity reflected the plasticity of stimuli processing in specific regions, as only smaller ensembles of expert neurons would be activated (Bergerbest et al., 2004; Ohl & Scheich, 2005).
- b. Use of different methods to present acoustic stimuli caused activation bilaterally in auditory cortices that were at approximately the same level in both musician and non-musician groups. However, the left-ear stimulus produced a strong contralateral response in the right AC across the musicians' group. Earlier studies reported that both auditory cortices worked together at a central level, and that this cooperation resulted in an inter-hemispheric interaction (Beerends & Houtsma, 1989; Suzuki et al., 2002; Sinai & Pratt, 2003). Furthermore, the current study indicated that the hemispheric lateralisation was influenced by the musical practice level that the musicians undertook, as the contralateral functional activation was more significant in the group of musicians.

10.2.2.3 Structural alterations

- a. The VBM analysis did not reveal any significant differences in GM volume across auditory regions between musicians and non-musicians.
- b. The FreeSurfer analysis showed that the central part of the CC in musicians was smaller in volume than the non-musicians. This reduction in tract volume may indicate the influence of musical proficiency on the ventral stream morphology, as suggested by Oechslin et al. (2018), who found that smaller tract volume in the middle temporal gyrus and pars opercularis pathway was associated with musical expertise.
- c. Another FreeSurfer result was that the musicians showed a thicker right STG than the non-musicians and it was correlated with their behavioural performance. Similarly in the investigation by Foster and Zatorre (2010), it was shown an increase in cortical thickness of the right AC among musicians and that this was correlated with the level of their accuracy in pitch perceptual performance.

10.2.2.4 Water diffusivity alterations

No significant differences were found in the WM tract between musicians and non-musicians.

A summary that compares the changes in neuroplasticity and psychoacoustic performances, either between musicians and non-musicians or between the non-musician results that were obtained before and after training, has been found to result from short-term training in pitch discrimination are represented in Table 10.1.

Training-related variable	Musicians vs. non- musicians (participants pre-training)	Trainees (pre vs. post- training)
Psychoacoustic performance (discrimination threshold)	Musicians have lower discrimination threshold than non-musicians	Reduction in threshold after training
Functional activation (BOLD response)	Musicians have lower BOLD response than non-musicians	Reduction in BOLD response after training
Structural changes (GM volume and cortical thickness)	Thicker R-STG in musicians compared with non-musicians	Trend of increase in R-STG thickness after training
WM diffusivity	No significant change between musicians and non-musicians	FA elevation, reduction in RD and MD in the right WM pathways, including the SLF, CST and CR tracts

Table 10.1. Summary of comparison of the changes that were found in neural plasticity (structural and functional) and psychoacoustic performance that resulted from short-term training on pitch discrimination according to length of experience. BOLD: Blood Oxygenation Level Dependent; GM: grey matter; WM: white matter; R-STG: right superior temporal gyrus; FA: Fractional anisotropy; RD: radial diffusivity; MD: mean diffusivity; SLF: superior longitudinal fasciculi; CR: corona radiata; CST: corticospinal tract.

10.3 Overall Conclusion and Novel Findings

The results of the current study fill a research gap in short-term auditory learning effects that previously existed. The results suggest that improvements in the function, structure and psychoacoustic performance of the auditory area make a small but significant contribution to short-term pitch discrimination learning. Most previous research works compared the learning that was related to neuroplasticity in musicians and controls. However, the current study provides a novel comparison between the short-term and long-term learning effects on brain structure and function. Alterations in the auditory regions that were found to result from short-term auditory training among novices were in line with those that occurred in those proficient

musicians with long experience. Another useful finding of the current study was that the correlation between individual behavioural performance and brain structure could be used as an indicator of learning outcomes, such as behavioural performance gains and structural change at the end of the training. Therefore, the current study results extend our understanding of the neuroplasticity mechanisms induced by short-term auditory learning. This will help in the development of knowledge to achieve the best neuroplasticity applications in skill perfection, and clinical fields.

10.4 Limitations and Future Recommendations

Although there was success in the research that is described in this thesis, the research had some limitations.

The results that are described in Chapter nine offer an insight into the long-term impact of auditory learning in the musician's brain. However, the study was conducted over a small sample size of musicians, as the data recruitment was stopped due to the COVID-19 pandemic. This reduced the statistical power of the findings. A further study limitation was that no significant correlation was found between the observed neuroplastic changes and psychoacoustic performance. This finding could be improved by the use of intense and more challenging auditory training.

Although DTI is a state-of-the-art tool for the study of white matter, DTI is not adequate for identifying cellular processes in neural tissue. Therefore, the improvement of MRI morphological resolution (Nakada et al., 2008; Duyn, 2010) as well as the use of additional advanced analysis models, such as AxCaliber (Assaf et al., 2008) and ActiveAx (Alexander et al., 2010), is required for application in future research to offer insight into the biological processes that control the white matter plasticity that is associated with short-term learning and its related relationship to diffusion measures.

Therefore, for any future investigation, it is recommended that a large sample size and more challenging (difficult) and more intense pitch discrimination training be used as these changes would be expected to lead to a better learning outcome.

References

- Abdul-Kareem, I. A., Stancak, A., Parkes, L. M., & Sluming, V. (2011). Increased gray matter volume of left pars opercularis in male orchestral musicians correlate positively with years of musical performance. *Journal of Magnetic Resonance Imaging*, 33(1), 24-32.
- Abdulkareem, I. A. (2012). Investigating structural plasticity in musicians' brains using structural magnetic resonance and diffusion tensor imaging techniques. Doctoral dissertation, University of Liverpool.
- Alais, D., Morrone, C., & Burr, D. (2006). Separate attentional resources for vision and audition. *Proceedings of the Royal Society B: Biological Sciences*, 273(1592), 1339-1345.
- Alexander, A. L., Lee, J. E., Lazar, M., & Field, A. S. (2007). Diffusion tensor imaging of the brain. *Neurotherapeutics: the journal of the American Society for Experimental NeuroTherapeutics*, 4(3), 316–329. <https://doi.org/10.1016/j.nurt.2007.05.011>
- Alexander, D. C., Hubbard, P. L., Hall, M. G., Moore, E. A., Ptito, M., Parker, G. J., & Dyrby, T. B. (2010). Orientationally invariant indices of axon diameter and density from diffusion MRI. *Neuroimage*, 52(4), 1374-1389.
- Alghamdi, J. S. (2012). A multi-modal investigation of structural and functional neural bases of pitch discrimination in musicians and non-musicians. Doctoral dissertation, University of Liverpool.
- Alho, K., Connolly, J. F., Cheour, M., Lehtokoski, A., Huotilainen, M., Virtanen, J., ... & Ilmoniemi, R. J. (1998). Hemispheric lateralization in preattentive processing of speech sounds. *Neuroscience letters*, 258(1), 9-12.
- Alho, K., Rinne, T., Herron, T. J., & Woods, D. L. (2014). Stimulus-dependent activations and attention-related modulations in the auditory cortex: a meta-analysis of fMRI studies. *Hearing research*, 307, 29-41.
- Altenmüller, E., Gruhn, W., Parlitz, D., & Liebert, G. (2000). The impact of music education on brain networks: evidence from EEG-studies. *International journal of music education*, (1), 47-53.
- Amaro, E., & Barker, G. J. (2006). Study design in fMRI: basic principles. *Brain and cognition*, 60(3), 220-232.
- Amitay, S., Hawkey, D. J., & Moore, D. R. (2005). Auditory frequency discrimination learning is affected by stimulus variability. *Perception & psychophysics*, 67(4), 691-698.
- Andersson, J. L., Skare, S., & Ashburner, J. (2003). How to correct susceptibility distortions in spin-echo echo-planar images: application to diffusion tensor imaging. *Neuroimage*, 20(2), 870-888.
- Ashburner, J. (2015). VBM Tutorial. [online] Available at: <https://www.fil.ion.ucl.ac.uk/~john/misc/VBMclass15.pdf> [Accessed 13 Oct. 2019].
- Ashburner, J., & Friston, K. J. (2000). Voxel-based morphometry—the methods. *Neuroimage*, 11(6), 805-821.
- Assaf, Y., Blumenfeld-Katzir, T., Yovel, Y., & Basser, P. J. (2008). AxCaliber: a method for measuring axon diameter distribution from diffusion MRI. *Magnetic Resonance in*

Medicine: An Official Journal of the International Society for Magnetic Resonance in Medicine, 59(6), 1347-1354.

- Bach, M., Laun, F. B., Leemans, A., Tax, C. M., Biessels, G. J., Stieltjes, B., & Maier-Hein, K. H. (2014). Methodological considerations on tract-based spatial statistics (TBSS). *Neuroimage*, 100, 358-369.
- Bailey, J. A., Zatorre, R. J., & Penhune, V. B. (2014). Early musical training is linked to grey matter structure in the ventral premotor cortex and auditory-motor rhythm synchronization performance. *Journal of cognitive neuroscience*, 26(4), 755-767.
- Baker, R. A., & Osgood, S. W. (1954). Discrimination transfer along a pitch continuum. *Journal of Experimental Psychology*, 48(4), 241.
- Bandettini, P. A., Jesmanowicz, A., Van Kylen, J., Birn, R. M., & Hyde, J. S. (1998). Functional MRI of brain activation induced by scanner acoustic noise. *Magnetic resonance in medicine*, 39(3), 410-416.
- Bangert, M., & Altenmüller, E. O. (2003). Mapping perception to action in piano practice: a longitudinal DC-EEG study. *BMC neuroscience*, 4(1), 1-14.
- Bangert, M., & Schlaug, G. (2006). Specialization of the specialized in features of external human brain morphology. *European Journal of Neuroscience*, 24(6), 1832-1834.
- Barrick, T. R., Charlton, R. A., Clark, C. A., & Markus, H. S. (2010). White matter structural decline in normal ageing: a prospective longitudinal study using tract-based spatial statistics. *Neuroimage*, 51(2), 565-577.
- Basser, P. J., & Pierpaoli, C. (1996). Microstructural and physiological features of tissues elucidated by quantitative-diffusion-tensor MRI. *Journal of magnetic resonance, Series B*, 111(3), 209-219.
- Basser, P. J., Mattiello, J., & LeBihan, D. (1994a). MR diffusion tensor spectroscopy and imaging. *Biophysical journal*, 66(1), 259-267.
- Baumann, S., Griffiths, T. D., Rees, A., Hunter, D., Sun, L., & Thiele, A. (2010). Characterisation of the BOLD response time course at different levels of the auditory pathway in non-human primates. *Neuroimage*, 50(3), 1099-1108.
- Beaulieu, C. (2002). The basis of anisotropic water diffusion in the nervous system—a technical review. *NMR in Biomedicine: An International Journal Devoted to the Development and Application of Magnetic Resonance In Vivo*, 15(7-8), 435-455.
- Beerends, J. G., & Houtsma, A. J. (1989). Pitch identification of simultaneous diotic and dichotic two-tone complexes. *The Journal of the Acoustical Society of America*, 85(2), 813-819.
- Belin, P., Zatorre, R. J., Hoge, R., Evans, A. C., & Pike, B. (1999). Event-related fMRI of the auditory cortex. *Neuroimage*, 10(4), 417-429.
- Bengtsson, S.L., Nagy, Z., Skare, S., Forsman, L., Forssberg, H., Ullen, F., 2005. Extensive piano practicing has regionally specific effects on white matter development. *Nat Neurosci*; 8(9):1148-50.
- Benner, J., Wengenroth, M., Reinhardt, J., Stippich, C., Schneider, P., & Blatow, M. (2017). Prevalence and function of Heschl's gyrus morphotypes in musicians. *Brain Structure and Function*, 222(8), 3587-3603.

- Bergamino, M., Farmer, M., Yeh, H. W., Paul, E., & Hamilton, J. P. (2017). Statistical differences in the white matter tracts in subjects with depression by using different skeletonized voxel-wise analysis approaches and DTI fitting procedures. *Brain research*, 1669, 131-140.
- Bergerbest, D., Ghahremani, D. G., & Gabrieli, J. D. (2004). Neural correlates of auditory repetition priming: reduced fMRI activation in the auditory cortex. *Journal of cognitive neuroscience*, 16(6), 966-977.
- Bermudez, P., Lerch, J. P., Evans, A. C., & Zatorre, R. J. (2009). Neuroanatomical correlates of musicianship as revealed by cortical thickness and voxel-based morphometry. *Cerebral cortex*, 19(7), 1583-1596.
- Bever, T. G. (1975). Cerebral asymmetries in humans are due to the differentiation of two incompatible processes: Holistic and analytic. *Annals of the New York Academy of Sciences*, 263(1), 251-262.
- Bever, T. G., & Chiarello, R. J. (1974). Cerebral dominance in musicians and nonmusicians. *Science*, 185(4150), 537-539.
- Bi, T., Chen, J., Zhou, T., He, Y., & Fang, F. (2014). Function and structure of human left fusiform cortex are closely associated with perceptual learning of faces. *Current Biology*, 24(2), 222-227.
- Bianchi, F., Hjortkjær, J., Santurette, S., Zatorre, R. J., Siebner, H. R., & Dau, T. (2017). Subcortical and cortical correlates of pitch discrimination: Evidence for two levels of neuroplasticity in musicians. *Neuroimage*, 163, 398-412.
- Bianchi, F., Santurette, S., Wendt, D., & Dau, T. (2016). Pitch discrimination in musicians and non-musicians: Effects of harmonic resolvability and processing effort. *Journal of the Association for Research in Otolaryngology*, 17(1), 69-79.
- Blumenfeld-Katzir, T., Pasternak, O., Dagan, M., and Assaf, Y. (2011). Diffusion MRI of structural brain plasticity induced by a learning and memory task. *PLoS One* 6, e20678.
- Bode, D., & Carhart, R. (1973). Measurement of articulation functions using adaptive test procedures. *IEEE Transactions on Audio and Electroacoustics*, 21(3), 196-201.
- Bolinger, D. (1978). Intonation across languages. *Universals of human language*, 2, 471-524.
- Brattico, E., Nääätänen, R., & Tervaniemi, M. (2001). Context effects on pitch perception in musicians and nonmusicians: Evidence from event-related-potential recordings. *Music Perception*, 19(2), 199-222.
- Brechmann, A., & Scheich, H. (2005). Hemispheric shifts of sound representation in auditory cortex with conceptual listening. *Cerebral Cortex*, 15(5), 578-587.
- Bullmore, E., Fadili, J., Breakspear, M., Salvador, R., Suckling, J., & Brammer, M. (2003). Wavelets and statistical analysis of functional magnetic resonance images of the human brain. *Statistical methods in medical research*, 12(5), 375-399.
- Bushberg, J. T., Seibert, J. A., Leidholdt Jr, E. M., Boone, J. M., & Goldschmidt Jr, E. J. (2003). The essential physics of medical imaging. *Medical Physics*, 30(7), 1936-1936. Retrieved 8 May 2017, from http://199.116.233.101/index.php/MRI_Physics_and_Principles
- Butz, M., Wörgötter, F., & van Ooyen, A. (2009). Activity-dependent structural plasticity. *Brain research reviews*, 60(2), 287-305.

- Buxton, R. B., Wong, E. C., & Frank, L. R. (1998). Dynamics of blood flow and oxygenation changes during brain activation: the balloon model. *Magnetic resonance in medicine*, 39(6), 855-864.
- Callan, D. E., Tajima, K., Callan, A. M., Kubo, R., Masaki, S., & Akahane-Yamada, R. (2003). Learning-induced neural plasticity associated with improved identification performance after training of a difficult second-language phonetic contrast. *Neuroimage*, 19(1), 113-124.
- Carcagno, S., & Plack, C. J. (2011). Subcortical plasticity following perceptual learning in a pitch discrimination task. *Journal of the Association for Research in Otolaryngology*, 12(1), 89-100.
- Cariani, P. A., & Delgutte, B. (1996). Neural correlates of the pitch of complex tones. I. Pitch and pitch salience. *Journal of neurophysiology*, 76(3), 1698-1716.
- Cariani, P. A., & Delgutte, B. (1996). Neural correlates of the pitch of complex tones. II. Pitch shift, pitch ambiguity, phase invariance, pitch circularity, rate pitch, and the dominance region for pitch. *Journal of neurophysiology*, 76(3), 1717-1734.
- Catani, M., & ffytche, D. H. (2005). The rises and falls of disconnection syndromes. *Brain*, 128(10), 2224-2239.
- Chavhan, G. B. (2013). *MRI made easy*. JP Medical Ltd, London, UK.
- Chen, J. L., Penhune, V. B., & Zatorre, R. J. (2008). Listening to musical rhythms recruits motor regions of the brain. *Cerebral cortex*, 18(12), 2844-2854.
- Chermak, G. D., & Musiek, F. E. (Eds.). (2013). *Handbook of central auditory processing disorder, volume II: Comprehensive intervention* (Vol. 2). Plural Publishing, San Diego, California, US.
- Chung, S., Fieremans, E., Kucukboyaci, N. E., Wang, X., Morton, C. J., Novikov, D. S., ... & Lui, Y. W. (2018). Working memory and brain tissue microstructure: white matter tract integrity based on multi-shell diffusion MRI. *Scientific reports*, 8(1), 1-7.
- Crippa, A., C. P. Lanting, et al. (2010). A Diffusion Tensor Imaging Study on the Auditory System and Tinnitus. *Open Neuroimage Journal* 4: 16-25.
- Crossman, A. R., & Neary, D. (2018). *Neuroanatomy E-Book: An Illustrated Colour Text*. Elsevier Health Sciences.
- Darwin, C. J. (2005). Pitch and auditory grouping. In *Pitch* , pp. 278-305. Springer, New York, NY.
- Delhommeau, K., Micheyl, C., & Jouvent, R. (2005). Generalization of frequency discrimination learning across frequencies and ears: implications for underlying neural mechanisms in humans. *Journal of the Association for Research in Otolaryngology*, 6(2), 171-179.
- Delhommeau, K., Micheyl, C., Jouvent, R., & Collet, L. (2002). Transfer of learning across durations and ears in auditory frequency discrimination. *Perception & psychophysics*, 64(3), 426-436.
- Demany, L. (1985). Perceptual learning in frequency discrimination. *The Journal of the Acoustical Society of America*, 78(3), 1118-1120.

- Di Salle, F., Formisano, E., Seifritz, E., Linden, D. E., Scheffler, K., Saulino, C., ... & Marciano, E. (2001). Functional fields in human auditory cortex revealed by time-resolved fMRI without interference of EPI noise. *Neuroimage*, 13(2), 328-338.
- Dixon, W. J., & Mood, A. M. (1948). A method for obtaining and analyzing sensitivity data. *Journal of the American Statistical Association*, 43(241), 109-126.
- Dohn, A., Garza-Villarreal, E. A., Chakravarty, M. M., Hansen, M., Lerch, J. P., & Vuust, P. (2015). Gray-and white-matter anatomy of absolute pitch possessors. *Cerebral cortex*, 25(5), 1379-1388.
- Dosher, B., & Lu, Z. (2005). Mechanisms of Perceptual Learning. *Neurobiology of Attention*, Chap.78, 471-476.
- Draganski, B., Gaser, C., Busch, V., Schuierer, G., Bogdahn, U., and May, A. (2004). Neuroplasticity: changes in grey matter induced by training. *Nature* 427, 311–312.
- Eickhoff, S. B., Heim, S., Zilles, K., & Amunts, K. (2006). Testing anatomically specified hypotheses in functional imaging using cytoarchitectonic maps. *Neuroimage*, 32(2), 570-582.
- Eluvathingal, T. J., Hasan, K. M., Kramer, L., Fletcher, J. M., & Ewing-Cobbs, L. (2007). Quantitative diffusion tensor tractography of association and projection fibers in normally developing children and adolescents. *Cerebral cortex*, 17(12), 2760-2768.
- Embleton KV, Haroon HA, Morris DM, Ralph MAL, Parker GJM. (2010). Distortion correction for diffusion-weighted MRI tractography and fMRI in the temporal lobes. *Human Brain Mapping*. 31(10):1570-87.
- Encyclopedia Britannica. (1997) Inner ear anatomy. Retrieved 7 December 2020, from <https://www.britannica.com/science/inner-ear#ref196743>
- Engel, A., Hijmans, B. S., Cerliani, L., Bangert, M., Nanetti, L., Keller, P. E., & Keysers, C. (2014). Inter-individual differences in audio-motor learning of piano melodies and white matter fiber tract architecture. *Human brain mapping*, 35(5), 2483-2497.
- Fahle, M. (2001). Perceptual Learning. In *International Encyclopedia of the Social & Behavioral Sciences*, eds. Neil J Smelser and Paul B Baltes. Oxford: Pergamon, 11224–27. <http://www.sciencedirect.com/science/article/pii/B0080430767014625>.
- Feldman, D. E. (2009). Synaptic mechanisms for plasticity in neocortex. *Annual review of neuroscience*, 32, 33-55.
- Fields, R. D. (2008). White matter in learning, cognition and psychiatric disorders. *Trends in neurosciences*, 31(7), 361-370.
- Fields, R. D. (2015). A new mechanism of nervous system plasticity: activity-dependent myelination. *Nature Reviews Neuroscience*, 16(12), 756-767.
- Filippi, M., Cercignani, M., Inglese, M., Horsfield, M. A., & Comi, G. (2001). Diffusion tensor magnetic resonance imaging in multiple sclerosis. *Neurology*, 56(3), 304-311.
- Filley, C. M., & Fields, R. D. (2016). White matter and cognition: making the connection. *Journal of neurophysiology*, 116(5), 2093-2104.
- Fiorentini, A., & Berardi, N. (1980). Perceptual learning specific for orientation and spatial frequency. *Nature*, 287(5777), 43-44.
- Fischl, B. (2012). FreeSurfer. *Neuroimage*, 62(2), 774-781.

- Fischl, B., & Dale, A. M. (2000). Measuring the thickness of the human cerebral cortex from magnetic resonance images. *Proceedings of the National Academy of Sciences*, 97(20), 11050-11055.
- Fischl, B., Salat, D. H., Busa, E., Albert, M., Dieterich, M., Haselgrove, C., ... & Montillo, A. (2002). Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. *Neuron*, 33(3), 341-355.
- Fischl, B., Salat, D. H., Van Der Kouwe, A. J., Makris, N., Ségonne, F., Quinn, B. T., & Dale, A. M. (2004). Sequence-independent segmentation of magnetic resonance images. *Neuroimage*, 23, S69-S84.
- Fischl, B., Van Der Kouwe, A., Destrieux, C., Halgren, E., Ségonne, F., Salat, D. H., ... & Caviness, V. (2004). Automatically parcellating the human cerebral cortex. *Cerebral cortex*, 14(1), 11-22.
- Foster, N. E., & Zatorre, R. J. (2010). A role for the intraparietal sulcus in transforming musical pitch information. *Cerebral Cortex*, 20(6), 1350-1359.
- Foster, N. E., & Zatorre, R. J. (2010). Cortical structure predicts success in performing musical transformation judgments. *Neuroimage*, 53(1), 26-36.
- Frank, S. M., Reavis, E. A., Greenlee, M. W., & Tse, P. U. (2016). Pretraining cortical thickness predicts subsequent perceptual learning rate in a visual search task. *Cerebral Cortex*, 26(3), 1211-1220.
- Friederici, A. D. (2011). The brain basis of language processing: from structure to function. *Physiological reviews*, 91(4), 1357-1392.
- Gaab, N., Gaser, C., & Schlaug, G. (2006). Improvement-related functional plasticity following pitch memory training. *Neuroimage*, 31(1), 255-263.
- Gaab, N., Tallal, P., Kim, H., Lakshminarayanan, K., Archie, J. J., Glover, G. H., & Gabrieli, J. D. E. (2005). Neural correlates of rapid spectrotemporal processing in musicians and nonmusicians. *Annals of the New York Academy of Sciences*, 1060(1), 82-88.
- García-Pérez, M. A. (1998). Forced-choice staircases with fixed step sizes: asymptotic and small-sample properties. *Vision research*, 38(12), 1861-1881.
- Gaser, C., & Schlaug, G. (2003). Brain structures differ between musicians and non-musicians. *Journal of Neuroscience*, 23(27), 9240-9245.
- Geissler, A., Lanzenberger, R., Barth, M., Tahamtan, A. R., Milakara, D., Gartus, A., & Beisteiner, R. (2005). Influence of fMRI smoothing procedures on replicability of fine scale motor localization. *Neuroimage*, 24(2), 323-331.
- George, R., Dela Cruz, J., Singh, R., Ilangoan, R. (1998). MRI physics. Retrieved 3 July 2020, from <https://mrimaster.com/physics%20intro.html>
- Giacosa, C., Karpati, F. J., Foster, N. E., Penhune, V. B., & Hyde, K. L. (2016). Dance and music training have different effects on white matter diffusivity in sensorimotor pathways. *Neuroimage*, 135, 273-286.
- Gockel, H. E., Moore, B. C., Carlyon, R. P., & Plack, C. J. (2007). Effect of duration on the frequency discrimination of individual partials in a complex tone and on the discrimination of fundamental frequency. *The Journal of the Acoustical Society of America*, 121(1), 373-382.

- Goldstein, J. L. (1973). An optimum processor theory for the central formation of the pitch of complex tones. *The Journal of the Acoustical Society of America*, 54(6), 1496-1516.
- Golestani, N., Price, C. J., & Scott, S. K. (2011). Born with an ear for dialects? Structural plasticity in the expert phonetician brain. *Journal of Neuroscience*, 31(11), 4213-4220.
- Green, D. M., Richards, V. M., & Forrest, T. G. (1989). Stimulus step size and heterogeneous stimulus conditions in adaptive psychophysics. *The Journal of the Acoustical Society of America*, 86(2), 629-636.
- Griffiths, T. D., Büchel, C., Frackowiak, R. S., & Patterson, R. D. (1998). Analysis of temporal structure in sound by the human brain. *Nature neuroscience*, 1(5), 422-427.
- Griffiths, T. D., Uppenkamp, S., Johnsrude, I., Josephs, O., & Patterson, R. D. (2001). Encoding of the temporal regularity of sound in the human brainstem. *Nature neuroscience*, 4(6), 633-637.
- Hall, D. A., & Plack, C. J. (2009). Pitch processing sites in the human auditory brain. *Cerebral cortex*, 19(3), 576-585.
- Hall, D. A., Edmondson-Jones, A. M., & Fridriksson, J. (2006). Periodicity and frequency coding in human auditory cortex. *European Journal of Neuroscience*, 24(12), 3601-3610.
- Hall, D. A., Haggard, M. P., Summerfield, A. Q., Akeroyd, M. A., Palmer, A. R., & Bowtell, R. W. (2001). Functional magnetic resonance imaging measurements of sound-level encoding in the absence of background scanner noise. *The Journal of the Acoustical Society of America*, 109(4), 1559-1570.
- Hall, D. A., Haggard, M.P., Akeroyd, M.A., Palmer, A.R., Summerfield, A.Q., Elliott, M.R., Gurney, E.M., and Bowtell, R.W. "Sparse" temporal sampling in auditory fMRI. *Human brain mapping* 7, no. 3 (1999): 213-223.
- Hall, D. A., Summerfield, A. Q., Gonçalves, M. S., Foster, J. R., Palmer, A. R., & Bowtell, R. W. (2000). Time-course of the auditory BOLD response to scanner noise. *Magnetic Resonance in Medicine: An Official Journal of the International Society for Magnetic Resonance in Medicine*, 43(4), 601-606.
- Han, Y., Yang, H., Lv, Y.T., Zhu, C.Z., He, Y., Tang, H.H., Gong, Q.Y., Luo, Y.J., Zang, Y.F., Dong, Q., 2009. Gray matter density and white matter integrity in pianists' brain: a combined structural and diffusion tensor MRI study. *Neurosci. Lett.* 459, 3-6.
- Han, Y., Yang, H., Lv, Y.T., Zhu, C.Z., He, Y., Tang, H.H., Gong, Q.Y., Luo, Y.J., Zang, Y.F., Dong, Q., Hashemi, R. H., Bradley, W. G., & Lisanti, C. J. (2012). *MRI: the basics*. Lippincott Williams & Wilkins.
- Hashimoto, R., Homae, F., Nakajima, K., Miyashita, Y., & Sakai, K. L. (2000). Functional differentiation in the human auditory and language areas revealed by a dichotic listening task. *Neuroimage*, 12(2), 147-158.
- Haueisen, J., & Knösche, T. R. (2001). Involuntary motor activity in pianists evoked by music perception. *Journal of cognitive neuroscience*, 13(6), 786-792.
- Heinz, M. G., Colburn, H. S., & Carney, L. H. (2001). Evaluating auditory performance limits: I. One-parameter discrimination using a computational model for the auditory nerve. *Neural computation*, 13(10), 2273-2316.

- Herholz, S. C., & Zatorre, R. J. (2012). Musical training as a framework for brain plasticity: behavior, function, and structure. *Neuron*, 76(3), 486-502.
- Hickok, G., & Poeppel, D. (2007). The cortical organization of speech processing. *Nature reviews neuroscience*, 8(5), 393-402.
- Hoare, D. J., Kowalkowski, V. L., & Hall, D. A. (2012). Effects of frequency discrimination training on tinnitus: results from two randomised controlled trials. *Journal of the Association for Research in Otolaryngology*, 13(4), 543-559.
- Hoch, L., & Tillmann, B. (2010). Laterality effects for musical structure processing: A dichotic listening study. *Neuropsychology*, 24(5), 661.
- Hofstetter, S., Friedmann, N., & Assaf, Y. (2017). Rapid language-related plasticity: microstructural changes in the cortex after a short session of new word learning. *Brain Structure and Function*, 222(3), 1231-1241.
- Hofstetter, S., Tavor, I., Moryosef, S. T., & Assaf, Y. (2013). Short-term learning induces white matter plasticity in the fornix. *Journal of Neuroscience*, 33(31), 12844-12850.
- Hsu, J. L., Van Hecke, W., Bai, C. H., Lee, C. H., Tsai, Y. F., Chiu, H. C., ... & Leemans, A. (2010). Microstructural white matter changes in normal aging: a diffusion tensor imaging study with higher-order polynomial regression models. *Neuroimage*, 49(1), 32-43.
- Hubel, D. H., & Wiesel, T. N. (1965). Binocular interaction in striate cortex of kittens reared with artificial squint. *Journal of neurophysiology*, 28(6), 1041-1059.
- Humphries, C., Liebenthal, E., & Binder, J. R. (2010). Tonotopic organization of human auditory cortex. *Neuroimage*, 50(3), 1202-1211.
- Husain, F. T., Medina, R.E., et al. (2011). Neuroanatomical changes due to hearing loss and chronic tinnitus: A combined VBM and DTI study. *Brain Research* 1369(0): 74-88.
- Hutchinson, S., Lee, L. H. L., Gaab, N., & Schlaug, G. (2003). Cerebellar volume of musicians. *Cerebral cortex*, 13(9), 943-949.
- Hyde, K. L., Peretz, I., & Zatorre, R. J. (2008). Evidence for the role of the right auditory cortex in fine pitch resolution. *Neuropsychologia*, 46(2), 632-639.
- James, C. E., Oechslin, M. S., Van De Ville, D., Hauert, C. A., Descloux, C., & Lazeyras, F. (2014). Musical training intensity yields opposite effects on grey matter density in cognitive versus sensorimotor networks. *Brain Structure and Function*, 219(1), 353-366.
- James, W. (1890). The perception of reality. *Principles of psychology*, 2, 283-324.
- Jäncke, L., Gaab, N., Wüstenberg, T., Scheich, H., & Heinze, H. J. (2001). Short-term functional plasticity in the human auditory cortex: an fMRI study. *Cognitive brain research*, 12(3), 479-485.
- Jansen, A., Menke, R., Sommer, J., Förster, A. F., Bruchmann, S., Hempleman, J., ... & Knecht, S. (2006). The assessment of hemispheric lateralization in functional MRI—robustness and reproducibility. *Neuroimage*, 33(1), 204-217.
- Jellison, B. J., Field, A. S., Medow, J., Lazar, M., Salamat, M. S., & Alexander, A. L. (2004). Diffusion tensor imaging of cerebral white matter: a pictorial review of physics, fiber tract anatomy, and tumor imaging patterns. *American Journal of Neuroradiology*, 25(3), 356-369.

- Jenkinson, M., & Chappell, M. (2018). *Introduction to neuroimaging analysis*. Oxford University Press, UK.
- Jenkinson, M., Pechaud, M., & Smith, S. (2005, June). BET2: MR-based estimation of brain, skull and scalp surfaces. In *Eleventh annual meeting of the organization for human brain mapping* (Vol. 17, p. 167).
- Johnsrude, I. S., Penhune, V. B., & Zatorre, R. J. (2000). Functional specificity in the right human auditory cortex for perceiving pitch direction. *Brain*, 123(1), 155-163.
- Jones, M. R. (2010). Music perception: Current research and future directions. In *Music perception* (pp. 1-12). Springer, New York, NY.
- Jung, B. A., & Weigel, M. (2013). Spin echo magnetic resonance imaging. *Journal of Magnetic Resonance Imaging*, 37(4), 805-817.
- Kanabus, M., Szelag, E., Rojek, E., & Poppel, E. (2002). Temporal order judgement for auditory and visual stimuli. *Acta neurobiologiae experimentalis*, 62(4), 263-270.
- Karmarkar, U. R., & Buonomano, D. V. (2003). Temporal specificity of perceptual learning in an auditory discrimination task. *Learning & Memory*, 10(2), 141-147.
- Karni, A., & Sagi, D. (1991). Where practice makes perfect in texture discrimination: evidence for primary visual cortex plasticity. *Proceedings of the National Academy of Sciences*, 88(11), 4966-4970.
- Khalfa, S., Veillet, E., & Collet, L. (1998). Influence of handedness on peripheral auditory asymmetry. *European Journal of Neuroscience*, 10(8), 2731-2737.
- Kiernan, J. A. (2012). Anatomy of the temporal lobe. *Epilepsy research and treatment*, 2012. <https://doi.org/10.1155/2012/176157>
- King-Smith, P. E., Grigsby, S. S., Vingrys, A. J., Benes, S. C., & Supowitz, A. (1994). Efficient and unbiased modifications of the QUEST threshold method: theory, simulations, experimental evaluation and practical implementation. *Vision research*, 34(7), 885-912.
- Kishon-Rabin, L., Amir, O., Vexler, Y., & Zaltz, Y. (2001). Pitch discrimination: Are professional musicians better than non-musicians?. *Journal of basic and clinical physiology and pharmacology*, 12(2), 125-144.
- Kleim, J. A., & Jones, T. A. (2008). Principles of experience-dependent neural plasticity: implications for rehabilitation after brain damage. *Journal of speech, language, and hearing research*. 51(1):S225-39.
- Klein, A., Andersson, J., Ardekani, B. A., Ashburner, J., Avants, B., Chiang, M. C., ... & Song, J. H. (2009). Evaluation of 14 nonlinear deformation algorithms applied to human brain MRI registration. *Neuroimage*, 46(3), 786-802.
- Koelsch, S., & Siebel, W. A. (2005). Towards a neural basis of music perception. *Trends in cognitive sciences*, 9(12), 578-584.
- Koelsch, S., Fritz, T., Schulze, K., Alsop, D., Schlaug, G., 2005. Adults and children processing music: an fMRI study. *NeuroImage* 25, 1068–1076.
- Koelsch, S., Gunter, T., Friederici, A. D., & Schröger, E. (2000). Brain indices of music processing: "nonmusicians" are musical. *Journal of cognitive neuroscience*, 12(3), 520-541.

- Koerte, I. K., & Muehlmann, M. (2014). Diffusion tensor imaging. In *MRI in Psychiatry* (pp. 77-86). Springer, Berlin, Heidelberg.
- Kolb, B. (1999). Towards an ecology of cortical organization: experience and the changing brain. In *Neuronal plasticity: Building a bridge from the laboratory to the clinic* (pp. 17-34). Springer, Berlin, Heidelberg.
- Konorski, J. (1948). Conditioned reflexes and neuron organization. Cambridge University Press, New York.
- Lampit, A., Hallock, H., Suo, C., Naismith, S. L., & Valenzuela, M. (2015). Cognitive training-induced short-term functional and long-term structural plastic change is related to gains in global cognition in healthy older adults: a pilot study. *Frontiers in aging neuroscience*, 7, 14.
- Langers, D. R. (2014). Assessment of tonotopically organised subdivisions in human auditory cortex using volumetric and surface-based cortical alignments. *Human brain mapping*, 35(4), 1544-1561.
- Langers, D. R., & van Dijk, P. (2012). Mapping the tonotopic organization in human auditory cortex with minimally salient acoustic stimulation. *Cerebral Cortex*, 22(9), 2024-2038.
- Langers, D. R., Backes, W. H., & van Dijk, P. (2007). Representation of lateralization and tonotopy in primary versus secondary human auditory cortex. *Neuroimage*, 34(1), 264-273.
- Langers, D. R., Sanchez-Panchuelo, R. M., Francis, S. T., Krumbholz, K., & Hall, D. A. (2014). Neuroimaging paradigms for tonotopic mapping (II): the influence of acquisition protocol. *NeuroImage*, 100, 663-675.
- Lappe, C., Herholz, S. C., Trainor, L. J., & Pantev, C. (2008). Cortical plasticity induced by short-term unimodal and multimodal musical training. *Journal of Neuroscience*, 28(39), 9632-9639.
- Levitt, H. (1971). Transformed up-down methods in psychoacoustics. *The Journal of the Acoustical society of America*, 49(2B), 467-477.
- Limb, C. J. (2006). Structural and functional neural correlates of music perception. The Anatomical Record Part A: Discoveries in Molecular, Cellular, and Evolutionary Biology: An Official Publication of the American Association of Anatomists, 288(4), 435-446.
- Liu, T. (2011). A few thoughts on brain ROIs. *Brain imaging and behavior*, 5(3), 189.
- Lledo, P. M., Alonso, M., & Grubb, M. S. (2006). Adult neurogenesis and functional plasticity in neuronal circuits. *Nature Reviews Neuroscience*, 7(3), 179-193.
- Long, M. (2014). *Architectural acoustics*. Elsevier.
- Lopes, F. C. R., Alves-Leon, S. V., Godoy, J. M., de Souza Batista Scherpenhuijzen, S., Fezer, L., & Gasparetto, E. L. (2015). Optic neuritis and the visual pathway: Evaluation of neuromyelitis Optica Spectrum by resting-state fMRI and diffusion tensor MRI. *Journal of Neuroimaging*, 25(5), 807-812.
- Lopez-Poveda, E. A. (2014). Why do I hear but not understand? Stochastic undersampling as a model of degraded neural encoding of speech. *Frontiers in Neuroscience*, 8, 348.

- Loui, P., Alsop, D., & Schlaug, G. (2009). Tone deafness: a new disconnection syndrome?. *Journal of Neuroscience*, 29(33), 10215-10220.
- Loui, P., Li, H. C., & Schlaug, G. (2011). White matter integrity in right hemisphere predicts pitch-related grammar learning. *Neuroimage*, 55(2), 500-507.
- Lynch, M. P., & Eilers, R. E. (1991). Children's perception of native and nonnative musical scales. *Music Perception*, 9(1), 121-131.
- Maess, B., Koelsch, S., Gunter, T. C., & Friederici, A. D. (2001). Musical syntax is processed in Broca's area: an MEG study. *Nature neuroscience*, 4(5), 540-545.
- Maguire, E. A., Gadian, D. G., Johnsrude, I. S., Good, C. D., Ashburner, J., Frackowiak, R. S., & Frith, C. D. (2000). Navigation-related structural change in the hippocampi of taxi drivers. *Proceedings of the National Academy of Sciences*, 97(8), 4398-4403.
- Marin, O. S., & Perry, D. W. (1999). Neurological aspects of music perception and performance. In *The psychology of music* (pp. 653-724). Academic Press.
- Markham, J. A., & Greenough, W. T. (2004). Experience-driven brain plasticity: beyond the synapse. *Neuron glia biology*, 1(4), 351.
- Marmel, F., Plack, C. J., Hopkins, K., Carlyon, R. P., Gockel, H. E., & Moore, B. C. (2015). The role of excitation-pattern cues in the detection of frequency shifts in bandpass-filtered complex tones. *The Journal of the Acoustical Society of America*, 137(5), 2687-2697.
- Mathys, C., Loui, P., Zheng, X., & Schlaug, G. (2010). Non-invasive brain stimulation applied to Heschl's gyrus modulates pitch discrimination. *Frontiers in psychology*, 1, 193.
- Mazziotta, J. C., Phelps, M. E., Carson, R. E., & Kuhl, D. E. (1982). Tomographic mapping of human cerebral metabolism: auditory stimulation. *Neurology*, 32(9), 921-921.
- McClaskey, C. M. (2016). *Factors affecting relative pitch perception*. Doctoral dissertation, University of California Irvine.
- McRobbie, D. W., Moore, E. A., Graves, M. J., & Prince, M. R. (2017). *MRI from Picture to Proton*. Cambridge University Press.
- Mechelli, A., Crinion, J. T., Noppeney, U., O'Doherty, J., Ashburner, J., Frackowiak, R. S., & Price, C. J. (2004). Structural plasticity in the bilingual brain. *Nature*, 431(7010), 757-757.
- Meyer, G. F., Harding, S., & Perez, E. (2006). Multi-Resolution Analysis in Speech Perception. *Dynamics of Speech Production and Perception*, 374, 113.
- Micheyl, C., Delhommeau, K., Perrot, X., & Oxenham, A. J. (2006). Influence of musical and psychoacoustical training on pitch discrimination. *Hearing research*, 219(1-2), 36-47.
- Miller, S. E., Schlauch, R. S., & Watson, P. J. (2010). The effects of fundamental frequency contour manipulations on speech intelligibility in background noise. *The Journal of the Acoustical Society of America*, 128(1), 435-443.
- Mišić, B., Betzel, R. F., Griffa, A., De Reus, M. A., He, Y., Zuo, X. N., ... & Zatorre, R. J. (2018). Network-based asymmetry of the human auditory system. *Cerebral Cortex*, 28(7), 2655-2664.

- Moore, B. C. (1973). Frequency difference limens for short-duration tones. *The Journal of the Acoustical Society of America*, 54(3), 610-619.
- Moore, B. C. (2012). *An introduction to the psychology of hearing*. Brill, Leiden, The Netherlands.
- Moore, E., Schaefer, R. S., Bastin, M. E., Roberts, N., & Overy, K. (2014). Can musical training influence brain connectivity? Evidence from diffusion tensor MRI. *Brain sciences*, 4(2), 405-427.
- Moore, E., Schaefer, R. S., Bastin, M. E., Roberts, N., & Overy, K. (2017). Diffusion tensor MRI tractography reveals increased fractional anisotropy (FA) in arcuate fasciculus following music-cued motor training. *Brain and cognition*, 116, 40-46.
- Moreno, S., Bialystok, E., Barac, R., Schellenberg, E. G., Cepeda, N. J., & Chau, T. (2011). Short-term music training enhances verbal intelligence and executive function. *Psychological science*, 22(11), 1425-1433.
- Mori, S., Wakana, S., Nagae-Poetscher, L. M., & Van Zijl, P. C. M. (2006). MRI atlas of human white matter. *American Journal of Neuroradiology*, 27(6), 1384.
- Morosan, P., Rademacher, J., Schleicher, A., Amunts, K., Schormann, T., & Zilles, K. (2001). Human primary auditory cortex: cytoarchitectonic subdivisions and mapping into a spatial reference system. *Neuroimage*, 13(4), 684-701.
- Moseley, M. E., Cohen, Y., Kucharczyk, J., Mintorovitch, J., Asgari, H. S., Wendland, M. F., ... & Norman, D. (1990). Diffusion-weighted MR imaging of anisotropic water diffusion in cat central nervous system. *Radiology*, 176(2), 439-445.
- Moseley, M. E., Kucharczyk, J., Mintorovitch, J., Cohen, Y., Kurhanewicz, J., Derugin, N., ... & Norman, D. (1990). Diffusion-weighted MR imaging of acute stroke: correlation with T2-weighted and magnetic susceptibility-enhanced MR imaging in cats. *American Journal of Neuroradiology*, 11(3), 423-429.
- Müller, B. W., Stude, P., Nebel, K., Wiese, H., Ladd, M. E., Forsting, M., & Jueptner, M. (2003). Sparse imaging of the auditory oddball task with functional MRI. *Neuroreport*, 14(12), 1597-1601.
- Müller, R.A., Kleinhans, Courchesne, E., 2001. Broca's area and the discrimination of frequency transitions: a functional MRI study. *Brain Lang.* 76, 70e76.
- Münte, T. F., Altenmüller, E., & Jäncke, L. (2002). The musician's brain as a model of neuroplasticity. *Nature Reviews Neuroscience*, 3(6), 473-478.
- Nichols, T. E., & Holmes, A. P. (2002). Nonparametric permutation tests for functional neuroimaging: a primer with examples. *Human brain mapping*, 15(1), 1-25.
- Norman-Haignere, S., Kanwisher, N., & McDermott, J. H. (2013). Cortical pitch regions in humans respond primarily to resolved harmonics and are located in specific tonotopic regions of anterior auditory cortex. *Journal of Neuroscience*, 33(50), 19451-19469.
- Nudo, R. J., Wise, B. M., SiFuentes, F., & Milliken, G. W. (1996). Neural substrates for the effects of rehabilitative training on motor recovery after ischemic infarct. *Science*, 272(5269), 1791-1794.
- Oechslin, M. S., Gschwind, M., & James, C. E. (2018). Tracking training-related plasticity by combining fMRI and DTI: the right hemisphere ventral stream mediates musical syntax processing. *Cerebral Cortex*, 28(4), 1209-1218.

- Oechslin, M. S., Imfeld, A., Loenneker, T., Meyer, M., & Jäncke, L. (2010). The plasticity of the superior longitudinal fasciculus as a function of musical expertise: a diffusion tensor imaging study. *Frontiers in Human Neuroscience*, 3, 76.
- Ogawa, S., Lee, T. M., Kay, A. R., & Tank, D. W. (1990). Brain magnetic resonance imaging with contrast dependent on blood oxygenation. *Proceedings of the National Academy of Sciences*, 87(24), 9868-9872.
- Ohl, F. W., & Scheich, H. (2005). Learning-induced plasticity in animal and human auditory cortex. *Current opinion in neurobiology*, 15(4), 470-477.
- Ohnishi, T., Matsuda, H., Asada, T., Aruga, M., Hirakata, M., Nishikawa, M., ... & Imabayashi, E. (2001). Functional anatomy of musical perception in musicians. *Cerebral Cortex*, 11(8), 754-760.
- Oldendorf, W. (1988). Advantages and Disadvantages of MRI. In *Basics of Magnetic Resonance Imaging* (pp. 125-138). Springer, Boston, MA.
- Olulade, O., Hu, S., Gonzalez-Castillo, J., Tamer Jr, G. G., Luh, W. M., Ulmer, J. L., & Talavage, T. M. (2011). Assessment of temporal state-dependent interactions between auditory fMRI responses to desired and undesired acoustic sources. *Hearing research*, 277(1-2), 67-77.
- Ontaneda, D., Sakaie, K., Lin, J., Wang, X., Lowe, M. J., Phillips, M. D., & Fox, R. J. (2014). Identifying the start of multiple sclerosis injury: a serial DTI study. *Journal of Neuroimaging*, 24(6), 569-576.
- Ostertagová, E. (2012). Modelling using polynomial regression. *Procedia Engineering*, 48, 500-506.
- Oxenham, A. J. (2008). Pitch perception and auditory stream segregation: implications for hearing loss and cochlear implants. *Trends in amplification*, 12(4), 316-331.
- Oxenham, A. J. (2013). Revisiting place and temporal theories of pitch. *Acoustical science and technology*, 34(6), 388-396.
- Pantev, C., Oostenveld, R., Engelien, A., Ross, B., Roberts, L. E., & Hoke, M. (1998). Increased auditory cortical representation in musicians. *Nature*, 392(6678), 811-814.
- Park, I. S., Lee, K. J., Han, J. W., Lee, N. J., Lee, W. T., & Park, K. A. (2009). Experience-dependent plasticity of cerebellar vermis in basketball players. *The cerebellum*, 8(3), 334.
- Patterson, R. D., Uppenkamp, S., Johnsrude, I. S., & Griffiths, T. D. (2002). The processing of temporal pitch and melody information in auditory cortex. *Neuron*, 36(4), 767-776.
- Perception Lecture Notes: Auditory Pathways and Sound Localization. (2001). Retrieved 7 December 2020, from <http://www.cns.nyu.edu/~david/courses/perception/lecturenotes/localization/localization.html>
- Peterson, A. J., Huet, A., Bourien, J., Puel, J. L., & Heil, P. (2018). Recovery of auditory-nerve-fiber spike amplitude under natural excitation conditions. *Hearing Research*, 370, 248-263.
- Pickles, J. (2013). *An introduction to the physiology of hearing*. Brill, Leiden, The Netherlands.

- Pickles, J. O. (2015). Auditory pathways: anatomy and physiology. In *Handbook of clinical neurology*, Vol. 129, pp. 3-25. Elsevier.
- Pietrasik, W., Cribben, I., Olsen, F., Huang, Y., & Malykhin, N. V. (2020). Diffusion tensor imaging of the corpus callosum in healthy aging: Investigating higher order polynomial regression modelling. *NeuroImage*, 116675.
- Pinterest. 2020. *Structures Of The Ear / In Chapter 04: Senses / From Psychology: An Introduction By Russ Dewey / Ear Anatomy, Human Ear Diagram, Human Ear Anatomy*. [online] Available at: <<https://www.pinterest.co.uk/pin/465770786461810962/>> [Accessed 1 December 2020].
- Plack, C. J., & Oxenham, A. J. (2005). The psychophysics of pitch. In *Pitch*, pp. 7-55. Springer, New York, NY.
- Popper, A. N., & Fay, R. R. (2005). *Sound source localization* (pp. 272-316). New York: Springer.
- Prins, N. (2016). *Psychophysics: a practical introduction*. Elsevier Academic Press, Cambridge, Massachusetts, US.
- Purves, D., Augustine, G., Fitzpatrick, D., Katz, L., LaMantia, A., McNamara, J., & Williams, S. (2001). *Neuroscience* 2nd edition. Sinauer Associates, Sunderland, MA.
- Quizlet. (2020, 14 April). Major Fibers in Brain Lateral View Diagram. Retrieved from <https://quizlet.com/305008690/major-fibers-in-brain-lateral-view-diagram/>
- Rademacher, J., Morosan, P., Schormann, T., Schleicher, A., Werner, C., Freund, H. J., & Zilles, K. (2001). Probabilistic mapping and volume measurement of human primary auditory cortex. *Neuroimage*, 13(4), 669-683.
- ReconAllDevTable - Free Surfer Wiki. (2020). Retrieved 22 November 2019, from <https://surfer.nmr.mgh.harvard.edu/fswiki/ReconAllDevTable>.
- Roth, D. A. E., Avrahami, T., Sabo, Y., & Kishon-Rabin, L. (2004). Frequency discrimination training: is there ear symmetry?. *Journal of basic and clinical physiology and pharmacology*, 15(1-2), 15-28.
- Rüber, T., Lindenberg, R., & Schlaug, G. (2015). Differential adaptation of descending motor tracts in musicians. *Cerebral cortex*, 25(6), 1490-1498.
- Sagi, Y., Tavor, I., Hofstetter, S., Tzur-Moryosef, S., Blumenfeld-Katzir, T., & Assaf, Y. (2012). Learning in the fast lane: new insights into neuroplasticity. *Neuron*, 73(6), 1195-1203.
- Sargolzaei, S., Sargolzaei, A., Cabrerizo, M., Chen, G., Goryawala, M., Noei, S., ... & Adjouadi, M. (2015). A practical guideline for intracranial volume estimation in patients with Alzheimer's disease. *BMC bioinformatics*, 16(7), S8.
- Schaefer, P. W., Grant, P. E., & Gonzalez, R. G. (2000). Diffusion-weighted MR imaging of the brain. *Radiology*, 217(2), 331-345.
- Scheffler, K., Bilecen, D., Schmid, N., Tschopp, K., & Seelig, J. (1998). Auditory cortical responses in hearing subjects and unilateral deaf patients as detected by functional magnetic resonance imaging. *Cerebral cortex (New York, NY: 1991)*, 8(2), 156-163.
- Schlaug, G. (2001). The brain of musicians: a model for functional and structural adaptation. *Annals of the New York Academy of Sciences*, 930(1), 281-299.

- Schlaug, G., Jancke, L., Huang, Y., & Steinmetz, H. (1995). In vivo evidence of structural brain asymmetry in musicians. *Science*, 267(5198), 699-701.
- Schlaug, G., Jäncke, L., Huang, Y., Staiger, J. F., & Steinmetz, H. (1995a). Increased corpus callosum size in musicians. *Neuropsychologia*, 33(8), 1047-1055.
- Schmithorst, V. J., & Holland, S. K. (2003). The effect of musical training on music processing: a functional magnetic resonance imaging study in humans. *Neuroscience Letters*, 348(2), 65-68.
- Schmithorst, V. J., & Holland, S. K. (2004). Event-related fMRI technique for auditory processing with hemodynamics unrelated to acoustic gradient noise. *Magnetic Resonance in Medicine: An Official Journal of the International Society for Magnetic Resonance in Medicine*, 51(2), 399-402.
- Schneider, P., Scherg, M., Dosch, H. G., Specht, H. J., Gutschalk, A., & Rupp, A. (2002). Morphology of Heschl's gyrus reflects enhanced activation in the auditory cortex of musicians. *Nature neuroscience*, 5(7), 688-694.
- Schneider, P., Sluming, V., Roberts, N., Scherg, M., Goebel, R., Specht, H. J., ... & Rupp, A. (2005). Structural and functional asymmetry of lateral Heschl's gyrus reflects pitch perception preference. *Nature neuroscience*, 8(9), 1241-1247.
- Scholz, J., Klein, M.C., Behrens, T.E., and Johansen-Berg, H. (2009). Training induces changes in white-matter architecture. *Nat. Neurosci* 12, 1370–1371.
- Schönwiesner, M., Krumbholz, K., Rübsamen, R., Fink, G. R., & von Cramon, D. Y. (2007). Hemispheric asymmetry for auditory processing in the human auditory brain stem, thalamus, and cortex. *Cerebral Cortex*, 17(2), 492-499.
- Schouten, J. F. (1940). The residue and the mechanism of hearing. In *Proc. K. Ned. Akad. Wet.* 43, 991-999.
- Schouten, J. F., Ritsma, R. J., & Cardozo, B. L. (1962). Pitch of the residue. *The Journal of the Acoustical Society of America*, 34(9B), 1418-1424.
- Schulze, K., Zysset, S., Mueller, K., Friederici, A.D., Koelsch, S., 2011. Neuroarchitecture working memory in nonmusicians and musicians. *Hum. Brain Mapp.* 32 (5), 771–783.
- Schwarz, C. G., Reid, R. I., Gunter, J. L., Senjem, M. L., Przybelski, S. A., Zuk, S. M., ... & Thompson, P. M. (2014). Improved DTI registration allows voxel-based analysis that outperforms tract-based spatial statistics. *Neuroimage*, 94, 65-78.
- Sebastian. (2011). Temporal lobe, gyri and sulci (diagrams). Retrieved June 22, 2020, from <https://commons.wikimedia.org/wiki/File:TempCapts.png>
- Sergeant, D. (1973). Measurement of pitch discrimination. *Journal of Research in Music Education*, 21(1), 3-19.
- Shahin, A., Roberts, L. E., & Trainor, L. J. (2004). Enhancement of auditory cortical development by musical experience in children. *Neuroreport*, 15(12), 1917-1921.
- Siebert, W. M. (1970). Frequency discrimination in the auditory system: Place or periodicity mechanisms?. *Proceedings of the IEEE*, 58(5), 723-730.
- Sinai, A., & Pratt, H. (2003). High-resolution time course of hemispheric dominance revealed by low-resolution electromagnetic tomography. *Clinical Neurophysiology*, 114, 1181–1188.

- Sluming, V., Barrick, T., Howard, M., Cezayirli, E., Mayes, A., & Roberts, N. (2002). Voxel-based morphometry reveals increased gray matter density in Broca's area in male symphony orchestra musicians. *Neuroimage*, 17(3), 1613-1622.
- Smith, S. M., Jenkinson, M., Johansen-Berg, H., Rueckert, D., Nichols, T. E., Mackay, C. E., ... & Behrens, T. E. (2006). Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. *Neuroimage*, 31(4), 1487-1505.
- Smith, S.M., Jenkinson, M., Woolrich, M.W., et al. Advances in functional and structural MR image analysis and implementation as FSL. (2004). *Neuroimage* 23(suppl 1):S208–19.
- Smith, S.M., Nichols, T.E., 2009. Threshold-free cluster enhancement: addressing problems of smoothing, threshold dependence and localisation in cluster inference. *NeuroImage* 44, 83–98.
- Snell, R. S. (2010). *Clinical neuroanatomy*. Lippincott Williams & Wilkins. Philadelphia, US.
- Specht, K., & Reul, J. (2003). Functional segregation of the temporal lobes into highly differentiated subsystems for auditory perception: an auditory rapid event-related fMRI-task. *Neuroimage*, 20(4), 1944-1954.
- Spiegel, M. F., & Watson, C. S. (1984). Performance on frequency-discrimination tasks by musicians and nonmusicians. *The Journal of the Acoustical Society of America*, 76(6), 1690-1695.
- Sprawls, P. (2000). *Magnetic resonance imaging: principles, methods, and techniques*. Medical Physics Publishing. Retrieved 8 May 2017, from http://199.116.233.101/index.php/MRI_Physics_and_Principles
- Stave, E. A., De Bellis, M. D., Hooper, S. R., Woolley, D. P., Chang, S. K., & Chen, S. D. (2017). Dimensions of attention associated with the microstructure of corona radiata white matter. *Journal of child neurology*, 32(5), 458-466.
- Steele, C. J., Bailey, J. A., Zatorre, R. J., & Penhune, V. B. (2013). Early musical training and white-matter plasticity in the corpus callosum: evidence for a sensitive period. *Journal of Neuroscience*, 33(3), 1282-1290.
- Stojanovic, J. (2010). Cortical functional activations in musical talents and nontalents in visuomotor and auditory tasks: implications of the effect of practice on neuroplasticity. Doctoral dissertation, Julius Maximilians University, Würzburg, Germany.
- Sundgren, P. C., Dong, Q., Gomez-Hassan, D., Mukherji, S. K., Maly, P., & Welsh, R. (2004). Diffusion tensor imaging of the brain: review of clinical applications. *Neuroradiology*, 46(5), 339-350.
- Suzuki, M., Kitano, H., Kitanishi, T., Itou, R., Shiino, A., Nishida, Y., ... & Kitajima, K. (2002). Cortical and subcortical activation with monaural monosyllabic stimulation by functional MRI. *Hearing research*, 163(1-2), 37-45.
- Takahashi, T., Wood, S. J., Yung, A. R., Walterfang, M., Phillips, L. J., Soulsby, B., ... & Pantelis, C. (2010). Superior temporal gyrus volume in antipsychotic-naïve people at risk of psychosis. *The British Journal of Psychiatry*, 196(3), 206-211.
- Talavage, T. M., Edmister, W. B., Ledden, P. J., & Weisskoff, R. M. (1999). Quantitative assessment of auditory cortex responses induced by imager acoustic noise. *Human brain mapping*, 7(2), 79-88.

- Talbot, K., Louneva, N., Cohen, J. W., Kazi, H., Blake, D. J., & Arnold, S. E. (2011). Synaptic dysbindin-1 reductions in schizophrenia occur in an isoform-specific manner indicating their subsynaptic location. *PloS one*, 6(3), e16886.
- Tanaka, H., Fujita, N., Watanabe, Y., Hirabuki, N., Takanashi, M., Oshiro, Y., & Nakamura, H. (2000). Effects of stimulus rate on the auditory cortex using fMRI with ‘sparse’ temporal sampling. *Neuroreport*, 11(9), 2045-2049.
- Tervaniemi, M., Just, V., Koelsch, S., Widmann, A., & Schröger, E. (2005). Pitch discrimination accuracy in musicians vs nonmusicians: an event-related potential and behavioral study. *Experimental brain research*, 161(1), 1-10.
- Tervaniemi, M., Medvedev, S. V., Alho, K., Pakhomov, S. V., Roudas, M. S., van Zuijen, T. L., & Näätänen, R. (2000). Lateralized automatic auditory processing of phonetic versus musical information: a PET study. *Human brain mapping*, 10(2), 74-79.
- Thomas, C., & Baker, C. I. (2013). Teaching an adult brain new tricks: a critical review of evidence for training-dependent structural plasticity in humans. *NeuroImage*, 73, 225-236.
- Tillmann, B., Koelsch, S., Escoffier, N., Bigand, E., Lalitte, P., Friederici, A. D., & von Cramon, D. Y. (2006). Cognitive priming in sung and instrumental music: activation of inferior frontal cortex. *Neuroimage*, 31(4), 1771-1782.
- Vital-Durand, F., & Jeannerod, M. (Eds.). (1975). *Aspects of neural plasticity (Plasticité nerveuse): colloque, Lyon-Pérouges, 11-12 avril 1975* (Vol. 43). Editions de l'Institut national de la santé et de la recherche médicale.
- Warren, J. D., & Griffiths, T. D. (2003). Distinct mechanisms for processing spatial sequences and pitch sequences in the human auditory brain. *Journal of Neuroscience*, 23(13), 5799-5804.
- Watanabe, T., & Sasaki, Y. (2015). Perceptual learning: toward a comprehensive theory. *Annual review of psychology*, 66, 197-221.
- Watson, A. B., & Fitzhugh, A. (1990). The method of constant stimuli is inefficient. *Perception & psychophysics*, 47(1), 87-91.
- Wengenroth, M., Blatow, M., Heinecke, A., Reinhardt, J., Stippich, C., Hofmann, E., & Schneider, P. (2014). Increased volume and function of right auditory cortex as a marker for absolute pitch. *Cerebral Cortex*, 24(5), 1127-1137.
- Wetherill, G. B., & Levitt, H. (1965). Sequential estimation of points on a psychometric function. *British Journal of Mathematical and Statistical Psychology*, 18(1), 1-10.
- Whitwell, J. L., Crum, W. R., Watt, H. C., & Fox, N. C. (2001). Normalization of cerebral volumes by use of intracranial volume: implications for longitudinal quantitative MR imaging. *American Journal of Neuroradiology*, 22(8), 1483-1489.
- Woldorff, M. G., Tempelmann, C., Fell, J., Tegeler, C., Gaschler-Markefski, B., Hinrichs, H., ... & Scheich, H. (1999). Lateralized auditory spatial perception and the contralaterality of cortical processing as studied with functional magnetic resonance imaging and magnetoencephalography. *Human brain mapping*, 7(1), 49-66.
- Wright, B. A., & Zhang, Y. (2009). A review of the generalization of auditory learning. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 364(1515), 301-311.

- Wright, B. A., Buonomano, D. V., Mahncke, H. W., & Merzenich, M. M. (1997). Learning and generalization of auditory temporal–interval discrimination in humans. *Journal of Neuroscience*, 17(10), 3956-3963.
- Wyatt, R. F. (1945). Improvability of pitch discrimination. *Psychological Monographs*, 58(2), i.
- Yacoub, E., Shmuel, A., PfeuVer, J., Van De Moortele, P. F., Adriany, G., Ugurbil, K., et al. (2001). Investigation of the initial dip in fMRI at 7 Tesla. *NMR in Biomedicine*, 14, 408–412.
- Yetkin, F. Z., Roland, P. S., Christensen, W. F., & Purdy, P. D. (2004). Silent functional magnetic resonance imaging (fMRI) of tonotopicity and stimulus intensity coding in human primary auditory cortex. *The Laryngoscope*, 114(3), 512-518.
- Yost, W. A. (2009). Pitch perception. *Attention, Perception, & Psychophysics*, 71(8), 1701-1715.
- Zaeble, T., Schmidt, C. F., Meyer, M., Baumann, S., Baltes, C., Boesiger, P., & Jancke, L. (2007). Comparison of “silent” clustered and sparse temporal fMRI acquisitions in tonal and speech perception tasks. *Neuroimage*, 37(4), 1195-1204.
- Zatorre, R. J., & Samson, S. (1991). Role of the right temporal neocortex in retention of pitch in auditory short-term memory. *Brain*, 114(6), 2403-2417.
- Zatorre, R. J., Belin, P., & Penhune, V. B. (2002). Structure and function of auditory cortex: music and speech. *Trends in cognitive sciences*, 6(1), 37-46.
- Zatorre, R. J., Chen, J. L., & Penhune, V. B. (2007). When the brain plays music: auditory–motor interactions in music perception and production. *Nature reviews neuroscience*, 8(7), 547-558.
- Zatorre, R. J., Evans, A. C., & Meyer, E. (1994). Neural mechanisms underlying melodic perception and memory for pitch. *Journal of neuroscience*, 14(4), 1908-1919.
- Zatorre, R. J., Perry, D. W., Beckett, C. A., Westbury, C. F., & Evans, A. C. (1998). Functional anatomy of musical processing in listeners with absolute pitch and relative pitch. *Proceedings of the National Academy of Sciences*, 95(6), 3172-3177.
- Zatorre, R.J., 1988. Pitch perception of complex tones and human temporal-lobe function. *J. Acoust. Soc. Am.* 84, 566–572.
- Zeitlin, L. R. (1964). Frequency discrimination of pure and complex tones. *The Journal of the Acoustical Society of America*, 36(5), 1027-1027.
- Zhang, Y. X., Moore, D. R., Guiraud, J., Molloy, K., Yan, T. T., & Amitay, S. (2016). Auditory discrimination learning: Role of working memory. *PloS one*, 11(1).
- Zilles, K. (1992). Neuronal plasticity as an adaptive property of the central nervous system. *Annals of Anatomy-Anatomischer Anzeiger*, 174(5), 383-391.

Appendix A – Result Tables

Section 1) The Global Activation of the Functional Experiments at Baseline:

Contrast Name	Region Label	MNI Coordinates			
		t-value	x	y	z
Task>Rest	L Middle Temporal Gyrus	12.39	-60	-28	6
	L Heschl's Gyrus	11.75	-34	-32	13
	L Superior Temporal Gyrus	7.22	-59	-32	7
	R Superior Temporal Gyrus	11.60	56	-20	2
	R Superior Temporal Gyrus	8.09	62	-18	1
	R Heschl's Gyrus	10.48	42	-27	10
	L Posterior-Medial Frontal	9.65	-4	4	60
	R Ventral Dorsal Caudate	9.01	10	-20	-8
	L Ventral Dorsal Caudate	7.91	-12	-24	-4
	L Precentral Gyrus	7.69	-28	-24	48
	L Putamen	7.07	-20	0	0
	R Putamen	6.68	20	4	-2
	R Thalamus Proper	7.481	-10	-20	4

Table 1.1 shows the average global activation of the fMRI ‘task-related’ model (modelling pitch discrimination tasks in all four acoustic stimuli conditions) of all participants at baseline. Map threshold is set at $t > 6.28$ (FWE corrected, $p < 0.05$). Regions were automatically labelled using the AnatomyToolbox atlas. x , y , and z =Montreal Neurological Institute (MNI) coordinates in the left-right, anterior-posterior, and inferior-superior dimensions, respectively.

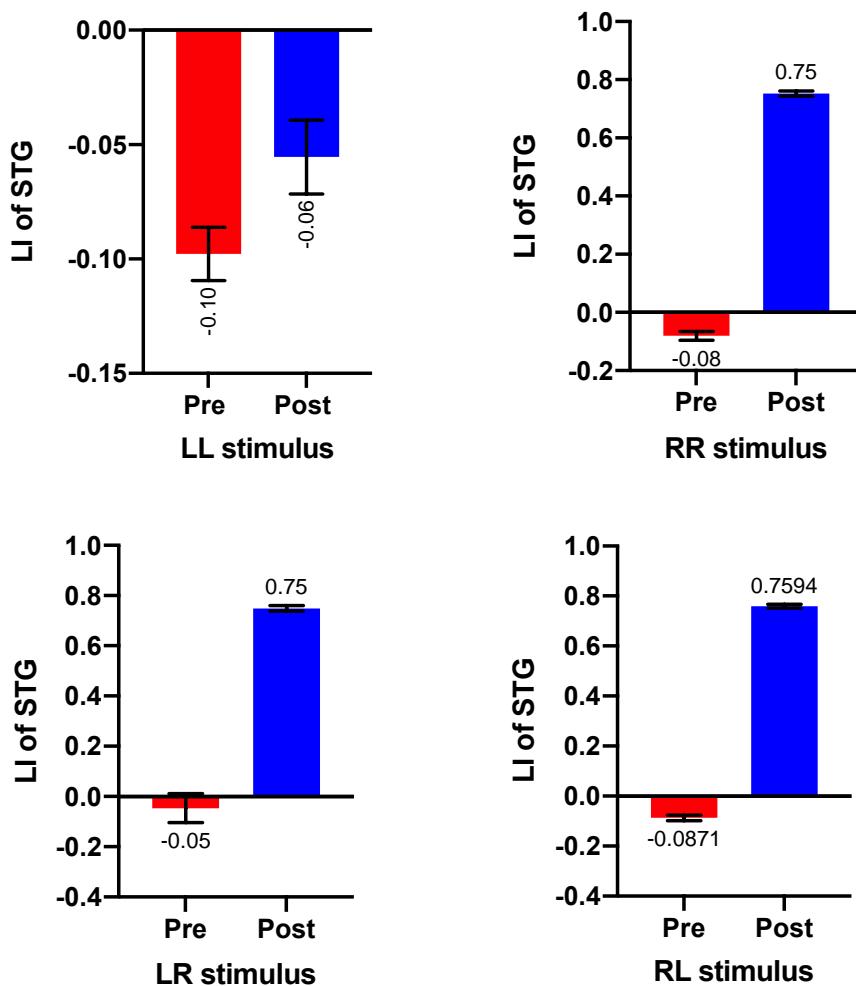


Figure 1.1 Graphs illustrates a comparison of lateralisation indices (LI) of different stimuli presentations both before and after training. The functional activity became left lateralised after the training in RR, LR and RL stimuli, but not after LL stimulus. Negative LI demonstrates right-hemisphere dominance, whereas positive LI means left-hemisphere dominance and an LI around zero is considered to show bilateral evenness effect. LL: both tones to the left ear; RR: both tones to the right ear; LR: first tone to the left ear and second tone to the right ear; RL: first tone to the right ear and second tone to the left ear; STG: superior temporal gyrus. Error bars represent the standard error of the mean.

**Section 2) Diffusion Scalar Metrics Comparison Result Tables for Controls
Before and After the Auditory Training Period using DTI - ROIs Analysis
Based on Anatomical Masks:**

ROI	Pre	Post	Controls
	Mean (SD)	Mean (SD)	Paired t test (df= 14)
<u>FA (Post > Pre)</u>			
R CR	0.54 (0.02)	0.54 (0.02)	t = 1.30, p = 0.22
L CR	0.54 (0.02)	0.54 (0.02)	t = 0.66, p = 0.52
R CST	0.54 (0.02)	0.54 (0.02)	t = 0.19, p = 0.85
L CST	0.57 (0.02)	0.57 (0.02)	t = 0.26, p = 0.80
R SLF	0.56 (0.03)	0.56 (0.03)	t = 0.59, p = 0.56
L SLF	0.56 (0.02)	0.57 (0.03)	t = 0.50, p = 0.63
BCC	0.72 (0.02)	0.72 (0.03)	t = 0.95, p = 0.36
GCC	0.76 (0.02)	0.76 (0.02)	t = 0.30, p = 0.77
SCC	0.80 (0.02)	0.80 (0.02)	t = 0.25, p = 0.80

Table 2.1 FA measurement comparison for controls before and after the auditory training period across anatomical masks of ROIs. CST: corticospinal tract; CR: anterior corona radiata; SLF: superior longitudinal fasciculi; BCC: body of corpus callosum; GCC: genu of corpus callosum; SCC: splenium of corpus callosum.

ROI	Pre-training	Post-training	Controls
	Mean (SD)	Mean (SD)	Paired t test (df= 14)
<u>MD (Pre>Post)</u>			
R CR	0.76 (0.02)	0.76 (0.02)	t = 0.81, p = 0.43
L CR	0.74 (0.03)	0.75 (0.01)	t = 0.12, p = 0.90
R CST	0.71 (0.01)	0.71 (0.02)	t = 0.83, p = 0.42
L CST	0.71 (0.01)	0.70 (0.02)	t = 0.41, p = 0.69
R SLF	0.70 (0.02)	0.71 (0.02)	t = 1.73, p = 0.11
L SLF	0.70 (0.02)	0.70 (0.02)	t = 0.22, p = 0.83
BCC	0.82 (0.03)	0.82 (0.03)	t = 0.98, p = 0.34
GCC	0.77 (0.03)	0.77 (0.03)	t = 0.61, p = 0.55
SCC	0.74 (0.02)	0.74 (0.02)	t = 0.02, p = 0.98

Table 2.2 MD measure comparison for controls before and after the auditory training period across anatomical masks of ROIs. MD Mean (in 10^3) and SD (in 10^{-3}) mm^2/s .

ROI	Pre-training	Post-training	Controls
	Mean (SD)	Mean (SD)	Paired t test (df= 14)
<u>RD(Pre>Post)</u>			
R CR	0.51(0.02)	0.51(0.02)	t = 0.55, p = 0.59
L CR	0.50 (0.03)	0.49 (0.01)	t = 1.02, p = 0.32
R CST	0.46 (0.02)	0.45 (0.02)	t = 1.92, p = 0.08
L CST	0.45 (0.02)	0.45 (0.01)	t = 1.33, p = 0.21
R SLF	0.46 (0.03)	0.46 (0.02)	t = 1.33, p = 0.21
L SLF	0.45 (0.02)	0.45 (0.02)	t = 0.07, p = 0.95
BCC	0.39 (0.03)	0.39 (0.03)	t = 1.23, p = 0.24
GCC	0.34 (0.03)	0.33 (0.03)	t = 0.53, p = 0.61
SCC	0.28 (0.02)	0.28 (0.02)	t = 0.18, p = 0.86
<u>AD (Pre>Post)</u>			
R CR	1.27 (0.04)	1.26 (0.03)	t = 1.12, p = 0.28
L CR	1.25 (0.03)	1.24 (0.03)	t = 1.64, p = 0.12
R CST	1.19 (0.02)	1.18 (0.02)	t = 1.43, p = 0.17
L CST	1.17 (0.03)	1.17 (0.03)	t = 1.85, p = 0.09
R SLF	0.12 (0.04)	0.12 (0.05)	t = 1.73, p = 0.11
L SLF	1.20 (0.04)	1.20 (0.04)	t = 1.94, p = 0.07
BCC	0.17 0.04)	0.17 (0.05)	t = 0.56, p = 0.59
GCC	1.64 (0.04)	1.64 (0.05)	t = 0.68, p = 0.51
SCC	1.65 (0.04)	1.65 (0.04)	t = 0.22, p = 0.83

Table 2.3 Diffusion scalar metrics (RD and AD) comparison for controls before and after the auditory training period across anatomical masks of ROIs. MD Mean (in 10^3) and SD (in 10^{-3}) mm 2 /s.

Section 3) Correlation Between the Change in Psychoacoustic Performance and the Change in Diffusion Measures in Trainees

ROI	Pearson r	p value	Pearson r	p value	Pearson r	p value	Pearson r	p value
BCC	-0.08	0.69	-0.04	0.86	-0.09	0.66	0.06	0.76
GCC	-0.09	0.67	-0.01	0.97	0.05	0.79	-0.10	0.61
SCC	0.01	0.99	-0.21	0.30	-0.26	0.19	-0.10	0.62
R SLF	0.03	0.88	0.18	0.39	-0.54	0.35	-0.15	0.47
L SLF	FA	0.02	0.92	MD	-0.03	0.90	RD	-0.03
R CR	0.24	-0.17	-0.24	0.23	-0.62	0.13	-0.09	0.65
L CR	-0.18	0.37	-0.11	0.58	-0.12	0.56	-0.122	0.55
R CST	0.04	-0.84	-0.15	0.47	-0.49	0.52	-0.14	0.50
L CST	0.24	-0.17	0.001	0.99	-0.02	0.89	0.03	0.89

Table 3.1 shows the correlation between the change (post-pre) in psychoacoustic performance and the change (post-pre) in FA, MD, AD and AD measures.

Appendix B – Participants’ Instructions Letter.

Section 1) Participant Instructions Letter.

Section 2) LiMRIC MRI Screening Form.

Section 3) Edinburgh Handedness Form.

Appendix C

Section 1) Psychoacoustic Training Codes (used for training in the lab).

Section 2) fMRI Auditory Task Code (used inside MRI scanner).