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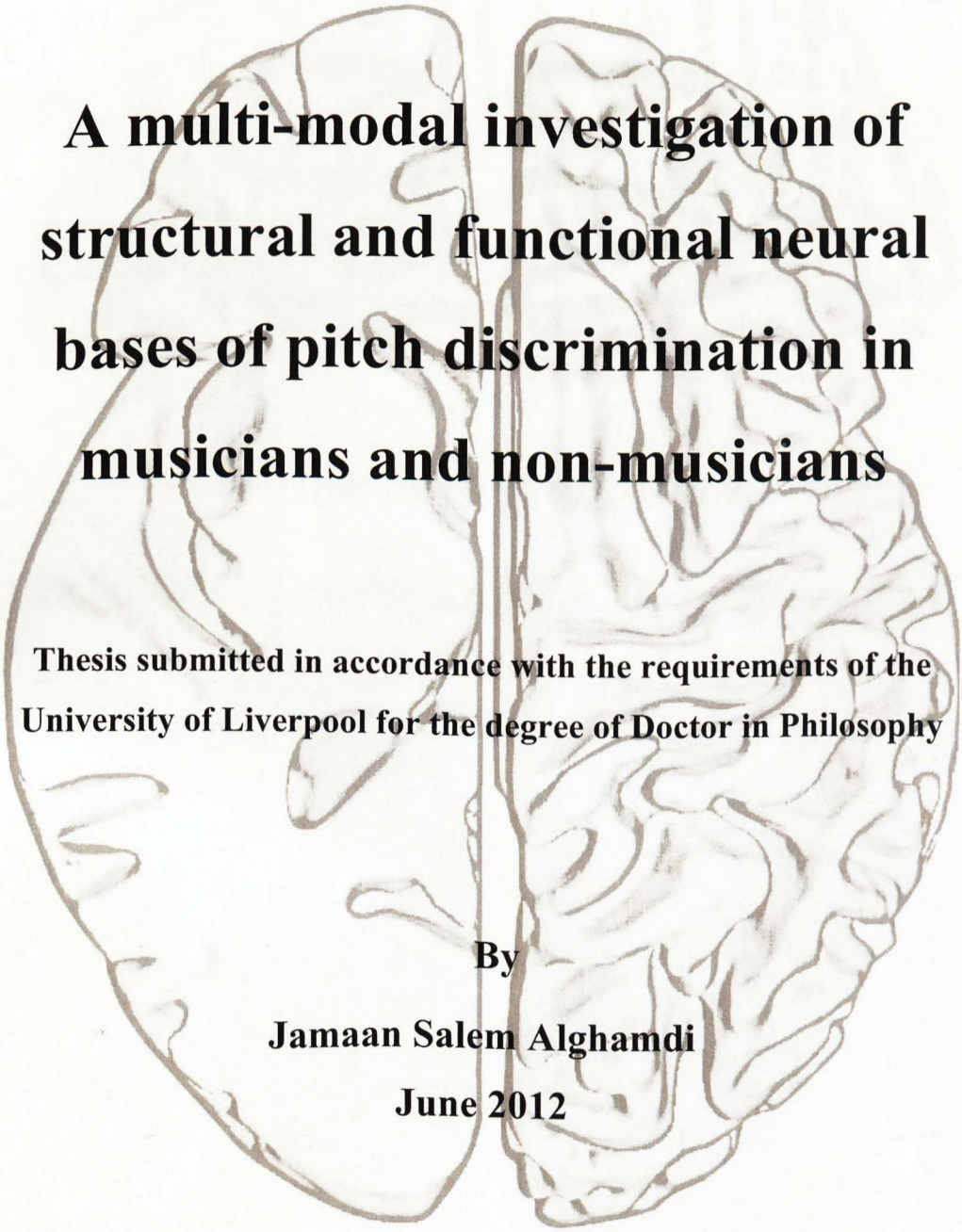

A multi-modal investigation of structural and functional neural bases of pitch discrimination in musicians and non-musicians

Thesis submitted in accordance with the requirements of the University of Liverpool for the degree of Doctor in Philosophy

By

Jamaan Salem Alghamdi

June 2012

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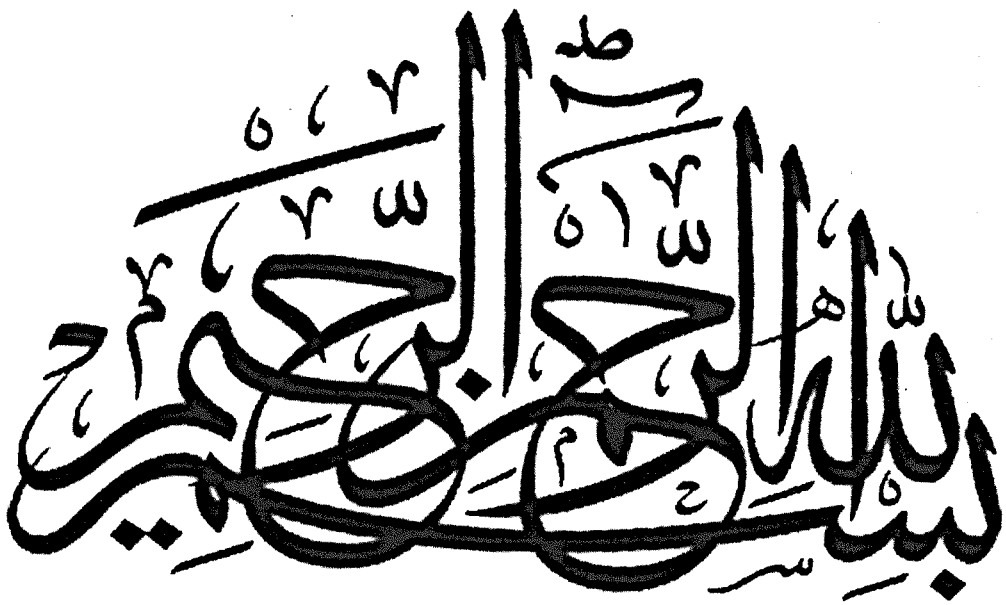

In the Name of Allah,

the Most Gracious, the Most Merciful

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Declaration

The work presented in this thesis is the result of my own work. The material contained in this thesis has not been presented, nor is currently being presented, either wholly or in part, for any other degree or qualification.

Jamaan Salem Alghamdi

Dr. Vanessa Sluming

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My warmest thanks go to my parents, my brothers and my sisters, who were always willing to listen and supported me in so many ways. I hope I have made them proud and continue to do so.

Finally, my deepest thanks go to my wife and my kids for their love, patience and support during this research project.

Jamaan 2012

Publications

Papers

- ALDHAFEERI, F. M., MACKENZIE, I., KAY, T., ALGHAMDI, J. & SLUMING, V. 2012. Neuroanatomical correlates of tinnitus revealed by cortical thickness analysis and diffusion tensor imaging. Neuroradiology.

- Aldhfeeri F, Mackenzie I, Kaye A, Alghamdi J and Sluming V (2012) Regional brain responses to pleasant and unpleasant IAPS pictures: different networks. Neuroscience Letters. 512(2):94-8

- STANCAK, A., ALGHAMDI, J. & NURMIKKO, T. J. 2011. Cortical Activation Changes during Repeated Laser Stimulation: A Magnetoencephalographic Study. PLoS One, 6, e19744.

- Abdul-Kareem I, Stancak A, Parkes L, Al-Ameen M, Alghamdi J, Aldhafeeri F, Embleton K, Morris D, Sluming V (2011) Plasticity of the superior and middle cerebellar peduncles in musicians revealed by quantitative analysis of volume and number of fibers based on diffusion tensor tractography. Cerebellum.

Conference Proceedings

- Alghamdi J and Sluming V (2012) Neuroanatomical correlates of musicianship in the right hippocampus. Proceedings of the European Congress of Radiology. ESR, Vienna pp xx **(Certificate of merit)**

- Aldhafeeri F, Alghamdi J, Sluming V (2011) Functional MRI of regional brain responses to pleasant and unpleasant IAPS pictures: different networks. Proceedings of the European Congress of Radiology. ESR, Vienna pp xx

- Alghamdi J, Stancak A, Parkes L, Lightfoot G, Adams V and Sluming V (2010) Multimodal imaging of frequency coding in the human auditory cortex. Proceedings of 16th Annual Meeting of the Organization for Human Brain Mapping. Elsevier, Barcelona pp xx

- Alghamdi J, Stancak A, Parkes L, Lightfoot G, Adams V and Sluming V (2010) Multimodal imaging of frequency coding in the human auditory cortex. Proceedings of 16th Annual Meeting of the Organization for Human Brain Mapping. Elsevier, Barcelona pp xx

- Stancak A, Alghamdi J, Turo Nurmikko (2010) A magnetoencephalographic study of temporal summation of pain. Annual Meeting of the Organization for Human Brain Mapping. Elsevier, Barcelona pp xx

- Alghamdi J, Stancak A, Parkes L, Sluming V (2009) Tonotopic Mapping using fMRI and MEG: A Multimodal Study of the Auditory Cortex in Pitch Discrimination. Auditory Cortex: Current Concepts in Human and Animal Research. ICAC, Magdeburg pp 67

- Alghamdi J, Stancak A, Parkes L, Sluming V. (2009) Tonotopic Mapping Using Both fMRI and MEG Scans. Proceedings of the National Meeting of the British Neuroscience Association. BNA, Liverpool pp 1

Scripts and tools

- **Multiple DICOM to NIfTI converter using dcm2nii and AppleScript**
  http://www.cabiatl.com/mricro/mricron/install.html
  http://www.easyneuroimaging.com

- **Using bash script and Applescript to convert freesurfer stats2table (asegstats2table & aparcstats2table)**
  http://surfer.nmr.mgh.harvard.edu/fswiki/freesurferstats2table
  http://www.easyneuroimaging.com

- **Easyfreesurfer and multi mri_convert**
  http://www.freesurfer.net/fswiki/Easyfreesurfer
  http://www.easyneuroimaging.com

- **Some other scripts were written for Brainvoyager QX and FSL**
  http://www.easyneuroimaging.com

Abstract

Musicians represent an ideal model for understanding experience-driven neuroplasticity in the human brain, especially in auditory and motor domains. Musicians exert intensive and durable practice of various multimodal skills (e.g., motor, auditory, visual and memory). It has been reported that certain regions of the adult musicians' brains are structurally larger than non-musicians. Also musicians demonstrate more sensitive pitch discrimination abilities compared to non-musicians because pitch labelling plays an important role in music. Music is made of a highly structured and complex succession of tones that arranged in a specific rhythm and played at specific pitch.

In this thesis I aimed to; (1) Explore the influence of musical proficiency on pitch discrimination ability with investigating the laterality pitch discrimination ability and exploring some factors that could affect pitch discrimination ability such as aging, type of musical instrument and duration of musical proficiency. (2) Investigate anatomical plasticity of selected brain structures in musicians with exploring musical proficiency and the instrument type effect on sulcal and gyral topography. (3) Study the correlations between pitch discrimination performance and some cortical features of selected brain structures. (4) Investigate tonotopic mapping in the human auditory cortex using functional magnetic resonance imaging and (fMRI) and magnetoencephalography (MEG). (5) Examine the influence of musical proficiency expertise on frequency organization and cortical activation of the human auditory cortex.

Different structural methods were implemented to study differences between musicians and non-musicians in some structural features. FMRI and MEG were used to study tonotopic mapping in the human auditory cortex.

During pitch discrimination tasks, musicians demonstrated more sensitivity than non-musicians. Musicians also showed significantly larger volume in various brain regions and shape differences in sulcal and gyral anatomy and the right hippocampus. Additionally, there were significant correlations between pitch discrimination performance and different structural measurements. Musicians had stronger BOLD fMRI in the medial and lateral part of the left HG. ANOVA tests of the amplitude of neuromagnetic N100 component showed a group effect of borderline significance.

Results clearly show behavioural, structural and functional differences between these two groups. These results indicate that the morphology and neurophysiology of various brain regions and the pitch labelling have an essential role in musical proficiency.

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Abbreviations

- AELLF Auditory Evoked Long Latency Fields
- AEMLF Auditory Evoked Short to Middle Latency Fields
- AF Arcuate Fasciculus
- amHG Anteromedial Portion of HG
- ANOVA Analyses of Variance
- AP Absolute Pitch
- B_0 External Magnetic field applied in MRI
- BE Both Ears
- BF Best Frequency
- BM Basilar Membrane
- BOLD Blood Oxygenation Level Dependent
- CC Corpus Callosum
- CF Characteristic Frequency
- CER Conventional Event Related
- CP Corticospinal Projections
- CSF Cerebrospinal Fluid
- DL Difference Limen
- DLF Difference Limen for Frequency
- DTI Diffusion Tensor Imaging
- EEG Electroencephalography
- EPI Echo Planar Image
- EPSP Excitatory Postsynaptic Potential
- FA Fractional Anisotropy
- FDR False Discovery Rate
- FM Frequency-Modulated
- FMDL Frequency Modulation Detection Limen
- FMRI Functional Magnetic Resonance Imaging
- FWHM Full Width at Half Maximum
- GD Gyrus Dentatus
- GLM General Linear Model
- GM Grey matter
- HDE Hybrid Depth Electrode
- HG Heschl's Gyrus
- HP Hippocampus Proper
- HRF Hemodynamic Response Function
- JND Just Noticeable Difference
- IPL Inferior Parietal Lobule
- IPSP Inhibitory Postsynaptic Potential
- ISI Interstimulus Interval
- HRF Hemodynamic Response Function

- LE Left Ear
- LH Left Hemisphere
- lHG Lateral Aspect of HG
- MEG Magnetoencephalography
- MEP Motor Evoked Potentials
- MMN Mismatch Negativity
- MNI Montreal Neurological Institute
- MRI Magnetic Resonance imaging
- NMR Nuclear Magnetic Resonance
- NMV Net Magnetization Vector
- PAC Primary Auditory Cortex
- PDP Pitch Discrimination Performance
- PET Photon Emission Tomography
- PSP Postsynaptic Potential
- PT Planum Temporal
- rCBF Regional Cerebral Blood Flow
- RE Right Ear
- RH Right Hemisphere
- RHipp Right Hippocampus
- SD Standard Deviation
- SER Silent Event Related
- SICI Short-Latency Intracortical Inhibition
- SIMEX Simultaneous Multi-Slice Excitation
- SL Strong-Learners
- SMG Supramarginal Gyrus
- SNR Signal To Noise Ratio
- SQUIDs Superconducting Quantum Interference Devices
- SPET Single Photon Emission Tomography
- SSF Steady-State Fields
- STG Superior Temporal Gyrus
- STS Superior Temporal Sulcus
- T1 Longitudinal Relaxation Time
- T2 Dephasing Relaxation Time
- $T2^*$ Transverse Magnetization Time
- TE Echo Time
- TIV Total Intracranial Volume
- TR Repetition Time
- VBM Voxel-Based Morphometric
- WL Weak-Learners
- WM White Matter

Chapter 1 : Introduction

1.1 Introduction

Expert musical performance is one of humankind's most complex and extensive multimodal activities, as professional musicians practice their rehearsal exercises with high attention and long lasting commitment. While playing an instrument the musician integrates various sensory modalities and cognitive processes comprehensively and extremely efficiently. These processes activate multiple brain regions (Langheim et al., 2002, Lotze et al., 2003, Meister et al., 2004, Bangert et al., 2006, Sluming et al., 2007a, Groussard et al., 2010a, Herdener et al., 2010). Therefore professional musicians are an ideal population to investigate brain functions and connectivity. Different studies showed induced cortical plasticity in both pitch memory and musical training in studies that investigated brain structure/function before and after a prescribed training programs (Fujioka et al., 2006, Gaab et al., 2006, Lappe et al., 2008, Hyde et al., 2009, Schlaug et al., 2009a, Herdener et al., 2010). Differences between musicians and non musicians regional brain structure and function have also been reported to be attributed to musical skill development (Schlaug et al., 1995a, Pantev et al., 1998, Schlaug, 2001, Schneider et al., 2002, Gaab and Schlaug, 2003, Gaser and Schlaug, 2003, Schulz et al., 2003, Bangert et al., 2006, Musacchia et al., 2007, Bermudez et al., 2009, Abdul-Kareem et al., 2011a, Halwani et al., 2011, Loui et al., 2011).

Pitch discrimination is one of the important skills for musicianship. Pitch plays a key role in audition, especially in the perception of speech and music (Plack et al., 2005). Theoretically brain processes pitch depending on either the spatial

(Helmholtz and Ellis, 1954) or temporal (Rutherford, 1886) patterns of excitation in the auditory periphery. However, using either model alone would not provide a complete explanation of pitch perception (Bendor, 2011). Some recent studies reported that pitch perception is based on spatiotemporal excitation patterns (Oxenham et al., 2004, Cedolin and Delgutte, 2010). During pitch discrimination tasks, musicians showed superior performance comparing with non-musicians (Kishon-Rabin et al., 2001, Tervaniemi et al., 2005, Micheyl et al., 2006).

The main aim of this thesis was to investigate the tonotopic mapping and the neuroanatomical and neurofunctional correlates of musicianship and neuroanatomical correlates of pitch discrimination performance (PDP) in the human auditory cortex.

Specific objectives include to:

- Investigate the influence of musical proficiency on PDP.
- Explore the neuroanatomical correlates of both musicianship and PDP in some brain regions that associated with pitch memory and at the same time I explored the effects of type of instrument on sulcal and gyral topography.
- Implement several novel features. Firstly, it is the first cross-sectional study that incorporated behavioural, anatomical and functional investigations on the same participants to study the differences between musicians and non-musicians. Second novel feature was using a multi-method approach (VBM, sulcal depth and cortical thickness measurements, sulcal and gyral topography and hippocampus shape) to investigate the neuroanatomical correlates of musicianship and PDP. Finally, it is the first study that

integrated multimodality (fMRI and MEG) in investigating tonotopic mapping in humans.

The literature review, experiments and the summary are presented in the following chapters that are organised as follows:

Chapter 2 gives a brief overview of physiology of the auditory pathway, pitch processing and pitch memory in the human brain. Also it presents anatomy and functional organisation of brain regions supporting pitch discrimination in the human brain e.g. auditory cortex, hippocampus and Inferior parietal lobule. It then presents a relevant literature about structural and functional plasticity in musicians.

Chapter 3 presents a basic fundamental overview of the physical principles of MRI, fMRI and MEG. It then presents a relevant literature about paradigm designs that have been implemented in some recent studies to overcome the confounding effect of scanner noise. In the last part, results of different optimised designs are discussed.

Chapter 4 gives a literature about pitch perception, pitch discrimination and the difference in pitch discrimination between musicians and non-musicians. It also explores the influence of musical performance expertise on pitch discrimination ability with taking in account laterality effect of pitch discrimination ability. Then it discusses the effect of different factors such as aging and period of musical experience on PDP.

Chapter 5 uses a multi-method approach to investigate the neuroanatomical correlates of musicianship and PDP. Different anatomical techniques are applied to explore plasticity of different brain regions by measuring various cortical features including; grey matter density, cortical thickness and sulcal depth cortical volume and surface area, and hippocampal volume and shape differences. In addition, the effect of instrument type on sulcal and gyral topography is studied.

Chapter 6 investigates tonotopic mapping in the human auditory cortex using fMRI. It also, explores the influence of musical performance expertise on frequency organization and on cortical activation of the human auditory cortex.

Chapter 7 studies tonotopic mapping in the human auditory cortex using MEG. It also, investigates the effect of musical proficiency on frequency organization and on cortical activation of the human auditory cortex.

Chapter 8 summarises and discusses the main findings of this thesis.

Chapter 2 : The Physiology of the Auditory Pathway, Pitch Processing and Pitch Memory in Human Brain

2.1 Aims

Specific aims of this chapter were to describe the:

i) Physiology of the auditory pathway, pitch processing and pitch memory in the human brain,

ii) Anatomy and functional organisation of brain regions supporting pitch processing and pitch memory in the human brain including;

   a. Auditory cortex.

   b. Hippocampus.

   c. Inferior parietal lobule.

iii) Structural and functional plasticity in musicians.

2.2 Physiology of the auditory pathway

Auditory signals travel from the tympanic membrane of each ear to the cochlear nuclei in the respective hemispheres through auditory nerve fibres. These nuclei, known as the ventral and the dorsal nuclei, are located on each side of the medulla. Each auditory nerve fibre splits to project in both nuclei. These nuclei show specific frequency response characteristics and are organized into subdivisions. High frequency sound waves are processed in the dorsal, caudal and medial parts of each cochlear nucleus, while the ventral, rostral, and lateral subdivisions act in response to low frequency sound waves. From the cochlear nuclei, the majority of auditory fibres project in a group of nuclei also located in the basal brainstem known as the superior olivary complex. Each superior olive receives projections from both the ipsilateral and contralateral cochlear nucleus. The medial and lateral superior olive nuclei play an important role in sound-source localization. Time difference is processed in the medial superior olive while lateral superior olive nucleus responds to phase differences (amplitude difference of sound waves). This information is subsequently transformed in an auditory spatial map located in the inferior colliculus (Bazwinsky et al., 2003, Goldstein et al., 2005).

Fibres connect between the superior olivary complex and the inferior colliculus through the lateral lemniscus tract then two distinct pathways arise from the inferior colliculus to project at the ventral and dorsal regions of the medial geniculate nuclei of the thalamus and alternatively, projections from the dorsal

medial geniculate nucleus reach the secondary auditory cortex, which is known as the final output from the auditory pathways (Figure 2.1) (Bazwinsky et al., 2003, Goldstein et al., 2005).

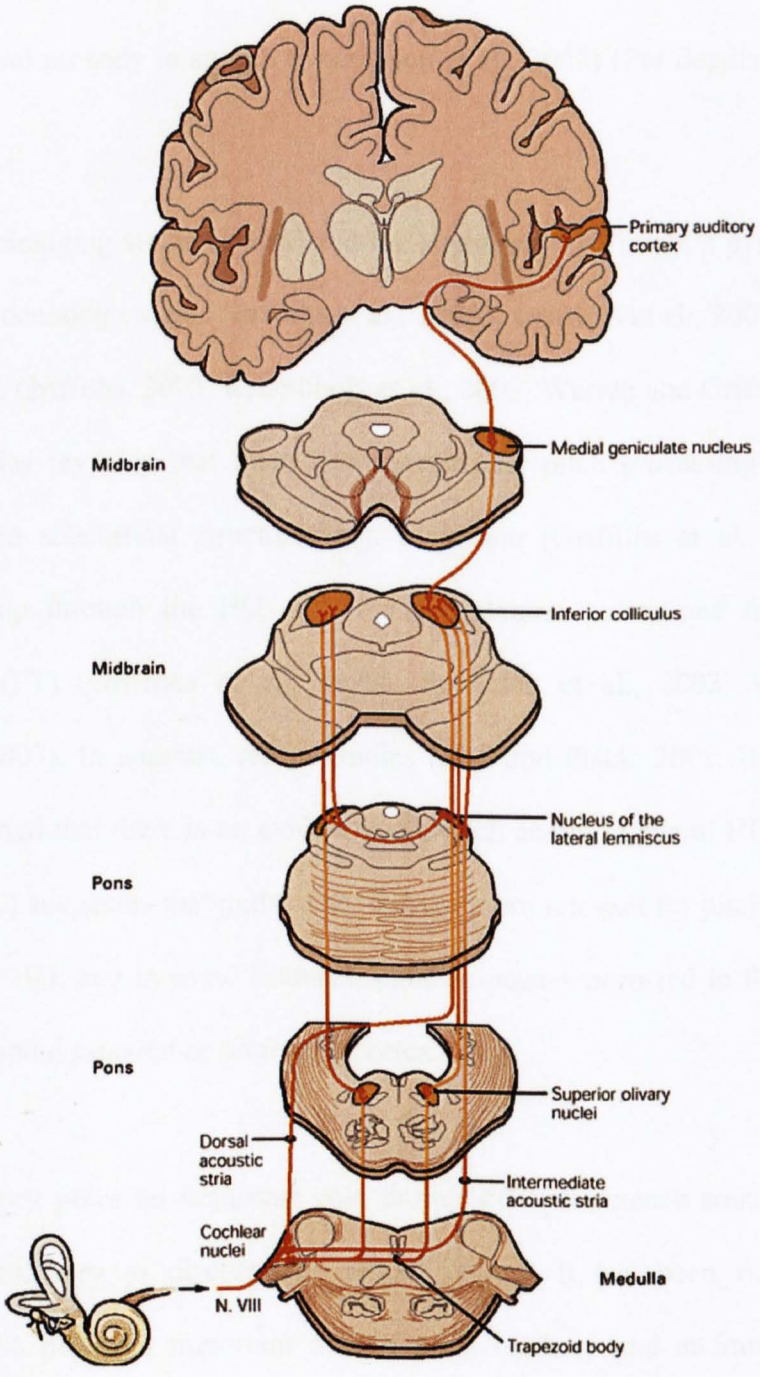

Figure 2.1 The central auditory pathways extend from the cochlear nucleus to the auditory cortex (Adapted from Kandel 2000)

2.3 Pitch processing, pitch memory and pitch discrimination in human brain

Pitch plays an important role as a fundamental auditory attribute in auditory communication, as a part of the basis of melody in music (Moore, 2003, Jones et al., 2010) and prosody in speech (Thompson et al., 2003) (For details see section 4.3).

Some neuroimaging studies considered the lateral part of Heschl's gyrus (HG) as the pitch processing centre (Griffiths et al., 1998a, Griffiths et al., 2001, Patterson et al., 2002, Griffiths, 2003, Krumbholz et al., 2003, Warren and Griffiths, 2003). These studies revealed that there is a hierarchical pitch processing in humans beginning in subcortical structures e.g. brainstem (Griffiths et al., 2001) and extending up through the HG out onto the planum polare and the planume temporale (PT) (Griffiths et al., 1998a, Patterson et al., 2002, Warren and Griffiths, 2003). In contrast, recent studies (Hall and Plack, 2009, Barker et al., 2011) reported that there is no evidence of a pitch centre in lateral HG. Hall and Plack (2009) suggested that parts of the PT are more relevant for pitch processing than lateral HG, and in some listeners, pitch responses occurred in the temporo-parieto-occipital junction or prefrontal cortex.

Pitch memory plays an important role during PDP. Reference sounds must be stored in memory to discriminate target pitches. It has been reported that hippocampus plays an important role in pitch memory and auditory temporal information in animal (Sakurai, 2002) and human (Watanabe et al., 2008).

O'Mara et al. (2009) showed that the dorsal part of subiculum, which considered as part of the hippocampus, is relatively more concerned with space and memory. Different studies reported that inferior parietal lobule (including supramarginal gyrus (SMG) and angular gyrus) plays an important role in the auditory and verbal short memory (Paulesu et al., 1993, Salmon et al., 1996, Binder et al., 1997, Celsis et al., 1999, Gaab et al., 2003, Gaab et al., 2006, Romero et al., 2006, Vines et al., 2006, Rinne et al., 2009). Additionally, it has been reported that pitch discrimination processes take place in the HG (Tramo et al., 2002, Brown et al., 2004, Gaab et al., 2006). Mathys et al. (2010) used transcranial direct current stimulation to address the problem of causality in pitch discrimination functions and found that both left and right HG are involved in pitch discrimination process with stronger contributor from right HG.

2.3.1 Pitch processing in musicians

Pitch discrimination is regarded as a fundamental ability for a successful musician. Musicians show better auditory capability compared to non-musicians, which has sparked multi discipline research interests in hearing science, psychology and neuroimaging. Various explanations have been suggested to describe how musicians present better pitch discrimination performance than non-musicians. Musicians may have an improved overall auditory capability. This may be related to their ability to ignore the interference of dubious timbral attribute of a tone, which could bias pitch perception. Additionally, playing music professionally requires performing fine pitch discrimination tasks in order to tune

musical instruments. The human brain processes pitch in a hierarchal manner starting in the primary auditory cortex to discriminate frequencies moving to higher level processes. Higher level processes include segregation of pitch contour and group of tones into melodies and harmony patterns which originate in the secondary auditory cortex, SMG, inferior frontal gyrus, and superior parietal lobe.

During pitch discrimination task, Gaab and Schlaug (2003) showed that musicians seem to rely more on a neural network that contain SMG and superior parietal cortex, while non-musicians use HG and hippocampal gyrus. In contrast, Schmithorst and Holland (2003) investigated melodic and harmonic processing. Both musicians and non-musicians showed activation similarity for melodic processing in the most anterior part of the STG. Additionally, musicians presented activation in the inferior parietal lobules for both tasks. Brattico et al (2001) used electroencephalography (EEG) to investigate pitch perception in musicians and non-musicians and reported that musicians had a faster neural response for pitch changes than the non-musicians. Although, non-musicians have an innate knowledge of musical regularities, musical practice creates a larger number of explicit memory representations. Therefore, it can be reported that auditory pitch perception for higher level processes are influenced by musical context and syntax (Brattico et al., 2001, Koelsch et al., 2002b).

2.4 Anatomy and functional organisation of brain regions supporting pitch processing and pitch memory

2.4.1 Auditory cortex

2.4.1.1 The anatomy of the auditory cortex

Auditory cortex of non-human primates can be divided into a core of primary areas, a surrounding belt and a parabelt region just lateral to the belt on the superior temporal gyrus (Figure 2.2). The core is subdivided into three fields (A1, R and RT), while the belt is subdivided into seven fields that surround the core along the upper surface of the superior temporal gyrus (Figure 2.2) (Hackett et al., 1998, Kaas and Hackett, 2000, Rauschecker and Scott, 2009).

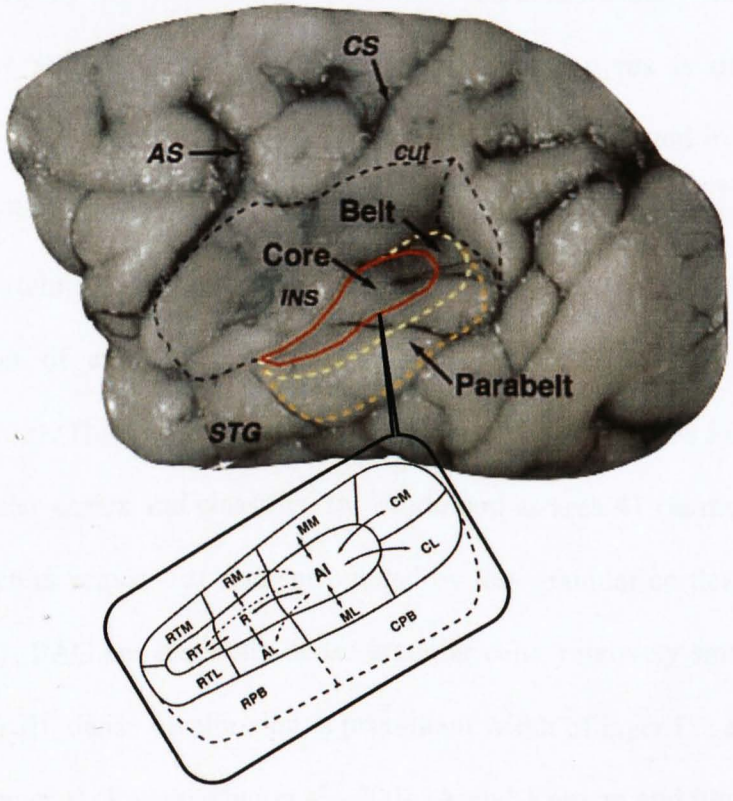

Figure 2.2 Dorsolateral view of the macaque cerebral cortex after removal of the overlying parietal cortex, exposing the ventral bank of the lateral sulcus and insula. The approximate locations of the core region (solid red line), caudal and lateral portions of the belt region (dashed yellow line), and the parabelt region (dashed orange line) are shown. The schematic diagram shows the subdivisions of core, belt and parabelt regions (Adapted from Kaas and Hackett 2000).

The core is characterized by koniocortical architecture and dense myelination. Pyramidal cells of the belt area are larger than those of the core, but cell density, columnar spacing and myelination are lesser in the belt than in the core (Hackett et al., 1998, Kaas and Hackett, 2000). In contrast, human auditory areas can be divided -based on gross morphological criteria- into the primary auditory cortex (PAC) and non-primary auditory cortex (Hall et al., 2003) (see Figure 2.3).

Human primary auditory cortex

PAC occupies posteromedial portion of the HG that located on the superior temporal gyrus (STG) in the temporal lobe Figure 2.3 It is surrounded laterally and posteriorly by non-PAC areas, while it is separated medially from the insula by a narrow strip of prokoniocortex. The transverse gyrus is often partially duplicated. If there are multiple transverse gyri, PAC is located in the anterior-most gyrus (Rademacher et al., 2001). It is essential to use a combination of cyto- and myelo-architectonic and histochemical markers to provide best reliable determination of anatomical borders (Hall et al., 2003, Abdul-Kareem and Sluming, 2008). The cytoarchitecture of the PAC is described as koniocortex or highly granular cortex and classified by Brodmann as area 41 (termed BA 41). It is also known as region Te1 and surrounded by less granular cortices, areas Te2, Te3, and TI1. PAC has distinctly dense granular cells, relatively small pyramidal cells in layer III, dense myelination, a prominent width of layer IV, and a relative cell-sparse layer V (Rademacher et al., 2001, Abdul-Kareem and Sluming, 2008). The position, the extent and the absolute size of this area vary across individuals and between the left and right hemispheres in one individual (Rademacher et al.,

2001). Comparing to the right hemisphere (RH) the PAC is located more posteriorly in the left hemisphere (LH). Auditory cortical areas in one hemisphere are connected to the reciprocal areas in the other hemisphere through corpus callosum. It has been reported that there are sex differences in the activation and size of the PAC (Morosan et al., 2001, Ruytjens et al., 2007). Furthermore, these authors reported that the transverse temporal gyrus has a larger volume in the left than in the RH.

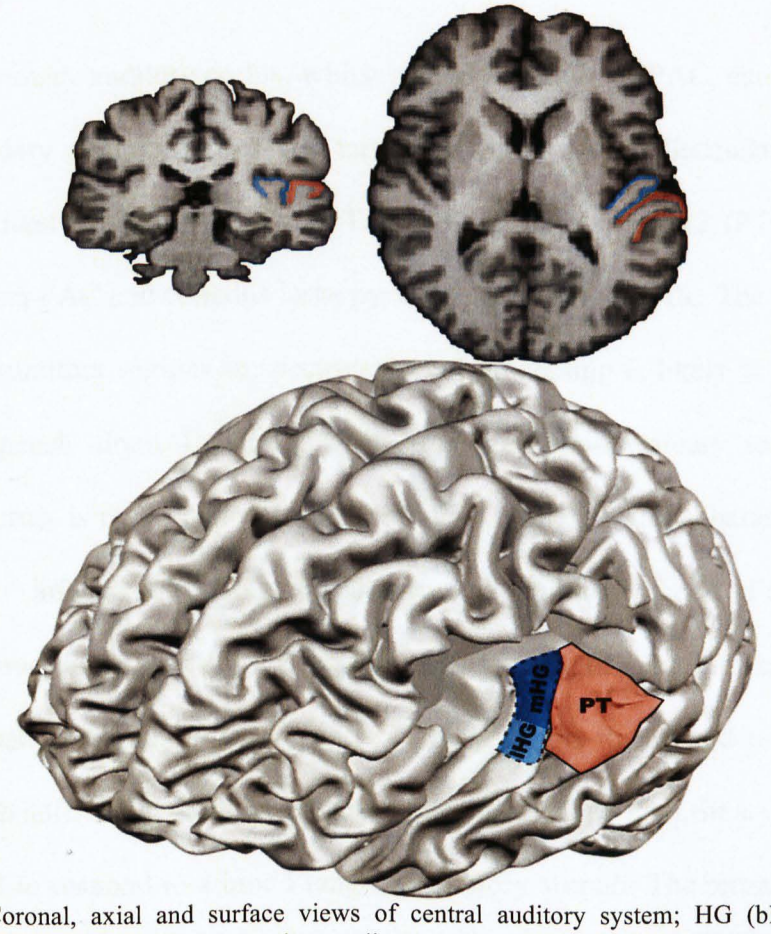

Figure 2.3 Coronal, axial and surface views of central auditory system; HG (blue), primary auditory cortex (dark blue) and secondary auditory cortex (red), mHG and lHG are medial and lateral HG respectively (subject C13. 3D mesh reconstructed for illustration purpose using BrainVoyager QX 2.3).

PAC contains neurons that respond to a limited range of frequency and register the characteristics of sound identification or perceptual processing, such as

loudness, pitch and timbre. The response of neurons in the PAC to specific sound wave frequencies is narrow and binaural (Reser et al., 2000). Some neurons are excited by stimulation from both ears while others respond to one ear and are inhibited by stimulation from the other. PAC is organized in vertical columns. The cells in each column are sensitive to a similar main sound frequency and neighbouring columns are mapped tonotopically (Reser et al., 2000).

Human non-primary auditory cortex

The non-primary auditory cortex, which situated laterally to PAC, can be divided into secondary auditory cortex and tertiary auditory cortex. Secondary auditory cortex is classified histologically as Te2 or Brodmann's area 42 (PT). It is less granular than PAC and contains large pyramidalcells in layer IIIc. The function of secondary auditory regions in spectrotemporal processing is likely to be broader than for speech alone. In addition, the transition from primary to secondary auditory cortex is responsible of transformation of the physical characteristics of sound into information about objects in the auditory scene. Furthermore, secondary auditory cortex plays a big role in processing of harmonic, melodic and rhythmic patterns. Finally, the secondary cortex seems to respond preferably to stimuli with sufficiently complex spectral dynamics, while the primary cortex has been found to respond to a broad range of auditory stimuli. The tertiary auditory cortex is located on the superior temporal gyrus and the superior temporal sulcus (STS) within the temporal lobe. This cortex supposedly integrates everything into the overall experience of music (Reser et al., 2000).

2.4.1.2 The functional organization of the auditory cortex

Many studies have been used to assess the functional organization of the auditory regions in mammals including humans. Most of these studies examine tonotopic (Merzenich and Brugge, 1973, Howard et al., 1996, Recanzone et al., 1999), amplitopic (Pantev et al., 1989, Bilecen et al., 2002) and spatiotopic (Griffiths et al., 1998b, Zatorre et al., 2002b) maps of the auditory regions. These maps can be defined as the spatial distribution of neurons that are maximally responsive to certain stimulus frequencies, intensities and position respectively. The following section will provide a detailed overview about the tonotopic mapping of the auditory cortex.

2.4.1.2.1 Tonotopic mapping of the human auditory cortex

In the auditory cortex, higher frequencies are located in more anterior medial regions while the posterior lateral regions responding to lower frequencies (Howard et al., 1996). Tonotopic mapping has been well examined using microelectrode recordings in various animal species (Merzenich and Brugge, 1973, Merzenich et al., 1975, McMullen and Glaser, 1982, Galazyuk, 1990, Schreiner, 1991, Kosaki et al., 1997, Recanzone et al., 1999, Bendor and Wang, 2005, Kalatsky et al., 2005). For example; seven tonotopic mappings and four or more have been observed in the cat and monkey cortices respectively (Merzenich and Brugge, 1973, Merzenich et al., 1975, Schreiner, 1991, Kosaki et al., 1997, Recanzone et al., 1999).

In the auditory cortex of nonhuman primates, each of the three divisions of the core area show tonotopic gradients that are mirror symmetric to each other (Merzenich and Brugge, 1973, Kosaki et al., 1997, Kaas and Hackett, 2000, Bendor and Wang, 2008). Additionally, tonotopic gradients have also been exhibited in the belt area (Kosaki et al., 1997, Kaas and Hackett, 2000, Petkov et al., 2006, Kusmierek and Rauschecker, 2009, Petkov et al., 2009).

However, the number and location of tonotopic organizations within human auditory cortex are still unclear either anatomically or functionally. Compared to animals, humans were shown to process additional complex sound patterns, such as language or music. Various neuroimaging modalities have been used to detect a frequency-depth tonotopic organization. Most of those studies can be divided into two groups, those using two stimulus frequencies and those using more than two frequencies. Studies using two stimulus frequencies have demonstrated that the cortical location of peak response is frequency dependent. On the other hand, studies that used more than two acoustic frequencies generally observed a covariance of position of response with stimulus frequency (Talavage et al., 2004).

Hybrid depth electrode (HDE)

HDE has provided a direct demonstration of tonotopic mapping along the HG. Howard et al (1996) implanted this technique in epilepsy surgery patients who required depth electrode placement as part of their standard clinical treatment

plan. The authors found a lateral progression in frequency sensitivity from high frequency (3360 Hz) to lower frequency (1480 Hz).

Positron and single photon emission computed tomography (PET) and (SPECT)

In 1985, Lauter et al. used stimuli with sine tones of 500 Hz and 4000 Hz. The authors measured the regional cerebral blood flow (rCBF) and metabolic rates of oxygen and glucose consumption upon both stimuli quantitatively. They could not localize the activated regions in the cortex precisely however; the rCBF changes induced by a 4000 Hz tone were located deeper and posterior to those induced by 500 Hz tone (Lauter et al., 1985). Additionally, Ottaviani et al (1997) showed similar results using SPECT.

EEG and MEG

Both systems have been used to investigate tonotopic mapping of human auditory cortex since early eighties (Romani et al., 1982a, Romani et al., 1982b). Different designs have been implemented to investigate tonotopic mapping of the auditory cortex in humans.

Auditory evoked steady-state fields (SSF)

Auditory steady-state stimuli are amplitude- or frequency-modulated tones with a modulation rate of 35–40 Hz yielding the maximum response energy. The first demonstration of tonotopy in humans using steady-state field (SSF) showed that the source of the response in HG moves more laterally as frequency decreases. (Romani et al., 1982a) Furthermore, Pantev et al. (1996) used sequences of

Gaussian tone pulses with a repetition rate of 39 Hz and carrier frequencies of 250, 500, 1000, 2000, and 4000 Hz, respectively to obtain SSF of the human auditory cortex. The authors found that the depth of the estimated source shifted medially with increasing carrier frequency. Their findings were confirmed by recent SSF studies (Ross et al., 2000, Weisz et al., 2004).

Auditory evoked short to middle latency fields (AEMLF)

Middle latency evoked fields occur about 25–50 ms post-stimulus and originate in PAC with P30m and P50m representing the most permanent components. While short latency components start in the range of 15 to 30 ms after stimulus and originates in upper brainstem and/or auditory cortex, the N19m-P30m components are distributed in the medial half to the first transverse temporal gyrus of Heschl (Liegeois-Chauvel et al., 1991, Liegeois-Chauvel et al., 1994, Schneider, 2001, Schneider et al., 2002, Lütkenhöner et al., 2003a). Pantev et al. (1995) presented data in the range from middle to long latencies. However, only the P30m/P30 (30 ms) and N100m/N100 (89 ms) were consistently present in all stimulus conditions and all subjects. This was the first study to use multi-channel data of both MEG and EEG recordings to study tonotopic mapping of the human auditory cortex. The source of the P30m/P30 components was in the medial part of HG and shifted laterally by increasing frequencies.

Auditory evoked long latency fields (AELLF)

The long latency cortical auditory fields start 50 to 200 ms post-stimulus; originating in the auditory cortex with the N100m representing the most

permanent components. Pantev et al. (1995) reported that the tonotopic gradient of N100m/N1mm components was found posterior to the HG in the PT and have opposite orientation compared to P30m/P30 components. This suggests that there is a mirror tonotopic organisation in human auditory cortex with sources of P30m/P30 and N100m/N100 located in the primary and secondary auditory cortices, respectively. Yamamoto et al. (1988) showed that a dipole source analysis of the major component of the long auditory evoked field (N100m) was informative about the tonotopic organization of the human auditory cortex. In addition, Lütkenhöner and Steinstrater (1998) explored the tonotopic mapping of the N100m components in single subject extensively. The authors registered the estimated dipole sources to three-dimensional reconstruction of the cortical surface derived from magnetic resonance images. Tones of 500 ms duration with frequencies of 250, 500, 1000, and 2000 Hz were presented, and the total number of stimuli presented per condition was about 3600. The tonotopic organization of N100m sources were consistent with all of the previous studies (Lütkenhöner and Steinstrater, 1998). The authors also demonstrated specific temporal patterns in each source. This indicates involvement of multiple areas in the generation of N100m. They proved that the source locations of P200m (150-200 ms) components were also shown to be dependent on the frequency of auditory stimulus (Lütkenhöner and Steinstrater, 1998). In contrast, Lütkenhöner et al. (2003b) showed that tonotopic organization of the N100m source of a large interindividual variability. Schneider (2001) observed a mirror tonotopic

organisation in the human primary and secondary auditory cortices with opposite gradients of sources reported by Pantev et al. (1995).

fMRI

Studying tonotopic organization in the human auditory cortex is a challenge as a frequency change by an octave is associated with a change in location by about 2-3 mm which is at the current limit of spatial resolution of fMRI protocols (Romani et al., 1982a, Pantev et al., 1988, Yamamoto et al., 1988, Pantev et al., 1996, Lütkenhöner et al., 2003b). FMRI has relatively high spatial resolution comparing with other non-invasive modalities e.g. EEG, MEG and PET. Advances in hardware, paradigm designs and data-analysis approaches of fMRI have made it the most widely used modality to examine tonotopic mapping in human in the past decade.

Several stimulus paradigm designs and delivery methods have been used to investigate tonotopic mapping, which can be broadly divided into block and event related (ER) designs. The block design involves ON/OFF conditions where stimuli are presented during ON conditions with subsequent rest periods, each condition is typically of 20–40 seconds duration (Rosen et al., 1998, Amaro et al., 2002). In contrast, ER design involves the presentation of discrete events at a certain interstimulus interval. In this design, discrete events would produce different BOLD responses in the same brain region in the case of sampling the full hemodynamic response function (HRF) curve. The ER design provides better temporal resolution than a block design (Amaro and Barker, 2006). In addition, it

is more flexible than the block design, however it has less statistical power (Rosen et al., 1998, Amaro et al., 2002) and comparatively low volume coverage (Yang et al., 2000). Using a block design, Wessinger et al. (1997) obtained a tonotopic map where low-frequency tones were located more anteriorly and laterally than those for high-frequency tones. Strainer et al. (1997) obtained multiple tonotopic mapping using four pure tones. Additionally, Talavage et al. (2000) demonstrated eight regions of response; each exhibiting a greater sensitivity to either lower or higher frequency stimulation. Seifritz et al. (2006) produced tonotopic mirror-symmetric maps in the auditory cortex, however, the gradient axis of the maps varied across subjects. Additionally, Striem-Amit et al. (2011) represented multiple mirror-symmetric tonotopic maps covering most of the core and high-order human auditory cortex, stretching all the way to the superior temporal sulcus. Yang et al. (2000) used conventional event related (CER) and silent event related (SER) to study tonotopic mapping in the human auditory cortex although the CER design could not detect any frequency gradient, the SER showed distinct spatial shifts in the lateral part of HG with changing frequency. Le et al. (2001) used three designs in the one study; a block, a CER and an SER designs. This study provided evidence for tonotopic organization in the human auditory cortex using both CER and SER, but not using block design. The low-frequency tones were located more lateral and anterior than high frequency tones. In addition, other studies used "stroboscopic" (Belin et al., 1999) event related design (Belin et al., 1999, Formisano et al., 2003, Upadhyay et al., 2007) to produce more detailed frequency organization regions in subdivisions of the auditory cortex. In

this design, auditory stimuli are presented in a pseudorandomised manner at different delays before each volume acquisition (0, 2, 3, 4, 5, 6, 7 and 9 s) (Belin et al., 1999). For instance, Formisano et al. (2003) found two mirror-symmetric representations of the sound frequencies. These maps move from the posterior-medial regions of the Heschl's sulcus (HS) to anterior-lateral locations along the first transverse sulcus. Formisano et al. (2003) and Upadhyay et al. (2007) used the same range of frequencies 0.3, 0.5, 0.8, 1, 2, and 3 kHz with a sound intensity set to approximately 70-dB sound pressure level for each subject. While Formisano et al. (2003) used binaural 3 s sine tones pulsed with an 8 Hz square wave, Upadhyay et al. (2007) used 1.5 s pure tones. In both studies, a single shot echo planar imaging (EPI) sequence with TR of 20 s (Formisano et al., 2003) and 25 s (Upadhyay et al., 2007) was collected with an auditory stimulus being presented at 8 variable offsets.

In contrast, Da Costa et al. (2011), Humphries et al. (2010), Langers and van Dijk (2011) and Woods et al. (2009) presented mirror-symmetric tonotopic fields along an anterior–posterior axis of the HG, while the lateral part of HG occupied by lower frequencies. Higher frequencies regions were located posterior and anterior to HG. Similar mirror-symmetric tonotopic patterns were demonstrated in both hemispheres. Results of these studies were inconsistent with older studies such as Formisano et al. (2003) and Seifritz et al. (2006) which showed that the gradients of those two fields are parallel to HG. The authors also found that the central region of the auditory cortex shows larger differences between preferred and non-preferred frequencies while lateral parts present smaller differences (Woods et al.,

2009, Humphries et al., 2010). Humphries et al. (2010) used a sparse temporal sampling method (Hall et al., 1999) with TR of 9.6 s to present 8 s trains of complex tone bursts with six centre frequencies: 200, 400, 800, 1600, 3200, and 6400 Hz. In contrast, Woods et al. (2009) used both continuous (TR = 2.9s) and sparse sampling (TR = 10.8 s) to present tone patterns of 750 ms that consisted of three different 250 ms tones of different frequency (225, 900, and 3600 Hz). In addition, the sparse sampling design was used in nonhuman primates (Petkov et al., 2006, Petkov et al., 2009). The authors presented 11 fields containing neurons tuned for the frequency of sounds where three of them are located in the primary auditory cortex.

Most of the previous studies (Formisano et al., 2003, Talavage et al., 2004, Woods et al., 2009, Humphries et al., 2010) suggested that human auditory cortex conforms to the general primate model. In this model, two mirror-symmetric tonotopic maps are located in the primary auditory core and belt areas. This model will be examined on participants later in this thesis.

2.4.2 Hippocampus

In humans, the hippocampus is a major component of the brains that belongs to the limbic system and located in the medial temporal lobe. It is responsible for some crucial functions e.g. long-term memory and spatial navigation (Watanabe et al., 2008). It has a curved tube (sea horse) shape with larger anterior-inferior

portion near the base of the temporal lobe than the posterior-superior part at the top (Tamraz and Comair, 2000, Andersen, 2007).

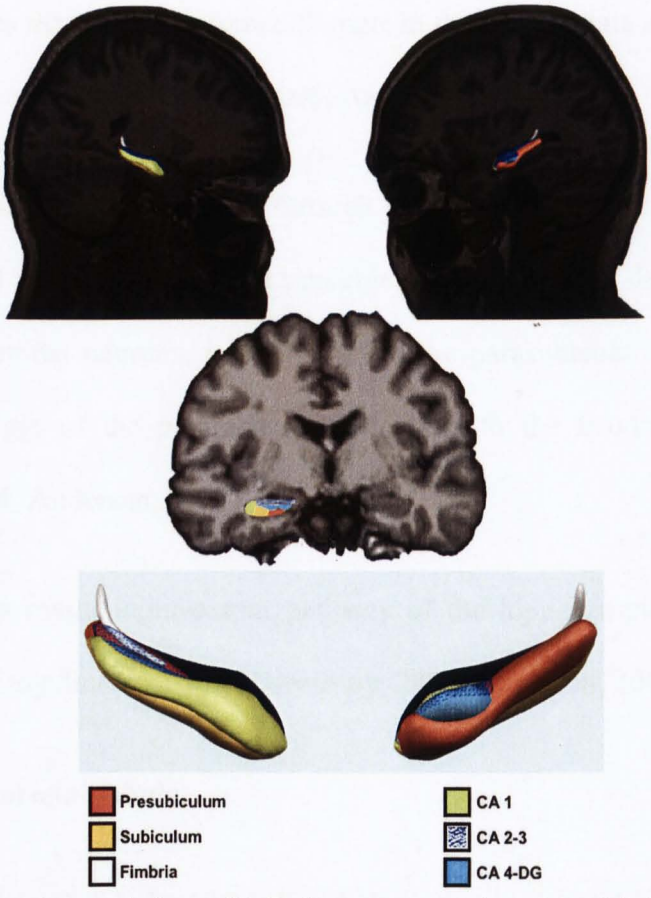

Figure 2.4 Sagittal and coronal views of 3–D shape reconstruction of the right hippocampal white matter (WM)/GM subfields (subject C17) segmented subfields was imported from freesurfer 5.1 and reconstructed for illustration purpose using BrainVoyager QX 2.3.

The hippocampus consists of the hippocampus proper (HP) (which has four fields named CA1–CA4) and the gyrus dentatus (GD) (Duvernoy, 2005) and the subicular complex (prosubiculum, subiculum, presubiculum, and parasubiculum) as shown in Figure 2.4 (Lopes da Silva and Arnolds, 1978). The HP is connected the rest of the temporal lobe at the subfield CA1 via the subiculum. CA1 has scattered triangular pyramidal somata and connected to CA2 that, composed of large, ovoid and densely packed somata. CA3, which connect between CA2 and

the area dentate (involving CA4 and the GD), has similar pyramidal somata with less density comparing with CA2. It is connected to the area dentate via fine, non-myelinated fibres named mossy fibres. Somata in the area dentate are ovoid, large, less dense and scattered (Duvernoy, 2005, Andersen, 2007).

The subiculum is connected to CA1 through prosubiculum at one side and to the presubiculum at the other side. The presubiculum, which has denes, small and superficial pyramidal neurons, is connected to the parasubiculum, which passes around the margin of the parahippocampal gyrus to the Brodmann's area 28 (Duvernoy, 2005, Andersen, 2007).

The fimbria is a major input-output pathway of the hippocampus that contains accumulation of myelinated axons (Duvernoy, 2005, Andersen, 2007).

2.4.3 Inferior parietal lobule

The inferior parietal lobule (IPL) lies below the horizontal segment of the intraparietal sulcus, superior to the lateral fissure and behind the lower part of the postcentral sulcus. It consists of three regions: the supramarginal gyrus (Brodmann's area 40), the angular gyrus (Brodmann's area 39) and the posterior parietal cortex, separated by two intermediate sulci. The SMG arches over the upturned end of the lateral fissure; anterior to the postcentral gyrus, and posterior to the STG, the angular gyrus, arches over the posterior end of the superior temporal sulcus (Tamraz and Comair, 2000) (Figure 2.5). The total cortical thickness of the SMG varies between 3.0–3.5 mm. Its layer I is rich in cells

particularly in the superficial sublayer. It has extremely thick II layer with small true granule cells, whereas layer III contains numerous small cells, mostly medium-sized pyramidal cells with large pyramidal cells sporadically disseminated in the deeper zones of this layer. Layer IV is very thick with dens cells in the middle of the layer, whereas layer V is relatively thin with a compact arrangement of its pyramidal cells with spindle cells of layer VI. The border between layer VI and the WM is very sharp and clear. In contrast, the angular gyrus is thinner than the SMG with a variation of cortical thickness from 2.9 to 3.3 mm. The cellular structure is very similar to the STG, with a tendency for the deeper sublayers of the overall thinner layer III to become magnocellular (Economo and Triarhou, 2009).

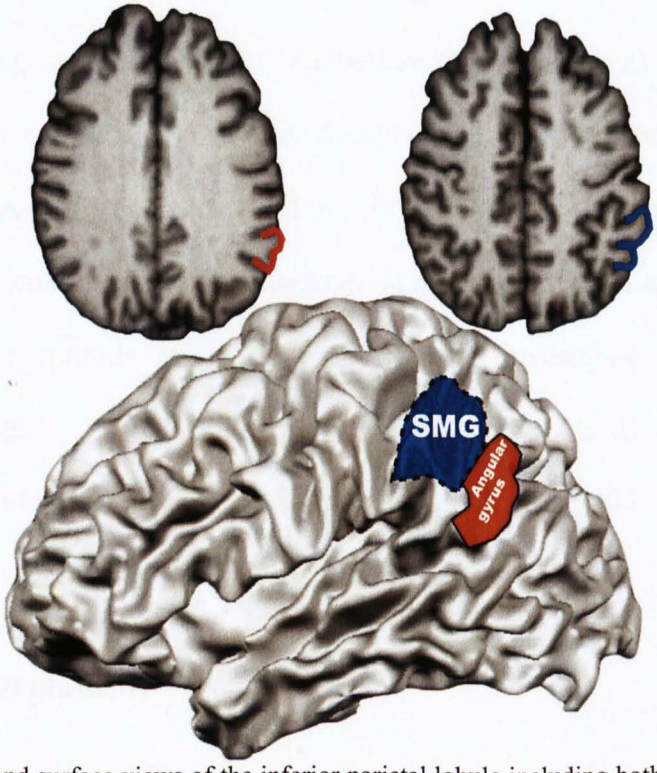

Figure 2.5 Axial and surface views of the inferior parietal lobule including both two main regions the SMG (blue) and the angular gyrus (red) (subject C13). 3D mesh reconstructed for illustration purpose using BrainVoyager QX 2.3.

The IPL involved in the comprehension of language, numerical processing, the perception of emotions in facial stimuli and interpretation of sensory information . It is also associated with auditory short memory (Celsis et al., 1999, Gaab et al., 2003, Rinne et al., 2009). In addition, the anterior portion of the SMG is considered to be the center for muscular sense and stereognosis (Economo and Triarhou, 2009). Stoeckel et al. (2009) demonstrated that SMG contributes in visual word recognition.

2.5 Plasticity in musicians

Musicians run multi function processes using multi-modal integration of auditory, motor, and cognitive tasks extensively on a daily basis during musical performance. These comprehensive demanding tasks and skills activate multiple brain regions e.g. the motor cortex, cerebellum (Langheim et al., 2002, Lotze et al., 2003, Meister et al., 2004), inferior frontal cortex, the STG and SMG (Bangert et al., 2006), Broca's area (Sluming et al., 2007a) and hippocampus (Groussard et al., 2010a, Herdener et al., 2010). Research on music perception and on musicians with high-level aptitude is an excellent tool to investigate brain plasticity (Altenmüller, 2001, Pantev et al., 2001, Pascual-Leone, 2001, Schlaug, 2001, Munte et al., 2002, Pantev et al., 2003, Zatorre and McGill, 2005, Groussard et al., 2010a, Herdener et al., 2010, Wan and Schlaug, 2010).

2.5.1 Structural plasticity

Differences in brain structure of musicians, in comparison to non-musicians, may indicate adaptations in response to intense and early commencement and continual

long-term practice including the repetitive rehearsal of musical skills. Several studies have reported structural differences in brain between musicians and non-musicians. Schlaug et al. (1995a) reported that the anterior portion of corpus callosum (CC) was significantly larger in musicians compared to non-musicians with a strong correlation with the age of commencement of musical practice. Significant gender × musicianship interaction was found for anterior and posterior CC size; male musicians had a larger anterior CC than non-musicians (Lee et al., 2003). Schlaug et al. (2009a) tested their hypothesis on the effect of instrumental music training in the size of particular subareas of the CC using diffusion tensor imaging (DTI) on a sample of 31 children aged 5–7, that was divided into three groups: high-practicing, low-practicing, and controls. Increased CC area was found after an average of 29 months of observation in the high-practicing group in the anterior midbody of the CC. In a longitudinal study by Hyde et al. (2009), musically trained children (15 months of musical training in early childhood) showed significant structural brain differences in CC, right precentral gyrus (primary motor area) and right HG compared with matched control group. Additionally, Bangert and Schlaug (2006) tested instrumental effect on string and keyboard players and found that string players display a prominent omega shape (Yousry et al., 1997) of the central sulcus on the RH only, the keyboard player shows a left more than right prominence of the omega shape.

Hutchinson et al. (2003) measured the volume of the cerebellum in musicians (keyboard players) and non-musicians and showed that male musicians have larger cerebellar volumes than matched non-musicians where the relative

cerebellar volume in the male musician was correlated with lifelong musical experience. Using diffusion tensor imaging, Bengtsson et al. (2005) investigated effects of extensive piano practice on WM across the life span. The authors found positive correlations between practicing and fibre tract organization in different regions for each age period (childhood, adolescence and adulthood). Also the authors found a highly organised fibre tract in the right posterior internal capsule in pianists compared to non-musicians. Another study by Abdul-Kareem et al. (2011a) presented that musicians have larger WM volume of the whole right cerebellum, and specifically larger volume in right middle cerebellar peduncles and increased right superior cerebellar peduncles volume and number of streamlines.

Han et al. (2009) investigated both GM distribution and WM integrity in pianists and non-musicians. The authors demonstrated that musicians have higher GM density in the left primary sensory-motor cortex and right cerebellum and higher WM integrity in the right posterior limb of the internal capsule. It has been shown that musicians presented a larger right motor cortex than non-musicians with a negative correlation between the size of motor cortex of both hemispheres and age at which the person began musical training (Amunts et al., 1997).

Gaser & Schlaug (2003) used voxel based morphometry (VBM) analysis to investigate whole brain structural differences and found increased GM density in motor, auditory and visuospatial cerebral areas in musicians. Another study by Sluming et al. (2002) found that VBM identified an increased GM in Broca's area in the left inferior frontal gyrus in musicians with a positive correlation between

years of playing and this increase in GM distribution in under-50-year-old musicians. Abdul-Kareem et al. (2011b) showed similar results to a previous study using manual morphometry (stereology) on the same data.

In a morphologogical study of HG, Schneider et al. (2002) reported that the GM volume of the anteromedial portion of HG (amHG) was 130% larger in professional musicians as compared to non-musicians. Additionally, the GM volume of amHG was highly correlated with musical aptitude in professional musicians and amateur musicians. Musicians with perfect pitch revealed increased leftward asymmetry in PT than non-musicians or musicians without perfect pitch (Schlaug et al., 1995b). Bermudez et al. (2009) found greater cortical thickness in musicians with peaks in superior temporal and dorsolateral frontal regions with right-lateralized focus of greater GM concentration in musicians centred on the posterolateral aspect of HG. Aydin et al. (2005) reported significant between musicians and non-musicians in the neurometabolite concentrations in the left PT using quantitative proton MR spectroscopic.

VBM was performed to investigate the structural differences of the hippocampus between musicians and non-musicians. It has been reported that GM density of the hippocampus was higher in musicians than in non-musicians, which indicates that musical expertise critically modifies long-term memory processes (Groussard et al., 2010a). Sluming et al. (2007b) found a significant gender by musicianship interaction in the hippocampal volumes. Male musicians had larger GM concentration in the posterior portion of the right hippocampus (RHipp) and larger

hippocampal volumes bilaterally compared to male non-musicians. Authors showed that hippocampal volume correlated positively with number of years of orchestral playing in male musicians under 50 years of age. In addition, male musicians performed significantly better on visual memory tasks than non-musicians, and this was significantly positively correlated with the right hippocampal volume.

Using VBM, it has been reported that male musicians with absolute pitch (AP) were more leftward lateralized in the anterior region of the PT than male non-AP musicians (Luders et al., 2004). AP musicians showed heightened connectivity in WM between auditory perception and association cortices predominantly in bilateral superior temporal regions (Loui et al., 2011).

Halwani et al. (2011) used DTI to measure tract volume and fractional anisotropy of the arcuate fasciculus, which connects temporal and frontal brain regions, in musicians (singers and instrumentalists) and non-musicians. Musicians had larger tract volume and higher fractional anisotropy values of the right and left arcuate fasciculus than non-musicians.

2.5.2 Functional plasticity

Differences in functional cerebral characteristics between musicians and non-musicians have been investigated using different modalities. Elbert et al. (1995) used MEG to study somatosensory evoked magnetic fields in string players. The authors found that the cortical representation of the digits of the left hand was

larger in musicians than in controls with no differences in the right hand. Also the authors reported that the cortical reorganization of the representation of the fingers increased with earlier musical training. Transcranial magnetic stimulation was used to measure motor evoked potentials (MEP), corticospinal projections (CP) curve and short-latency intracortical inhibition (SICI) curve. The authors applied paired associative stimulation with interstimulus interval of 25 or 10 ms to test change of synaptic effectiveness. Musicians showed steeper curve of MEP and SICI with greater amplitudes and slope at both interstimulus intervals (Rosenkranz et al., 2007).

MEG has been used to investigate processing of multisensory stimuli in professional trumpet players. When stimulating the lip, the authors found that trumpet players showed a positive peak at 33 ms, which was not found in the control group (Schulz et al., 2003).

Using MEG, Pantev et al. (1998) investigated the evoked magnetic fields of a pseudorandom sequence of piano and pure tones matched in frequency and loudness in musicians and non-musicians. The only different was in the strength of cortical activation for piano tones, which was 25% greater in musicians. Musicians also showed a strong correlation with the age of commencement of musical practice. Schneider et al. (2002) used MEG to compare the processing of sinusoidal tones in the auditory cortex of non-musicians, professional musicians and amateur musicians. The authors found neurophysiological differences between groups. Comparing professional musicians and non-musicians, the

activity evoked in primary auditory cortex (19–30 ms after stimulus onset) was 102% larger in professional musicians. Pantev et al. (2001) showed that musical education and training is reflected in the organization of auditory and somatosensory representational cortex in musicians. The intensive experience of musicians with musical instruments formed representations for musical instruments in and adjacent to auditory association cortex (Hoenig et al., 2011).

Rüsseler et al. (2001) used mismatch negativity (MMN) to investigate the evoked potentials component in auditory cortex of musicians and non-musicians. The authors suggested that temporal integration might be more precise in musicians since musicians showed MMN for regularly spaced tones mistimed by 20 milliseconds, where non-musicians needed longer than 50 milliseconds. Lappe et al. (2008) reported that sensorimotor-auditory training causes plastic reorganizational changes in the auditory cortex over and above changes introduced by auditory training alone. In this study, the authors investigated the difference in MMN response between 'sensorimotor-auditory' group who, learned to play a musical sequence on the piano and 'auditory listened to' group and made judgments about the music that had been played by participants of the sensorimotor-auditory group. The authors showed that first group had significantly enlarged response.

Using fMRI Bangert et al. (2006) investigated cortical auditory motor coupling during the acoustic and the mute motion-related tasks in professional pianists. The professional pianists showed increased activity compared to the non-musicians in

a distributed cortical network during both tasks. Applying conjunction analysis showed that either task type coactivated a distinct musicianship-specific network comprised of dorsolateral and inferior frontal cortex (including Broca's area) the STG, the SMG, and supplementary motor and premotor areas. Sluming et al. (2007a) reported that professional musicians showed enhanced performance on a visuospatial task compared to non-musicians, associated with increased activation in Broca's area.

In another study, fMRI has been used to examine developmental aspects and effects of musical training on three different groups; 10-year-old children with varying degrees of musical training, adults non-musicians, and adult musicians. Both adults groups showed larger activations than children in prefrontal and temporal areas, and in the SMG. Musical training was correlated with stronger activations in the frontal operculum and the anterior portion of the STG in both adults and children (Koelsch et al., 2005).

It has been shown that changes in functional organization also extend to subcortical sensory structures. Musacchia et al. (2007) demonstrated that musicians had earlier and larger auditory and audiovisual brainstem responses to speech and music stimuli with a positive correlation between years of musical practice and strength of brainstem response to speech stimulus. Groussard et al. (2010a) and Herdener et al. (2010) identified plastic capabilities of the hippocampus in musicians. Herdener et al. (2010) observed enhanced neural responses to temporal novelty in the anterior left hippocampus in professional

musicians. The authors also reported enhanced neural responses to temporal novelty in music students with one-year intensive aural skills training. They also found that musical abilities boost hippocampal sensitivity to temporal novelty. Groussard et al. (2010a) found that musical expertise induced supplementary activations in the hippocampus, medial frontal gyrus, and superior temporal areas on both sides. The authors suggested that there is a broad combination of the neural networks involved in episodic and semantic memory.

Brain activation patterns of pitch memory task were investigated in musicians using fMRI. Musicians and non-musicians showed bilateral activation of superior parietal lobe, the STG, SMG, posterior middle gyrus and inferior frontal gyrus. Musicians showed more activation in the right temporal and SMG, while more activation was shown in right primary and left secondary auditory cortices in musicians. The authors suggested that musicians prefer to use brain regions specialized in short-term memory while non-musicians rely more on brain regions that important for pitch discrimination (Gaab and Schlaug, 2003). Gaab et al. (2006) examined functional activation patterns of an auditory working memory task prior to and after training. The training group was divided into Strong-Learners (SL) and Weak-Learners (WL), with no significant functional or structural brain differences prior to training. Pre-post training comparisons showed a significant signal increase in the left HG, the left posterior superior temporal and SMG for the SL group, while the WL group showed significant signal increases in the left HG, anterior insular cortex and in a lingual–orbitofrontal–parahippocampal network. Applying a random effects analysis

comparisons between both groups showed increased activation only in the left SMG but not in HG. It has been suggested that the activation of the SMG reflects its importance in the short-term storage of auditory material (Gaab et al., 2006).

2.5.2.1 Plasticity of the auditory cortex and tonotopic reorganisation

Early experience of sounds with spectral patterning develops the tonotopic mapping of auditory cortex. Many studies demonstrated evidence for this hypothesis. For example, Harrison, Stanton et al. (1993) demonstrated that, distorted tonotopic organization is caused by induced high-frequency hearing loss in neonatal kittens with expanded cortical space devoted to frequencies near the frequency of the hearing loss. Early intensive musical experience has a great effect on brain development (Shahin et al., 2004). However, it is possible to obtain musical expertise later in life. These could change the number of neurons involved in processing, the timing of synchronization and the number and strength of excitatory and inhibitory synaptic connections. However, musical training does not provide a specific change in the responses to noise stimuli (Fujioka et al., 2006). In animals, different studies showed that frequency reorganisation can be induced after exposing to noise (Nakahara et al., 2004, Eggermont, 2005, Pienkowski and Eggermont, 2011) or by training (Recanzone et al., 1993), by mechanical damage to the cochlea (Robertson and Irvine, 1989), by exposing to environmental contaminate (Kenet et al., 2007) and by electrical stimulation of the auditory cortex (Valentine and Eggermont, 2003, Eggermont, 2005). In humans, some population sowed expanded or altered tonotopic organisations such as; blind people (Elbert et al., 2002), schizophrenia patients (Rojas et al., 2002), people

who have develop high-frequency hearing loss from acoustic trauma or sudden hearing loss (Dietrich et al., 2001) and following stabilized changes of the acoustic input entering the central nervous system (Tecchio et al., 2000). In addition, Suga and Ma (2003) found an enlarged representation of the frequency of stimulus. The authors applied a microstimulation in primary auditory cortex of gerbils and echolocating bats because best frequency (BF) of neurons surrounding the stimulation site shifted towards that of the neurons at the stimulation site. These lead to a suggestion of auditory discrimination training. For example, reorganization of the auditory cortex can be approached by training tinnitus patients to discriminate some features of acoustic stimuli that close to the tinnitus frequency (Muhlnickel et al., 1998, Flor et al., 2004). Moreover, both high frequency and low frequency environmental sounds conferred benefit on reorganisation compared with normal acoustic environment. However, high frequency sound is more effective in reducing hearing loss and map reorganization (Eggermont and Roberts, 2004). In contrast, Flor et al. (2004) demonstrated some limitations in their study. Firstly, short training period only provides an initial evaluation of the effects of the training. Secondly, The authors did not collect physiological data, which could give an indication of the specific effects of the training on auditory cortex. Third, the role of nonspecific effects in the alteration of tinnitus severity cannot be determined because they did not employ a control group. Finally, there was an overestimating of the true effects of the training, which could be because corrections were not applied on computation of multiple tests (Flor et al., 2004). Two recent studies approved that auditory

discrimination training could partially reverse the wrong changes in tonotopic representation and improve tinnitus (Herraiz et al., 2007, Herraiz et al., 2009). In addition, it have been reported that, rapid changes can occur in the tuning of neurons in the auditory cortex of adult human following manipulation of the acoustic environment (Pantev et al., 1999) and tonotopic maps change happened during paying selective attention to differences in pitch of the tones (Ozaki et al., 2004). Also, intensive short-term training of pitch discrimination results in a change in the hemodynamic response of the human auditory cortex (Jäncke et al., 2001).

Chapter 3 : The Technology of Functional Neuroimaging and Experimental Paradigms Optimisation

3.1 Aims

Specific aims of this chapter were to:

1- Consider the technological aspects in investigating tonotopic mapping in the human auditory cortex using fMRI and MEG.

2- Optimise the experimental designs.

3.2 Introduction

During the last two decades, advances in neuroimaging technologies have provided enormous information about brain structure and function. Exploiting the superior temporal resolution of EEG/MEG and reasonably good spatial resolution of fMRI could improve our understanding of the neural mechanisms that involved in various sensory and cognitive processes. FMRI measures local changes in brain hemodynamics induced by cognitive or perceptual tasks with high spatial resolution. Conversely, electrophysiological methods M/EEG measure instantaneously the current flows induced by synaptic activity.

3.3 Magnetic Resonance imaging (MRI)

MRI is one of the most important medical advances during last few decades. It is the most preferable system in neuroimaging because of: minimal invasiveness, no radioactivity, widespread availability, and virtually unlimited study repetitions. It also provides anatomical and functional information for brain regions. Historically, Paul Lauterbur used back projection technique to demonstrate MRI in 1973. In 1974, Sir Peter Mansfield's group invented selective excitation technique. One year later Richard Ernst's group in Zurich invented two-dimensional Fourier transform imaging. In 1980, Edelstein and Hutchison developed the first practical 2D FT imaging method (McRobbie, 2003).

3.3.1 Magnetic components and larmor frequency

MRI uses property of nuclear magnetic resonance (NMR) to image nuclei of atoms inside the body. Because water and fat are the biggest source of protons in the body, NMR depends on the spinning of hydrogen atom (a single proton). Spinning protons produce small magnetic fields in random distribution. Applying an external magnetic field, make protons align their spin states either with or against the external magnetic field ($\mathbf{B_0}$) as shown in Figure 3.1. Protons obey the Botzmann statistics and therefore majority of protons aligns with the magnetic field, the total magnetic field of the excess protons is called net magnetization vector (NMV) (M_0). The spinning protons precess about the axis of the external field with an angular frequency ($\boldsymbol{\omega_0}$) proportional of the strength of the magnetic field (McRobbie, 2003) as shown in larmor equation (3.1).

$$\boldsymbol{\omega_0} = \gamma \mathbf{B_0} \qquad 3.1$$

$\boldsymbol{\omega_0}$ = Angular frequency γ = Gyromagnetic ratio
$\mathbf{B_0}$ = External magnetic field in tesla

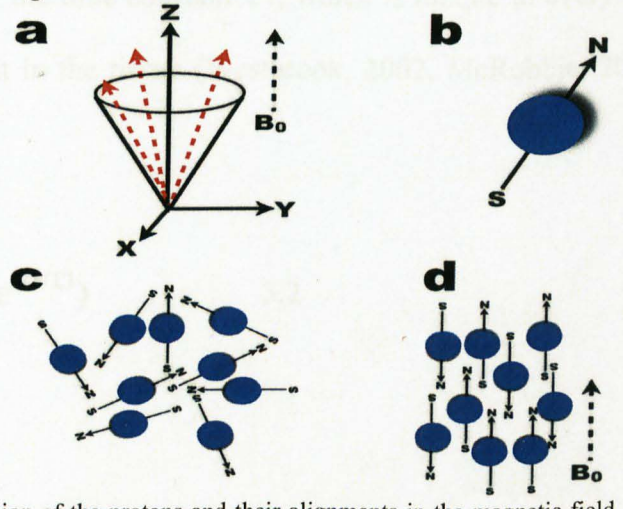

Figure 3.1 Precession of the protons and their alignments in the magnetic field. a) Precession of protons (hydrogen atom), b) Spinning proton, c) Spinning proton with no magnetic field present, d) Spinning proton if external magnetic field applied.

Applying electromagnetic radio frequency (RF) pulse cause protons to jump between high and low energy states which result in a change in the NMV of protons inducing a voltage in a coil of wire perpendicular to that field as identified by Faraday's law (McRobbie, 2003).

3.3.2 Relaxation times

The absorbed RF energy is retransmitted at the angular frequency by turning off RF in order to produce the NMR signal. The excited protons begin to return to the relaxation state where energy absorbed by the excited protons is released back into the surrounding lattice in a process called T1 relaxation, which mostly used in anatomical images. In this configuration, Z component of magnetization M_Z equals M_0 with no transverse (M_X or M_Y) magnetization. The time that it takes for the system to return to relaxation state is described mathematically by an exponential curve (equation 3.2 and Figure 3.2). This recovery rate is characterized by the time constant T1, which is unique to every tissue depending on water amount in the tissue (Westbrook, 2002, McRobbie, 2003, Bernstein et al., 2004).

$$M_Z = M_0 (1 - e^{-t/T1}) \qquad 3.2$$

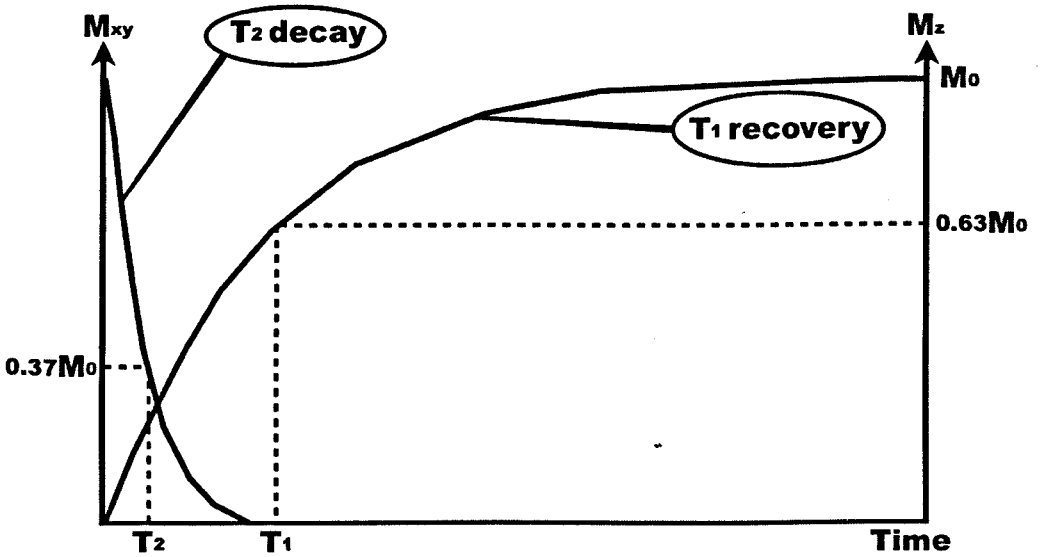

Figure 3.2 T1 recovery curve and T2 decay curve, T2 is much quicker than T1.

The second relaxation type depends on de-phasing of the excited protons which is called T2 and $T2^*$ relaxation. The time that it takes for the system to return to equilibrium of the transverse magnetization is described mathematically by an exponential curve (Westbrook, 2002, McRobbie, 2003, Bernstein et al., 2004) (see equation 3.3 and Figure 3.2).

$$M_{XY} = M_{XY_o} e^{-t/T2} \qquad 3.3$$

Usually, protons spin at different rates and hence they get out of phase leading to NMR signal decay depending on interacting magnetic field. Magnetic fields of two nearby protons interact with each other (spin-spin interaction). The temporary and random interaction between two protons causes a cumulative loss in phase resulting in an overall loss of signal which known as T2 relaxation (Westbrook, 2002, McRobbie, 2003, Bernstein et al., 2004).

3.3.3 Blood oxygenation level dependent (BOLD) fMRI

Generally, BOLD fMRI measurements reflect the hemodynamic changes related to the input and intracortical processing of a given area rather than its spiking output (Logothetis et al., 2001, Goense and Logothetis, 2008). This technique, which makes use of blood as an intrinsic contrast, has functional sensitivity in MRI. Gradient echo, which was introduced in 1992 and based on $T2^*$ is the most widely used BOLD sequence in fMRI because of its sensitivity to the magnetic field inhomogeneity. Excitation of neurons leads to a local increase in energy and oxygen consumption in stimulated areas. This makes blood flow increases so much, that the venous and capillary concentration of deoxyhemoglobin actually decreases with an increase in oxyhaemoglobin, This process causes an increased field homogeneity and thus a higher signal intensity in a series of $T2^*$ weighted images. Change of the oxygenated blood flow to/from a region in the brain cause an increase in MR signal by increasing intravoxel $T2^*$. This leads to the image intensity difference between the rest and the task for active regions of the brain (McRobbie, 2003, Stippich et al., 2007).

3.3.4 Study design considerations

FMRI of the auditory system has been regarded as challenging because of the loud gradient switching noise. Scanner noise not only masks the presentation of the stimulus and affects the perception of the auditory stimulus, but also the repetitive nature of scanner noise determined by repetition time (TR) could cause activation of the auditory cortex (Bandettini et al., 1998, Ulmer et al., 1998, Shah et al.,

1999, Hall et al., 2000, Shah et al., 2000). Scanner acoustic noise is mainly produced by the mechanical oscillation of the gradient coils placed in a magnetic field. Switching the electrical current on and off through the gradient coils induces Lorentz forces and makes the coils move.

Different factors affect this displacement such as; voltage applied, strength of the static magnetic field, the amplitude frequency and waveform of the switching (Hedeen and Edelstein, 1997, Mansfield et al., 1998, Shellock et al., 1998, Moelker and Pattynama, 2003). Various techniques have been implemented to eliminate the actual sources of scanner acoustic noise. Passive noise reduction methods such as; earplug, earmuff, and helmet; are the most widely used methods (Amaro et al., 2002, Moelker and Pattynama, 2003). Combination of these methods could effectively reduce acoustic noise by up to 60 dB (Moelker and Pattynama, 2003). In addition, reengineering MR hardware by incorporating the gradient coils in vacuum enclosures (Katsunuma et al., 2002) combined with a magnet with a non conducting inner bore cryostat (Edelstein et al., 2002) or multiple active gradient shields (Edelstein et al., 2005) effectively interrupt acoustic noise propagation. MR systems with vacuum enclosed gradient and insulators have become commercially available for a decade (Excelart, Toshiba Corporation, Tochigi, Japan, and Signa Twinspeed, General Electric, Milwaukee). Toshiba has implemented a breakthrough technology called pianissimo which leads to an acoustic noise reduction more than 90% of conventional MRI systems (Vantage, Toshiba Corporation, Tochigi, Japan).

Alternatively, several image acquisition techniques have been studied to overcome the confounding effect of scanner noise such as; sparse temporal sampling (Hall et al., 1999), clustered volume acquisition (Talavage et al., 1999), behaviour-interleaved acquisition (Eden et al., 1999), silent simultaneous multi-slice excitation (SIMEX) (Loenneker et al., 2001) and silent event related (SER) (Yang et al., 2000, Le et al., 2001, Yetkin et al., 2003). In addition, Schmidt et al. (2008) optimized low-noise EPI for auditory fMRI measurements using a block design. This design produces a narrow-band acoustic frequency spectrum therefore; the authors found that the acoustic noise reduction amounts to up to 20 dB comparing to standard EPI sequence.

Hall et al. (1999) used a long repetition time TR (14 s) with alternating intervals of 14 sec of speech and 14 sec of silence. This method shows a greater MR signal change than continuous scanning. The response of the primary auditory cortex peaked 4-5 s after stimulus onset and decayed after an additional 5-8 s (Hall et al., 1999, Hall et al., 2000). Baumann et al. (2010) studied characterisation of the BOLD response and reported that the BOLD response peaked around 4 s after the onset of 2 s stimuli. In contrast, Belin et al. (1999) found that activation peaked approximately 3s after stimulus onset and lasted for 3s. The authors used shorter effective TR (10 s) and varied the delay between a short auditory stimulus and the MR acquisition. Although sparse imaging shows greater auditory response, continuous imaging could better reveal organizational properties such as aspects of the hierarchical organization of auditory cortex (Petkov et al., 2009).

In clustered volume acquisition (Talavage et al., 1999), slice acquisitions are clustered at the end of TR period to prevent a response from being induced by the volume acquisition itself. Extra gradient readouts are introduced to detect the cortical responses to the scanner noise where acoustic stimulation is presented immediately prior to the acquisition of a cerebral volume. The number of extra gradient readouts controls the duration of acoustic stimulation. This method yields greater measures of dynamic range of the signal change (Talavage et al., 1999).

Eden et al. (1999) used behaviour-interleaved acquisition for non-auditory tasks and showed that it would be useful for the studies involving auditory stimulation. The authors delayed data acquisition to a period immediately after task completion, to utilize the physiological delay in order to disperse between neuronal activity and its resulting hemodynamic lag.

Loenneker et al. (2001) implemented SIMEX pulses to improve the intrinsic low volume coverage of the silent sequence and compared it with a standard noisy technique using auditory and visual stimulation paradigms. The scanner noise was reduced below the range of the ambient noise of the magnet room during the silent part of the experiment, while there was a trend of decreased activated areas for the noisy part.

SER design limits image acquisition to a single volume following an auditory stimulus administered during the 'silent' period. This acquires an image at a point close to the peak of the HRF; 5 s (Le et al., 2001) or 4 s (Yetkin et al., 2003) after stimulus onset or even two time points in the peak period of the stimulus induced

HRF curve and also in the baseline period (Yang et al., 2000). Compared to other designs (block and conventional event related), SER shows larger MR signal change (Yang et al., 2000) and a greater signal to noise ratio (SNR) (Amaro et al., 2002). The main disadvantage of this design that it needs a longer total acquisition time because of its longer TR -at least 20 s for the best optimization- (Amaro et al., 2002, Hall et al., 2000, Le et al., 2001) therefore, it is more susceptible to motion artefacts (Le et al., 2001). It mostly depends on two time points at the peak and baseline of HRF or even one time point at the peak therefore, resultant images will lack temporal information (Amaro et al., 2002). Another disadvantage is that the HRF is excessively affected by medications (Seifritz et al., 2000), age (Yousem et al., 1999), and vascular diseases (Rother et al., 2002), while the peak time for the HRF is estimated by assuming that it will be constant across all subjects and trials. Introducing a jittering scheme overcomes the lack of temporal information. This method permits full sampling of HRF curve by collecting data at different time points on the HRF curve at jittered intervals post stimulus manner (Josephs et al., 1997, Belin et al., 1999, Hall et al., 2000, Amaro et al., 2002), resulting in a total acquisition time which is even longer than that of normal SER. Furthermore, averaging of time points combines the signals of correct and erroneous trials.

3.4 MEG

MEG is a neuroimaging technique that is extremely sensitive to the minimal changes in the magnetic fields produced by small changes in the electrical activity within the brain. Usually, information is transferred between neurons as electric

currents, which in turn produce magnetic fields, which are detectable outside the head. It is a direct and real time measurement of neural activity (Hansen et al., 2010).

3.4.1 Electrophysiological Basis of MEG Signals

A stimulus activates part of the cortex and hence induces time-varying electrical currents at the level of cellular membranes. These currents consist of an action potential and postsynaptic potential (PSP). The contribution of the action potential to MEG signals is minimal to that of compared to that of PSP, due to its short duration (≈1ms) and because action potential attenuates much more strongly than PSP. The PSP can be classified into an excitatory postsynaptic potential (EPSP) and inhibitory postsynaptic potential (IPSP). Detectable MEG signals are produced by EPSP and partially by IPSP (Niedermeyer and Silva, 2005). Here we will consider two types of neurons: pyramidal and stellate. Pyramidal neurons have long apical dendrites that help in generating coherent magnetic fields when activated with a certain degree of synchrony. The cortex is folded into gyri and sulci. Therefore, apical dendrites of some populations of neurons are roughly perpendicular to the overlying skull (gyral neurons), whereas others are roughly parallel to the skull, i.e., (sulcal neurons). Sulcal neurons produce currents that have a component oriented tangentially to the skull, while gyral neurons produce radial currents (Figure 3.3). Tangential currents produce detectable magnetic field by MEG because their magnetic fields are perpendicular to the skull (Hämäläinen

et al., 1993, Vrba and Robinson, 2001, Lu and Kaufman, 2003, Hansen et al., 2010).

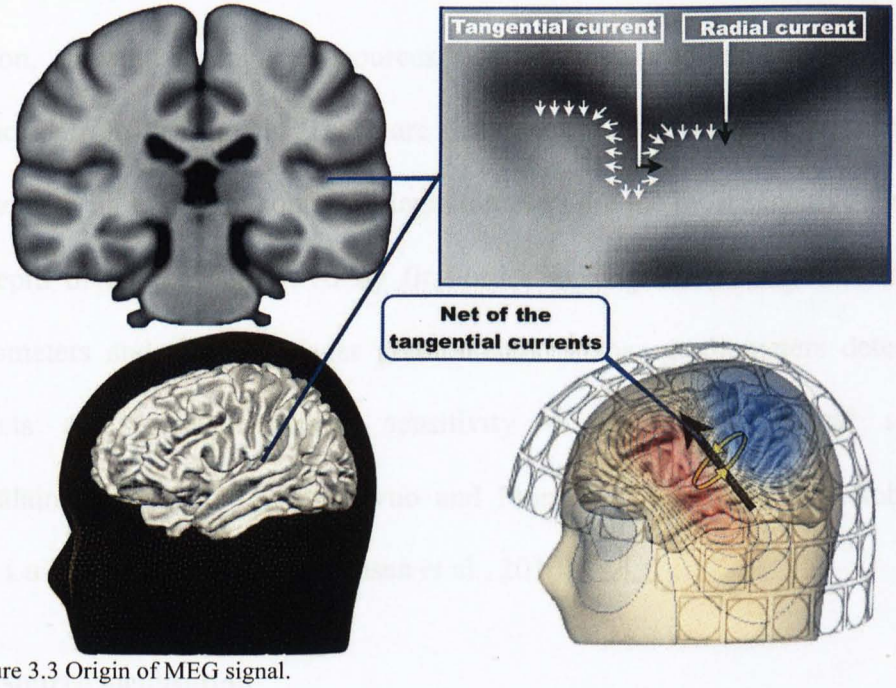

Figure 3.3 Origin of MEG signal.

3.4.2 MEG measurement

The magnetic fields that generated by brain are very weak (in the range of several tens to hundreds femto tesla) (Ono and Ishiyama, 2008), which only can be detected by a highly sensitive magnetic detector that named superconducting quantum interference devices (SQUIDs). Environmental noise is about a factor of 1 million to 1 billion larger than the MEG signals, which need very accurate noise cancellation methods. Different approaches have been used to isolate MEG signal. The most effective and important method is employing a passive magnetically shielded room. Another technique is using active noise compensation systems by measuring the interference field and generates a compensating field. Further noise

reduction techniques have to be applied inside the shielded room; gradiometrization (using multiple magnetometers) is one of them. The gradiometers protects the MEG sensors from far-away magnetic sources. In addition, unwanted magnetic sources can be measured explicitly and then subtracted from the signals. There are different types of magnetic sensors have vary sensitivity to distant sources. Magnetometers are the most sensitive sensor to the depth of sources, followed by first-order axial gradiometers, second-order gradiometers and, finally, planar gradiometers. Planar gradiometers detect less artefacts and have maximum sensitivity to superficial cortical sources (Hämäläinen et al., 1993, Malmivuo and Plonsey, 1995, Vrba and Robinson, 2001, Lu and Kaufman, 2003, Hansen et al., 2010).

3.4.3 Source localisation

Localising electric activity within the brain that induces magnetic fields outside the head is a great challenge in MEG. Source localization can be done by computing what the output of the MEG sensors would be if a certain region of cortex were active "forward problem" or by estimating the location of the activity from MEG signal "inverse problem". The forward problem determines the magnetic fields that result from primary current sources, while the inverse problem estimates the location of these primary current sources. Although, solving the forward problem show diversity of approaches that have been applied, it is crucial for performing source localisation (Yaroslav O. Halchenko et al., 2005). In the inverse problem, there are infinite possible answers, which introduce

the difficulty of defining the best solution. Therefore, prior knowledge of brain activity and anatomy are needed. The source models can be either over-determined or under-determined. The over-determined estimation assumes that a single current dipole or several current dipoles exist in a head conductor. These models are suitable for a primary sensory response. However, in the case of a complicated neuromagnetic field e.g. spontaneous or high cognitive function, under-determined estimation is required considering multiple or widely distributed cortical areas. The under-determined solution can be divided into norm estimation and spatial filter models (Hämäläinen et al., 1993, Lu and Kaufman, 2003, Hansen et al., 2010). Additionally, time and frequency amplitude analysis, coherence analysis and three-dimensional mapping of source power are considered as solution techniques as well (Vrba and Robinson, 2001).

3.5 Combining fMRI and MEG

Although, neuroimaging is a very young science, multimodal neuroimaging has already advanced our understanding of the spatiotemporal pattern of brain activation and connectivity underlying perception, motion and cognition. MEG and fMRI are innovative functional brain imaging techniques. MEG signals are directly coupled to neuronal electrical activity (Hämäläinen et al., 1993, Dale et al., 2000). It reflects the magnetic field resulting primarily from synaptic trans-membrane currents in neuronal dendrites. In contrast, fMRI signals are limited by the indirect nature of the coupling between the observed signals and the underlying neuronal electrical activity (Dale and Buckner, 1997). MEG has good

temporal resolutions with poor spatial resolution whereas fMRI has good spatial resolution with poor temporal resolution due to the limited rate of change in the hemodynamic response. These two modalities present different views of the neural activity; therefore integrating them would improve our understanding of brain activity. It has been shown that BOLD contrast mechanism reflects the synaptic processing of a given area rather than its spiking output (Logothetis et al., 2001, Goense and Logothetis, 2008). Additionally, Arthurs et al. compared the evoked EEG potential and the fMRI response to somatosensory stimulation and found a similar increase in the somatosensory evoked potential amplitude and the BOLD signal with increasing stimulus intensity (Arthurs and Boniface, 2002, Arthurs and Boniface, 2003, Arthurs et al., 2007). Im et al. (2005) investigated spatiotemporal pattern of brain activation of language judgment task and found better localization of the language area on the left hemisphere in the fMRI-constrained data as compared with the distributed sources based on MEG alone. Although, tonotopic mapping is not a complex cognitive task therefore; combination of fMRI and MEG should be truly integrated analyses, it is rather a challenging process to investigate spatiotemporal components of neural activity of frequency organisation as recent studies showed multiple tonotopic fields in time (Liegeois-Chauvel et al., 1991, Liegeois-Chauvel et al., 1994, Pantev et al., 1995, Schneider, 2001, Schneider et al., 2002, Lütkenhöner et al., 2003a) and space (Talavage et al., 2000, Formisano et al., 2003, Seifritz et al., 2006, Woods et al., 2009, Humphries et al., 2010, Da Costa et al., 2011, Langers and van Dijk, 2011).

3.6 Experimental Design optimisation

In the pilot study, I investigated and optimised different designs to examine tonotopic mapping in the human auditory cortex using both fMRI and MEG. Also I used different groups of frequencies.

3.6.1 Acoustic stimulation

I used different auditory stimuli with nine frequencies (130.8, 164.81, 207.65, 523.25, 659.26, 830.61, 2093, 2637 and 3322.4 Hz) from three notation groups (C, E and G#/A ♭) in the form of an octave interval. Sound pressure level of the stimulus was set to 70 dB sound pressure level (SPL) for all stimuli and for every subject. Each stimulus was formed in a train of sine waves (rise/fall time 10 ms, plateau 30 ms, interstimulus interval (ISI) 50 ms).

I changed the acoustic stimulations to the following frequencies (247, 440, 784, 1175, 2637 and 4186 Hz) that allocated to the following musical notation groups (B3, A4, G5 D6 E7, C8 respectively) at the same sound level (70 dB SPL). The later group of frequencies was selected depending on the calibration process of sound delivery systems in both modalities (MRI and MEG scanners). 247 and 4186 Hz were the lowest and the highest frequencies that were presented at 60 dB SPL in MEG system. This sound pressure level was characterised and measured by Dr. Guy Lightfoot from department of audiology at the Royal Liverpool University Hospital. This extended the range of frequencies (247-4186 Hz) and reduced the overall fMRI scanning time e.g. in high-resolution stroboscopic event

related (SER), scanning time of each run was reduced from 13 minutes to 9 minutes. Therefore, this design became less susceptible to gross motion artefacts. In MEG design, more stimuli of each frequency were presented.

3.6.2 FMRI experiments

In order to investigate tonotopic mapping of the human auditory cortex, five subjects were tested using four designs of fMRI; low-resolution SER, high-resolution SER, low-resolution block and high-resolution block designs. All experiments were performed using a 3T Trio whole body scanner (Siemens, Erlangen, Germany) with an eight-channel phased-array head coil.

SER

Stimuli were presented randomly during the silent part of the image acquisition. Acquisition of the EPI data was taken in a randomised manner at 8 distinct time points (0, 3, 4, 5, 6, 7, 8 and 11 s) after the onset of the stimulus to permit sampling at different time-points on the HRF curve (Josephs et al., 1997, Belin et al., 1999). Tone duration was 3s and the scanning time was 9 minutes. This design has been optimised for two types of resolutions. In the low resolution SER, the following scanner parameters have been used; (TR) = 20 s, echo time (TE) = 35 ms; delaying TR = 18196 ms; echo spacing 0.45; imaging resolution = 3 × 3 × 3 mm^3; flip angel= 90°; number of axial slices 28; matrix size 256 × 256; bandwidth = 2605 Hz/px. However in high resolution SER, I used the following scanner parameters: (TR/TE) = 20000/35 ms; delaying TR = 17170 ms; echo spacing 0.7; phase partial Fourier = 6/8; imaging resolution = 2 × 2 × 2 mm^3; flip

angel= 90°; number of axial slices 28; matrix size 256 × 256; bandwidth 1628 Hz/px.

Block design

This design involves ON-period and OFF-period with duration of 20 sec each period. The duration of the stimulus was 500ms and the duration of rest was 500ms which means each On-period contains a repetition of each stimulus for twenty times. On-periods were repeated twice for each tone. The following scanner parameters have been used for lower resolution design; TR= 2.5 s; TE= 30 ms; matrix size = 64 × 64; flip angle = 90°; echo spacing 0.45; field of view 190 × 190; number of slices = 36 and bandwidth = 2605 Hz/px with voxel size 3 × 3 × 3 mm^3. Scanning session lasted for about 12 min. In contrast, the higher resolution design has the following scanner parameters; number of slices = 30; TR = 3 s; TE= 32 ms; matrix size = 64 × 64; flip angle = 90°; field of view 190 × 190; number of slices = 36 and bandwidth = 1628 Hz/px; phase partial Fourier = 6/8; echo spacing 0.8; voxel size 1.5 × 1.5 × 2 mm^3; matrix size 128 × 128. This session lasted for about 13 minutes.

3.6.3 MEG experiments

In the first design, I used the same frequencies that have been used in fMRI experiment where every stimulus was presented 200 times with duration of 500 ms, and interstimulus interval ranging from 450 to 550 ms, this session lasts up to 39 min. In the newer design, each frequency was formed in 150 ms sine wave

(rise/fall time 20 ms, plateau 110 ms) with an interstimulus interval randomized between 300 and 500 ms. Every stimulus was presented 1000 times.

3.7 Results

3.7.1 FMRI results

For each subject activated regions were those regions with activated voxels above a significance of adjusted False Discovery Rate (FDR) (Benjamini and Hochberg, 1995, Genovese et al., 2002) $P < 0.01$. Some subjects had a strong response to the tones, with significance of adjusted FDR $P < 0.001$. The obtained *P* values were corrected for multiple comparisons using a cortex-based adjustment. Moreover, maps of the frequency and octave that evoked the highest BOLD response (best tonotopic and octave maps) were represented on folded and morphed inflated polygon meshes representing the subjects' cortical sheet (Figures 3.4 and 3.5) by implementing a three colour coding scheme; high-octave maps were represented in blue, whereas medium octave frequencies maps was represented in a yellow colour, and low octave was illustrated in red colour. I have applied the technique used by Parkes et al. (2009) for colour tuning in the visual cortex to tonotopic mapping in the auditory cortex.

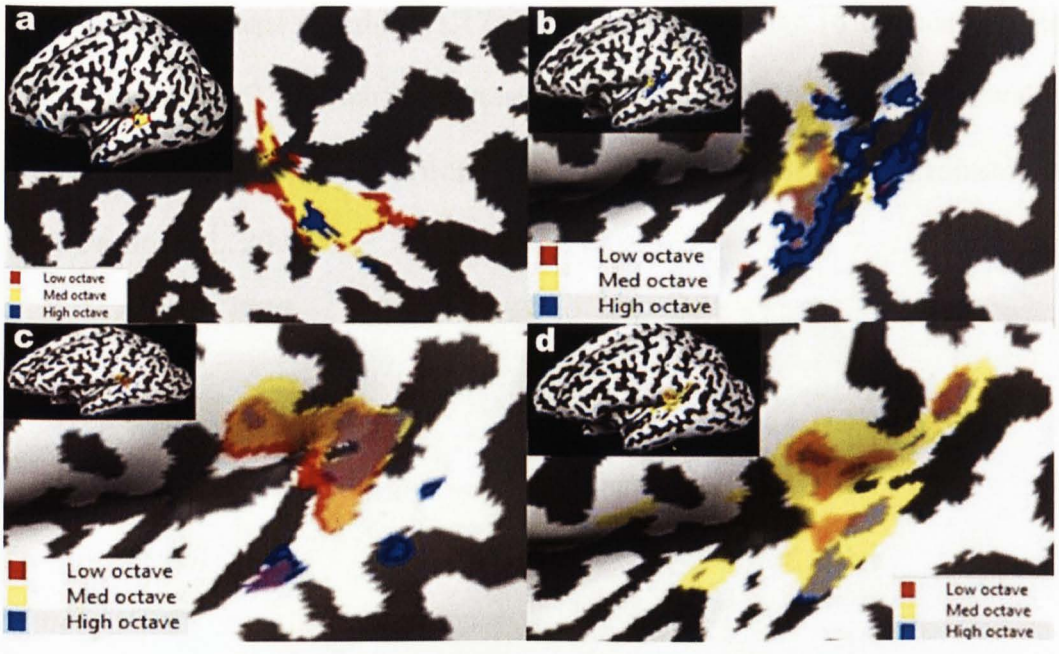

Figure 3.4 Best-octave maps in the auditory cortex (subject C17, P<0.01 FDR adjusted), layout maps are superimposed on a mesh reconstruction of the subject's cortex. a) low-resolution block design, b) high-resolution block design, c) low-resolution SER, d) high-resolution SER.

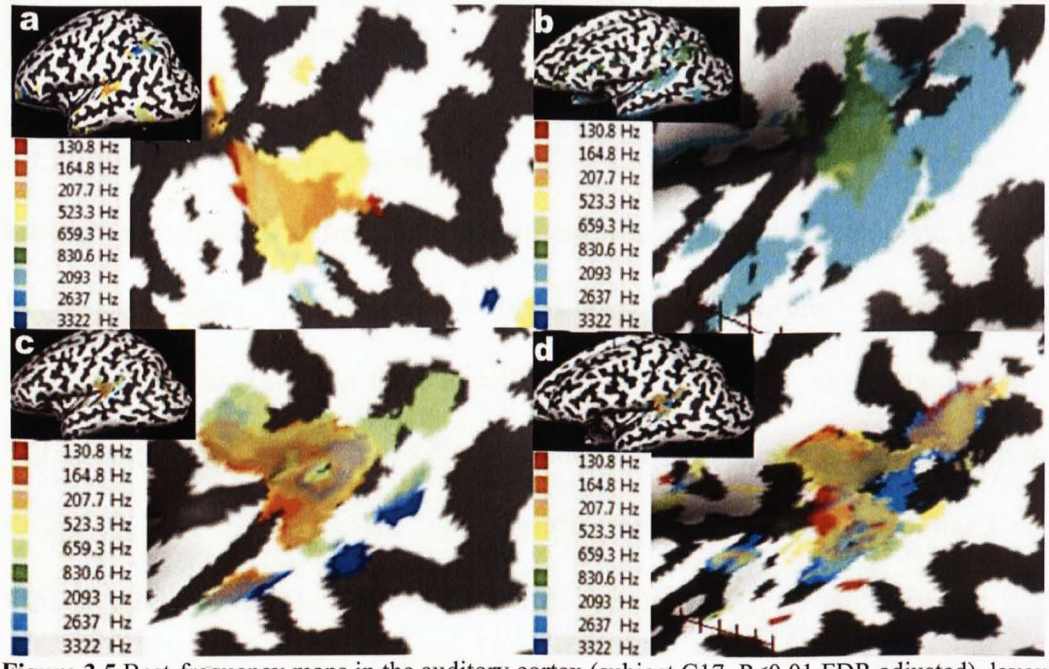

Figure 3.5 Best-frequency maps in the auditory cortex (subject C17, P<0.01 FDR adjusted), layout map is superimposed on a mesh reconstruction of the subject's cortex. a) low-resolution block design, b) high-resolution block design, c) low-resolution SER, d) high-resolution SER.

Best-frequency maps of subject C17 with the newest design (6 frequencies and voxel size of 2 × 2 × 2 mm^3) are presented in Figure 3.6. The obtained p value was corrected for multi comparisons using a cortex-based Bonferroni adjustment (Formisano et al., 2002).

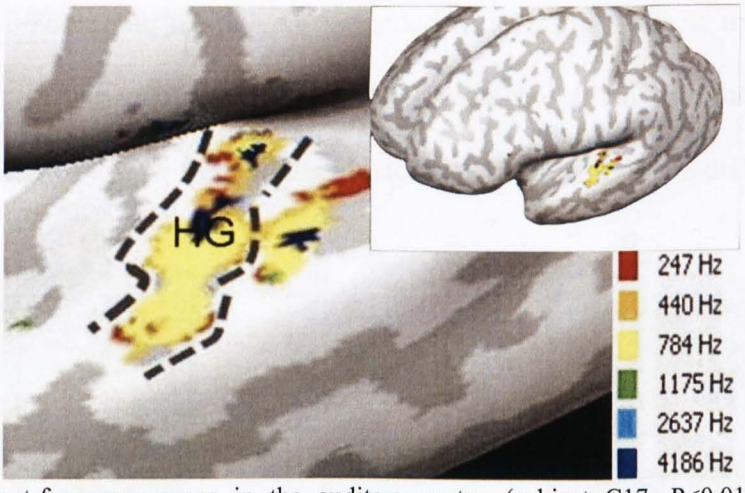

Figure 3.6 Best-frequency maps in the auditory cortex (subject C17, P<0.01 cortex-based Bonferroni adjustment (Formisano et al., 2002)), layout map is superimposed on a mesh reconstruction of the subject's cortex.

3.7.1.1 Defining frequency organization

Further investigation of frequency organisation was applied on subject C17. Best frequencies maps were projected on folded and morphed inflated mesh reconstruction representing the subject's auditory cortices to check the effect of HG orientation, and its degree of convolution on frequencies gradient directions (Figure 3.7). Tonotopic maps were clearly preserved in both convoluted and inflated auditory cortex. Mirror-Symmetric Tonotopic Maps were shown in both hemispheres in the medial part of HG along an axis roughly parallel to the HG axis. First high frequencies cluster (4186 Hz "dark blue" and 2637 Hz "light blue") can be observed in the medial edge of HG. The second high frequencies cluster was located in the middle of HG. A large cluster of low to mid range

frequencies (440 Hz "orange", 784 Hz "yellow" and 1175 Hz "green") was located in the middle between these high frequency regions. Another cluster of (247 Hz "red", 440 Hz "orange" and 784 Hz "yellow") was situated in the lateral aspect of HG. In the left HG, there was a third high frequency region at the lateral edge of HG. Tonotopic maps were extended to a single gradient in PT in both hemispheres. In this map, high frequencies cluster was situated in the lateral part of PT and the med to low frequencies cluster was located in the medial part of PT.

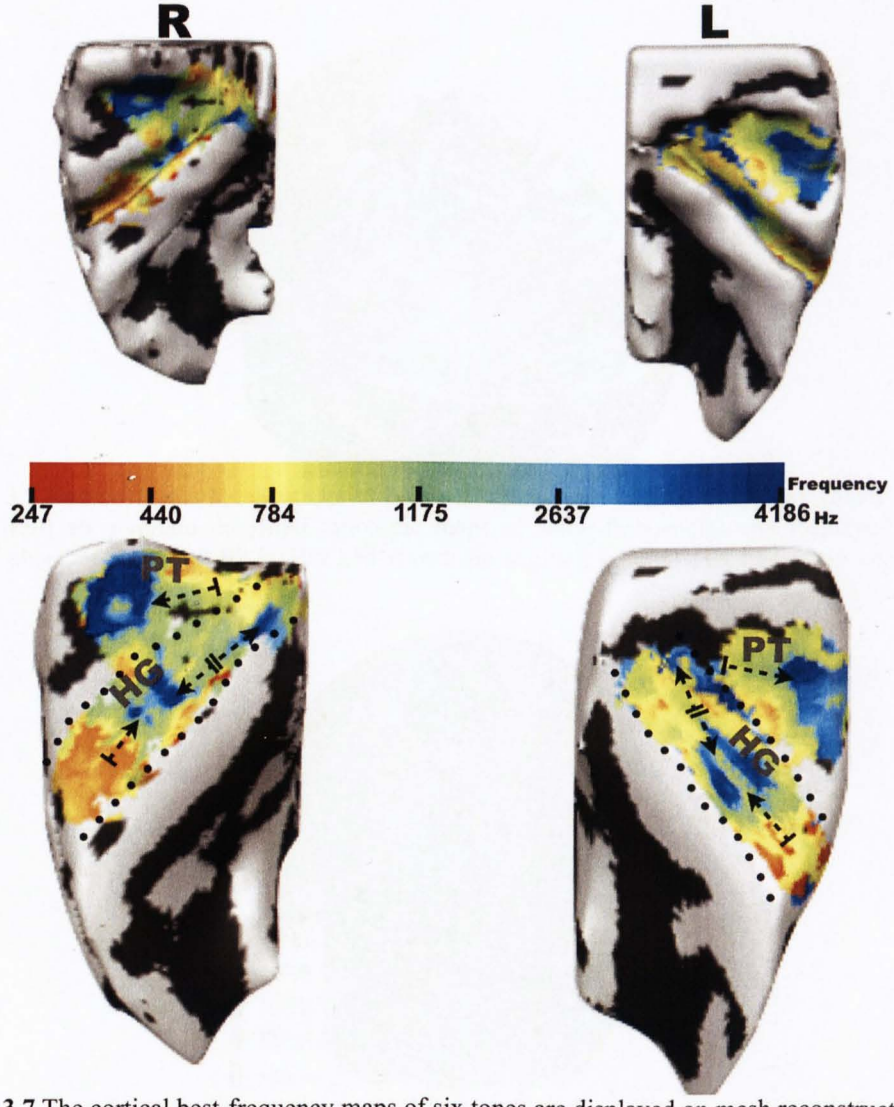

Figure 3.7 The cortical best-frequency maps of six tones are displayed on mesh reconstruction and inflated representation of the subject's auditory cortices, HG = Heschl's gyrus, (subject C17, P<0.01 FDR adjusted).

3.7.2 MEG results

Figures 3.7 and 3.8 show tonotopic mapping of N19m-P30m and N100m components respectively. Dipoles were colour-coded using six colours (ranging from dark blue for the highest frequency to red for the lowest one). Tonotopic mapping gradients of N100m components were located along the medial-lateral axis of PT posterior to HG. I managed to localize earlier auditory evoked field components (N19m-P30m) in the HG for two frequencies in one subject only.

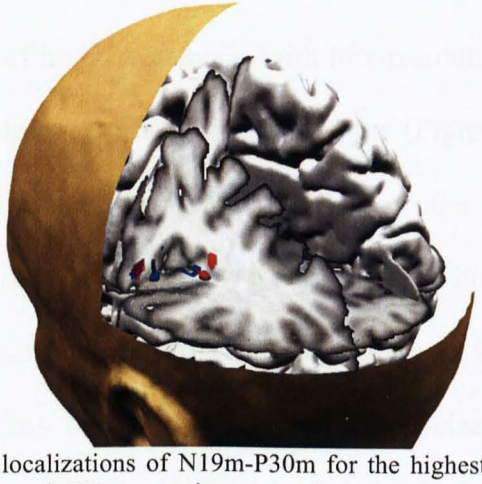

Figure 3.8 Source dipole localizations of N19m-P30m for the highest frequency (blue) and the lowest (red) are overlaid on fMRI tonotopic maps of same frequencies and displayed on the cortical sheet of subject # 02 in HG and shown on sagittal, coronal and transverse anatomical views.

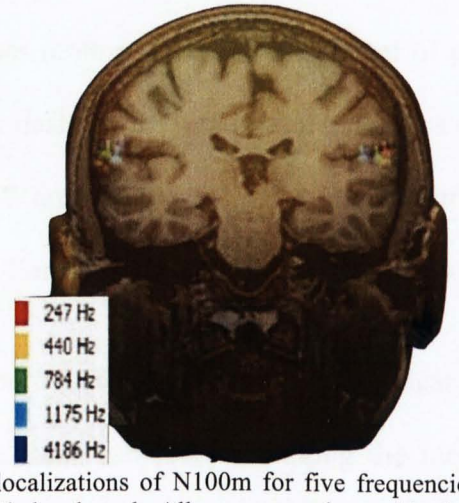

Figure 3.9 Source dipole localizations of N100m for five frequencies are presented on a mesh reconstruction of the subject's head mesh. All sources are located in the PT (subject # 03).

3.8 Discussion

In this pilot study, I implemented various designs using fMRI and MEG. Several methods have been developed to examine tonotopic mapping in the human auditory cortex using various pure tones from different notes and different octaves. Regarding fMRI design, both block designs were superior in statistical power in comparing with stroboscopic event related designs. However, activities were distributed over wide area outside the region of interest. In addition, because of interface between scanner noise and sound tones, some tones were not represented e.g. tones of high frequencies with low-resolutions block designs and low frequencies with high-resolution block designs (Figure 3.5 a-b). I only ran higher-resolution design on 3 subjects because of the load on the scanner acquiring high-resolution images during block design. This produced high noise produced during scanning session. Investigating technical reasons is out of scope for this study. In contrast, stroboscopic SER provided clearer maps (see Figures 3.5 c-d and 3.6). High-resolution stroboscopic SER with six tones produced the best tonotopic maps (Figure 3.6). This could be due to shorter scanning time, which leads to less gross motion artefacts, as number of presented frequencies is less than these of older designs. Multiple tonotopic maps of the optimised design as shown in Figure 3.7 are consistent with some recent studies (Pantev et al., 1995, Schneider, 2001, Formisano et al., 2003, Seifritz et al., 2006).

In contrast, in MEG part of the study, there were clear tonotopic gradients of N100m components in three subjects only along the medial-lateral axis of PT. Tonotopic maps of auditory evoked long latency fields are consistent with some

recent studies (Pantev et al., 1995, Schneider, 2001). I localised the earlier auditory evoked field components (N19m-P30m) in the HG for two frequencies in one subject only. Instability of localising N19m-P30m could be related the fact that middle latency auditory evoked field components require a minimum number of event per stimulus (Pantev et al., 1995, Schneider, 2001).

As a consequence of this optimization study, I decided to investigate influence of musical performance expertise on tonotopic mapping and cortical activation in the human auditory cortex using fMRI and MEG. Approval for the 'musical performance' study was obtained from the Local Research Ethics Committee at University of Liverpool. Number of participants of each study is listed in the table 3.1. Table 3.2 show detailed information of each subject.

Study	Number of participants							
	Musicians				Non-musicians			
	Participated		Excluded		Participated		Excluded	
	Males	Females	Males	Females	Males	Females	Males	Females
Auditory test	7	5	0	0	10	4	0	0
SMRI	7	5	0	0	10	4	0	0
FMRI	7	3	4	2	10	3	3	3
MEG	7	4	3	1	11	4	6	2

Table 3.1 The number of participants of each study.

Subject's ID	Age	Handedness	Gender	fMRI	MRI	MEG	Psychoacoustic tests
M01	57	R	M	✓*	✓	✓+	✓
M02	42	L	F	-	✓	✓+	✓
M03	57	R	M	✓*	✓	✓	✓
M04	19	R	F	✓*	✓	✓+	✓
M05	18	L	M	✓	✓	✓+	✓
M06	41	R	M	✓*	✓	✓	✓
M07	23	L	M	✓*	✓	✓	✓
M08	54	R	M	✓	✓	✓+	✓
M09	25	R	F	✓	✓	✓+	✓
M10	51	R	M	✓	✓	✓	✓
M11	31	R	F	✓*	✓	✓+	✓
M12	38	R	F	-	✓	-	✓
C01	57	R	M	✓	✓	✓	✓
C02	35	R	M	-	✓	✓+	✓
C04	36	R	M	✓*	✓	✓	✓
C05	38	R	M	✓	✓	✓+	✓
C06	21	L	M	✓	✓	✓	✓
C07	21	L	M	✓*	✓	✓+	✓
C08	20	R	F	✓	✓	✓	✓
C09	47	R	M	✓	✓	✓+	✓
C11	50	R	M	✓	✓	✓	✓
C12	22	R	F	✓	✓	✓	✓
C13	44	R	M	✓*	✓	✓	✓
C14	21	R	F	✓*	✓	✓	✓
C15	33	L	F	✓*	✓	✓+	✓
C16	56	R	M	-	✓	✓+	✓
C17	57	R	F	✓*	✓	✓+	✓

Table 3.2 Participants' details. M= Musicians, C= non-musicians. Right ticks are for subjects who participated in the studies. Asterisk flag and plus sign are for subjects who have been included in fMRI and MEG analysis respectively.

Chapter 4 : Investigating of Pitch discrimination ability in musicians and non-musicians

4.1 Aims

Specific aims of this chapter were to:

1- Explore the influence of musical performance expertise on pitch discrimination ability.

2- Investigate laterality effect of pitch discrimination ability.

3- Explore the aging effect and influence of musical experience on pitch discrimination ability.

4.2 Introduction

Pitch plays an important role in the perception of speech and music and in the segregation of concurrent sound sources (Plack et al., 2005). Pitch discrimination ability is highly variable among the general population. These individuals could either possess inherent abilities and/or they have gained this ability through musical training. It is still unclear what make individuals got good pitch discrimination ability without the benefit of formal musical training. It has been reported that pitch perception and discrimination accuracy are affected by musical education (Kishon-Rabin et al., 2001, Schön et al., 2004).

4.3 Pitch perception

Pitch labelling is an important ability in musicianship. Psychologically, pitch plays an important role as a fundamental auditory attribute in auditory communication including music and speech. Generally, it is defined as the perceptual correlation of periodicity in sounds (McDermott and Oxenham, 2008) that allows the ordering of sounds on a frequency related scale. While musically, it was defined by the American Standards Association as "that attribute of auditory sensation in terms of which sounds may be ordered on a musical scale" (ASA, 1960). It corresponds to the frequency for a pure tone and to the fundamental frequency for a periodic complex tone but it cannot be measured directly because it is not a purely objective physical property. For several decades, two basic theories of pitch perception have been proposed to explain how the

human hearing system locates and tracks changes in the fundamental frequency (f_0) of an input sound; 'place' theory and the 'temporal' theory. The place or resonance theory (Helmholtz and Ellis, 1954) states that each position on the basilar membrane (BM) is tuned with a particular characteristic frequency (CF). The frequency organisation is passed to the auditory cortex through the brainstem. Since the pitch of complex tones induces patterns of excitation along the BM with no single maximum the largest maximum may not be at the CF corresponding to the fundamental component of that pitch (Moore, 2003, Cheveigné, 2005, Warren, 2008). The temporal or frequency theory (Rutherford, 1886) assumes that pitch of a stimulus is determined by the time domain representation of the neural impulses induced by that stimulus (Moore, 2003, Cheveigné, 2005, Warren, 2008). This theory cannot work for a sinusoid tune at high frequencies because nerves do not fire fast enough (Moore, 2003, Cheveigné, 2005, Warren, 2008). Pitch discrimination in the auditory nervous system is dominated by the frequency code at low frequencies and the place code at high frequencies with both principles contributing at middle frequencies. (Wever, 1949, Gulick, 1971).

4.4 The frequency discrimination of pure tone

Humans can generally detect frequencies between 20 and 20 kHz, but the identifiable pitch sensation extends from 30 Hz to 5 kHz (the range of the fundamental frequencies of piano strings) (Deutsch, 1982). Frequency discrimination refers to the ability to detect changes of two nearly equal stimuli over time, which is often characterized by a difference limen (DL) or just

noticeable difference (JND) (Moore, 2003, Goldstein et al., 2004, Plack et al., 2005). The JND for pitch depends on the frequency, the sound level, the duration of the tone, and the suddenness of the frequency change (Moore, 2003).

Frequency discrimination are commonly done using two different methods; pitch matching (Goldstein et al., 1978, Moore et al., 1992) where listeners are asked to adjust the frequency of a tone to match the sound of interest, and the most commonly used method; the discrimination threshold (Srulovicz and Goldstein, 1983). The discrimination threshold method can be divided into two types. In the first measure, two successive steady tones with slightly different frequencies are presented randomly in multiple trials and the listener has to show whether the first or the second tone is higher in pitch. When the listener achieves a criterion percentage correct, for example 75%, the frequency DL between the tones will be called the difference limen for frequency (DLF). The second measure, which called the frequency modulation detection limen (FMDL), uses frequency-modulated (FM) tones at a low rate. Usually, two randomly ordered tones are presented successively; one is modulated and the other is un-modulated. The listener is asked to indicate which tone is modulated (Moore, 2003, Goldstein et al., 2004, Plack et al., 2005).

In 1970, Zwicker proposed a model based on space theory for discriminating tones separated by considerably less than a critical band (Moore, 2003, Goldstein et al., 2004, Plack et al., 2005, Warren, 2008). In this model, frequency discrimination and frequency selectivity (usually known as the ability to resolve

the frequency components of a complex sound) are related to each other. Here, frequency discrimination depends on the filtering process on the basilar membrane; hence, alternation of stimulus frequency evokes different excitation patterns (Moore, 2003, Goldstein et al., 2004, Plack et al., 2005). This model has difficulties handling very small JNDs for pure tones especially with frequencies from about 500 Hz to 2k Hz (Goldstein et al., 2004). Furthermore, Moore (1973) tested this model and found that its prediction for variation of the frequency DL with frequency is not accurate especially for short-duration tones below 5 kHz. Moore (1973) suggested an inclusion of temporal model especially for frequencies below 5 kHz. In contrast, the place model shows results that are more accurate for FMDLs especially for relatively high modulation rates (10k Hz and above). In summary, the temporal model determines DLFs for pure tones and FMDLs for very low modulation rates for frequencies up to about 4-5 kHz more accurately than the place model. While DLFs for pure tones of high frequency and FMDLs for medium to high modulation rates and for FMDLs for low modulation rates, when the carrier frequency is above about 5k Hz are determined by place model (Nordmark, 1968, Moore, 1973, Moore, 2003, Goldstein et al., 2004, Plack et al., 2005, Warren, 2008).

4.5 Pitch discrimination in musicians and non-musicians

Perception of pitch is evoked by a pure tone and hence pitch variations over time produce perception of melodies. Musical pitch has two dimensions, pitch height and pitch chroma. Pitch height represents the overall pitch level and provides a

basis for segregation of notes into streams and pitch chroma provides a basis for presenting melodies (Warren et al., 2003). Accordingly, musicians show superior auditory performance in tasks that involve discriminating sounds along both pitch dimensions (height and chroma) comparing with non-musicians. This has been reported in different studies reflecting specific aspects of music, such as timbre, rhythm, pitch discrimination, mistuned harmonics and the identification of musical intervals (Spiegel and Watson, 1984, Pitt, 1994, Burns and Houtsma, 1999, Koelsch et al., 1999, Kishon-Rabin et al., 2001, Fujioka et al., 2004, Fujioka et al., 2005, Tervaniemi et al., 2005, Seither-Preisler et al., 2007, Nikjeh et al., 2009, Zendel and Alain, 2009). However in some of the music characteristics, non-musicians with appropriate training (Kishon-Rabin et al., 2001, Amitay et al., 2006, Micheyl et al., 2006, Wright and Sabin, 2007) or repeated exposure to music (Bigand, 2003, Bigand and Poulin-Charronnat, 2006) can nearly obtain the achieved performance by experienced musicians.

In the present study, I attempted to maximize group separation. I included in the group of musicians only professional musicians who had 10 years or more of experience playing an instrument. Non-musicians had not played a musical instrument in the last 10 years and never performed professionally.

4.6 Materials and Methods

4.6.1 Subjects

Data was collected from 12 musicians (7 males and 5 females) with an age of 38 ± 14.07 (mean ± SD) years and 14 age matched non-musicians subjects (10 males

and 4 females) (the mean age: 37 years (SD = 16.62). Volunteers participated in the study after giving written informed consent. They had no history of any neurological or hearing impairment.

4.6.2 Stimuli and procedure

Three types of psychoacoustic tests were run; hearing threshold, loudness and pitch discrimination. In all tests, a pure tone of 500 Hz was used, unfortunately larger range of frequencies such as 125 to 15k Hz and 50 to 5k Hz for hearing threshold and pitch discrimination respectively could not be run due to time limitations. Sound stimuli were created and presented using custom-made scripts in MATLAB 7.0 (MathWorks, Natick, USA). Hearing threshold and loudness tests were used to ensure that all listeners are within certain range of hearing threshold and loudness. During all tests, a paradigm of three-alternative forced-choice was used. In this paradigm, three buttons were marked on the computer screen "1", "2" and "3". In the hearing threshold test, a single tone was presented and the task of the listener was to indicate which of the three buttons flash when the tone was heard. In the loudness test, three tones with different loudness levels were presented. The task of the listener was to indicate which of the three buttons flash when the loudest tone was heard. In the pitch discrimination test, three tones are presented with different pitch levels. The task of the listener was to indicate which of the three buttons flash when the highest pitch tone was heard. In all tests, listeners gave their responses by pressing "1", "2" or "3" on a computer keyboard. Three blocks were run for each test (right ear (RE), left ear (LE) and both ears

(BE) at the same time), each block lasted for about two minutes. The unit of pitch discrimination used to characterise responses to different tones was the "cent": a logarithmic unit used to measure musical intervals equal to a hundredth of a semitone.

4.6.3 Statistical analysis

Statistical analyses were performed using SPSS (for MAC, Rel18.0. 2010. Chicago: SPSS Inc.). Group comparisons of PDP of BE together, the right and left ears were performed using a 2-way ANOVA. A paired (samples) t-test was used to compare the means of PDP of the left and the right ears in each group. Parametric correlations analyses were performed between PDP and age, proficiency period and start of training age.

4.7 Results

ANOVA statistical test showed that there was a significant effect of musicianship on PDP of all tests (BE simultaneously, the RE and the LE independently), ($F(1,23) = 11.972$, $P = .002$), Figure 4.1. However, group-ear interaction effect was not statically significant ($F(1,23) = .000$, $P = .991$). The means of PDP in musicians were about 8 cents in the LE test, 9 cents in BE simultaneously tests and 11 cents in the RE test, Figure 4.1. In non-musicians, the means of PDP were just above 23 cents, just less than 28 cents and just above 32 during all tests (BE simultaneously, the RE and the LE independently), Figure 4.1.

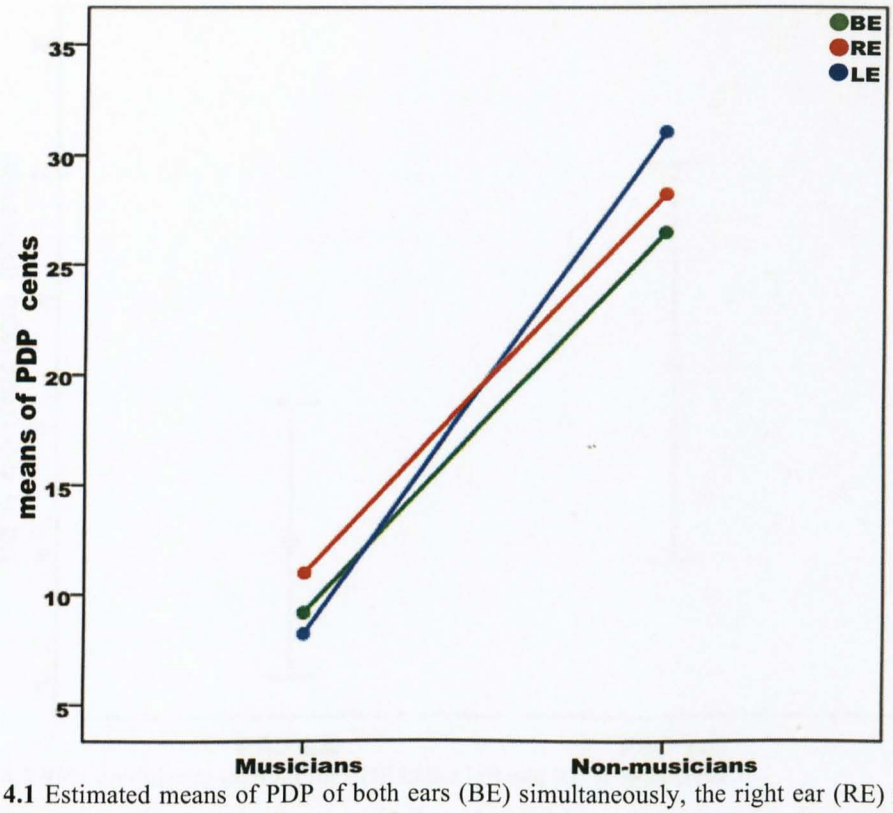

Figure 4.1 Estimated means of PDP of both ears (BE) simultaneously, the right ear (RE) and the left ear (LE) independently (Smaller score of pitch discrimination means better performance).

Paired (samples) t-test of the means of PDP showed that performance of the LE was statistically significant compared to the RE in musicians, t (11) = -2.352, $P = .041$, Figure 4.2. In contrast, non-musicians showed no significant difference in performance between BE, t (11) = .711, $P = .490$, Figure 4.3.

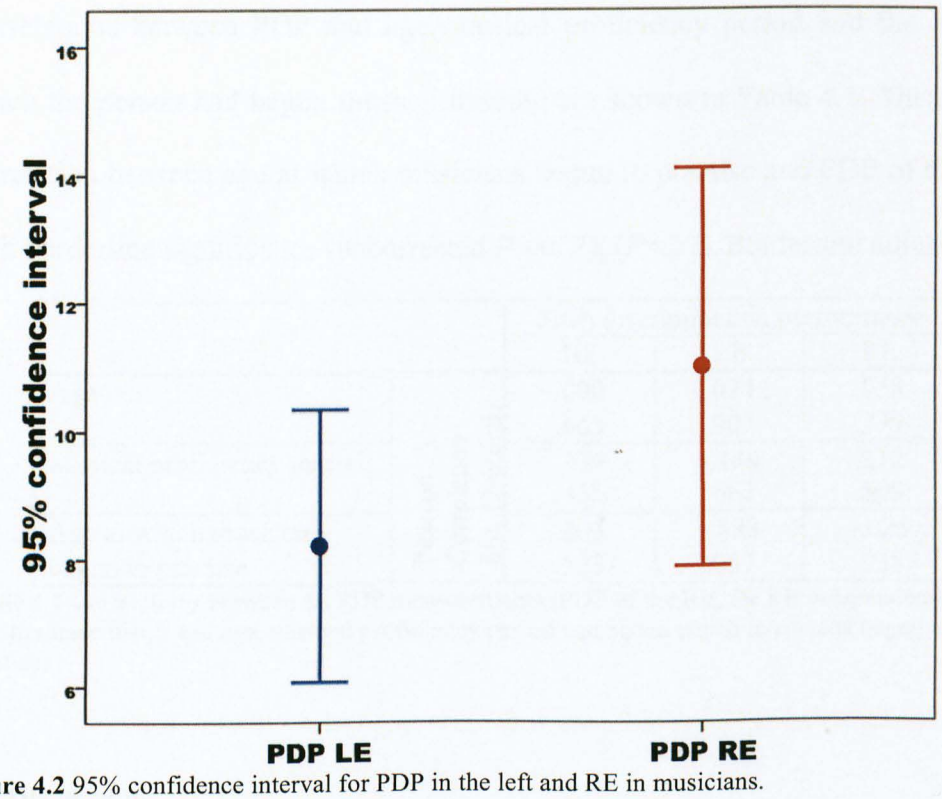

Figure 4.2 95% confidence interval for PDP in the left and RE in musicians.

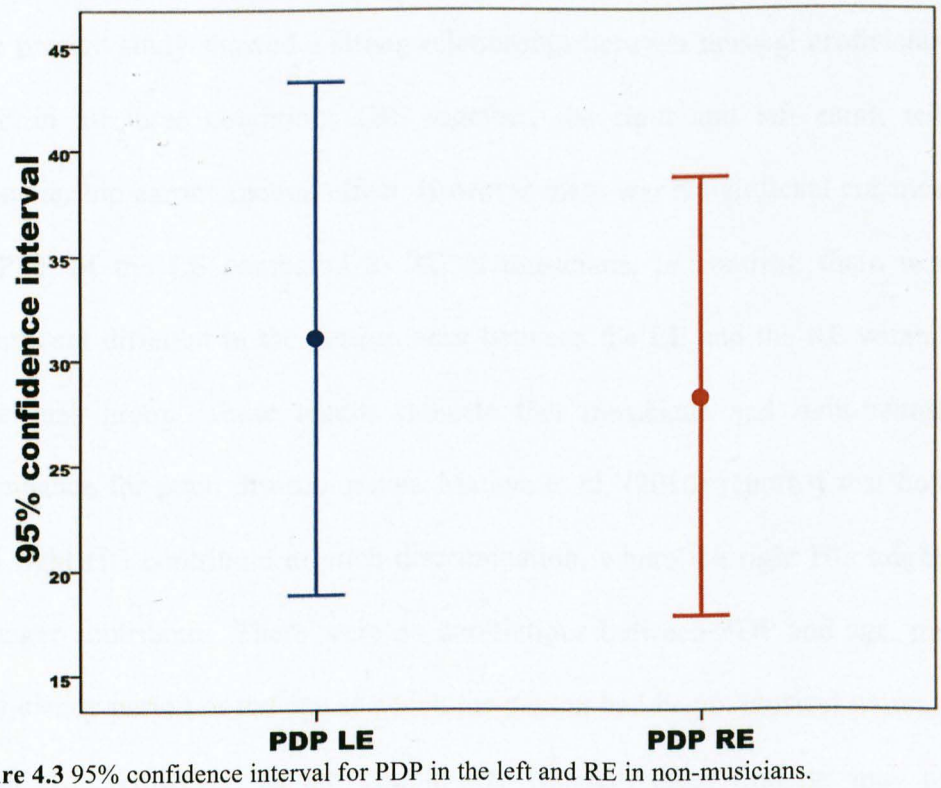

Figure 4.3 95% confidence interval for PDP in the left and RE in non-musicians.

Correlations between PDP and age, musical proficiency period and the age at which the person had begun musical training are shown in Table 4.1. There was correlation between age at which musicians begun to practise and PDP of the LE with borderline significance (uncorrected P=.057), (P=.171 Bonferroni adjusted).

		Pitch discrimination performance		
		BE	LE	RE
Age	Pearson Correlation	.090	.024	.058
	Sig. (2-tailed)	.663	.907	.779
Musical proficiency period	Pearson Correlation	.239	-.149	.212
	Sig. (2-tailed)	.455	.662	.509
Age at which musicians begun to practise	Pearson Correlation	.205	-.588	-.025
	Sig. (2-tailed)	.523	.057	.938

Table 4.1 Correlations between all PDP measurements (PDP of the RE, the LE independently and BE simultaneously) and age, musical proficiency period and age at which musicians begun to practise.

4.8 Discussion

The present study showed a strong relationship between musical proficiency and PDP in all three conditions (BE together, the right and left ears), with no musicianship ear interaction effect. However there was a significant enhancement in PDP of the LE compared to RE in musicians. In contrast, there were no significant different in the performance between the LE and the RE within non-musicians group. These results indicate that musicians had right-hemisphere dominance for pitch discrimination. Mathys et al. (2010) reported that both left and right HG contribute in pitch discrimination, where the right HG might be a stronger contributor. There were no correlations between PDP and age, musical proficiency period or the age at which the person had begun musical training (see Table 4.1). However, as the sample size is small these findings may not be

replicated for larger groups of experienced musicians. Work on larger sample size is needed to properly investigate instrumental effect on PDP as well as testing musicians' listening preferences.

4.9 Conclusion

Musicians showed better performance in pitch discrimination than non-musicians in all three conditions. Musicians performed better their left ear during PDP test. This result indicates that musicians had right-hemisphere dominance for pitch discrimination.

Chapter 5 : Neuroanatomical correlates of musicianship and PDP

5.1 Aims

Specific aims of this chapter were to:

1- Investigate anatomical plasticity of selected brain structures in musicians.

2- Explore the correlations between PDP and some cortical features of selected brain structures.

3- Explore the musical proficiency effect on sulcal and gyral topography.

4- Explore the instrument type effect on sulcal and gyral topography.

5.2 Introduction

The human brain has an excellent ability to reorganize neural pathways and to alter cortical patterns according to the context of the surrounding environment. (Naatanen and Winkler, 1999, Pantev et al., 1999, Tervaniemi et al., 2005, Munro, 2008, Rahne and Sussman, 2009, Tanaka et al., 2009, Trainor et al., 2011) Early intensive musical training affects brain development to a great extent (Shahin et al., 2004). It could change the number of neurons involved in processing, the timing of synchronization and the number and strength of excitatory and inhibitory synaptic connections (Schneider et al., 2002, Jones et al., 2010). Starting at early age, musicians integrate multi functions processes (e.g. auditory, motor, visual, and cognitive tasks) comprehensively during musical performance demanding activation of multiple brain regions. Several studies have reported structural changes in brains of musicians (For details see section 2.4.4.1).

In the current study, a multi-method approach has been used to investigate the neuroanatomical correlates of musicianship and PDP. Different anatomical techniques have been applied to explore plasticity of different cortical features including; GM density, cortical thickness and sulcal depth cortical volume and surface area, and hippocampal volume and shape differences. In addition, I studied the effect of instrument type on sulcal and gyral topography.

5.3 Materials and Methods

5.3.1 Subjects

Data was collected from 12 musicians (7 males and 5 females) with an age of 38 ± 14.07 (mean ± SD) years and 14 matched non-musicians subjects (10 males and 4 females) (the mean age: 37 years (SD = 16.62). Volunteers participated in the study after giving written informed consent. Additionally, the musician group was divided into two groups (string and non-string players) to investigate effect of instrument type on sulcal and gyral topography (Bangert and Schlaug, 2006).

5.3.2 Anatomical imaging sessions

Whole head 3D anatomical datasets were obtained for all subjects using a 1.5 T Symphony whole body scanner (Siemens, Erlangen, Germany) (176 slices, TR/TE= 1660/3.05 ms; 2 averages; flip angel = 8°, matrix size 256 x 256; voxel size = 1 × 1 × 1 mm3). The duration of scanning time was 14 minutes and 11 seconds. The 1.5T scanner was used because it produces T1-weighted images with reduced sensitivity to susceptibility and minimised distortions in anatomical images (McRobbie, 2003).

5.3.3 Anatomical investigation methods

5.3.3.1 Voxel based morphometry

Voxel based morphometry (VBM) is an automated method of identifying structural brain differences depending on voxel-wise comparison of local

concentrations of grey and white matter between two or more groups. It provides a comprehensive assessment of variation in anatomical distribution of tissues (Ashburner and Friston, 2000).

The first stage was performing spatial normalization by transforming brains of all subjects into the same stereotactic space (MNI asymmetrical average template of 305 subjects) by registering each image sets with the template image. Images were matched using a 12–parameter affine transformation with accounting for global non-linear shape differences by a linear combination of smooth spatial basis functions. All resultant images were relatively high resolution (1 mm isotropic voxels) to minimise the effects of partial volume. Then spatially normalised images were segmented into GM, WM and CSF. The normalised, segmented images were smoothed by convolving with a Gaussian kernel. Each voxel in the resultant image was an average of the tissue type from the neighbouring voxels in order to represent the local density of the tissue type at that voxel. This also helps in compensating for inter-individual gyral variation in the normalised and segmented images. Different smoothing kernel sizes were applied to provide optimal sensitivity for regions of interest (4 and 10) mm full width at half maximum (FWHM) Gaussian kernel. The final step was to apply voxel-wise parametric statistical tests on the normalised segmented and smoothed images of the groups selected (Ashburner and Friston, 2000). VBM analyses were carried out running MATLAB 7.9.0.529 (R2009b) (Mathworks Inc., Natick, MA, USA; http://www. mathworks.com/products/matlab) and VBM8 (http://dbm.neuro.uni-

jena.de/vbm), implemented as a toolbox in SPM8 software (Wellcome Department of Cognitive Neurology, London; http://www.fil.ion.ucl.ac.uk/spm).

Statistical analysis of VBM

Statistical group analysis was performed using 2-sample *t*–test. Analyses of covariance were performed, with global mean voxel value as a confounding covariate. This covariate corrected for the effect of summed difference in voxel intensity across scans, while preserving regional differences in tissue type. Two contrasts were defined to detect whether each voxel had a greater (or lesser) probability of being GM in the musicians group than had the equivalent voxel in non-musicians group, representing an increase or decrease in local GM density in musicians group. Significant foci above the $P<0.01$ level were characterised of their peak height (u) and spatial extent (k). Locations of significant clusters were assessed by localising their centre of gravity coordinates on template atlases using FSLView 3.1.8 (http://www.fmrib.ox.ac.uk/fsl) and SPM Anatomy toolbox (http://www2.fz-juelich.de/inm/index.php?index=194) (Eickhoff et al., 2005).

5.3.3.2 Cortical thickness and sulcal depth

Pre-processing

All image data preparation and pre-processing, cortex-based alignment and cortical thickness and sulcal depth analysis were carried out using BrainVoyager QX software package (Brain Innovation, Maastricht, The Netherlands; Version 2.3). The anatomical data (DICOM format) of each subject was converted into

BrainVoyager's internal data format. The data was resampled into 1 mm isotropic voxels, aligned with the ACPC plane and transformed into the Talairach coordinate system. The Talairach transformed image was used for automatic cortical surface reconstruction (Kriegeskorte and Goebel, 2001).

Advanced segmentation analysis

Talairach transformed image was resampled to 0.5 mm iso-voxels. The brain was segmented from surrounding head tissue using an automatic "brain peeling" tool (advanced segmentation tools). The cerebellum and subcortical structures were removed. Enhancement of tissue contrast and homogeneity was done using a sigma filter, which operates like a standard gaussian smoothing filter but excludes neighbour voxels with intensities too far away from the intensity of the currently considered voxel. The WM–GM border was set automatically using an adaptive region-growing step to separate white from GM voxels. The GM–cerebrospinal fluid (CSF) border was segmented using a dilation process, which controlled by computed gradient fields and histogram analysis of GM–CSF threshold values. The polishing process, which estimate a more correct GM / CSF contour was performed by calculating the magnitude map (Goebel et al., 2006).

Cortical based alignment

Reconstructed cortical surfaces were aligned using curvature information reflecting the gyral-sulcal folding pattern to improve the spatial correspondence mapping between subjects' brains, which reduces anatomical variability. First step was morphing the reconstructed folded cortical representations of each subject

and hemisphere into a spherical representation. The curvature map created from folded representation was overlaid on the spherical representation where each vertex on the sphere (spherical coordinate system) corresponds to a vertex of the folded cortex (Cartesian coordinate system) and vice versa. The curvature information was smoothed along the surface providing spatially extended gradient information to minimise the mean squared differences between the curvature of a source and a target sphere All brains were aligned using a moving target approach where the goal function is specified as a moving target computed repeatedly during the alignment process as the average curvature across all hemispheres at a given alignment stage. It starts with the coarsest curvature maps then with finer curvature maps (Goebel et al., 2006).

Cortical thickness and sulcal depth analysis

Cortical thickness identifies structural brain change depending on voxel intensity values. It can be calculated by selecting two different intensity values, one at the white-grey matter boundary and one at the grey-CSF boundary. A smoothed transition of intensities from one boundary to the other is resulted from applying Laplace's equation (Jones et al., 2000). Laplace's equation is a partial differential equation, which is used in many fields of science e.g. electromagnetism and fluid dynamics. Obtained smooth field can be used to calculate a gradient value at each voxel, which results in field lines by integrating along these gradient values. Calculating a cortical thickness value starts at any boundary voxel, and then a small step is performed along the gradient direction after checking the gradient. A re-evaluation of the gradient at the new point is done before performing the next

step along the gradient direction. This procedure is repeated until reaching the other boundary. Cortical thickness value is the sum of the performed small step sizes. Going in both directions (gradient directions) calculates a thickness value for any voxel in between boundary voxels producing cortical thickness volume maps that contain the thickness measures at cortical voxels.

Depth of sulci can be measured in the same way with the only difference that one boundary must be the boundary of the brain and the other boundary must be the white or grey matter. The computed field lines then travel from any WM or GM point through the sulci up to the boundary of the brain and the integrated path length values result in sulcal depth measures. This process produces sulcal depth volume containing the depth measures at sulcus voxels. Both cortical thickness and sulcal depth volume maps were used to efficiently calculate maps on cortical surface meshes producing cortex thickness and sulcal depth surface maps.

Locations of significant clusters were assessed by visual inspection and localising their centre of gravity coordinates on template atlases using BrainVoyager Brain Tutor 2.5 for MAC (http://www.brainvoyager.com/products/braintutor.html) and FSLView 3.1.8 (http://www.fmrib.ox.ac.uk/fsl).

5.3.3.3 Cortical volume and surface area

Aligned brains (resultant of cortical based alignment) were used to superimpose several regions of interest; STG, HG and PT. These regions were transformed into volume of interest and corrected manually using macro-anatomically defined anterior, posterior, medial and inferior boundaries as in method previously

published in (Rademacher et al., 2001, Hall et al., 2003, Abdul-Kareem and Sluming, 2008). Manual correction was carried out to minimise alignment errors. Next, corrected region and volume of interests were used to measure cortical surface area and volume respectively. Individual cortical surface area and volume values were exported to SPSS 18.0. Statistical analyses were performed using SPSS (for MAC, Rel18.0. 2010. Chicago: SPSS Inc.). Group comparisons of volume and cortical surface area values of auditory areas were performed using a 2-way ANOVA. Parametric correlations were performed between PDPs of all conditions (the LE, the RE and BE together) and cortical surface area or cortical volume of the following regions; PAC, PT, lateral aspect of HG and STG. *P* values of ($\leq$ 0.05) were considered statistically significant. Bonferroni multiple comparisons correction were performed on all *p* values (Salkind and Rasmussen, 2007).

5.3.3.4 Hippocampal shape and subfields volume

Segmentation of hippocampus

The anatomical T1 data (DICOM format) of each subject was converted into compressed NIfTI format using MRIcron (http://www.cabiatl.com/mricro/mricron). Using FSL (http://www.fmrib.ox.ac.uk/fsl) (Smith et al., 2004, Woolrich et al., 2009), the following tools were applied sequentially: brain extraction by the BET tool (Smith, 2002) to clear non-cerebral voxels; automated segmentation by the FIRST tool of the left and right hippocampi (Patenaude et al., 2011). FIRST tool is based on a template originating from manually segmented images, with

subcortical labels parameterized as surface meshes. First brain-extracted image was registered to the template via 12 degrees of freedom affine transformation (Jenkinson and Smith, 2001), and then 12 degrees of freedom registration to a standard MNI 152 template of subcortical mask. Hippocampi were labelled and segmented using subcortical mask depending on T1 image intensity. Registration and segmentation processes of both hippocampi were visually checked at each step to confirm accuracy of the results.

Analysis of the shape of the hippocampus

A multivariate Gaussian model of vertex location and intensity variation was used to automatically generate surface mesh for both hippocampi of each subject. The same number and labelling of vertices were used to enable point-to-point comparisons across all subjects. Corresponding vertex points of generated surface were aligned to the mean surface of the template hippocampus in MNI152 space. *F* statistics were then calculated to compare shape differences between musicians and non musicians (Patenaude et al., 2011).

Subfields volume of the hippocampus

The workflow for creating subcortical segmentations was processed using FreeSurfer version 5.1 (released May 24th, 2011; Martinos Center, Harvard University, Boston, MA) (http://surfer.nmr.mgh.harvard.edu) on a PC running Open SUSE 11.3 Linux. FreeSurfer's built-in mri_convert command was used to convert T1 images to FreeSurfer format (.mgz). Converted images were registered to Talairach space using 12 degrees of freedom affine transformation. Next,

fluctuations in scan intensity were corrected and scan intensities were adjusted to achieve a mean WM intensity of 110. The skull and meningeal surfaces were removed from the scan, leaving only the brain tissue. Segmentation labels were applied by aligning each image with the FreeSurfer atlas. Volume labels were applied to subcortical structures based on the prior probabilities of voxel identity assigned by the atlas, in addition to the probability of voxel identity based on the tissue class assignment of surrounding voxels, and volumetric statistics were computed (Fischl et al., 2002). Automated segmentation of the subfields of the hippocampus, was carried out using freesurfer models built from manual segmentations of the RHipp (Van Leemput et al., 2009). Individual subfields volume values were exported to SPSS. ANOVA for repeated measurements was used to compare hippocampal subfields volume values in both hemispheres. Parametric correlations were performed between PDPs of all conditions (the LE, the RE and BE) and volume of hippocampus subfields. *P* values of (≤ 0.05) were considered statistically significant. Bonferroni multiple comparisons correction were performed on all *P* values (Salkind and Rasmussen, 2007).

5.4 Results

5.4.1 Voxel based morphometry

In this study, I investigated differences in GM distribution between musicians and non-musicians on a voxel by voxel basis. 2-sample t–test was computed considering total intracranial volume (TIV) as a global variable at every voxel. Two contrasts were examined: 1) detecting local increases in GM distribution in musicians compared with non-musicians; 2) detecting local increases in GM distribution in non-musicians compared with musicians. Repeating previous tests, PDPs of each ear (chapter 3) were considered as numerical covariates in order to test their effect on local increase in GM density. Each test was carried out on previously smoothed images (with 10 mm smoothing kernel). Statistically significant clusters were corrected for repeated measures on cluster level threshold at $p<0.01$ and with spatial extent of 20 mm^3 or above. Cluster level correction, was performed using region of interest approach to improve statistic power. Regions of interest were defined using MarsBaR (http://marsbar.sourceforge.net) that implemented as a toolbox in SPM8 software (Wellcome Department of Cognitive Neurology, London; http://www.fil.ion.ucl.ac.uk/spm).

5.4.1.1 ANCOVA test with TIV as global variable

Musicians showed significant increased GM density compared to non-musicians in the left angular and supramarginal gyri (left IPL) and right postcentral as shown in Figure 5.1 and Table 5.1. Non-musicians showed no increased GM density compared with musicians.

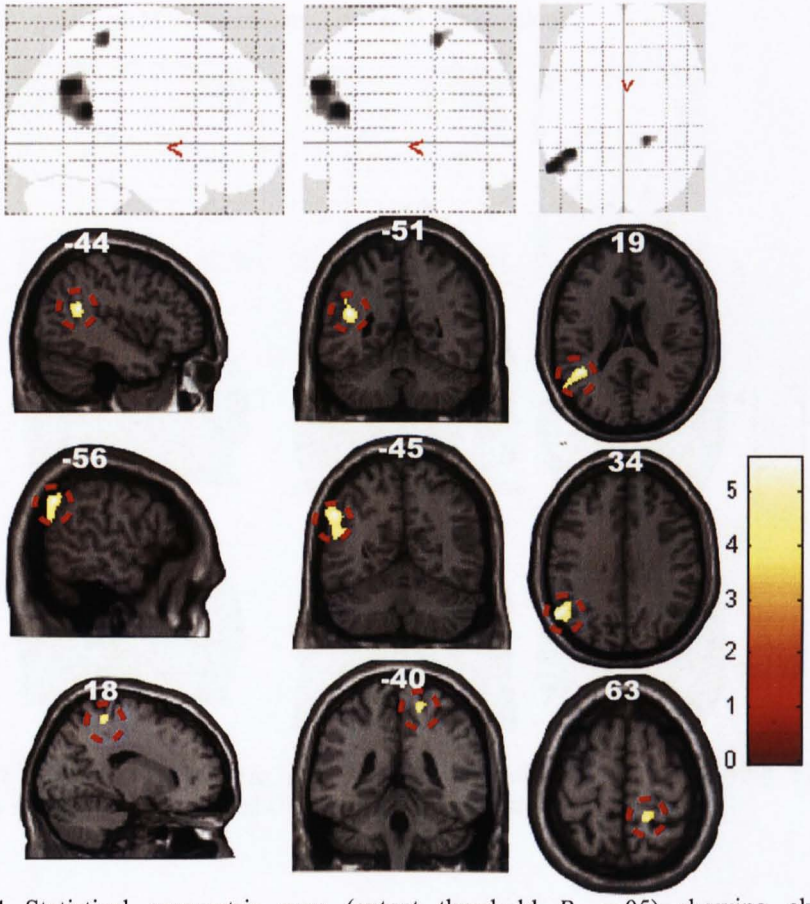

Figure 5.1 Statistical parametric map (extent threshold P_{corr}=.05) showing clusters with statistically significant of increased GM density in musicians.

Cluster peak region	Voxels	Zmax	P_{corr}	x	y	z
Left angular gyrus	612	4.34	.006	-44	-51	19
Left supramarginal gyrus	600	4.30	.007	-56	-45	34
Right postcentral gyru	102	3.80	.023	18	-40	63

Table 5.1 *P* values and MNI coordinates of cluster peak regions.

5.4.1.2 ANCOVA test with PDPs as covariates

Applying PDP of LE as a covariate showed a significant increase in regional GM density in the posterior region of musicians' RHipp (particularly in subiculum) and right angular gyrus as shown in Figure 5.2 and Table 5.2. Non-musicians showed no increased GM density.

Cluster peak region	Voxels	Zmax	P_{corr}	x	y	z
RHipp (subiculum)	38	3.39	.023	18	-32	-5
Right angular gyrus	15	3.45	.027	39	-54	29

Table 5.2 *P* values and MNI coordinates of cluster peak regions.

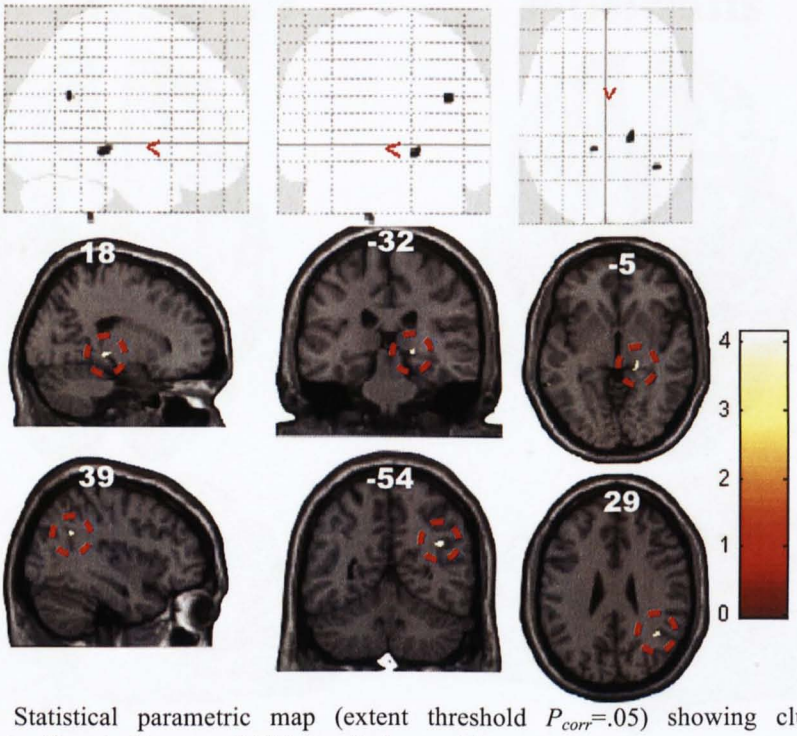

Figure 5.2 Statistical parametric map (extent threshold P_{corr}=.05) showing clusters with statistically significant of increased GM density in musicians.

5.4.2 Cortical thickness, sulcal depth and sulcal and gyral topography

5.4.2.1 Musical proficiency effect on sulcal and gyral topography

Figure 5.3 shows the average cortical surfaces generated for the musicians and non-musicians groups. Visual inspection of these representations suggested subtle group differences in sulcal and gyral patterning in different regions e.g. right central sulcus, right dorsal posterior cingulate (Brodmann's area 31), left calcarine sulcus and left and right SMG. For example, the right central sulcus was wider in musicians than in non-musicians. Surface patterns of the STGs were more folded in musicians as seen in Figure 5.3.

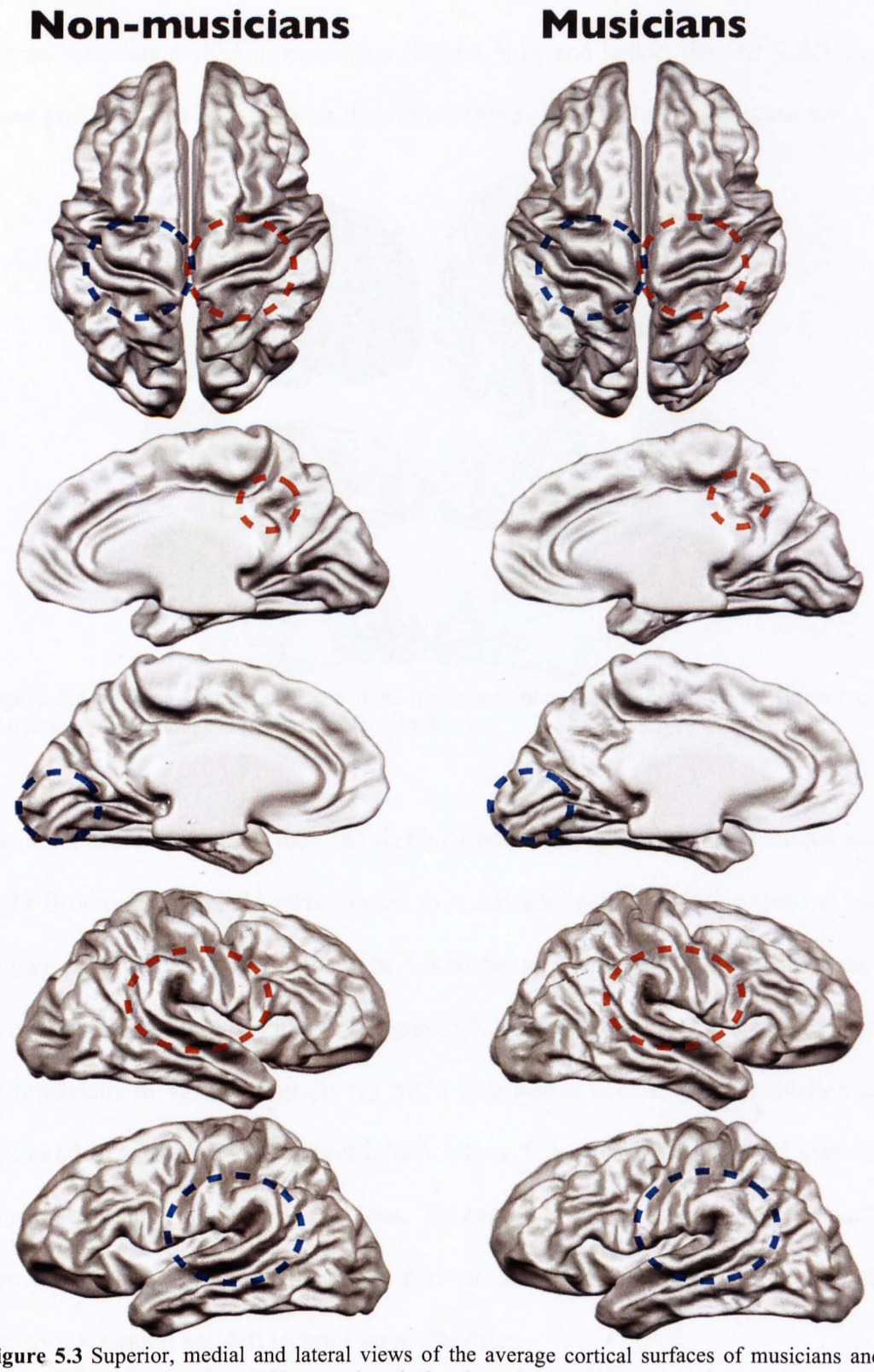

Figure 5.3 Superior, medial and lateral views of the average cortical surfaces of musicians and non-musicians. Circles show differences in sulcal and gyral topography.

The posterior ramus of the lateral sulcus was oriented more vertically in the LH of the non-musicians than in musicians (Figure 5.4), and hence, the left SMG was more posterior in non-musicians than musicians as shown clearly in Figure 5.4.

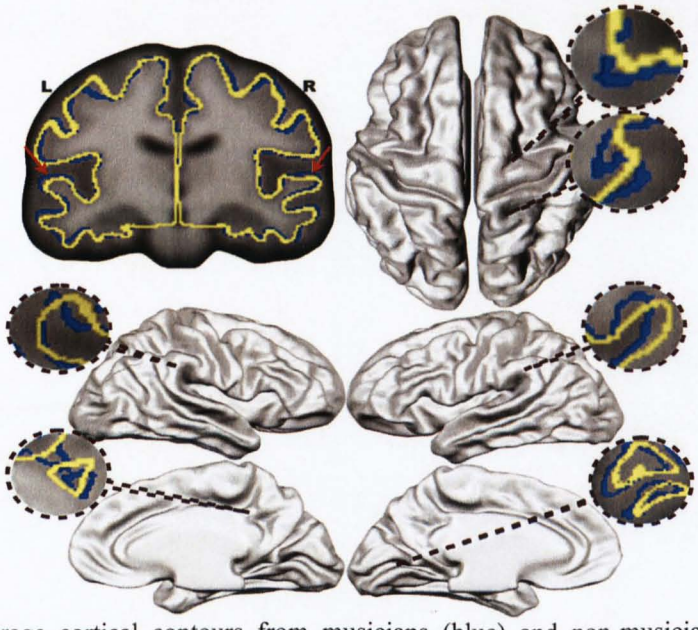

Figure 5.4 Average cortical contours from musicians (blue) and non-musicians (yellow) are superimposed on average target volume for all subjects.

Figures 5.3 and 5.4 show that, the depth of both the right postcentral sulcus and right Brodmann's area 31 were greater in musicians. Additionally, musicians had longer path of calcarine sulcus. The t-statistic maps of sulcal depth difference between both groups are shown on Figure 5.5. The cortex was significantly deeper in musicians in various regions e.g. right postcentral sulcus, anterior portion of right and lift cingulate sulci, right lateral sulcus, left calcarine sulcus and anterior portion of superior temporal sulcus. In contrast, non-musicians significantly showed deeper cortex in posterior part of left superior frontal sulcus, right superior temporal and left inferior temporal sulci.

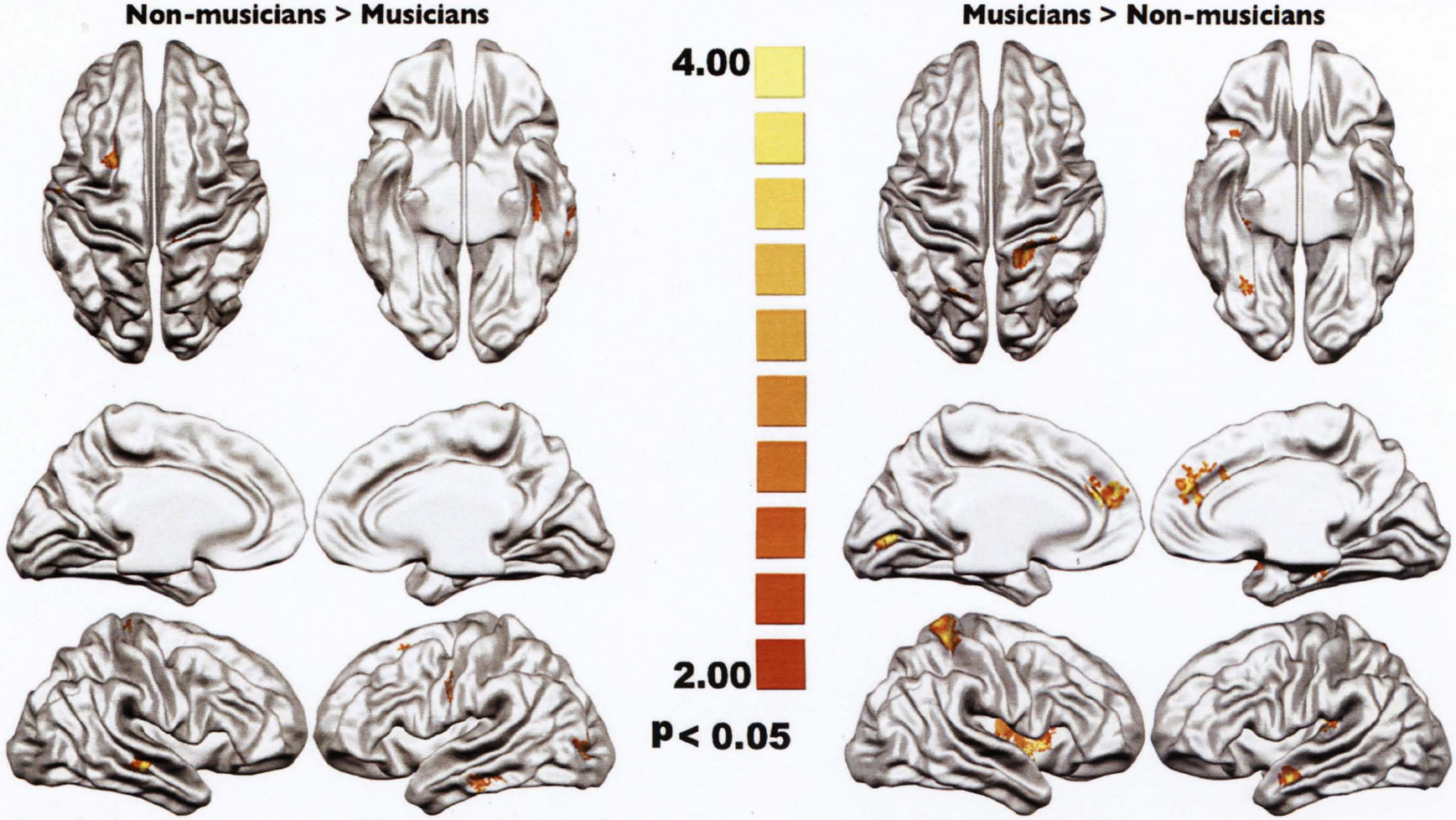

Figure 5.5 T-statistic maps of group difference in sulcal depth are superimposed on average target surface for all subjects.

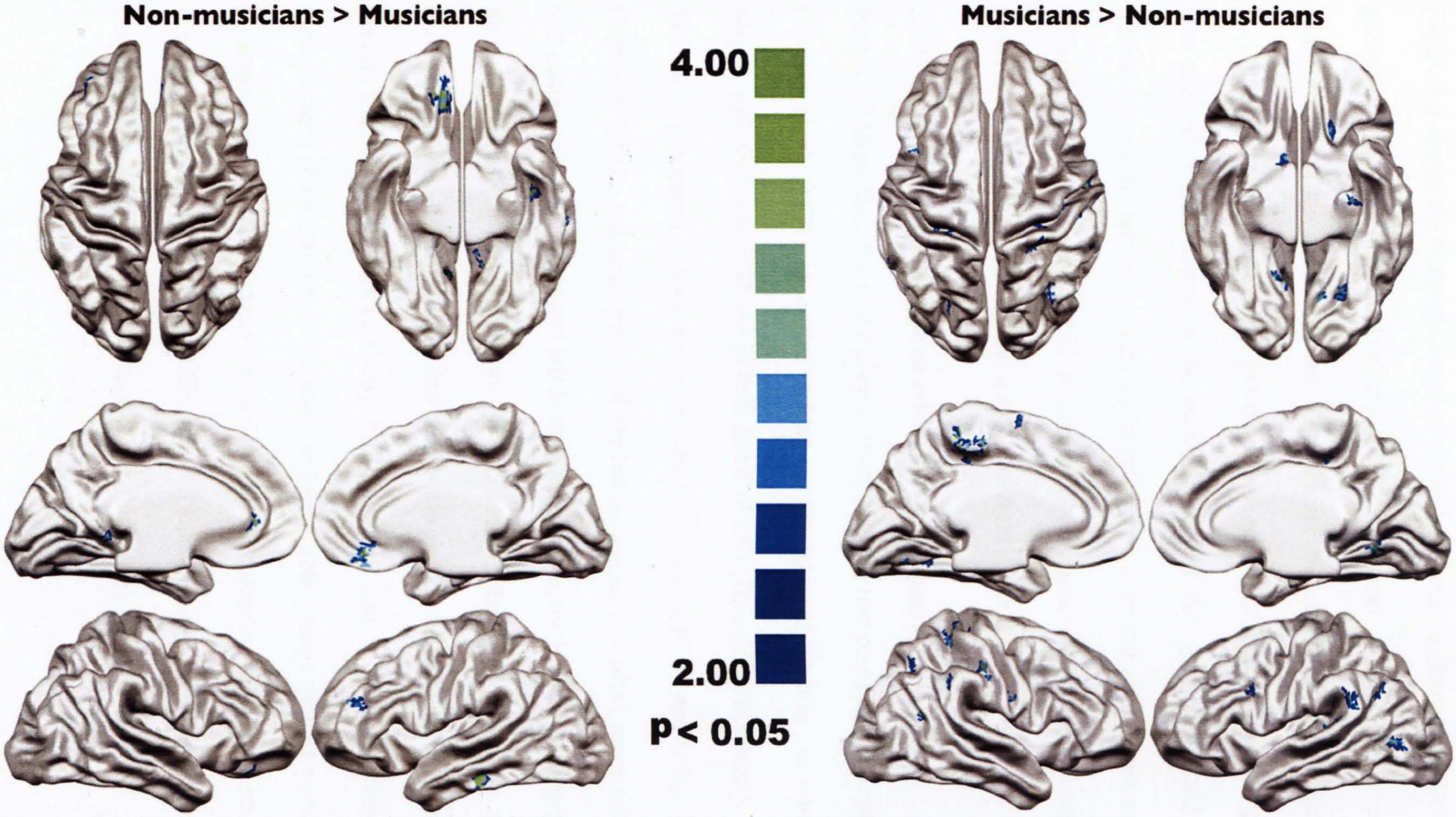

Figure 5.6 T-statistic maps of group difference in cortical thickness are superimposed on average target surface for all subjects.

Figure 5.6 shows the t-statistic maps of cortical thickness difference between both groups. Musicians had thicker cortex in SMG and angular gyrus in both hemispheres. Additionally, cortex was thicker in musicians in the posterior portion of left parahippocampal gyrus and left and right lingual gyrus. Musicians also showed thicker cortex in the posterior part of the right postcentral gyrus, medial part of the left postcentral gyrus and inferior frontal gyrus (posterior part of brodmann area 44) in the LH. In contrast, non-musicians had thicker cortex in anterior part of left middle frontal gyrus, and right gyrus rectus.

5.4.2.2 Effect of instrument type on sulcal and gyral topography

Figure 5.7 show that, the string players (6 musicians) had prominent omega shape (Yousry et al., 1997) of central sulcus on the RH only, while the non-string players preserve omega shape in both hemispheres (Bangert and Schlaug, 2006). The right precentral sulcus was extended more medially in non-string players (Figure 5.7). The posterior ramus of the lateral sulcus was tilted more anteriorly and posteriorly in the right and left hemispheres respectively in non-string players than those of string players (Figure 5.9). Therefore, the SMG was more anterior and more posterior in the right and left hemispheres respectively in non-string players than string players as shown in Figures 5.7 and 5.8. Additionally, some other regions show differences in shape between both groups such as right dorsal posterior cingulate (Brodmann's area 31) and left calcarine sulcus. In Figure 5.9, the t-statistic maps of group difference in sulcal depth show that non-string players had more regions with deeper cortex than string players.

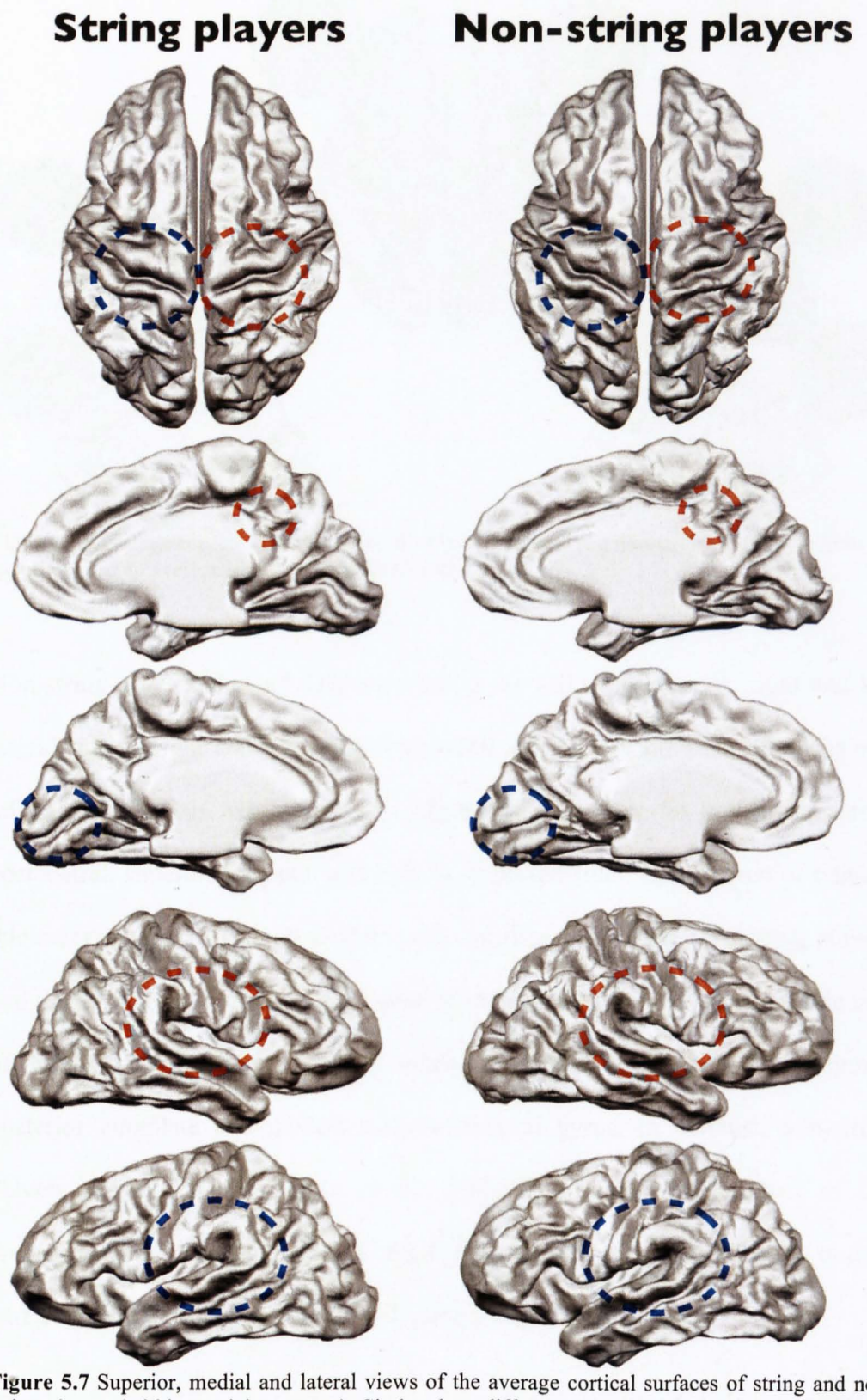

Figure 5.7 Superior, medial and lateral views of the average cortical surfaces of string and non-string players (within musicians group). Circles show differences in sulcal and gyral topography.

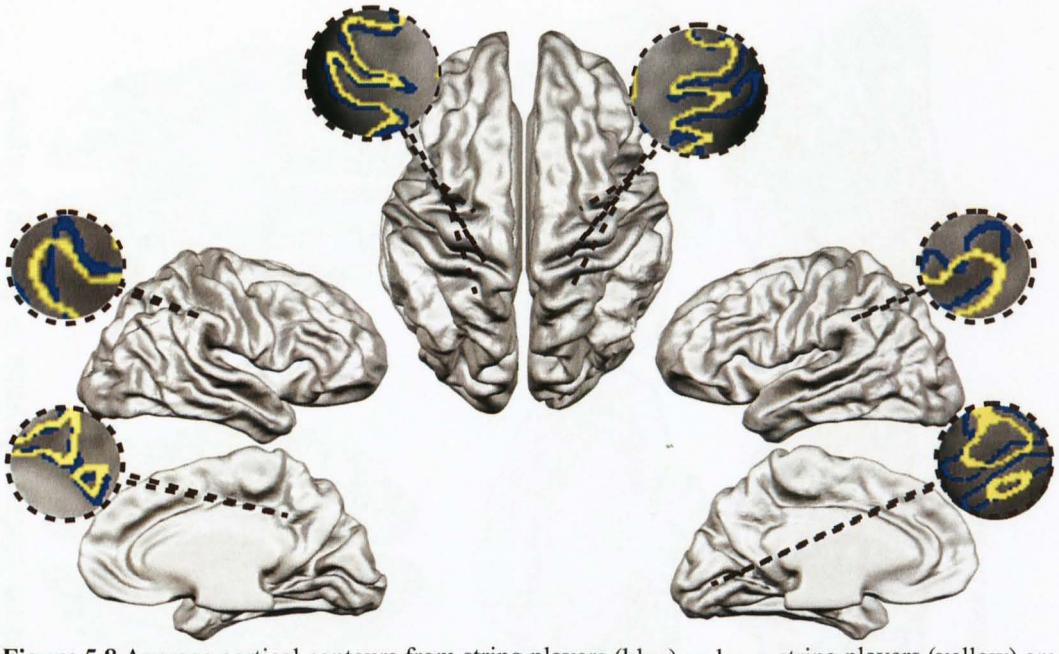

Figure 5.8 Average cortical contours from string players (blue) and non-string players (yellow) are superimposed on average target volume for all subjects.

Non-string players showed deeper cortex in the following regions; right and left lateral sulcus, right and left occipitotemporal sulcus, left intraparietal sulcus and left calcarine sulcus. While the string players had deeper cortex in the left central, postcentral, superior temporal and inferior temporal sulci. Comparison of cortical thickness maps shows small clusters with significant t-statistic. The string players had thicker cortex in the anterior region of right middle frontal gyrus, middle part of the left inferior temporal gyrus, medial region of orpital gyrus, right dorsal posterior cingulate and medial occipitotemporal gyrus. In contrast, non-string players showed thicker cortex in the following regions; medial part of left precentral gyrus, middle region of cingulate gyrus, right lingual gyrus and middle part of right parahippocampal gyrus Figure 5.10.

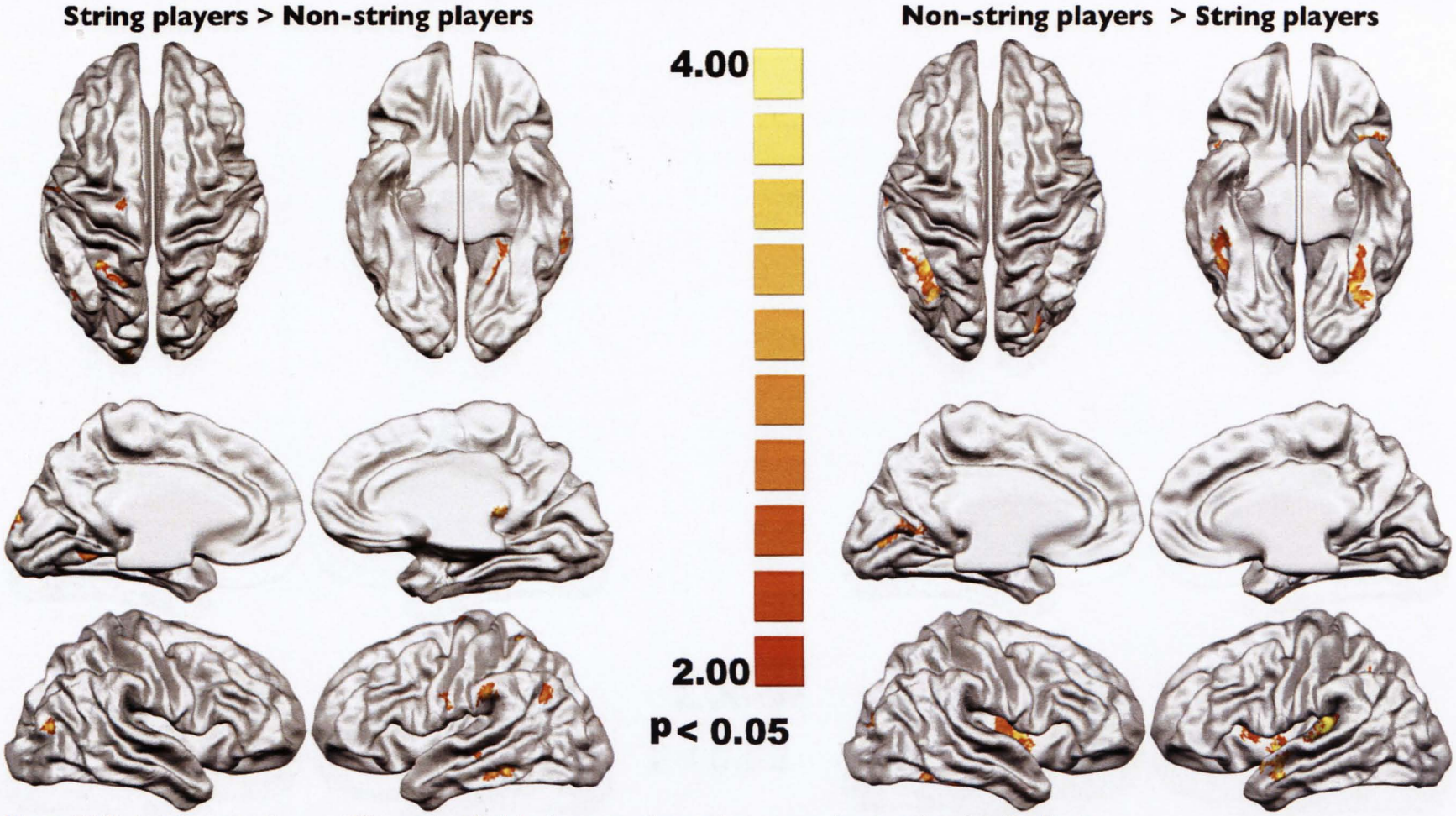

Figure 5.9 T-statistic maps of group difference in sulcal depth are superimposed on average target surface for all subjects.

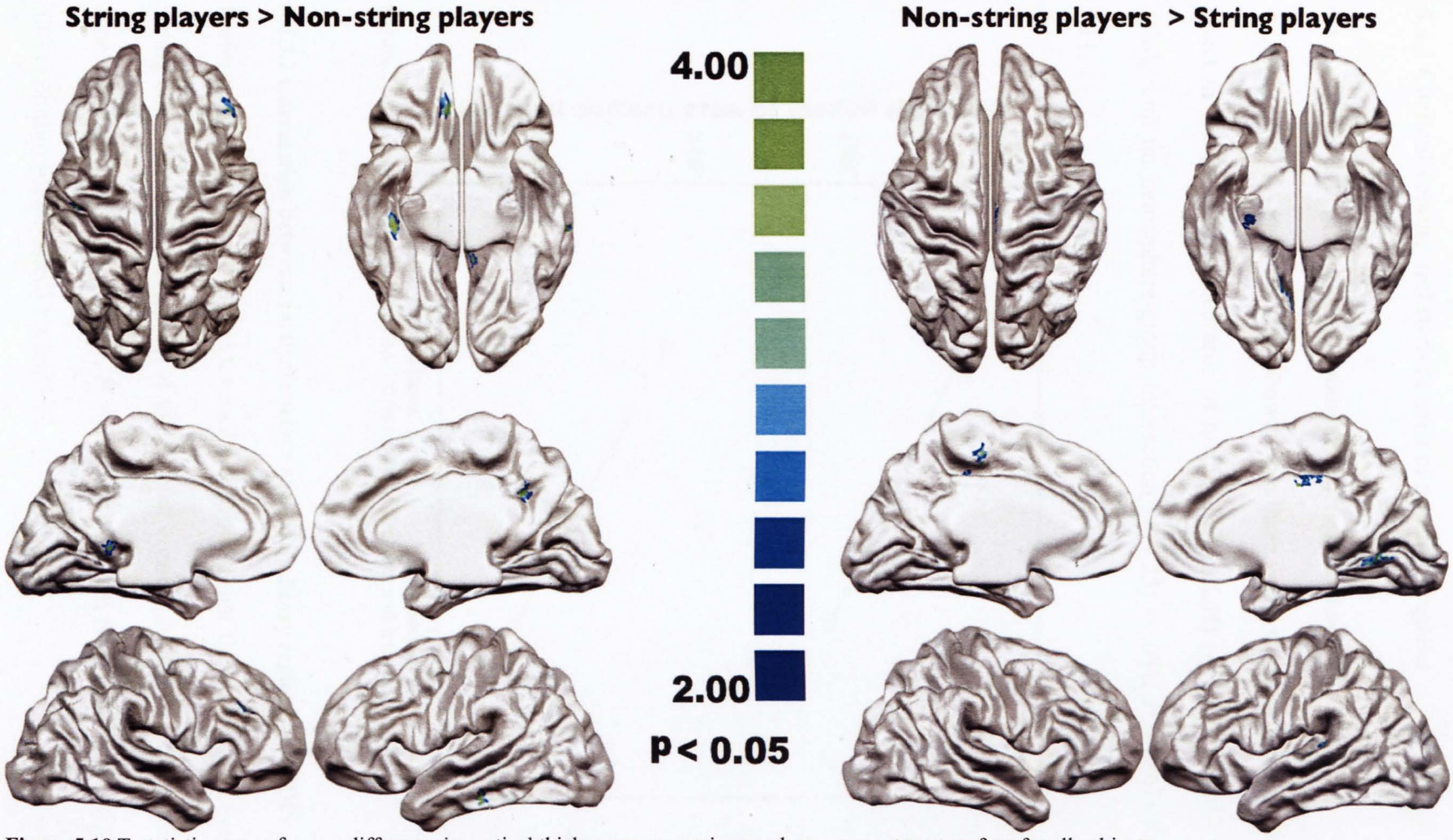

Figure 5.10 T-statistic maps of group difference in cortical thickness are superimposed on average target surface for all subjects.

5.4.3 Cortical volume and surface area of auditory regions

5.4.3.1 Influence of musical performance on cortical surface area

A 2-way ANOVA statistical test showed that there was a significant musicianship effect in the cortical surface area of medial HG (mGH) ($F(1,25) = 5.617$, $P = .026$), with no hemisphere-group interaction ($F(1,25) = .031$, $P = .861$) Figure 5.11.

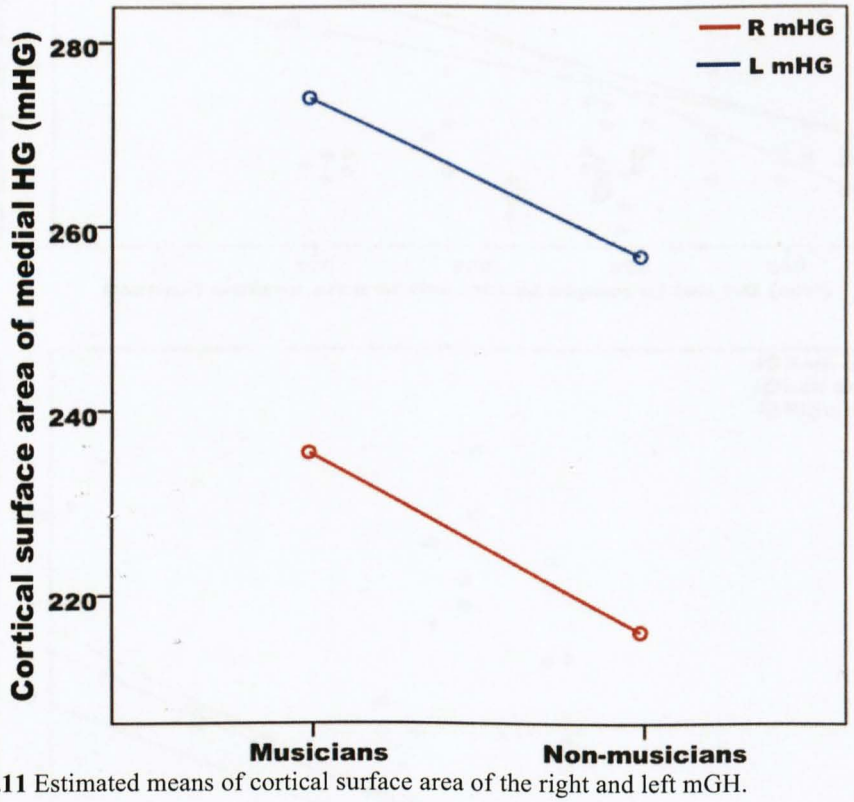

Figure 5.11 Estimated means of cortical surface area of the right and left mGH.

5.4.3.2 Correlation between cortical surface area of auditory regions and PDP

Performing parametric correlations analysis showed that there were positive and strong correlations between PDP of the RE and cortical surface area of the lateral aspect of left HG (r (26) = -.527, $P = .006$) and the left STG (r (26) = -.507, $P = .008$) (Bonferroni adjusted) Figure 5.12.

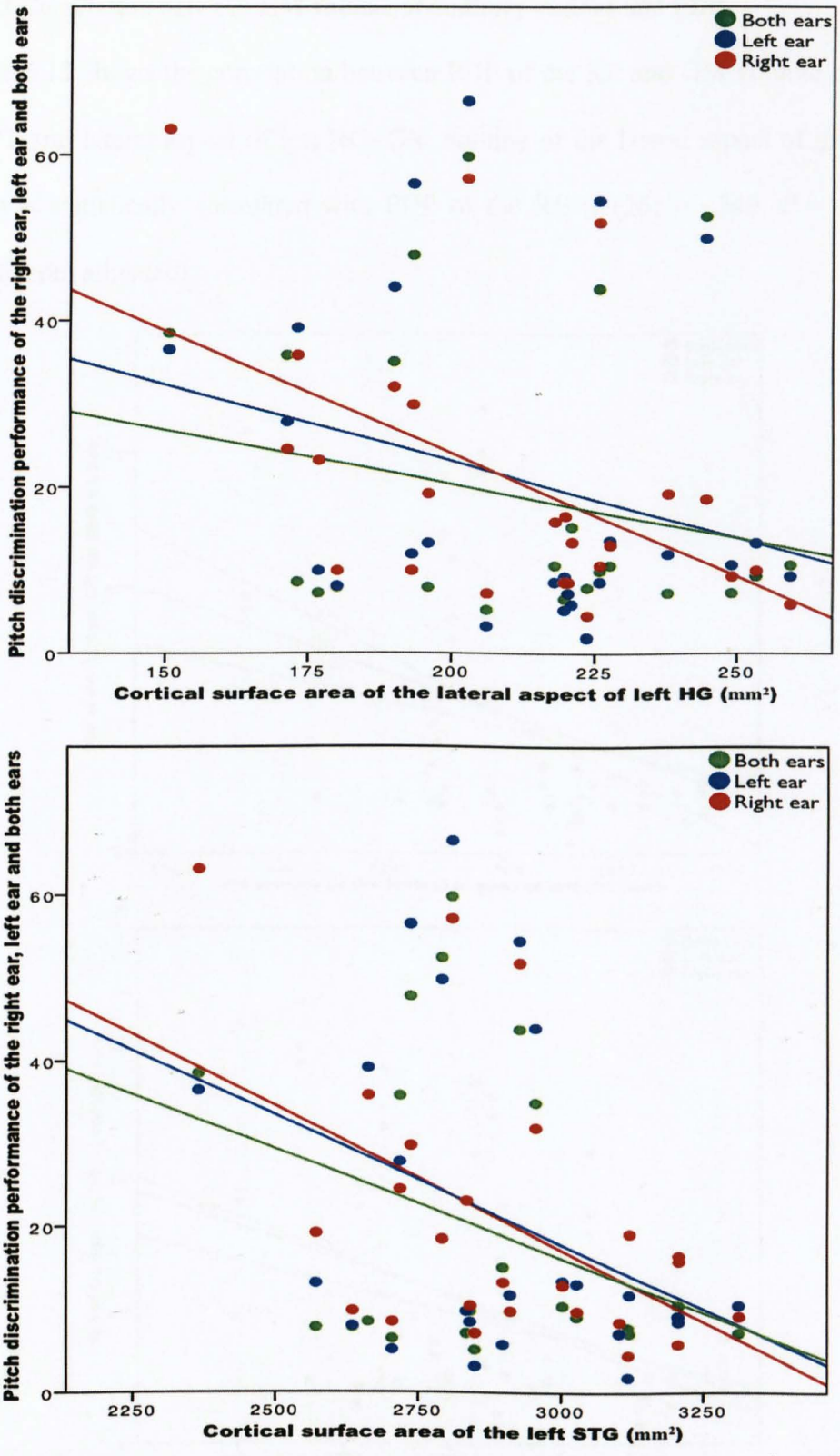

Figure 5.12 Correlation between PDP of all conditions and cortical surface area (mm^2) of the left STG and the lateral aspect of left HG. (Smaller score of pitch discrimination means better performance).

5.4.3.3 Correlation between GM volume of auditory regions and PDP

Figure 5.13 shows the correlation between PDP of the RE and GM volume of the left PT and lateral aspect of left HG. GM volume of the lateral aspect of the left HG was statistically correlated with PDP of the RE (r (26) = -.549, P = .004) (Bonferroni adjusted).

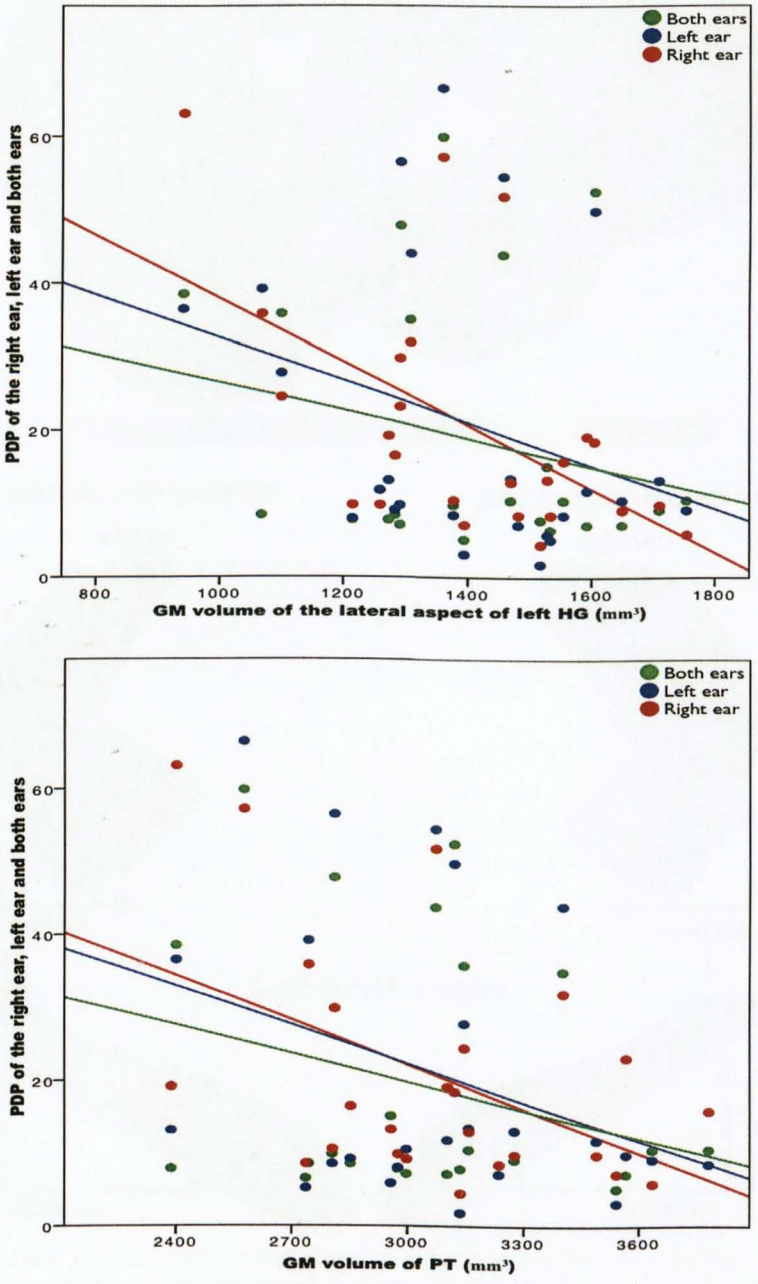

Figure 5.13 Correlation between PDP of the RE and cortical volume (mm^3) of the lateral aspect of left HG and left PT. (Smaller score of pitch discrimination means better performance)

5.4.4 Hippocampal shape difference and and subfields volume differences

5.4.4.1 Influence of musical performance on hippocampal surface shape

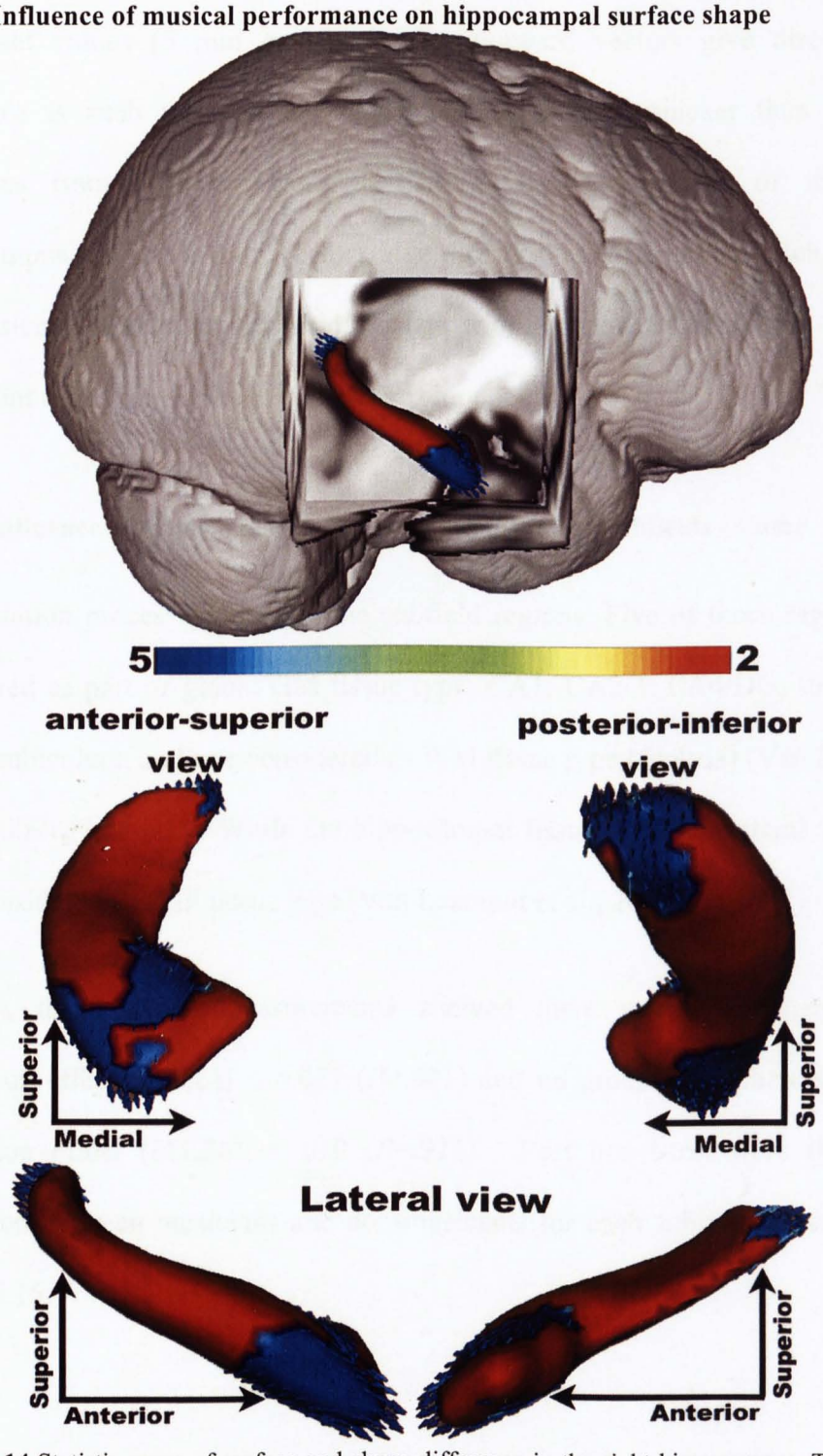

Figure 5.14 Statistic maps of surface and shape difference in the right hippocampus. The colour bar indicates the statistic values; an increase from red to blue is going from lower to higher statistical significance.

The group differences of hippocampi shape were significant only in the right hippocampus. Figure 5.14 shows that there were 3 regions (blue patches) with significant values (5 mm or more). The outward vectors give direction of difference is such that the musicians' RHipp is larger/thicker than in non-musicians (most posterior and the lateral anterior regions of the right hippocampus). While inward vectors give direction of difference is such that the non-musicians' RHipp is larger/thicker (superior anterior region). There were no significant differences of the right and left hippocampi volumes.

5.4.4.2 Influence of musical performance on hippocampal subfields volume

Segmentation process produced nine subfield regions. Five of those regions are considered as part of global GM tissue type; CA1, CA2/3, CA4/DG, subiculum and presubiculum, and one considered as WM tissue type (fimbria) (Van Leemput et al., 2009) Figure 2.2. While the hippocampal fissure, inferior lateral ventricle were considered as CSF tissue type (Van Leemput et al., 2009).

ANOVA for repeated measurements showed there were group-hemisphere interaction effect ($F(1,24) = 6.077$ (P=.021) and no group-hemisphere-subfields interaction effect ($F(1,24) = .010$ (P=.921). Post hoc t-test were therefore, conducted between musicians and non-musicians for each subfield separately in Figure 5.15.

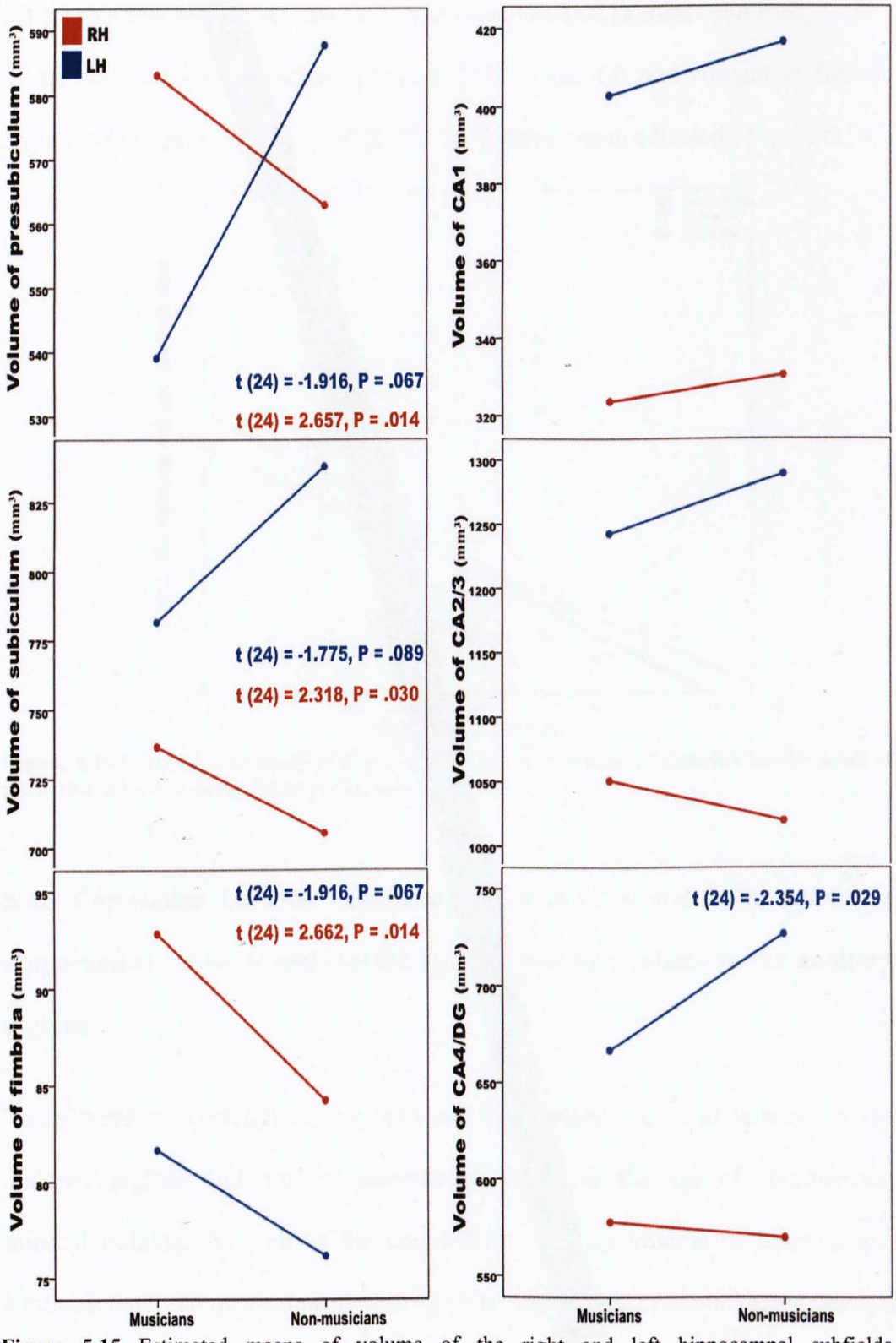

Figure 5.15 Estimated means of volume of the right and left hippocampal subfields (presubiculum, subiculum, fimbria, CA1, CA2/3 and CA4/DG).

5.4.4.3 Correlation between volume of right hippocampal subfields and PDP

There was positive correlation between PDP of the LE and volume of fimbria region in the RHipp (r (25) = -.497, P = .012) (Bonferroni adjusted), Figure 5.16.

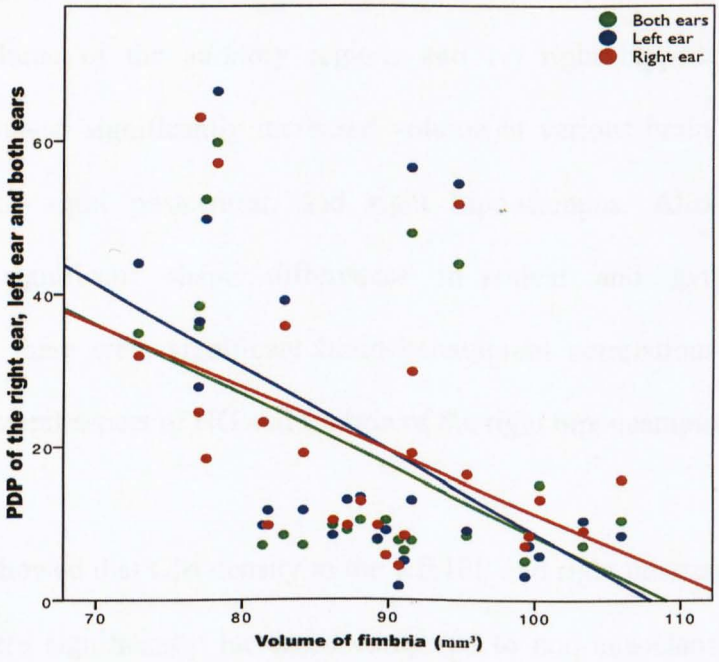

Figure 5.16 Correlation between PDP of all conditions and volume of fimbria (Smaller score of pitch discrimination means better performance).

5.4.5 Correlation between musicians' characteristics and both volume of hippocampal subfields and cortical surface area and volume in the auditory regions

There were no correlations between cortical surface area and volume in the auditory regions and musical proficiency period or the age of commencing musical training. As well as the correlations between volume of hippocampal subfields and both musical proficiency period and the age of commencing musical training were not statistically significant.

5.5 Discussion

This multi-methods study consisted of four different parts; i) VBM, ii) sulcal and gyral topography including cortical thickness and sulcal depth, iii) cortical surface area and volume of the auditory regions and iv) right hippocampal shape. Musicians showed significantly increased volume in various brain regions; left angular gyrus, right postcentral, and right hippocampus. Also there were statistically significant shape differences in sulcal and gyral anatomy. Additionally, there were significant brain–behavioural correlations in different regions e.g. lateral aspect of HG and fimbria of the right hippocampus.

VBM study showed that GM density in the left IPL and right postcentral gyrus of musicians were significantly increased compered to non-musicians while there was borderline significant increased GM distribution in the right angular gyrus in musicians compared to non-musicians as shown in Figure 5.1. Those regions are part of the auditory-motor coupling network (Gaab and Schlaug, 2003, Bangert et al., 2006, Gaab et al., 2006). VBM results had been further investigated using PDP of the LE as covariates showing significant large GM density in the right angular gyrus in musicians compared to non-musicians (Figure 5.2). IPL is considered as part of the pitch short memory network (Binder et al., 1997, Rinne et al., 2009).

Comparison of the topographic patterns of sulci and gyri in musicians and non-musicians showed that musicians had deeper cortex in the following sulci: right

postcentral right and left cingulate, right lateral and left calcarine sulci. Musicians also showed thicker cortex in multiple brain regions including the left parahippocampal gyrus, the left and right lingual gyrus, the posterior part of right postcentral gyrus, medial part of left postcentral gyrus, posterior part of the left Broca's area, the left and the right IPL (see Figures 5.3–5.6). Cortical thickness results closely agree with VBM results (particularly in the left IPL and the right postcentral gyrus). Sulcal and gyral topographic difference in musicians reflect multi-modal integration of auditory, motor, and cognitive tasks in response to daily extensive requirements of multi functions process; e.g. pitch perception, playing on instruments, remembering and musical sight-reading. In addition, sulcal and gyral topographic patterns indicate considerable within-musician differences (see Figures 5.7–5.10). These differences suggest an association between acquired sensory-motor skills and features of brain topographic patterns especially in the primary and pre-motors area and some brain regions that associated with motor tasks. Association of changes of the brain's external features with motor training has been reported previously in animals (Kleim et al., 1996, Anderson et al., 2002) and humans (Bengtsson et al., 2005, Bangert and Schlaug, 2006, Hyde et al., 2009, Schlaug et al., 2009a). Therefore, I interpret my findings of the differences in sulcal and gyral topography patterns (including sulcal depth and cortical thickness) between musicians and non-musicians to reflect use-dependent structural adaptation associated with expert musical skill acquisition.

Musicians had larger cortical surface area in the anteromedial portion of the left HG Figure 5.11. Additionally, this study showed positive brain–behavioural correlations in the auditory regions (STG, PT and lateral aspect of HG) in the LH in both groups and irrespective to musical proficiency (Figures 5.12–5.14). The strongest correlations were found between PDP of the RE and both cortical surface area and GM volume of the lateral aspect of left HG. The lateral part of HG is considered as the pitch-processing centre (Griffiths, 2003). Although the musical proficiency only influence anteromedial portion of the left HG the brain–behavioural correlations in non-primary auditory areas are irrespective to musical proficiency. Schneider et al. (2005) observed a strong relation between absolute magnitudes of structure and function at the early automatic processing level in anteromedial HG only. This suggests that genetic predisposition could influence the anatomical differences particularly in non-core auditory areas, which would be enhanced by training.

Of importance, musicianship affected the surface shape of some regions of the RHipp but not the whole hippocampus. Musicians' RHipp was thicker in the lateral anterior and the most posterior regions compared to non-musicians' RHipp Figure 5.14. No significance difference was found between musicians and non-musicians in the subfields volume in both hippocampi. But there were group-hemisphere interaction and a significant difference between two hemispheres Figure 5.15. Post hoc t-test showed significant difference between musicians and non-musicians in some subfield regions (fimbria, subiculum and presubiculum in the RHipp and CA4/DG in the left hippocampus). The findings of hippocampus

study and the VBM analysis including PDPs of the LE as a covariate strongly agree with each other. In VBM, musicians had increased GM density in the posterior portion of hippocampus compared to non-musicians using PDP of the LE as a covariate Figure 5.2 and Table 5.2. It has been reported that the posterior part of subiculum is relatively more concerned with space and memory (O'Mara et al., 2009). In addition, volume of fimbria region correlated positively with PDP of the LE (Figure 5.16). Hippocampus plays an important role in pitch memory and auditory temporal information in animal (Sakurai, 2002) and human (Watanabe et al., 2008). I propose that the correlation between volume of fimbria of the RHipp and PDP of the LE reflect an overall internal/external reorganization of hippocampal connections in response to increasingly demanding tasks and skills required to perform pitch discrimination tasks. The present study has not fully reported previous data (Sluming et al., 2007b) about the positive correlation between hippocampal volume and musical proficiency in male musicians under 50 years of age. This was possibly related to the small sample size.

5.6 Limitations

Each method has its own limitation. VBM method has a few limitations (Ashburner and Friston, 2000, Bookstein, 2001, Mechelli et al., 2005) including sensitivity to methodological choices in normalization, smoothing kernel and template. To assure the best results I used default setting of VBM8 toolbox during pre-processing step. Additionally, the quality of normalised and segmented images was visually inspected. I got similar results using two different smoothing

kernels (4 and 10 mm) providing optimal sensitivity for regions of interest. Another limitation is that size, position, and morphology are concurrently linked in VBM results (Bermudez et al., 2009). VBM results were verified using other anatomical methods e.g. cortical thickness, sulcal depth and cortical surface area. These methods have clearly comprehensible biological meanings than GM density.

Using BrainVoyager QX to calculate cortical thickness and sulcal depth, I performed surface-based registration, which offers an accurate gyral/sulcal topology and allows the preservation of the cortical anatomy of the original surface model (Fischl et al., 1999, Desai et al., 2005). All brains were aligned using a moving target approach (Goebel et al., 2006) without user intervention. In regions of high shape variability, the algorithm can force alignment process leading to a misalignment of the corresponding regions (Van Essen, 2005). It has been shown that BrainVoyager QX is not successful in aligning the curves (Pantazis et al., 2010). In addition, some regions e.g. frontal lobes are not performed accurately due to technical limitations of the cortical thickness algorithm (Geuze et al., 2008). Furthermore, there is an interindividual variation in cortical thickness in healthy control subjects of up to 15% (Haller et al., 2009). Although, misalignment of the cortical regions affects the measurements of cortical surface area and volume, manual correction would overcome any inadequate results. Correction procedure is an excruciatingly time consuming process.

For Hippocampus measurements a few data set have been excluded from further analysis due to major defects during automatic segmentation of hippocampus by both techniques; Freesurfer and FIRST. This can be explained by over-inclusion of part of boundary voxels, neighbour regions e.g. parahippocampal gyrus and some CSF. Segmentation algorithms of both techniques are sensitive to differences in contrast in boundary voxels especially in FIRST (Morey et al., 2009). Therefore quality of segmented images was carefully inspected and major defects were manually corrected. However, there is an underestimation of the volume of the hippocampal fissure by this method (Van Leemput et al., 2009). Therefore I excluded hippocampal fissure from further analysis. Additionally, the sequence that used in this study might be not optimum for the automated segmentation of hippocampal subfields because freesurfer models for both hippocampi were built from manual segmentations of the RHipp in $0.38 \times 0.38 \times 0.8\ mm^3$ (Van Leemput et al., 2009).

Additionally, the sample size was underpowered for calculation of correlation between some structure measurements and the age at which the person had begun musical training and musical proficiency period. For example, sample size was underpowered for the calculation of the correlation between age of commencing musical training and cortical surface area of the anteromedial portion of the left HG (Power = .62) (Faul et al., 2007, Faul et al., 2009).

5.7 Conclusion

Taken together, the results of the current study found that musicians showed increased cortical volume in the right postcentral gyrus and in the left IPL. These regions are part of the auditory-motor coupling network, which indicates that long term practicing may lead to GM adaptation in auditory-motor related regions. Additionally, there were changes in the RHipp surface shape, which indicates change of hippocampal volume according to musical proficiency. Further investigation showed brain–behavioural correlation of fimbria of the RHipp reflecting the importance of internal circuitry of the right hippocampal during PDP. Additionally, brain–behavioural correlations in the RHipp and non-primary auditory areas are irrespective to musical proficiency. Although, musical training could enhance shape and volume of these areas, these changes could be related to genetic predisposition. Only well designed future functional/structural experiments can determine the relative contribution of predisposition and practice.

Chapter 6 : Tonotopic Mapping of the Human Auditory Cortex and its Relationship with Musical Proficiency: an fMRI Study Using a Stroboscopic Event Related Design

6.1 Aims

Specific aims of this chapter were to:

1- Investigate tonotopic mapping in the human auditory cortex using fMRI.

2- Explore the influence of musical performance expertise and pitch discrimination ability on frequency organization.

3- Explore the influence of musical performance expertise and pitch discrimination ability on cortical activation of the human auditory cortex.

6.2 Introduction

The main advantages of using fMRI that brain activation and anatomy can be related directly in individual subjects, and it provides the best spatial resolution. The current study was undertaken to investigate tonotopic mapping in the human auditory cortex using fMRI and to explore the influence of pitch discrimination ability and musical proficiency on frequency organization and cortical activation of the human auditory cortex. Here, I used a stroboscopic event related design that optimised in the pilot study (For details see chapter 3).

6.3 Materials and Methods

6.3.1 Subjects

Data was collected from 10 musicians (7 males and 3 females) (the mean age: 37.6 years (SD = 16.19) and 13 matched non-musicians subjects (10 males and 3 females) with an age of 36 ± 13.59 (mean ± SD) years. Volunteers participated in the study after giving written informed consent. They had no history of any neurological or hearing impairment.

6.3.2 Stimuli

Subjects were binaurally presented with six sine tones varying in frequency (247, 440, 784, 1175, 2637 and 4186 Hz) from different musical notation groups (B3, A4, G5 D6 E7, C8 respectively). Each frequency was formed in a train of sine

waves (rise/fall time 10 ms, plateau 30 ms, interstimulus interval (ISI) 50 ms) as shown in Figure 6.1.

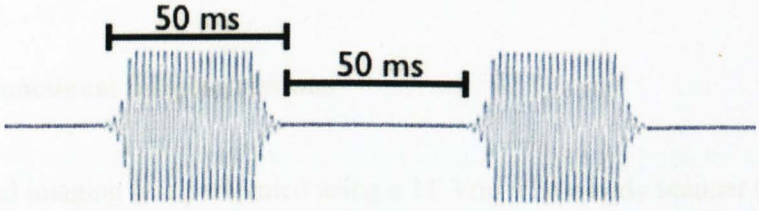

Figure 6.1 Waveform of one of the sine tones (440 Hz).

Tasks were programmed using Eprime (Psychology Software Tools, PST, Pittsburgh, PA). Stimuli were delivered through electrodynamic headphones using a system that included a personal computer, and a commercial MR-compatible device (MR Confon; MR confon GmbH, Magdeburg, Germany). This type of headphone has a high degree of acoustic attenuation to reduce scanner acoustic noise. The system accurately preserves tone frequencies in the range of the stimulation frequencies used (247–4186 Hz). The intensity of the output stimulus was set to 70 dB SPL for all subjects and for all the frequencies to produce maximum neuronal activation (Formisano et al., 2003, Woods et al., 2009).

6.3.3 Experiment Procedure

All subjects participated in four functional runs, each lasting 9 min, to increase the total number of trials in order to obtain the full sampling of HRF curve and to increase the statistical power in single subject analyses. During the fMRI sessions, subjects were instructed to lie still, listen to the tones and focus on a visually presented cross-hair. The cross-hair was of white colour and presented on a black

background. To maintain a stable level of alertness, subjects were asked to press a button when they saw a circle shape that was presented randomly for 12 times in each run. The circles were presented 6 times during an fMRI session.

6.3.3.1 Functional imaging sessions

Functional imaging was performed using a 3T Trio whole body scanner (Siemens, Erlangen, Germany) with an eight-channel phased-array head coil. FMRI parameters: pulse sequence = EPI; (TR/TE) = 20000/35 ms; delaying TR = 17170 ms; echo spacing 0.7; phase partial Fourier = 6/8; imaging resolution = 2 × 2 × 2 mm^3; flip angel= 90°; number of axial slices 28; matrix size 128 × 128; bandwidth 1628 Hz/px. Each EPI measurement was collected at regular 20s intervals with an auditory stimulus being presented at variable offsets (0, 3, 4, 5, 6, 7, 8, and 11 s) before each acquisition to obtain the full sampling of HRF curve (Josephs et al., 1997, Belin et al., 1999). Figure 6.2 shows presentations of (3 s) stimulus at three different time points (11, 7 and 5 s) before each acquisition. This acquisition scheme permits full sampling of HRF for each frequency.

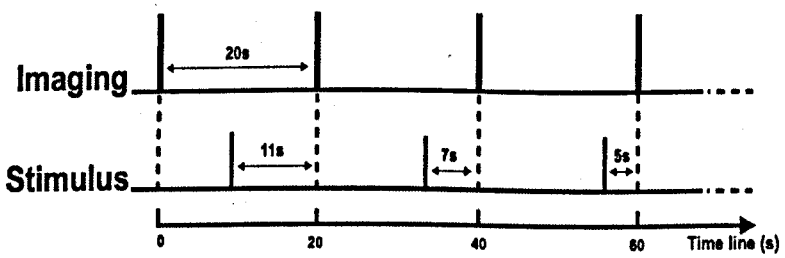

Figure 6.2 Schematic diagram of the stroboscopic event related design. The presentation of the tone occurred at variable offsets before each scan.

6.3.4 Statistical analysis

In the 2nd level analysis of musicianship effect, qualitative comparison was applied by creating percent overlay maps within subjects, then checking the overlay of "fixed effects" within group maps and overlaying single subject maps. Then beta weights were extracted from demarcated regions of interest (HG and PT) by averaging across all voxels in those regions. Alternative methods such as random effects analysis (McNamee and Lazar, 2004, Penny and Holmes, 2007) are not suitable for exploratory investigations in my data because of the small sample size (Seghier et al., 2008). Statistical analyses were performed SPSS (for MAC, Rel18.0. 2010. Chicago: SPSS Inc.) Group comparisons of the estimated beta values were performed using a 2-way ANOVA. *P* values of (≤ 0.05) were considered statistically significant.

6.3.5 FMRI and Anatomical Data Analysis

BrainVoyager QX software package was utilized for single subject fMRI and anatomical image analysis (Brain Innovation, Maastricht, The Netherlands; Version 2.3). Anatomical images were transformed into the Talairach coordinate system. The anatomical data sets were used for automatic cortical surface reconstruction (Kriegeskorte and Goebel, 2001), and inflation. Reconstructed cortical surfaces were then aligned for better match between corresponding brain regions (For details see section 5.3.3.2). The reconstructed cortical surface of the

HG and PT of each subject (For details see section 5.3.3.3) was used for the generation of cortical masks that were used as a constraint for the analysis of functional data sets (Formisano et al., 2002) in order to reduce the number of considered comparisons. Functional data sets were pre-processed with a 3D head motion correction procedure. The functional data sets for each subject were then co-registered to individual 3D anatomical images and inflated aligned brains. This allowed for the viewing of best frequency or tonotopic maps on anatomical data sets. Then the functional data was transformed into Talairach space producing volume time course. Statistical activation maps were obtained by computing a general linear model (GLM), with defining six predictors, one selected for each of those varying pure tones presented during a scanning session. Best frequency maps for each individual were computed by colouring each voxel according to the perceptual frequency using six colours (ranging from dark blue for the highest frequency to red for the lowest one) to which the voxel showed the largest BOLD response (Parkes et al., 2009).

6.3.5.1 The exclusion criteria

Eleven out of twenty three subjects (four musicians and seven non-musicians) were excluded from further analysis for different reasons. Three subjects had artefactual responses over large regions Figure (6.3). This exclusion criterion was performed in each subject before applying cortical masks on functional data to exclude subjects whose estimates were heavily biased by non-cognitive effects. I also excluded four subjects whose overall BOLD responses were very weak and

not statistically significant. For each subject activated regions were those regions with activated voxels above a significance of adjusted FDR (Benjamini and Hochberg, 1995, Genovese et al., 2002) $P < 0.01$.

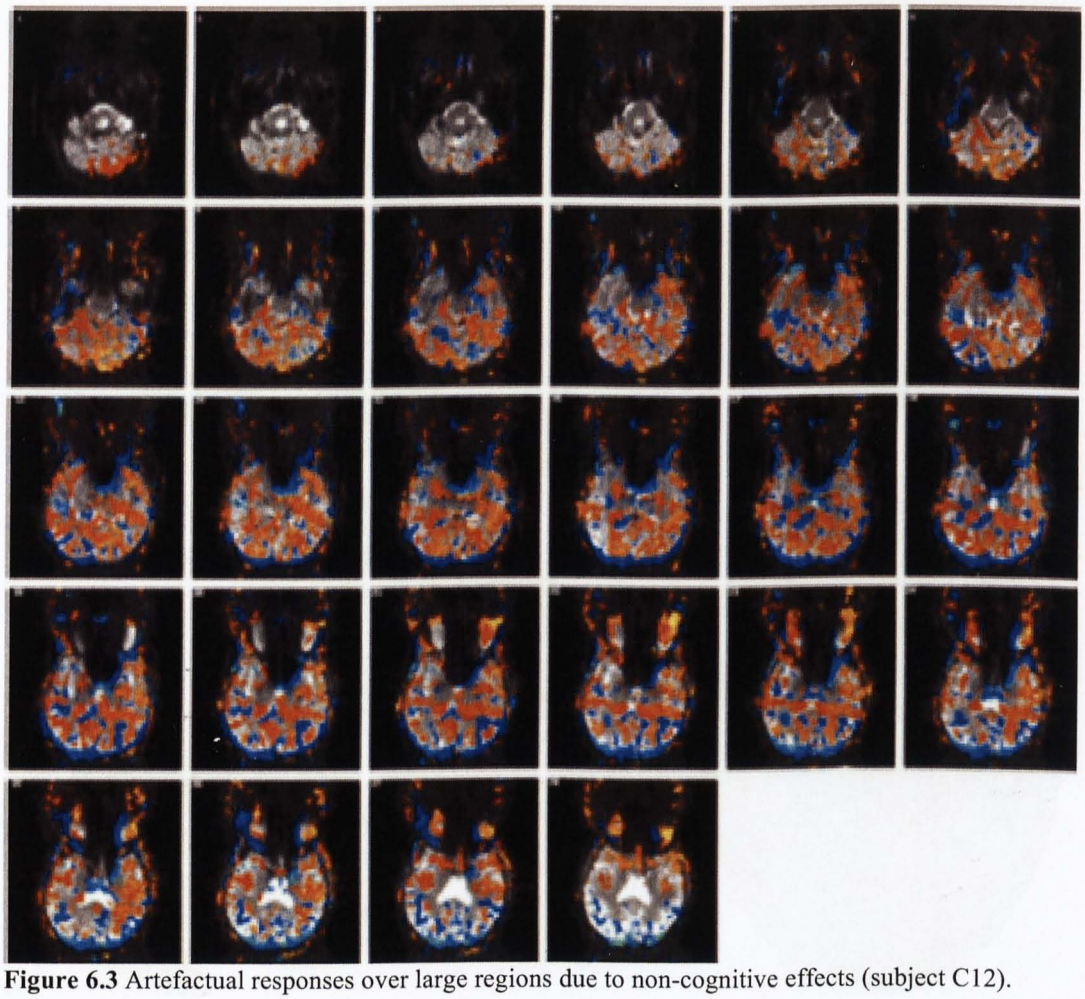

Figure 6.3 Artefactual responses over large regions due to non-cognitive effects (subject C12).

The FDR method is less conservative than Bonferroni correction, yet it is rigorous enough, especially when the data shows sparse activations. The Bonferroni correction, operating on voxel level, was employed in pilot computations and proved to be too stringent. Some subjects had a very strong response to the tones, with significance of adjusted FDR $P < 0.001$ across all BOLD responses as shown in Figure 6.4. However, the significance level across frequencies was set to FDR

$P < 0.01$ for all subjects. Unfortunately, the signal to noise ratio was very weak for some frequencies for four more subjects. Therefore, tonotopic maps were investigated only in six subjects in each group.

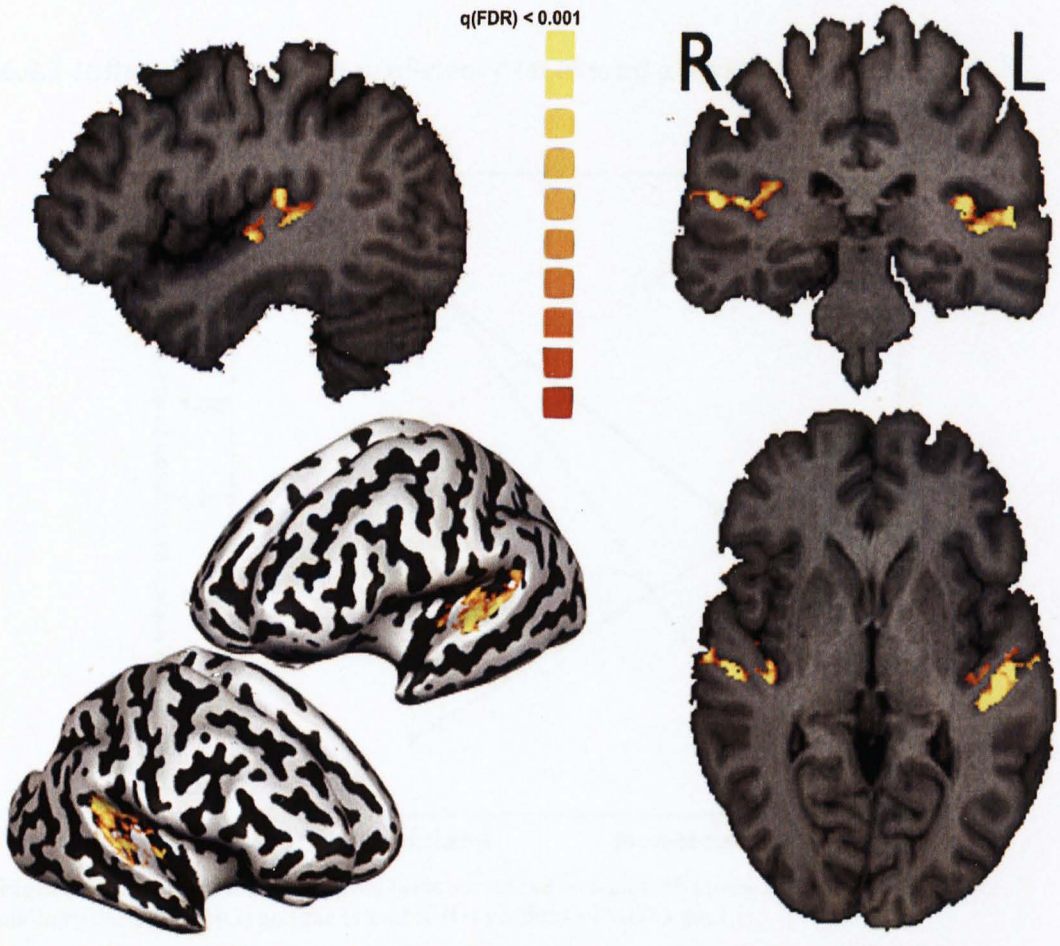

Figure 6.4 Statistical map of the overall auditory cortex response to six frequencies (subject C17) is superimposed on sagittal (LH), coronal and transverse anatomical slices in standard Talairach space, and on a mesh reconstruction of the subject's cortex.

6.4 Results

For each subject, a statistical map of the response of the auditory cortex to all the tones was computed. The activation was mainly located in the HG and secondary auditory cortex (PT).

6.4.1 Influence of musical proficiency on overall activation

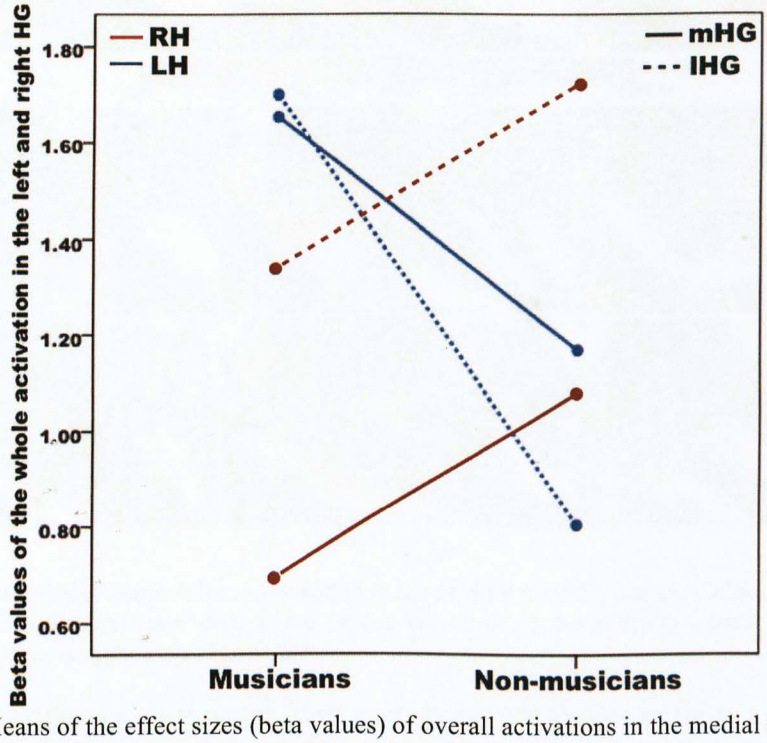

Figure 6.5 Means of the effect sizes (beta values) of overall activations in the medial (primary auditory cortex) (mHG) and the lateral (lHG) portions of HG in the LH.

Repeated measures ANOVA showed no significant effect of musicianship on beta values of overall activations in the medial and the lateral parts of HG ($F(1,10) = .267$, $P = .617$). Additionally there were hemisphere-group interaction ($F(1,10) = 8.155$, $P = .017$) and hemisphere-beta values interaction ($F(1,10) = 19.288$, $P = .001$), but no group-beta values interaction ($F(1,10) = .599$, $P = .457$) or hemisphere-group-beta values interaction ($F(1,10) = 1.258$, $P = .288$), Figure 6.7.

6.4.3 Tonotopic Organization

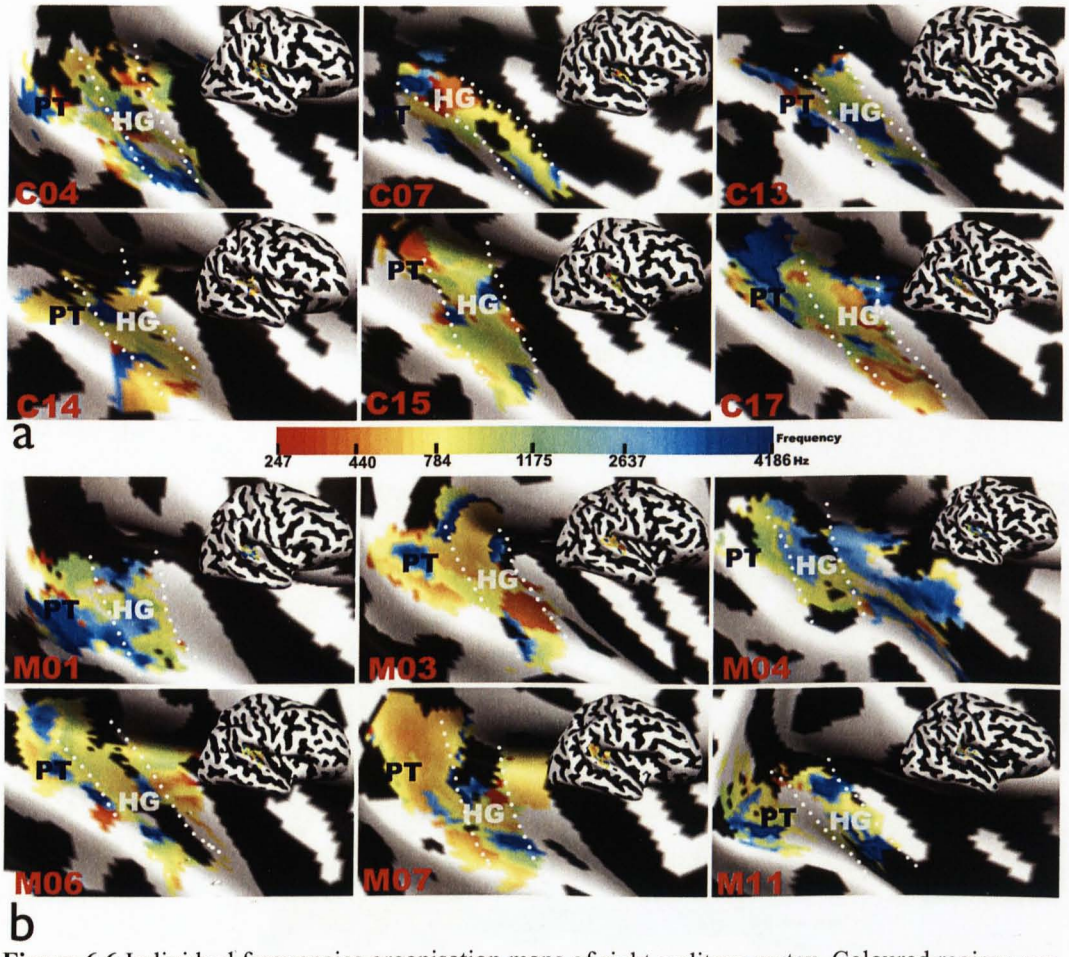

Figure 6.6 Individual frequencies organisation maps of right auditory cortex. Coloured regions are areas that showed significant differences across six tones in the auditory cortex (P<0.01 FDR adjusted). a) Non-musicians, b) Musicians.

Tonotopic maps of a participant from each group are shown in figures 6.6 and 6.7. Frequency gradient maps vary in location, orientations and sizes across all subjects. At least 2 prominent high-frequency areas with a maximal response to frequencies at 4186 and 2637 Hz (dark blue and light blue colours) can be observed medially and laterally or in the middle of HG along an axis roughly parallel to the HG axis in subjects (C04, C07, C13, C14, C15, C17, M3, M6 M07 and M11). With a broad cluster of (440, 784 and 1175 Hz) - orange, yellow and green colours respectively - located over a large portion in the middle of the HG.

Area with a maximal response to frequencies at 247 and 440 Hz (red and orange colours respectively) was situated in the middle of the right HG in subjects (C04, C17, M03 and M07) and the left HG in subjects (C04, C13, C15, M01 and M04). This low frequency region was located in the lateral part of the right HG in subject (C14) and the left HG in subjects (C07, C13, C15, C17 and M01). In contrast, there were single gradient maps in the right PT in subjects (C04, C07, C17, M01 and M11) and the left PT in subjects (C14, C15, C17, M03, M04, M06 and M07).

Figure 6.7 Individual frequencies organisation maps of left auditory cortex. Coloured regions are areas that showed significant differences across six tones in the auditory cortex (P<0.01 FDR adjusted). a) Non-musicians, b) Musicians.

6.5 Discussion

Although ANOVA test showed no significant effect of musicianship on beta values of overall activations in the medial and the lateral parts of HG, there were hemisphere-group interaction and hemisphere-beta values interaction. In contrast, there were no interaction relations either group-beta values or hemisphere-group-beta values.

In the current study, inter-individual variability was large in frequency gradient maps in location, orientations and sizes. These considerable variations have been reported in most previous studies (Formisano et al., 2003, Talavage et al., 2004, Seifritz et al., 2006, Woods et al., 2009, Humphries et al., 2010, Da Costa et al., 2011, Langers and van Dijk, 2011). This inconsistency of maps can be attributed to attributed to the individual gyral pattern of the position and the anatomy of HG and PT (Penhune et al., 1996, Hackett et al., 2001, Rademacher et al., 2001). Another possible source of variance are the differences in the physiologic state changes.

In some subjects (C07, C13, C14, C15, C17, M03, M06, M07 and M11 "right HG") and (C04, C13, C15, C17, M01, M06, M07 and M11 "left HG"), mirror-symmetric frequency gradients extending from a region in the middle of the HG that was most sensitive to lower frequencies. These gradients extended posterior-medial and anterior-lateral along the HG axis are similar to those observed by Formisano et al., (2003). These multiple frequency gradients could help explain the first stage of parallel processing of auditory information (Formisano et al.,

2003). I propose that there are multiple auditory fields in the HG and the PT which overlap in time representing a combination of results from two MEG studies (Pantev et al., 1995, Schneider, 2001) and supported by Liegeois-Chauvel et al., 1994, Gutschalk et al., 1999 and Lütkenhöner et al., 2003a.

Specifically, frequency maps of subject C17 is very similar to those described in macaque monkeys (Petkov et al., 2006, Petkov et al., 2009). It is clearly shown in Figure 3.7 (page 61). In their data, a low frequency band was located in the centre of the core area, similar to low frequencies areas roughly occupying the middle part of HG of subject C17. High frequency regions present immediately anterior and posterior to low frequency band.

6.6 Limitations

The total acquisition time of each run was long, taking into consideration that each scanning slot consisted of four runs. Therefore inter-runs and inter-subjects variability was seen in the number of significantly activated voxels and their preferred frequencies. Therefore, the maps in this study did show a high degree of variability across subjects and across hemispheres and hence, in the analysis of tonotopic organization of auditory cortex, no group comparison was done. There are some possible factors could cause those variances such as amount of head movement and alterations in attention and alertness. The latter factors affected results of this study to a great extent. Additionally, stroboscopic event related design has a lower statistical power compared with other designs (Rosen et al., 1998, Amaro et al., 2002). This design also needs longer time and multiple runs to

obtain the full sampling of HRF curve.

A number of datasets were excluded because of either their artefactual responses over large regions (Figure 6.3) or their response estimates were very weak and not statistically significant. Insignificant statistic response estimates could be related to reduction of attention and alertness level due to running multiple scans on the same subject in the same day (running fMRI experiments directly after a MEG scan). Taking in consideration, that MEG part lasted for more than two hours.

6.7 Conclusion

Although, ANOVA test of Influence of musical proficiency on overall activation showed no significant effect in the medial and the lateral parts of HG, there were hemisphere-group interaction and hemisphere-beta values interaction. Due to inter-individual variability of the tonotopic mapping of this study, group comparison was not possible. In most subjects, I observed gradients along the axis of HG similar to those produced by Formisano et al., (2003) but most recent studies (Woods et al., 2009, Humphries et al., 2010, Da Costa et al., 2011, Langers and van Dijk, 2011) showed gradients perpendicular to the long axis of HG. This discrepancy with the most recent studies could be partly due to differences in the stimuli and range of frequencies used. It could be related as well to the different methods that have been used. I used stroboscopic event related design which has been used by Formisano et al., (2003) while Humphries et al. (2010), Langers and van Dijk (2011) and Woods et al. (2009) used sparse temporal sampling method.

Chapter 7 : Tonotopic Mapping of the Human Auditory Cortex and its Relationship with Musical Proficiency: an MEG Study

7.1 Aims

Specific aims of this chapter were to:

1- Investigate tonotopic mapping in the human auditory cortex using MEG.

2- Explore the influence of musical performance expertise and pitch discrimination ability on frequency organization of the human auditory cortex.

3- Explore the influence of musical performance expertise and pitch discrimination ability on cortical activation of the human auditory cortex.

7.2 Introduction

MEG has been used to investigate tonotopic mapping of the auditory cortex in humans since 1982 (Romani et al., 1982a, Romani et al., 1982b). Most studies used different experimental designs based on the type of neuromagnetic response (For details see section 2.4.1.3).

7.2.1 Auditory evoked fields in musicians and non-musicians

Several studies showed that some components of evoked auditory potentials can be enhanced in musicians or by musical training. Musicians manifested larger N1c (peak at 138 ms) and P2 (peak at 185 ms) responses to all types of tonal stimuli (violin tones, piano tones, and pure tones) (Shahin et al., 2003). Pantev et al. (1998) investigated the evoked magnetic fields of a pseudorandom sequence of piano and pure tones matched in frequency and loudness in musicians and non-musicians. The only difference between musicians and non-musicians was in the strength of cortical activation for piano tones, which was 25% greater in musicians. Musicians also showed a strong correlation with the age of commencement of musical practice. Schneider et al. (2002) investigated the processing of sinusoidal tones in the auditory cortex of non-musicians, professional musicians and amateur musicians. The authors found neurophysiological differences between groups. Comparing professional musicians and non-musicians, the activity evoked in primary auditory cortex (AEMLF) was 102% larger in professional

musicians. Pantev et al. (2001) showed that musical education and training is reflected in the organization of auditory and somatosensory representational cortex in musicians. In addition, musicians had larger N2b (peak at 175 ms) and P300 (peak at 300 ms) amplitude during attentive listening (Tervaniemi et al., 2005).

The effect of auditory discrimination has been studied by Bosnyak et al. (2007) using single carrier frequency for 10 training sessions, alternating training and passive control blocks to explore whether competitive interactions among frequency representations in both primary and secondary auditory cortices. P2 (peak at 200 ms) amplitude increased across sessions on both passive listening and training blocks. In contrast, steady-state response amplitude was larger in training compared to passive blocks. Fujioka et al. (2006) reported that musically trained children had larger and earlier N250m peak in the LH in response to the violin sound compared with untrained children.

The current study was undertaken to investigate tonotopic mapping in the human auditory cortex using MEG and to explore the influence of pitch discrimination ability and musical experience on frequency organization and cortical activation of the human auditory. An additional aim was to investigate any hemispheric difference of tonotopic mapping of the human auditory cortex.

7.3 Materials and Methods

7.3.1 Subjects

Data was collected from 11 musicians (7 males and 4 females) with an average age of an age of 35 ± 14.09 (mean ± SD) years and 14 matched non-musicians subjects (10 males and 4 females) (the mean age: 38 years (SD = 11.59). Volunteers participated in the study after giving written informed consent. They had no history of any neurological or hearing impairment.

7.3.2 Stimuli

Six sine tones of varying frequencies (247, 440, 784, 1175, 2637 and 4186 Hz) were applied binaurally. The tones belonged to different musical notation groups (B3, A4, G5 D6 E7, C8 respectively). Tasks were programmed using Eprime (Psychology Software Tools, PST, Pittsburgh, PA). Stimuli were delivered through plastic tubes attached to ear tips using a system that included a personal computer, a multi-channel analogue amplifier. The system accurately preserves tone frequencies in the range of the stimulation frequencies used (247–4186 Hz). The intensity of the output stimulus was set to 60 dB SPL for all subjects and for all the frequencies. Each frequency was formed in 150 ms sine wave (rise/fall time 20 ms, plateau 110 ms) with an interstimulus interval randomized between 300 and 500 ms.

7.3.3 Experimental procedure

All subjects participated in 6 blocks of 10 min duration each. In every block, 200 tones of each frequency were presented. During the sessions subjects were instructed to lie still, listen to the tones and focus on a visually presented cross-hair. The cross-hair was of white colour and shown on black background. There was a 2 min break between successive blocks.

Whole- head MEG was recorded using 148 axial magnetometers encased in a plastic helmet (Magnes 2400, 4D Neuroimaging, San Diego, USA). The bandpass filter was 0–200 Hz, and the sampling rate was 640.78 Hz. Before the experiment, the 3-D positions of three fiducials (nasion and the left and right pre-auricular points) and five head coils were measured using Polhemus system (Polhemus Navigation, Inc., Colchester, USA). Vertical electrooculogram was recorded using silver electrodes filled with conductive gel and placed above and below the right eye. The electrocardiogram was recorded by two silver cup electrodes placed on the left and right shoulder.

7.3.5 Statistical analysis

Statistical analyses were performed using SPSS (for MAC, Rel18.0. 2010. Chicago: SPSS Inc.) Group comparison of the dipole amplitude of N100m response was performed using repeated measures analyses of variance (ANOVA). Parametric correlations analysis were performed between frequency gradient and x, y and z axes of Talairach coordinates in both

hemispheres. *P* values of (≤ 0.05) were considered statistically significant. Bonferroni multiple comparisons correction were performed on all *p* values (Salkind and Rasmussen, 2007).

7.3.6 MEG Data Analysis

MEG data were analysed using the Brain Electrical Source Analysis v. 5.1.8 program (BESA, Megis, GmbH, Germany). MEG signals were visually inspected to identify head motion artefacts and dead channels. Electrocardiographic and electrooculographic artefacts were removed by identifying their patterns and averaging all events of these patterns in MEG data. Clean MEG data were cut into epochs corresponding to 100 ms of the pre-stimulus and 400 ms of the post-stimulus timeframe. Triggers identifying the occurrences of individual stimuli were given order numbers so as to allow selective averaging of epochs. MEG data were averaged for all stimuli encompassing up to 1200 events for each frequency, then the averaged MEG waveforms were analysed using source dipole analysis in BESA program. Source reconstruction was based on a spherical head model. The digitized head shape of the individual was used to adjust the size of the sphere in every subject. The main source activity of N100m was analysed after applying zero phase shift band-pass filter from 3 Hz (6 dB/octave) to 30 Hz (12 dB/octave) (Schneider, 2001) then modelled with two equivalent dipoles -one in each hemisphere- located in the PT posterior to HG. Additionally, I analysed

earlier components of auditory evoked fields, such as N19m–P30m, which situated in HG using different filter values (20–120 Hz zero phase bandpass). Different patterns of equivalent dipole source (e.g. locations and orientations) have been estimated using source- fitting method. I exclude earlier components from further analysis because of difficulty of localising dipoles within HG in most subjects. This issue is related to limited number of events for each condition. The resultant dipole sources were transformed into Talairach space using BrainVoyager QX software package (Brain Innovation, Maastricht, The Netherlands; Version 2.3) as explained in section 5.3.3.2. Flux maps were used to visually view the spatial pattern of the activity observing apparent sources over the epoch of interest.

7.4 Results

7.4.1 Influence of musical performance on cortical activation

The N100m component was enhanced in musicians compared to non-musicians as shown in flux maps of grand average evoked fields (Figure 7.1). Visual inspections of flux maps within each group shows that middle range frequencies were greater than the highest and lowest frequencies. Activation of 1175 Hz is the greatest in both groups (Figure 7.1). Flux maps were larger in the LH than in the RH in both groups. Musicians had larger flux maps of 440, 784 and 1175 Hz than non-musicians while non-musicians had larger map of 2637 Hz.

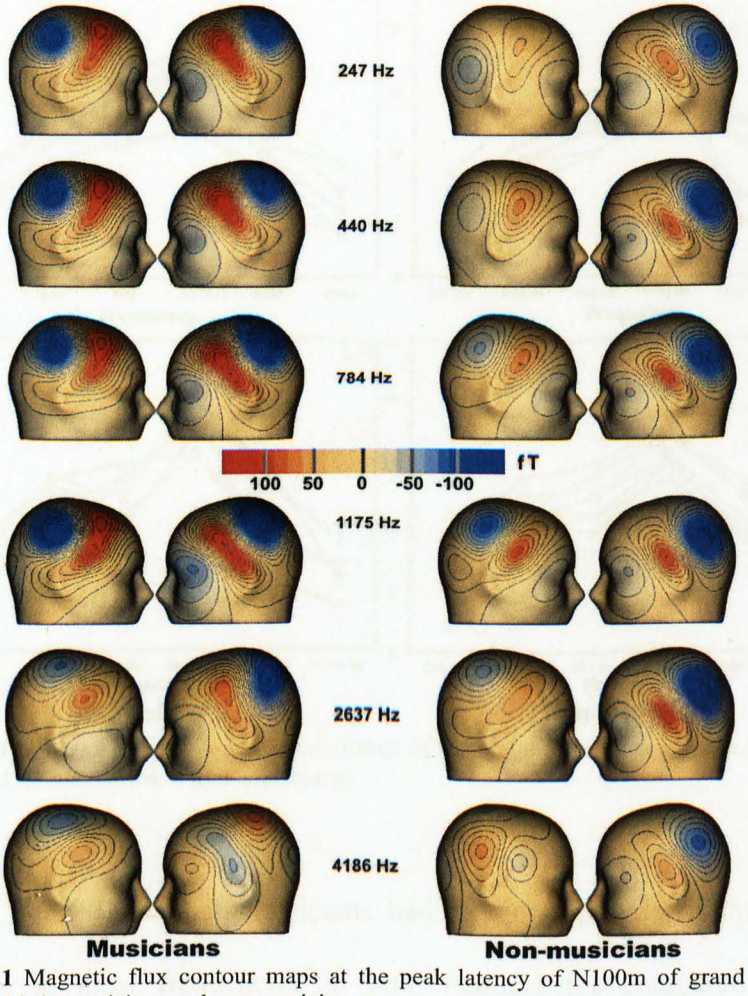

Figure 7.1 Magnetic flux contour maps at the peak latency of N100m of grand average evoked fields in musicians and non-musicians.

7.4.1.1 Dipole magnitude of cortical responses

The individual N100m baseline to peak dipole amplitudes are shown in Figure 7.3. There is a large variance in each group making it difficult to analyse the data, therefore I analysed the grand average of each group. Overall, source activity was largest around 1175 Hz in the LH as shown in Figure 7.4. In both groups, source activity was larger in left hemisphere within med range frequencies (440, 1175 and 2637 Hz).

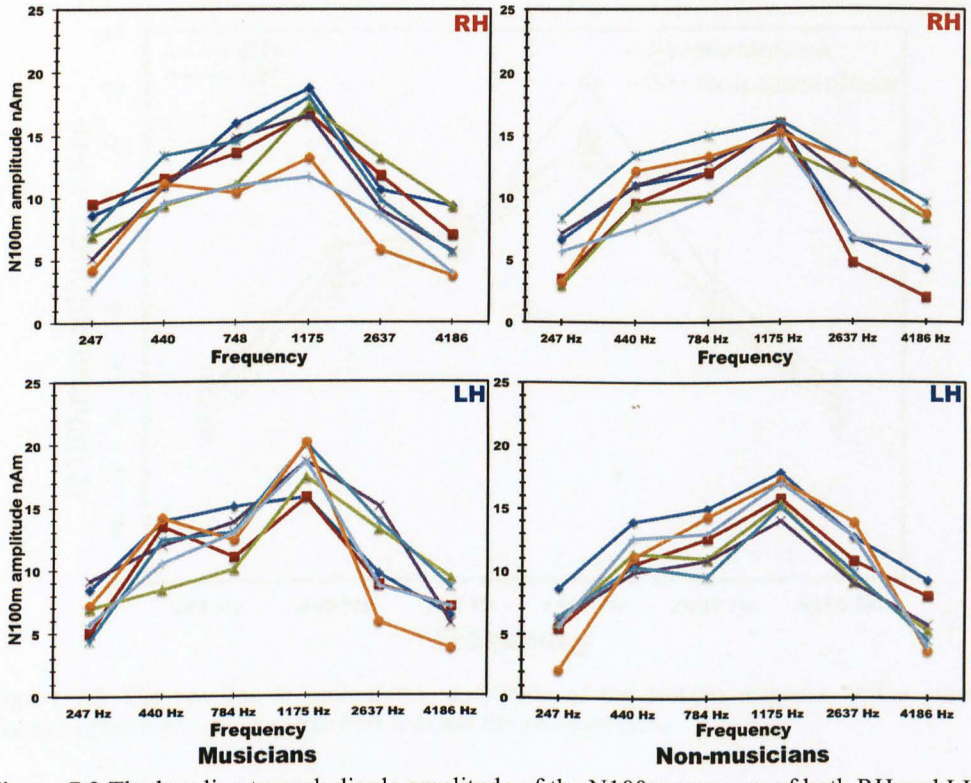

Figure 7.2 The baseline to peak dipole amplitude of the N100m response of both RH and LH of individual, (7 musicians, 7 non-musicians).

Figures 7.2–7.4 show that, musicians had larger amplitude of the N100m component at most frequencies in both hemispheres compared to non-musicians. However, ANOVA for repeated measurements showed no significance effect of musicianship (P=.07). Additionally there were no interaction effects either frequency-group interaction (P=.953), hemisphere-group interaction (P=.909), or even frequency-hemisphere interaction (P=.977).

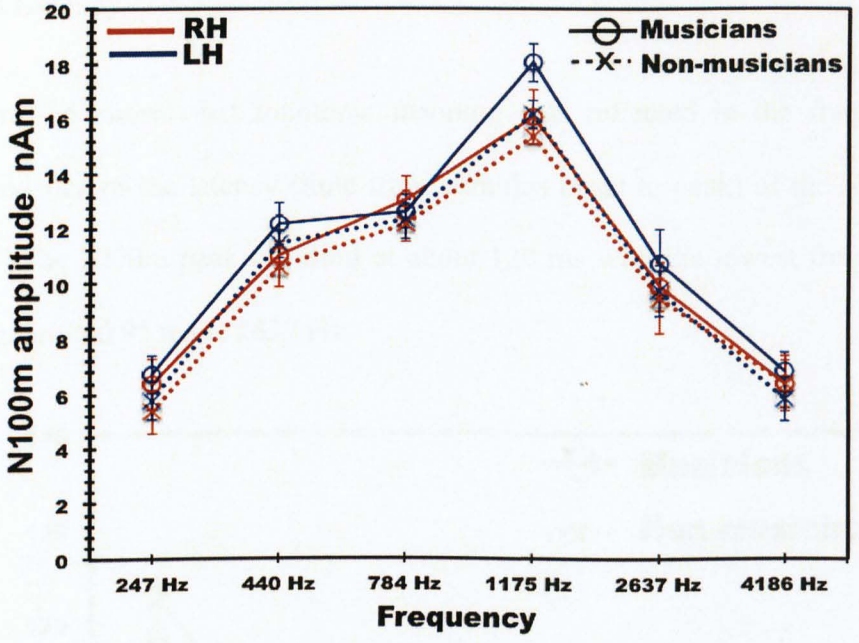

Figure 7.3 The baseline to peak dipole amplitude of the N100m response of the grand average of each group. The error bars indicate the standard error.

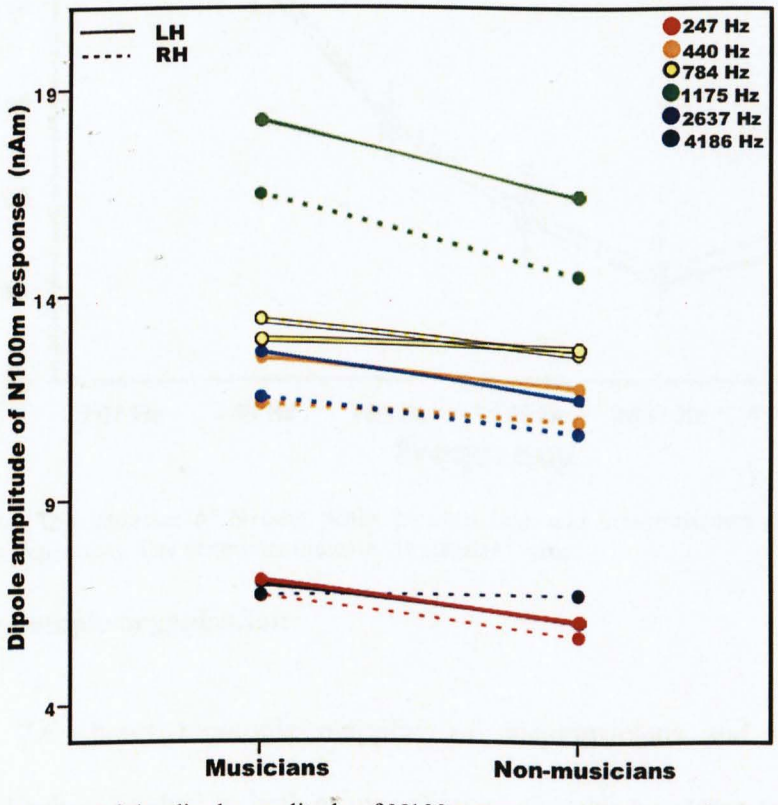

Figure 7.4 Means of the dipole amplitude of N100m response of the grand average of each group.

7.4.2 Latency

Figure 7.5 shows that tonotopic mapping was reflected in the frequency dependence of the latency (time from stimulus onset to peak) of the N100m peak. The Nl00m peak occurred at about 120 ms with the lowest frequency and at around 95 ms at 2637 Hz.

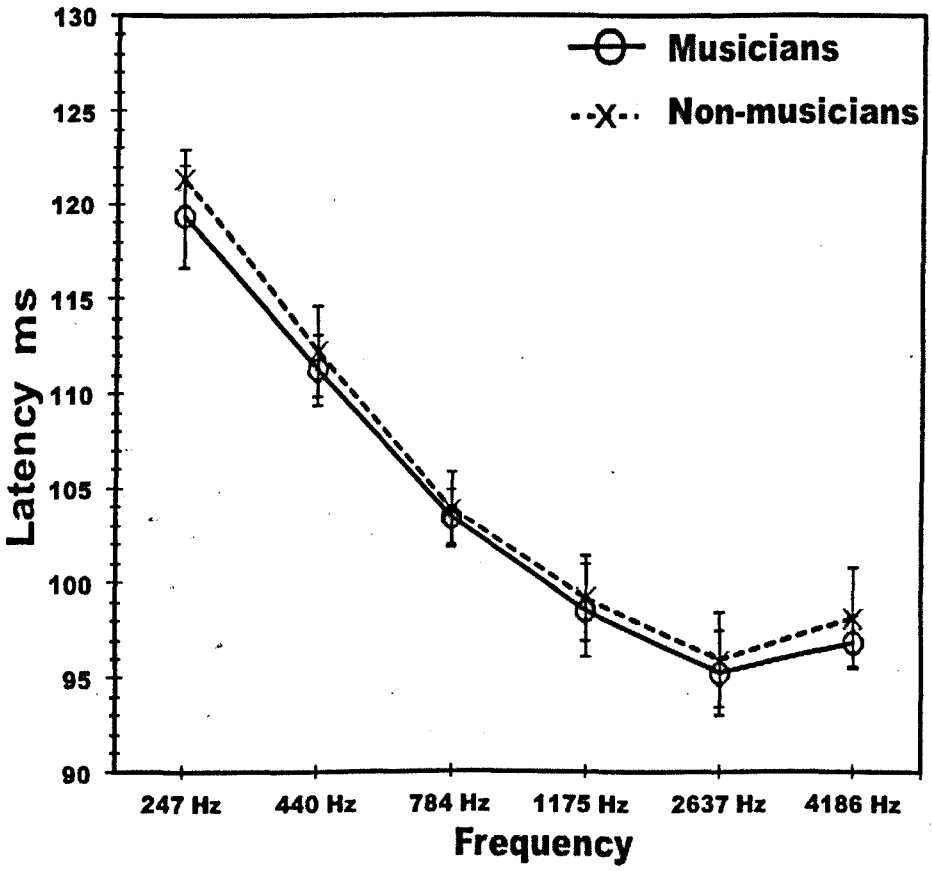

Figure 7.5 The latencies of N100m peaks of musicians and non-musicians are strongly frequency dependent. The error bars indicate the standard error.

7.4.3 Tonotopic organisation

Figures 7.6 shows tonotopic mapping of non-musicians and musicians groups. Each individual in both groups showed a strong tonotopic gradient of

N100m components along the medial-lateral axis of the PT in both hemispheres with no left-right asymmetry. This gradient was located in the lateral part of PT in most cases. I observed that the source of N100m components shifted laterally by increasing frequencies with an average about 1.5 mm per octave. Dipoles were colour-coded using six colours (ranging from dark blue for the highest frequency to red for the lowest one).

Additionally, N100m components of grand average of each group have been investigated. Tonotopic gradient was preserved in both groups as shown in (Figures 7.7–7.10) Visual inspections of tonotopic maps showed no differences between musicians and non-musicians. Performing parametric correlations analysis showed that both groups demonstrated positive and strong correlations between frequency gradient and the gradient along the medial-lateral axis of the PT only in both hemispheres (Table 7.1).

Group		Hemisphere	
		Right	Left
Musicians	Pearson Correlation	.940	-.920
	Sig. (2-tailed) N (6)	.005	.010
Non-musicians	Pearson Correlation	.945	-.909
	Sig. (2-tailed) N (6)	.004	.012

Table 7.1 Correlations between frequency gradient and the gradient along the medial-lateral axis of the PT, *P* values were corrected using Bonferroni adjustment.

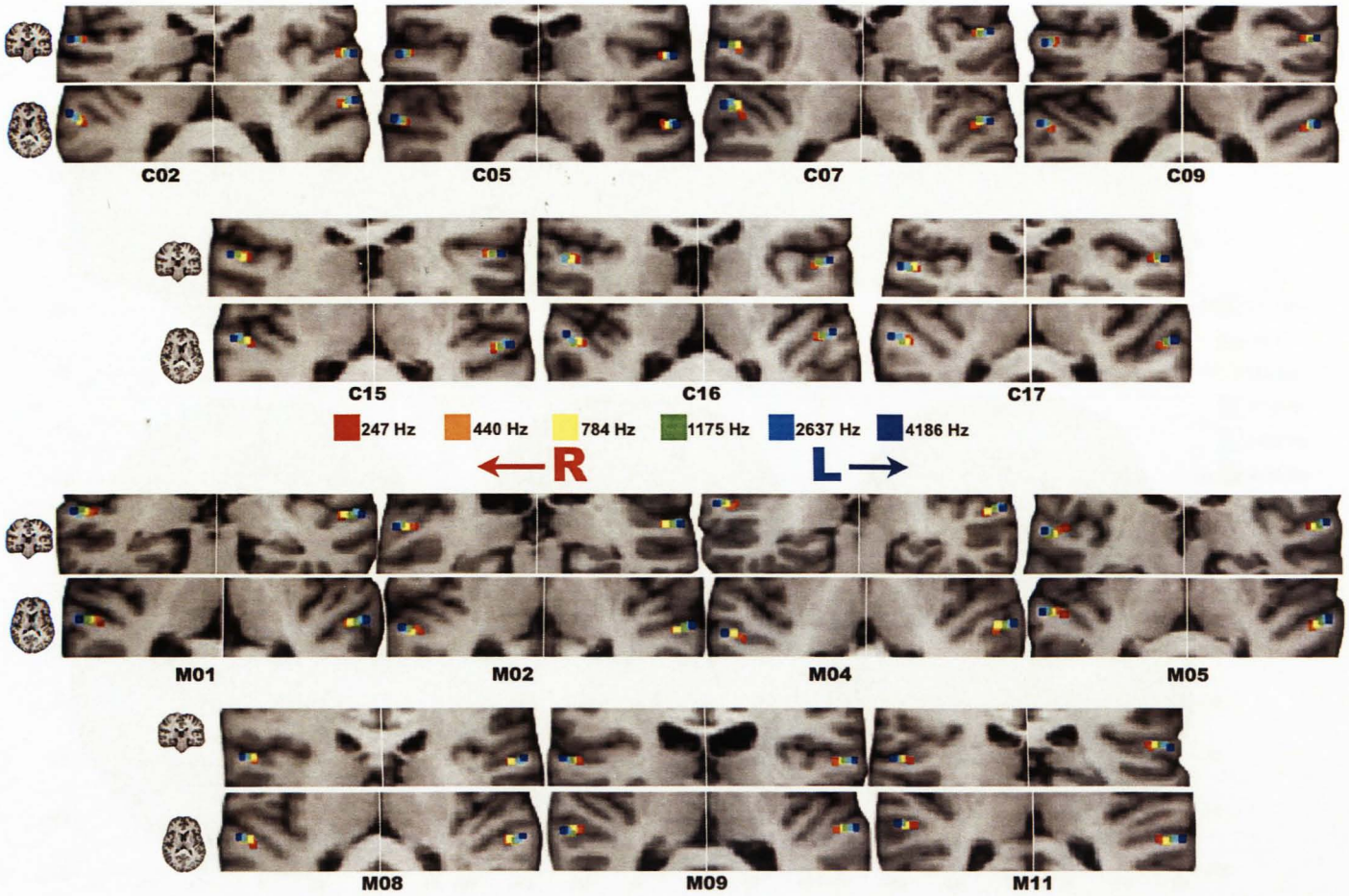

Figure 7.6 Individual tonotopic mapping of the N100m components in non-musicians (letter C) and musicians (letter M). Dipole loclisations are superimposed on coronal and transverse slices in standard Talairach space.

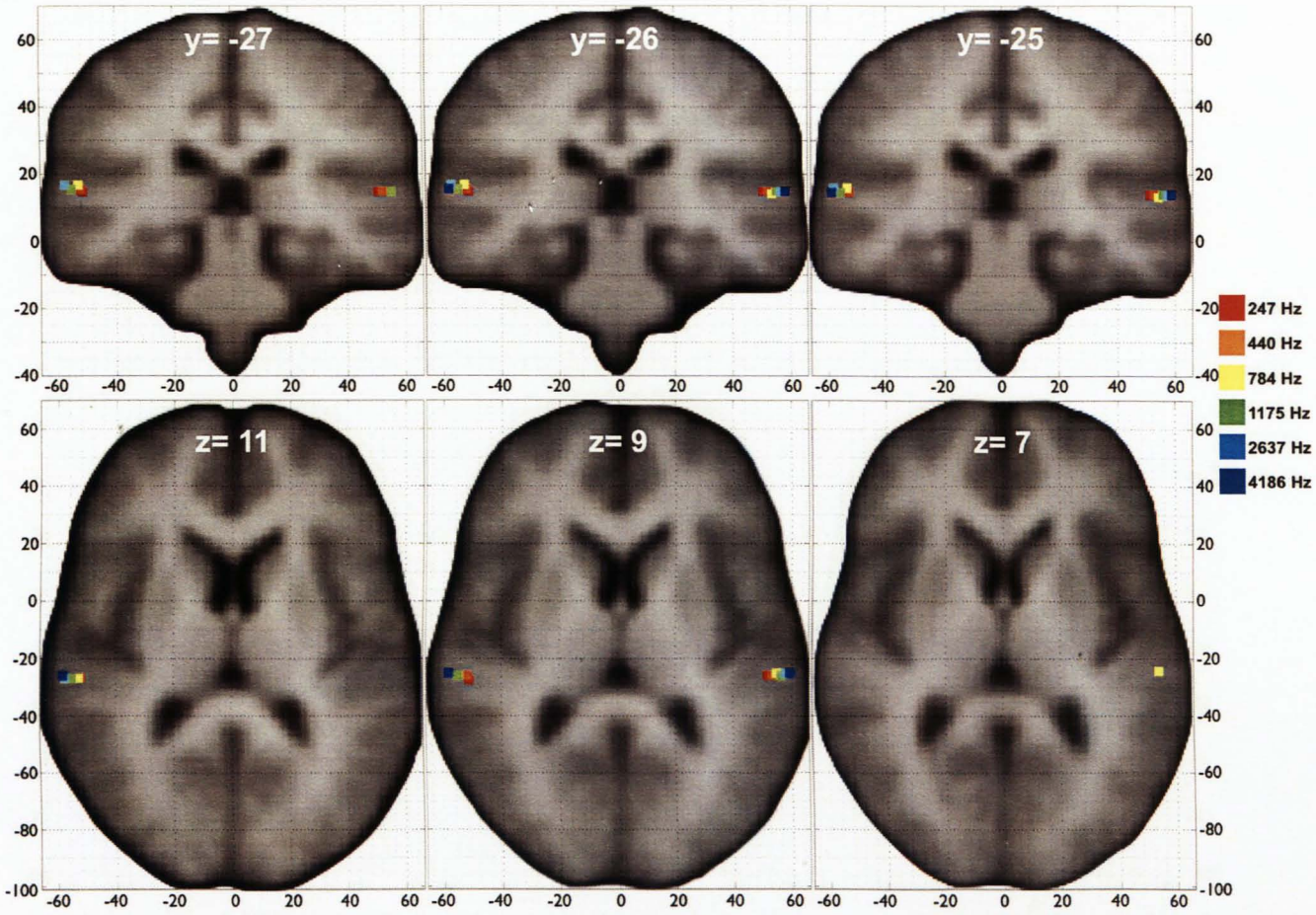

Figure 7.7 Tonotopic mapping of the N100m components in musicians. Dipole localisations are superimposed on coronal and transverse slices in standard Talairach space of an average volume of all participants.

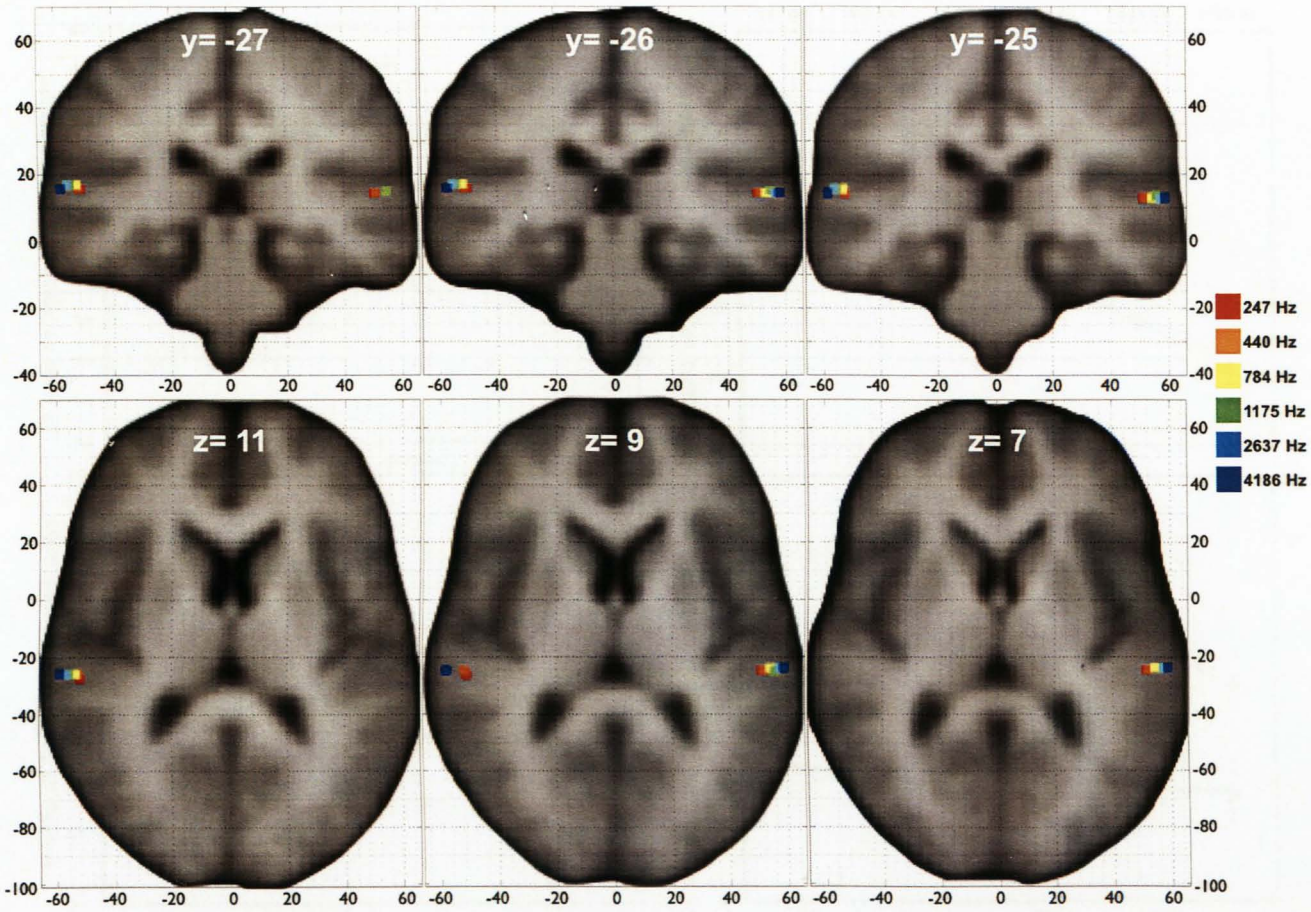

Figure 7.8 Tonotopic mapping of the N100m components in non-musicians. Dipole localisations are superimposed on coronal and transverse slices in standard Talairach space of an average volume of all participants.

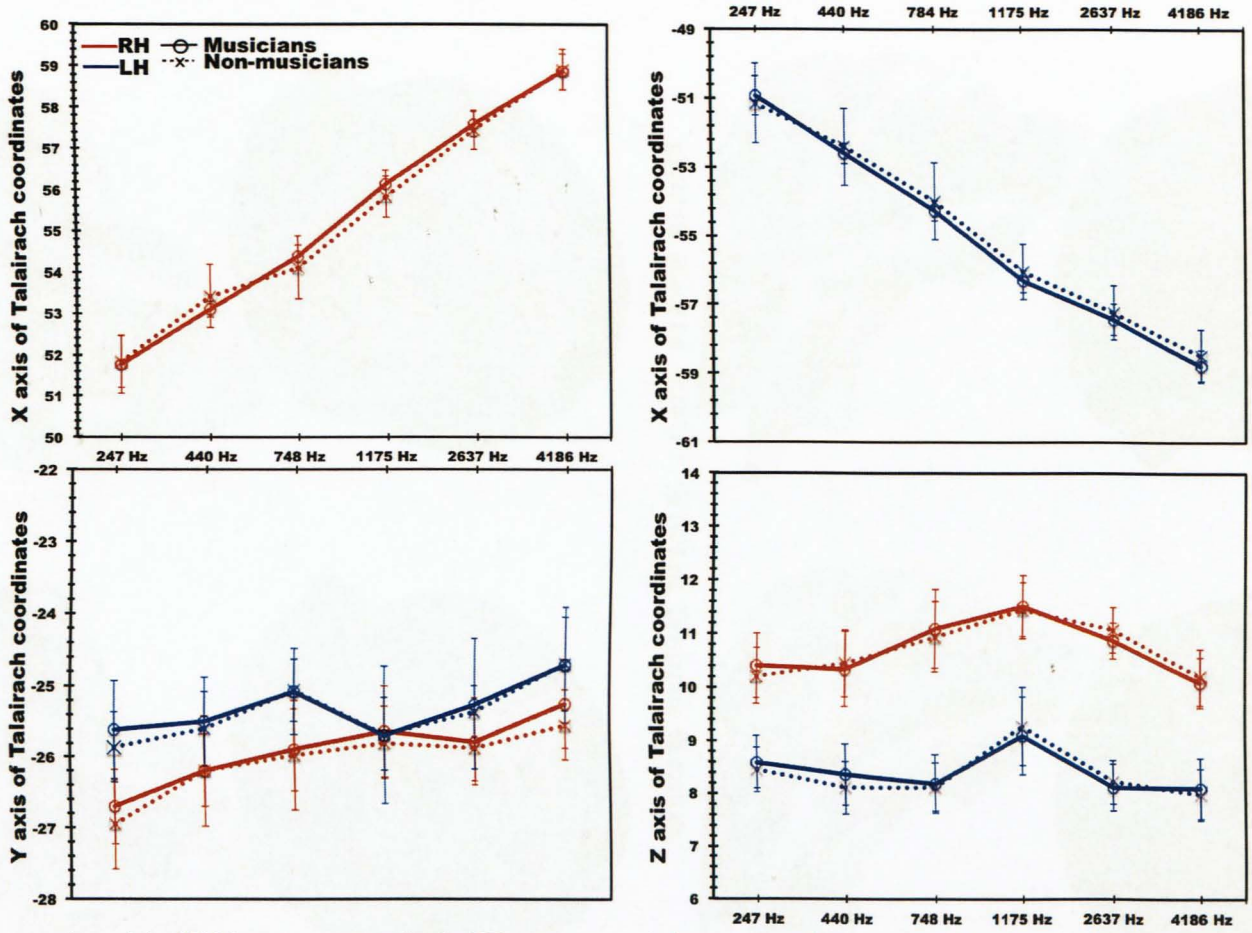

Figure 7.9 Tonotopic mapping of the N100m components in the PT are presented along x, y and z axis of Talairach coordinates in both hemispheres. The error bars indicate the standard error.

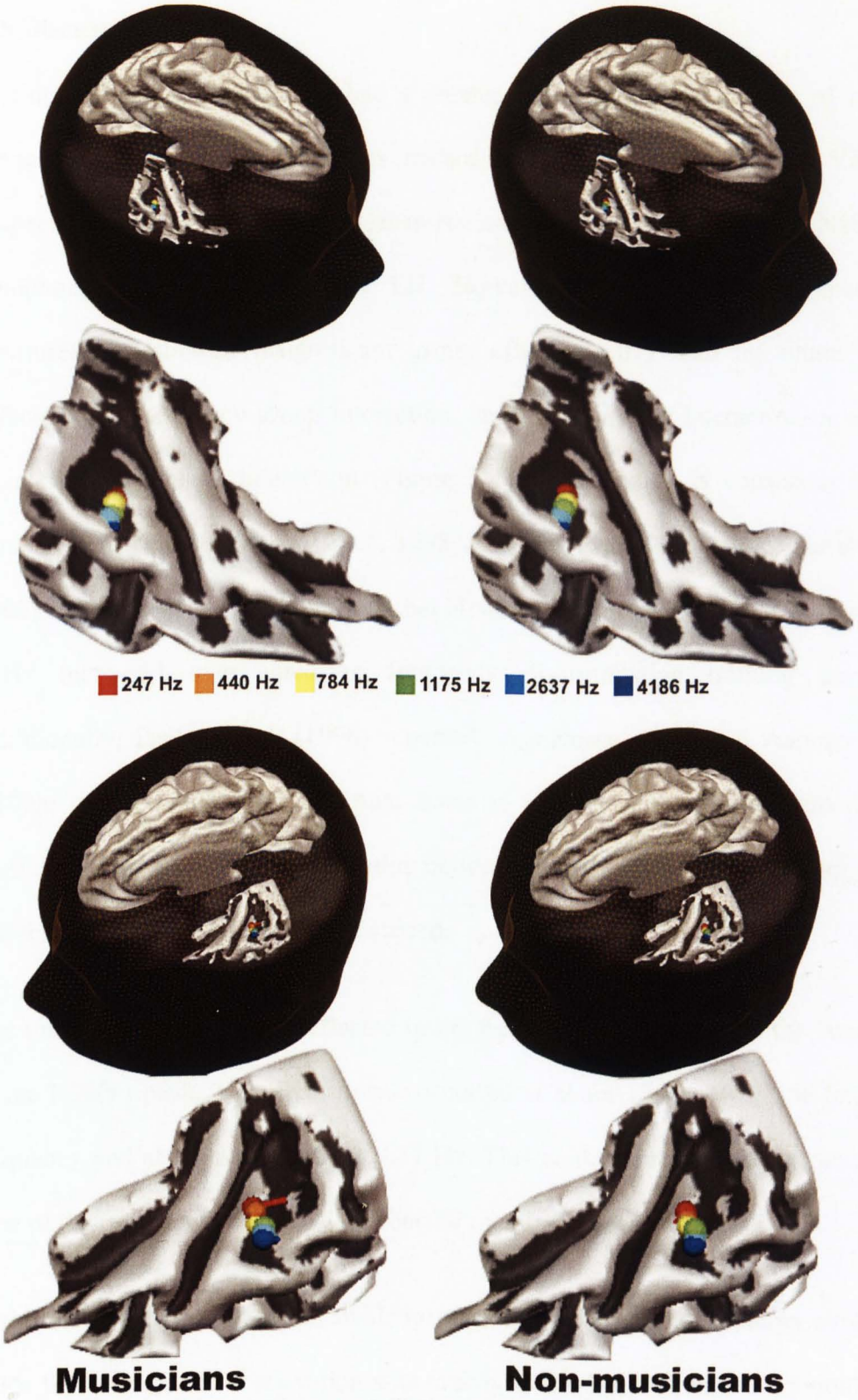

Figure 7.10 Tonotopic mapping of the N100m components of grand average of each group are displayed on mesh reconstructions of the right and left auditory cortex of one subject's (subject C17).

7.5 Discussion

Results showed that musicians had a greater neuromagnetic activation of most frequencies than non-musicians as shown in flux maps (Figure 7.1). Visual inspection of Figure 7.4 showed that musicians had greater amplitude of N100m components at 1175 Hz in the LH. However, the ANOVA for repeated measurements showed insignificant group effect (p=.07) with no interaction effects either frequency-group interaction, hemisphere-group interaction or even frequency-hemisphere interaction (Figure 7.4). This finding is consistent with some previous studies (Pantev et al., 1998, Menning et al., 2000, Schneider et al., 2002). Menning et al. (2000) showed that N100m source strength of a pure tone of 1kHz increased over intensive frequency discrimination training period. Additionally, Pantev et al. (1998) reported an increase of cortical response of N100m of piano tones but not pure tones in musicians comparing with non-musicians with a significant correlation between the mean N100m dipole moment and the age where musical training started.

The tonotopic mapping was reflected in the frequency dependence of the latency of the N100m peak. The Nl00m peak occurred at about 120 ms with the lowest frequency and at around 95 ms at 2637 Hz. This could be related to the running time of the travelling wave along the basilar membrane (Schneider, 2001).

In this study, I could not obtain stable response of middle latency auditory evoked fields therefore; cortical activation was mainly in the PT. I observed a tonotopic gradient of N100m components in the lateral part of the PT with no significant

group effect, where the highest frequency was located more laterally and the lowest one was situated more medially with a gradient average of 1.5 mm per octave. Results of this study are consistent with the tonotopic mapping of N100m response of (Schneider, 2001).

The gradient of N100m components is inconsistent with frequency gradients in the PT that resulted from fMRI part of this thesis. It might be explained by methodological differences or due to the large inter-individual variability especially in fMRI study and the comparatively small number of subjects precluded both averaging over subjects and comparison of fMRI and MEG tonotopic maps. Additionally, systematic error related to co-registration of averaged MEG data to an averaged brain could contribute in that variation.

7.6 Limitations

There are two noteworthy limitations regarding the present study. Firstly, the auditory evoked middle latency fields were very weak in most subjects because the total number of stimuli presented was low (in the range of 900 to 1000 per condition). Previous studies presented larger number of stimuli per condition - 3500 (Lütkenhöner and Steinstrater, 1998), 1500 (Pantev et al., 1995) and 12000 (Schneider, 2001)- to gain an enhanced response of the primary components. Primary components are very important because they are originated within the medial portion of the HG.

Another limitation was excluding data sets (4 musicians and 8 non-musicians)

from further analysis due to severe tilting of sensor locations as shown in Figure 7.11. In addition, technical abilities of the MEG system at the University of Liverpool limited the number and range of frequencies used.

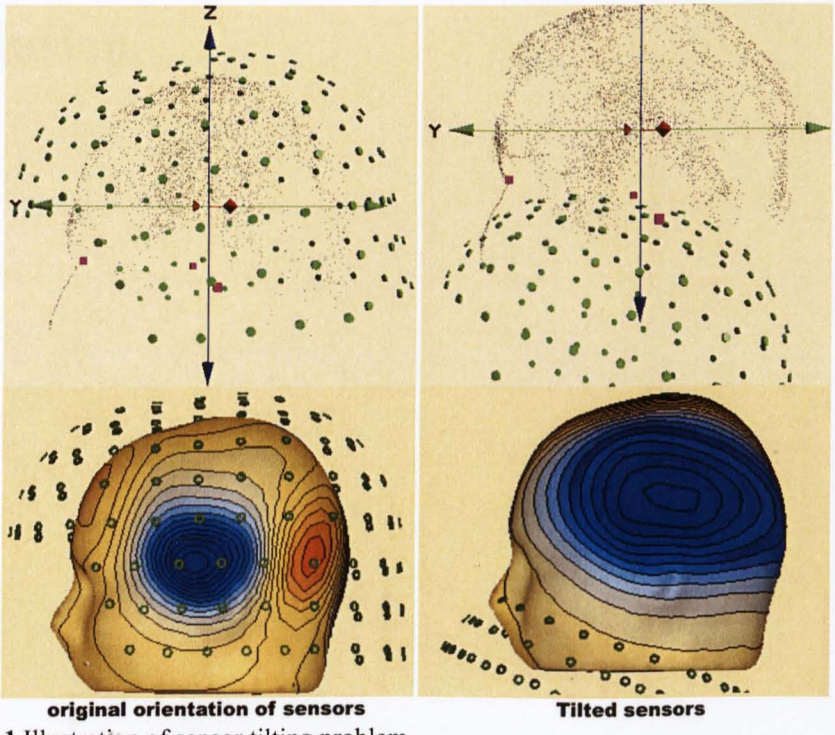

Figure 7.11 Illustration of sensor tilting problem.

7.7 Conclusion

In conclusion, musicians had greater amplitude of N100m component especially at 1175 Hz with no interaction effect. This shows that N100m components for pure tone can be used as a comparison tool for the neural response but only at a limited range of frequencies. Both groups demonstrated positive and strong correlations between frequency gradient and the gradient along the medial-lateral axis of the PT in both hemispheres The gradient of N100m components is inconsistence with fMRI part of the main study.

Chapter 8 : Summary, discussion and conclusion

8.1 Introduction

In this thesis, the main aim was to investigate the effect of musical proficiency on functional neural substrates of sine tone frequency processing and anatomical morphology in the human auditory cortex using multimodal neuroimaging methods (structural MRI, fMRI and MEG). I also explored neuroanatomical features in brain regions that are associated with pitch memory (IPL and hippocampus) with taking in consideration the effect of type of instrument on sulcal and gyral topography.

I assessed the possible links between pitch discrimination ability test scores (as defined in Chapter 4) and neuroanatomical features e.g. GM density, cortical surface area and volume (see Chapter 5).

8.2 Results and Interpretations

The results that I obtained for each study were described and interpreted separately within each chapter. The following subsections were related to the interpretation of results for analyses based around individual objectives.

1- Investigating PDP in musicians and non-musicians (chapter 4):

Musicians had better performance in pitch discrimination than non-musicians in all three conditions (both ears together, the right and left ears). In musicians, a statistically significant difference in PDP was observed with the left ear performing better than the right ear. This result might suggest that musicians had right-hemisphere dominance for pitch discrimination. Additionally, I may

consider that musicians' performance of the LE was related to the duration of musical proficiency.

2- Frequency organisation of the human auditory cortex (chapters 6 and 7):

In the fMRI study, group comparison was not possible because of inter-individual variability of the tonotopic mapping. In most subjects, I observed gradients along the axis of HG similar to those produced by Formisano et al., (2003). Formisano et al. (2003) suggested three different explanations for mirror-symmetric of frequency organisation of the human auditory cortex; a) it could be a presentation of two primary cortical fields that located closely to each other, b) tonotopic gradient of this mapping is oriented in opposite directions, and c) There is an overlapping between two fields in time. The authors supported first and second suggestions. Additionally, gradient of N100m components which occupied the lateral part of PT. In this study, I suggested that there were multiple auditory fields overlapping in time and perhaps representing combination of results from two MEG studies (Pantev et al., 1995, Schneider, 2001) and supported by (Liegeois-Chauvel et al., 1994, Gutschalk et al., 1999, Lütkenhöner et al., 2003a).

3- Neuroanatomical/functional correlates of musicianship in the human auditory cortex (chapters 5, 6 and 7):

Musicians had larger cortical surface area in the anteromedial portion of the left HG compared to non-musicians. Functionally, ANOVA of repeated measures of the amplitude of hemodynamic responses to neural activity of the medial and the lateral parts of HG showed hemisphere-group interaction and hemisphere-beta

values interaction. Functional correlates of musicianship in anteromedial portion of HG might be explained by the structural correlate of musicianship and hence the number of neurons that contributed in processing auditory stimuli. Furthermore, neuromagnetic activation showed musicianship effect of borderline significance on the amplitude of the N100m component. These results indicate the importance of the morphology and neurophysiology of auditory cortex in musical proficiency (Schneider et al., 2002).

4- Neuroanatomical correlates of PDP in the human auditory cortex (chapters 5 and 6):

There were positive correlations between PDP of the right ear and both cortical surface area in the left STG and the lateral aspect of left HG. PDP of the right ear was also significantly related to GM volume of the lateral aspect of left HG. The anatomical correlates of PDP of the right ear in the lateral part of left HG might suggest that increasing number of synchronised neurons that involved in pitch processing may improve PDP and reflecting its importance in pitch processing (Griffiths et al., 1998a, Griffiths et al., 2001, Patterson et al., 2002, Griffiths, 2003, Krumbholz et al., 2003, Warren and Griffiths, 2003).

5- Neuroanatomical correlates of musicianship and PDP in IPL and postcentral gyrus (chapter 5):

Musicians had larger GM distributions than non-musicians in the right postcentral gyrus and in the left IPL. Differences of sulcal and gyral topographic patterns indicate that musicians had deeper and thicker cortex than non-musicians in various sulci and gyri respectively such as right postcentral and the right and left

cingulate sulci, and the left parahippocampal gyrus, the posterior part of the left Broca's area and the left and the right IPL. In contrast, non-musicians had deeper cortex than musicians in the following sulci: posterior part of the left superior frontal, right superior temporal and left inferior temporal sulci. Non-musicians also had thicker cortex than musicians in the following gyri: the anterior part of left middle frontal gyrus, and the right gyrus rectus.

Sulcal and gyral topographic features in musicians may reflect multi-modal integration of auditory, motor, and cognitive processes in response to daily extensive requirements to perform music at professional level. Limiting my results to those regions that had significant difference in both anatomical methods (VBM and sulcal and gyral topographic patterns), GM distributions and sulcal and gyral topographic patterns results agree with each other in the left IPL and the right postcentral gyrus. These regions are considered as part of the auditory-motor coupling network (Gaab and Schlaug, 2003, Bangert et al., 2006, Gaab et al., 2006).

Larger GM density in the right angular gyrus in musicians compared to non-musicians were further explored by covarying with PDP of the left ear. Angular gyrus, which takes part in pitch short memory (Binder et al., 1997, Rinne et al., 2009), is considered as part of the semantic memory network (Platel et al., 2003, Platel, 2005, Groussard et al., 2010b).

6- Neuroanatomical correlates of musicianship and PDP in the right and left hippocampi (chapter 5):

It has been shown that there is a relation between musicianship and the surface shape of the RHipp indicating that musicians had thicker lateral anterior and the most posterior regions of the RHipp compared to non-musicians. Further investigation showed no significance difference between musicians and non-musicians in the subfields volume in both hippocampi with group-hemisphere interaction and a significant difference between two hemispheres. Post hoc t-test showed that musicians had significantly larger volume than non-musicians in fimbria, subiculum and presubiculum of the right hippocampus. In contrast, non-musicians had significantly increased volume of CA4/DG in the left hippocampus compared to musicians.

When PDP was included as a covariate in the VBM analysis, musicians had larger GM density compared to non-musicians in the posterior portion of hippocampus (particularly subiculum), which relatively more concerned with space and memory (O'Mara et al., 2009). In addition, volume of fimbria region in the RHipp correlated positively with PDP of the left ear reflecting the importance of hippocampal internal/external circuitry in pitch memory and auditory temporal information processing. It has been shown that the RHipp is associated with pitch memory and processing of auditory temporal information in animal (Sakurai, 2002) and human (Watanabe et al., 2008).

Covarying with PDP of the left and right ear in VBM study showed an associated increase in GM density in the RHipp and the right and left angular gyrus

respectively may suggest a network supporting the spatial processing required for pitch memory.

7- Brain effects of type of instrument (chapter 5):

Sulcal and gyral topographic patterns indicate considerable within-musician differences. String players (6 musicians) had prominent omega shape (Yousry et al., 1997) of central sulcus in the right hemisphere only, while the non-string players (6 musicians) preserved omega shape in both hemispheres (Bangert and Schlaug, 2006). These results reveal an association between acquired sensory-motor skills and features of brain topographic patterns. This has been reported previously in animals (Kleim et al., 1996, Anderson et al., 2002) and humans (Bengtsson et al., 2005, Bangert and Schlaug, 2006, Hyde et al., 2009).

8.3 General discussion

8.3.1 Multimodal imaging approach

Although, neuroimaging is a very young science, multimodal neuroimaging has already advanced our understanding of the spatiotemporal pattern of brain activation and connectivity underlying perception, motion and cognition. Combining fMRI and MEG offers a great tool for spatiotemporal mapping of brain activity (Dale et al., 2000, Dale and Halgren, 2001, He and Liu, 2008). In this thesis, I implemented both methods to investigate spatiotemporal excitation patterns of frequency organisation and simple tone pitch perception in the auditory cortex and to understand the neural basis of mirror-symmetric of frequency organizations of the human auditory cortex. In MEG part, unfortunately I could

not obtain stable response of middle latency auditory evoked fields, which situated in the HG; therefore cortical activation was mainly in the PT. Therefore it was not possible to examine spatiotemporal excitation patterns of frequency organization in the auditory cortex. I found that frequency organizations of N100m components occupied lateral part of frequency gradient that resulted from fMRI, which extended along the lateral-medial axis of the PT. This might be explained by assuming that there is an involvement of multiple areas in the PT in the generation of auditory fields, which is supported by previous MEG studies (Pantev et al., 1995, Lütkenhöner and Steinstrater, 1998, Schneider, 2001). However, the inconsistency in MEG and fMRI results could be also explained by methodological differences that related to the differences in physiological and physical rationales of both imaging modalities.

The detectable change of BOLD signal should last at least thousands of milliseconds to become observed by MRI, while MEG and EEG could detect shorter cortical activity. Exciting a small percentage of neurons could produce detectable electromagnetic signal and could lead to an unobserved change in metabolic consumption by fMRI. Spike timing-dependent synaptic plasticity is considered as linking patterns of pre- and postsynaptic activity to changes in synaptic strength (Froemke and Dan, 2002, Dan and Poo, 2006). Synaptic strength modifications alter representational patterns or reorganise neural connections in morphological or functional domains. MEG and EEG may detect early plasticity changes related to strengthening of synaptic but MRI could explore long-term brain plasticity reveal significant volumetric/regional changes. However diffusion

MRI can detect structural changes in cell morphology induced by plasticity within few hours (Le Bihan et al., 2006, Blumenfeld-Katzir et al., 2011). In this thesis, both fMRI and MEG revealed sort of asymmetric functional differences in the auditory cortex between musicians and non-musicians. Various anatomical techniques revealed significant difference in various cortical features in different brain regions between musicians and non-musicians. Results of anatomical studies strongly agree with each other.

8.3.2 Is it genetic predisposition for music?

Genetic and environmental factors influence brain structure and function to a great extent (Thompson et al., 2001, Brun et al., 2009, Jahanshad et al., 2010, Thompson et al., 2010, Kochunov et al., 2011, Yoon et al., 2011). Several studies showed the environmental and personal experience effect on structural characteristic of some brain regions (Maguire et al., 2000, Mechelli et al., 2004, Lazar et al., 2005, Aydin et al., 2007).

The main question remains whether structural and functional changes in musicians' brains are associated with musical training (Hyde et al., 2009, Herdener et al., 2010) or represent a genetic predisposition (Thompson et al., 2001, Jahanshad et al., 2010) for music?. The first factor is supported by a considerable literature. The structural and functional correlates of musicianship are highly correlated with the duration of musical proficiency and intensity of musical practice (Sluming et al., 2002, Hutchinson et al., 2003, Aydin et al., 2005, Abdul-Kareem et al., 2011b), with the age at which the person had begun musical

training (Elbert et al., 1995, Schlaug et al., 1995a, Monaghan et al., 1998, Pantev et al., 1998, Ohnishi et al., 2001, Gaser and Schlaug, 2003, Lotze et al., 2003, Bengtsson et al., 2005) and musical aptitude (Schneider et al., 2002, Gaser and Schlaug, 2003, Lotze et al., 2003). Additionally, the literature and this study showed that structural differences are directly related to type of instrument (Elbert et al., 1995, Schneider et al., 2005, Bangert and Schlaug, 2006). Pantev et al. (2003) reported functional correlates of the type of instrument. Investigation of the functional effect of type of instrument was beyond this thesis as I used simple tone stimuli during functional neuroimaging tasks. Furthermore, induced structural and functional plasticity were observed in several longitudinal studies (Jäncke et al., 2001, Pascual-Leone, 2001, Gaab et al., 2006, Lappe et al., 2008, Hyde et al., 2009, Herdener et al., 2010). The results of this thesis are consistent with some of sited studies above. Although, relation between structural differences and type of instrument has been observed effect of the duration of musical proficiency, intensity of musical practice and age of commencing musical training were not statically significant. This could be related to the lack of power and intersubject variability and will be considered further in the limitation section.

In this thesis, structural correlates of PDP, which were irrespective to musical proficiency, were found in various brain regions. This finding could support the assumption of the influence of environmental and genetic factors on particular brain regions (Lenroot et al., 2009, Deary et al., 2010, Davies et al., 2011). Exploring environmental and gentic effect is beyond the aims of this thesis.

8.4 Limitations

One of the limitations is that data size is too few to accurately account for measurements of some factors such as the age at which the person had begun musical training and musical proficiency period. For example, sample size was underpowered for the calculation of the correlation between age at which musicians begun to practise and PDP of the LE (Power = .52) (Faul et al., 2007, Faul et al., 2009). In contrast, power of the data was fairly enough in some other measurements e.g. Power of fMRI study was 0.9 (Desmond and Glover, 2002, Hayasaka et al., 2007). Additionally, this study might be affected by intersubject variability e.g. within the whole sample there are five and four females in musicians and non-musicians respectively and one left handed participant in each group. That may explain why this study is not fully consistent with some previous studies. Specific limitations of each method were discussed in sections (5.5, 6.5 and 7.5).

8.5 Conclusion

In this thesis, I investigated PDP and brain structure and function in a group of musicians in comparison with age, sex and handedness matched non-musicians. Different neuroimaging methods and image analyses approaches have been employed to study structural and functional difference in the auditory cortex and some brain regions that associated with pitch memory specifically hippocampus and IPL.

A statistically significant region of increased GM distribution was found in the right postcentral gyrus and in the right and the left IPL of musicians. IPL forms triangle-like functional structure with Broca's and Wernicke's areas (Catani et al., 2007). These regions are important for music and language (Zatorre et al., 1992, Binder et al., 1997, Koelsch et al., 2002a, Sluming et al., 2002, Tillmann et al., 2003) with taking in consideration the evidences of neural specializations for music and speech (Peretz et al., 1994, Tervaniemi et al., 1999, Maess et al., 2001, Zatorre et al., 2002a, Abrams et al., 2011, Rogalsky et al., 2011).

My findings of the difference in some brain structures between both groups might reflect multi-modal integration demands of auditory, motor, and cognitive tasks in response to daily extensive requirements for multisensory process; e.g. pitch perception, playing on instruments, remembering and musical sight-reading. In contrast, the functional and structural behavioural correlates in some brain regions that associated with pitch processing and memory, which were present irrespective of musical proficiency. Structure and function of these regions play essential role in musical proficiency, however these correlates could be related to innate predisposition (Thompson et al., 2001, Carmelli et al., 2002, Toga and Thompson, 2005).

Significant differences in brain structure were identified in regions that have functional relevance to musical proficiency and pitch discrimination ability with all techniques of image analyses employed. These differences suggest an indication of use-dependent adaptation of cortical tissue in reaction to the lifestyle

of professional musicians. Knowledge of training-induced anatomical and functional neuroplasticity might be applied to neurorehabilitation strategies in neurologically impaired patients (Jenkins, 2001, Flor et al., 2004, Schneider et al., 2007, Herraiz et al., 2009, Schlaug et al., 2009b). Early musical training may have transferable benefits which contribute towards achievement in verbal memory (Chan et al., 1998, Ho et al., 2003), verbal intelligence (Moreno et al., 2011), mathematical enhancement (Rauscher et al., 1997, Graziano et al., 1999) and fine motor skills (Forgeard et al., 2008).

8.6 Future work

Additional work on larger sample size is needed including performing longitudinal, multimodal and behavioural studies to separate apart the genetic effects from those of musical training. Designing specific spectral/temporal pitch processing/memory paradigms using fMRI and MEG in combination with ultra high resolution DTI and MRI would provide clear image about role of brain regions and the brain internal circuitry that involved in pitch processing and pitch memory.

This thesis could be considered as the first implementation of brain topographic patterns and shape change of subcortical regions in studying neuroanatomical correlates of musicianship. Combination of these methods is important to find out at which extent they can be used as disease indications such as Alzheimer senile dementia (Li et al., 2007, Tondelli et al., 2011) and schizophrenia (Csernansky et al., 2008).

Language and music share many common features (Patel et al., 1998, Patel, 2008, Fedorenko et al., 2009, Shahin, 2011). Therefore musical perception and processing may be relevant for understanding the neural bases of language only in specific cases such as the higher-order cognitive processes (Rogalsky et al., 2011) and complex sound structures (phonology) (Brown et al., 2006). Also musical training could help in extracting prosodic information from speech (Thompson et al., 2003, Thompson et al., 2004).

Distinctive neural processing is applied in human brain to process different languages. During reading tasks, native speakers of the Arabic language showed specific right hemisphere disability for Arabic, but not for Hebrew or English (Ibrahim and Eviatar, 2009). The authors used the divided visual field technique on native Arabic speakers who use Hebrew and English as second language. Arabic and English languages differ in reading direction, orthographic complexity (extensive use of dots and many letters with an identical structure in Arabic script) and morphological structure, which could cause the specific difficulty of the right hemisphere with Arabic. Boudelaa et al. (2010) investigated Arabic morphology using MMN. The authors reported that topographically, the root MMN has a symmetric fronto-central distribution, whereas the word pattern MMN lateralizes significantly to the left. It is really important to apply neuroimaging methods extensively in studying Arabic language, as neural basis of Arabic language is still not clear. This could help in knowing how a stroke affects language recovery in Arabic speakers and in diagnosing some learning and language disorders in

Arabic language e.g. aphasia, dyslexia and dysgraphia. Additionally, understanding neural basis of Arabic language would be essential in defining learning strategies especially for children.

In Arabic language, sounds are closely fused with meanings. This strong connection between sounds and meanings is one of the beauty and affectivity of Classical Arabic texts including Holy Qur'an. Arabic poetry is the main form of Arabic literature especially during pre-Islamic era. At the beginning of Islamic period, the Holy Qur'an reinforced phonologic and prosodic patterns in Arabic language. Al-Khalīl ibn Ahmad al-Farāhīdī (d.ca. A.H. 175/A.D.791) invented science of "Arūḍ" (prosody) depending on rhythmic nature of pre-Islamic poetry (Ryding, 1998). He wrote fifteen "Buhūr" (verse types) to measure the poems' structure imitating musical "iqa" (rhythmic mode). In most cases, Arabic poets start producing poems at the early age and continue production process until they die. Professional readers of the Holy Qur'an usually memorise the whole book (more than 600 page) before the age of ten. They read it from memory in the daily basis in a particular phonetic way "Tajweed". Implementing neuroimaging methods in studying neural structure and function of some brain regions in professional readers of the Holy Qur'an and poets may extend our knowledge about neural basis of language processing and production at least in the Arabic language and may be the Semitic languages. Additionally, language production and processing in poets might be more appropriate to be used as investigation tools for neural bases of language comparing with musical perception and processing.

It has been reported that memory training (Belleville et al., 2011) and bilingualism (Bialystok et al., 2007, Craik et al., 2010, Schweizer et al., 2011) may delay onset of dementia including Alzheimer diseases. Studying brain structure and function of people with impressive memory ability and extensive language use e.g. poets could help improving neurorehabilitation or delaying strategies of dementia.

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