PLASTICITY, HEMISPHERIC ASYMMETRIES AND THE NEURAL REPRESENTATION OF SOUND

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<th>Description</th>
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<tr>
<td>µV</td>
<td>microVolts</td>
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<tr>
<td>AC</td>
<td>Auditory Cortex</td>
</tr>
<tr>
<td>Ag/AgCl</td>
<td>Silver/Silver-Chloride</td>
</tr>
<tr>
<td>ANOVA</td>
<td>Analysis of Variance</td>
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<tr>
<td>AEF</td>
<td>Auditory Evoked Field</td>
</tr>
<tr>
<td>AEP</td>
<td>Auditory Evoked Potential</td>
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<tr>
<td>BOLD signal</td>
<td>Blood Oxygen Level Dependent signal</td>
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<tr>
<td>CAS</td>
<td>Central Auditory System</td>
</tr>
<tr>
<td>CN</td>
<td>Cochlear Nucleus</td>
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<tr>
<td>CNS</td>
<td>Central Nervous System</td>
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<tr>
<td>dB (HL/SL/SPL)</td>
<td>decibel (Hearing Level/ Sensation Level/ Sound Pressure Level)</td>
</tr>
<tr>
<td>EE/EI</td>
<td>Excitatory-Excitatory / Excitatory-Inhibitory</td>
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<tr>
<td>EEG</td>
<td>Electroencephalography</td>
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<td>EHI</td>
<td>Edinburgh Handedness Inventory</td>
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<td>EOG</td>
<td>Electrooculography</td>
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<tr>
<td>GFP</td>
<td>Global Field Power</td>
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<tr>
<td>Hz</td>
<td>Hertz</td>
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<tr>
<td>IC</td>
<td>Inferior Colliculus</td>
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<tr>
<td>kHz</td>
<td>kiloHertz</td>
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<tr>
<td>LED</td>
<td>Left Ear Deafness</td>
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<td>LI</td>
<td>Laterality Index</td>
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<tr>
<td>MEG</td>
<td>Magnetoencephalography</td>
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<tr>
<td>MGN</td>
<td>Medial Geniculate Nucleus</td>
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<tr>
<td>nAM</td>
<td>nanoAmpere-Meter</td>
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<tr>
<td>NHS</td>
<td>National Health Service</td>
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<tr>
<td>RED</td>
<td>Right Ear Deafness</td>
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<tr>
<td>RMS</td>
<td>Root-Mean-Square</td>
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<tr>
<td>SNR</td>
<td>Signal-to-Noise Ratio</td>
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<tr>
<td>SOC</td>
<td>Superior Olivary Complex</td>
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<td>WBN</td>
<td>Wide Band Noise</td>
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Abstract

The mature central nervous system (CNS) has the capacity to reorganise when there is a change in sensory input. However, studies using the N1 cortical auditory evoked potential, or its magnetic homolog N1m, have not consistently demonstrated evidence of plasticity in adults with late onset unilateral deafness. In addition, little is known about the time course of experience-related plasticity in adults with unilateral deafness. The aim of the studies described in this thesis was to investigate plasticity in adults with unilateral deafness, using N1 auditory evoked potentials. Deafness occurred as a result of surgery for the removal of an acoustic neuroma. The stimuli were 500-Hz and 4-kHz tones presented monaurally to the intact ear, and the data were analysed using global field power and dipole source analysis.

In the first study (Chapter 3), hemispheric asymmetries in the N1 response were measured in a group of 24 normally hearing adults at presentation levels of 40, 60 and 80 dB sensation level (SL). The results revealed that the mean hemispheric asymmetry was greater for the 4-kHz stimulus but there was no significant effect of presentation level. In addition, the results revealed that the magnitude of hemispheric asymmetry depended on the ear of stimulation; a trend for larger asymmetries was observed following stimulation of the left ear. The results of the study provide confidence that the methodology is suitable for measuring hemispheric asymmetries in individuals with unilateral deafness. The effect of stimulus level is important since this will vary in plasticity studies involving individuals with late onset unilateral deafness due to their pure tone sensitivity thresholds. Clarifying the effect of stimulus frequency in normally hearing adults is important since the effect of stimulus frequency on plasticity following unilateral deafness has not been reported previously.

In the second study (Chapter 4), N1 responses were measured in 19 adults with unilateral deafness (10 and 9 right- and left-sided deafness respectively). Stimuli were typically presented at 60 dB SL. The results revealed that there was significantly greater mean activity and a shift towards reduced hemispheric asymmetries compared with 19 audiogram-matched controls. Similar changes were apparent after both right- and left-sided deafness, and for both 500-Hz and 4-kHz stimuli. Therefore the results reveal evidence of experience-related plasticity that mirrors the findings reported in animal models. The reduced hemispheric asymmetries were reflected in the dipole source model used in this thesis by changes in dipole strength, location and orientation. These findings may explain the inconsistencies reported in previous studies that have used N1 or N1m, where dipole location and orientation have not always been taken into adequate consideration.

In the third study (Chapter 5), longitudinal measurements were made in six adults just prior to the onset of complete unilateral deafness, and at 1-, 3- and 6-months after the onset (4 right-sided and 2 left-sided deafness respectively). The results from the second study were further analysed by splitting the data into two groups: nine participants with <2 years deafness and 10 with ≥2 year’s deafness. The results from the longitudinal data revealed that there was a significant difference in mean activity across the four conditions. For both stimulus types an increase in mean activity occurred after the onset of deafness, and hemispheric asymmetries were reduced. The biggest changes occurred within 1-month, although further increases were noted in some individuals with ≥2 year’s duration of deafness. Changes that continue over this period of time suggest different physiological mechanisms for plasticity within the human central auditory system.
Declaration

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Chapter 1: Introduction

The adult mammalian central nervous system has the capacity for experience-related plasticity following a change in sensory input. This seems to be a common feature across the sensory modalities. For instance Merzenich et al. (1984) demonstrated changes in the neural representation of the hand in the primate somatosensory cortex following digit amputation and Gilbert and Wiesel (1992) showed analogous changes in the visual cortex of cats following lesions of the retina. In terms of the auditory cortex, changes in the neural representation of the cochlea in guinea pigs have been observed following restricted lesions of the sensory inner hair cells (i.e. introducing cochlear dead regions). The region of cortex deprived of its normal sensory input becomes responsive to the adjacent regions where input is still present (Robertson and Irvine, 1989). The capacity for experience-related plasticity in the adult central auditory system gives rise to a number of questions concerning the neurophysiological mechanisms involved, their perceptual consequences and the implications for the rehabilitation of deaf individuals. Willot (1996) described the possible relevance of experience-related plasticity in the rehabilitation of deaf individuals with regards to hearing aid use and subsequent acclimatisation. This also extends to assessing candidature for and maximising outcomes from other interventions such as cochlear implantation and auditory rehabilitation through training (Purdy, 2001; Irvine et al., 2001).

In addition to cochlear dead regions, another type of change in sensory input that drives plasticity in the central auditory system is that of complete unilateral deafness. Researchers interested in the effect of unilateral deafness have demonstrated altered responses of binaurally sensitive neurons in the auditory pathway (McAlpine et al., 1997). These can be observed via changes in the normal pattern of hemispheric asymmetry that results following monaural stimulation. Although the two hemispheres of the brain receive sensory input from both ears, presenting sounds to one ear alone has been shown to produce asymmetrical activation with a stronger response from the contralateral hemisphere (Woldorff et al., 1999; Suzuki et al., 2002a). Stimulation of the remaining intact ear following unilateral deafness typically results in a pattern of activation that is more symmetrical between the hemispheres (Popelar et al., 1994; Scheffler et al., 1998; Ponton et al., 2001). Individuals with unilateral deafness provide an ideal opportunity for studying experience-related plasticity in humans because of the large scale neurophysiological changes that can be expected to occur. Although
evidence for such plasticity has been clearly demonstrated in animals, the evidence is much less clear in humans. In particular, the normal pattern of hemispheric asymmetry has not always been found to change and evidence for the time course of events remains sparse and poorly understood. There are likely to be a number of factors that have contributed to this situation. For example methodological issues related to the use of non-invasive techniques that are necessary in the study of humans may be at least partly to blame. Conflicting results have also been attributed to the inter-subject variability caused by differences in the aetiology of deafness between individuals and due to the retrospective design typically used in studies involving humans. It is important to address these issues in order to ascertain the underlying neurophysiological mechanisms, inform future research into the perceptual consequences, and to help identify the potential clinical implications of experience-related plasticity.

The present thesis aims to study experience-related plasticity in adult humans following surgery for the removal of an acoustic neuroma. As a result of this surgery individuals suffer an abrupt and profound unilateral deafness that is similar to experimentally induced deafness in animal models. This offers an opportunity to overcome many of the limitations inherent in the design of previous studies. In particular this patient group offers the unique prospect of obtaining pre-surgical measurements in order to make pre- and post-onset comparisons. They also provide the opportunity for multiple post-onset measures which will reveal the time course of events. Such information is crucial in elucidating the physiological mechanisms that may underlie experience-related plasticity in humans.

A critical review of the literature is provided in Chapter 2. It starts with a brief overview of the central auditory system in order to explain why presenting sounds to one ear results in asymmetrical activation in favour of the contralateral hemisphere. In addition, the existing evidence for changes in this activation pattern following unilateral deafness is discussed. The review focuses on the main theoretical and methodological issues as well as attempting to identify and direct research towards the areas where understanding remains limited. Tables providing a comprehensive list of studies and summarising the findings have been included.

Subsequent chapters detail new work carried out on human participants. The first study, which is described in Chapter 3, addresses issues associated with measuring
contralateral dominance non-invasively using cortical auditory evoked potentials. This technique was then used to study the effects of unilateral deafness on the response of the central auditory system in adult humans (Chapter 4), as well as describing the time course of any changes (Chapter 5). The thesis concludes with Chapter 6, which gives an overview of the findings and provides suggestions for future research.
Chapter 2: Literature Review

2.1 Organisation of the mammalian central nervous system

The mammalian brain is divided into two halves called hemispheres. An observation is that each hemisphere controls the opposite side of the body. For instance a stroke victim with damage in the right hemisphere will typically suffer left-sided paralysis. This can be explained by the anatomical organisation of the brain. Each hemisphere is connected to the other by the Corpus Callosum and at many other places in the brainstem and spinal cord called commissures. A common feature of the organisation of the central nervous system is the decussation or “cross-over” of nerve fibres such that connections to and from one hemisphere innervate the sense organs and muscles on the contralateral side of the body. Whilst no conclusive evidence exists to explain why such a pattern of decussation exists, the most likely reason was initially presented by the Spanish histologist Ramon y Cajal (1898). It is based on the optical constraints of the lens in the eye, upon which the visual system relies. As light passes through the lens the image falling on the retina is both inverted and reversed. Unless addressed this reversal would cause a mismatch between the organism’s visual perception and the physical scene (e.g. objects observed on the left would be perceived as being located to the right and vice versa). Cajal reasoned that the general pattern of decussation of nerve tracts within the central nervous system may stem from initial evolutionary developments in the visual system. Decussation here may have been the most evolutionarily efficient way in which to restore congruence between the neural representation of the visual scene and the outside world itself. Indeed such decussation in the visual system is most apparent in animals without stereoscopic vision (i.e. eyes on opposite sides of the head). The visual field of each eye does not overlap with that of the other and so complete decussation of nerve fibres would be required to restore congruence with the outside world. However in animals with stereoscopic vision a partial (albeit more complicated) pattern of decussation is evident. This more complicated pattern is necessary in order to accurately combine the image of a single object seen in both eyes. It may be that the more generalised decussation of nerve tracts in the central nervous system has since been driven, in evolutionary terms, by the optical constraints in the visual system. For instance motor and sensory information must also cross the midline in order to stimulate the correct muscles and accurately relate other information such as touch to the visual
information, whilst allowing these various inputs to congregate in adjacent areas of the brain. Such a pattern of congregation sets the tone for the subsequent interaction of multiple sensory and motor modalities, culminating in the cortical association areas exhibited in the human central nervous system (Vulliemoz et al., 2005).

2.1.1 Anatomy and physiology of the ascending central auditory system

The anatomy of the central auditory system (CAS) follows this pattern of decussation accordingly. Ascending fibres of the auditory nerve send information from the ear to the ipsilateral cochlear nucleus in the brainstem. The main outflow of information from here crosses the midline and projects, via various sub-cortical nuclei, towards the auditory cortex on the contralateral side of the brain. However, a small proportion of nerve fibres leaving the cochlear nucleus (approximately 30%) do not cross the midline (Moore, 1991; McAlpine et al., 1997). Instead they relay information, again via the various sub-cortical nuclei, towards the auditory cortex on the ipsilateral side of the brain (see Figure 2.1, upper panel). Due to these contralateral and ipsilateral neural pathways, the auditory cortex in each hemisphere receives a complete neural representation of the auditory scene from both ears. However, the proportion of neurons that respond principally to each ear is greater in the auditory cortex on the contralateral hemisphere (Rosenzwieg, 1951).

A key principle in the function of the CAS is that the majority of neurons (at least 80%) exhibit binaural responses i.e. they are influenced by stimulation of either ear (Moore, 1991). For neurons in the ascending pathway the contralateral ear will generally provide the dominant input and this will be excitatory, whereas the ipsilateral ear may provide either excitatory or inhibitory input. Additional lateral connections from the contralateral ear normally inhibit the activity in neurons that respond primarily to stimulation of the ipsilateral ear (see Figure 2.1, upper panel). The overall neural activity therefore depends on the interactions between inputs from each ear and this occurs almost simultaneously at various levels of the auditory pathway. These so-called binaural interactions give rise to abilities such as localisation of sound sources, for example through inter-aural time and level difference cues. Other phenomena such as the masking level difference and the precedence effect also occur as a result of binaural
interactions; these latter two effects being involved in the detection and localisation of signals in noisy or reverberant environments.

2.1.2 Contralateral dominance

Since the majority of afferent activity crosses the midline, stimulation of one ear produces a bilateral but asymmetrical response within the CAS. The greatest activity occurs in the hemisphere contralateral to the ear being stimulated and this effect is termed here as contralateral dominance. Many studies have demonstrated contralateral dominance in the auditory systems of animals using electrophysiological techniques, the majority of which have focused on recording activity from the auditory cortex. Early studies used electrodes that were placed on or near the surface of exposed cortex on one side of the brain in various animal subjects such as dogs, squirrel monkeys and cats. In this way the neural activity evoked from the stimulation of either ear could be compared. The resulting activity was consistently larger in amplitude (with greater amplitudes indicating a greater number of neurons being activated) and/or covered a more extensive area of cortex when sounds were presented to the contralateral ear (e.g. Tunturi, 1946; Gross et al., 1967; Massopust et al., 1968; Musiek, 1986). Nevertheless, when recording from one side of the brain it is not possible to rule out alternative explanations such as differences in sensitivity between the ears. It is also difficult to distinguish any variation in the degree of contralateral dominance according to whether the left or right hemisphere is under investigation. However due to anatomical and functional variations between hemispheres this may often be the case (Firszt et al., 2006). In one famous early study Rosenzweig (1951) compared the cortical representation of each ear in a group of cats. Electrophysiological recordings were made from both hemispheres. The resulting waveforms were categorised according to their latency. Short latency activity was often found to be larger when recorded at the ipsilateral hemisphere relative to stimulation of each ear. However, this is not surprising since the short latencies would suggest the activity originated from peripheral sources such as the auditory nerve that are ipsilateral to the ear of stimulation. On the other hand longer latency activity (greater than 2 ms), whilst present over both hemispheres tended to be larger over the contralateral hemisphere, reflecting the subsequent crossing of the majority of ascending neural projections from the brainstem upwards. This was found to be the case when recording from either hemisphere, although the absolute amplitudes of activity varied according to the precise location of the recording electrodes. Later studies have used implantable electrodes to reduce the need to expose
the cortex (or sub-cortical nuclei) and unlike previously, these have enabled recordings in awakened animals that have recovered from surgery. This approach also avoids any ambiguity that may have arisen previously due to the effects of anaesthesia. Essentially these studies demonstrate converging evidence for contralateral dominance in the auditory system above the level of the cochlear nucleus. In particular this has been demonstrated at the inferior colliculi (Semple and Kitzes, 1985; Popelar et al., 1994), the medial geniculate nuclei (Altman et al., 1970) and at the auditory cortices (Di and Barth, 1993; Popelar et al., 1994).

Many studies have investigated contralateral dominance in adult humans receiving monaural stimulation. Early examples used surface electrodes in order to describe the scalp distribution of prominent compound auditory evoked potentials such as the auditory brainstem response (Levine and McGaffigan, 1983; Phillips and Thornton, 1995) and cortical auditory evoked potentials such as the N1 wave (Vaughan and Ritter, 1970; Wolpaw and Penry, 1977). More recent studies have employed techniques such as source modelling of electro- and magneto-encephalographic (EEG and MEG) derived N1 data, and indirect measures such as functional Magnetic Resonance Imaging (fMRI), all demonstrating qualitatively similar findings of contralateral dominance (Woldorff et al., 1999; Pantev et al., 1998; Hine and Debener, 2007). Nevertheless, some important issues that relate to the measurement of contralateral dominance have emerged that may be specific to humans. These include differences in the apparent degree of contralateral dominance that seem to depend at least partly on the measurement techniques used and on the ear of stimulation (Hine and Debener, 2007). This latter point may be related to evidence indicating functional specialisation within the auditory pathways (Firszt et al., 2006). Functional specialisation refers to the dominance of one hemisphere over the other with regard to a particular function. For example the human ability to understand and produce speech seems to be dependent on specialisation of the left cortical system for processing rapidly changing acoustic stimuli, whereas the right cortical system may be more sensitive to the spectral content of the stimuli (Zatorre et al., 2002). Further, these functional specialisations are associated with structural asymmetries in the supratemporal plane on a gross and micro-anatomical level, with asymmetries suggested in cortical and subcortical structures including at the level of the cochlea (Firszt et al., 2006; Devlin et al., 2003). Other issues such as the effects of stimulus level and frequency on the degree of contralateral dominance in humans are as yet unclear, although there are reasons to suspect that both
of these stimulus parameters could have an effect on the degree of measured contralateral dominance. However, it is clear that the degree of contralateral dominance measured in humans following monaural stimulation does not necessarily solely reflect anatomical asymmetries between the auditory pathways in each hemisphere (Schonwiesner et al., 2007). Consequently this may impact on the interpretation of any effects of experience-related plasticity in humans following unilateral deafness, and therefore warrants careful consideration. All of these issues will be discussed in more detail in Chapter 3.

2.2 Experience-related plasticity

Experience-related plasticity refers to changes in the response of neurons or the pattern of nervous system activity following altered sensory or motor input (Kleim and Jones, 2008). An essential feature of the central nervous system is the ability to reorganise through experience driven processes. These processes may be functional in which case the strengths of existing synapses are modified, or they may be anatomical, in which case the neuronal projections and/or the population of synapses changes. In either case the effect of experience-related plasticity is that the activity of the nervous system is altered to reflect the relative importance of the altered input. Traditionally this ability has been considered strongest in the developmental period during which time normal functions must first be learned and then maintained despite growth. For instance in the CAS the inter-aural difference cues must be correctly associated with a sound location for normal localisation abilities to be retained, despite these cues continually changing as the head grows (Moore and King, 2004).

Changes in input that occur beyond the developmental period, either as a result of training or following injury, can also induce experience-related plasticity in the central nervous system. It is this continued ability to reorganise into adulthood that has captured intense clinical interest and which motivates the current research, since the nature and effects of plasticity in the mature CAS are likely to be of key importance in rehabilitation strategies after injury or following intervention (Kleim and Jones, 2008).

Within the CAS, any changes in the response following acquired hearing loss can be addressed in two broad areas. The first area concerns characterising the precise nature of experience-related plasticity and the subsequent effects on auditory functionality. The
second concerns what further changes (and associated perceptual outcomes) are likely following the introduction of new auditory experience. This is important for guiding attempts to correct for any deficit in humans, and may be achieved through the introduction of a hearing aid or cochlear implant, or via other rehabilitative interventions such as auditory training exercises (Purdy, 2001; Irvine et al., 2001).

It is the first of these areas that is of present concern with regard to unilateral deafness in adult humans, since the evidence for any subsequent changes in the CAS remains unclear. Consideration will be given to the basic principles of experience-related plasticity, to the evidence from animal models of unilateral deafness and to the evidence gathered from humans with unilateral deafness.

2.2.1 Principles of experience-related plasticity following unilateral deafness

Experience-related plasticity appears to depend on several basic principles that are discussed in detail by Kleim and Jones (2008). Perhaps the most important is the so-called ‘use it or lose it’ principle. This describes how neural connections that are not actively involved in a task will eventually degrade. Essentially it is this principle that was first demonstrated in the visual deprivation experiments by Hubel and Wiesel (1963), and later in the other modalities such as the somatosensory system (Merzenich et al., 1984). A related principle is the strengthening of neural connections when their activity is temporally correlated (Hebb, 1949). Studies of cortical representational plasticity demonstrate that the outcome of sensory deafferentation is for the corresponding area of cortex to become responsive to the remaining, intact sensory input (Gilbert and Wiesel, 1992; Rajan et al., 1993; Robertson and Irvine, 1989; Merzenich et al., 1984). This is thought to be a result, at least initially, of the unmasking of afferent connections from adjacent sensory input (Buonomano and Merzenich, 1998). Unmasking refers to an immediate release from suppression of neural activity following the removal of inhibitory effects (and/or increase in the gain of existing synapses). Due to this unmasking, subsequent activity between intact sensory input and the area of cortex deprived of its normal input becomes increasingly more temporally correlated. This leads to increased responsiveness in the deprived cortex to the intact sensory input, effectively altering the cortical representation accordingly (Buonomano and Merzenich, 1998). Since unmasking constitutes a functional change in the way neurons respond, it
presumably occurs immediately following the onset of sensory deafferentation. However, much evidence relating to experience-related plasticity supports a model with multiple physiological mechanisms in addition to unmasking, since changes may continue over a wide time frame of weeks, months or even years. These mechanisms may include modifications in the efficacy of existing synapses, growth of new synapses at the existing axon terminals and intra-cortical axon sprouting, all occurring subsequently to unmasking (McAlpine et al., 1997). Since these mechanisms constitute physiological and anatomical changes in connectivity between neurons it is generally assumed that they will take a longer period of time than unmasking (Moore et al., 1997).

In the case of unilateral deafness, given the binaural interactions discussed in the previous section it follows that the loss of afferent input from one ear would lead to a prolonged imbalance in the input to binaurally sensitive neurons. That is, whereas previously the activity of these neurons was governed by input from both ears, subsequently they receive input from only one. This would be expected to drive physiological changes in the CAS based on the principles described above. The basic effects of any such changes should be an increased responsiveness of neurons to stimulation of the intact ear. However, when observing the activity in each hemisphere of the brain separately, this effect should be more apparent on the side opposite to the deafened ear by virtue of the contralateral dominance; there are a greater number of deafferented neurons on this side.

When this principle is considered from the perspective of the intact ear any experience-related changes will lead to an alteration in the normally observed pattern of contralateral dominance. Stimulation of the intact ear will activate neurons on the ipsilateral hemisphere to a greater extent than before, reducing contralateral dominance (Mossop et al., 2000; McAlpine et al., 1997; see also section 2.2.2). Consequently, experience-related plasticity following unilateral deafness can be studied through observation of changes in levels of activity and patterns of contralateral dominance upon stimulation of the intact ear. These changes are outlined in the schematic shown in Figure 2.1.
Figure 2.1 Upper Panel: Schematic showing contralateral and ipsilateral ascending pathways from the left cochlea (blue arrows) and the right cochlea (red arrows). The thick arrows denote the stronger influence of the respective ears on the ascending pathways. Black arrows represent lateral inhibitory effects of each ear on the other. The colours in each CAS nuclei represent the proportion of neurons primarily responsive to left ear (blue) or right ear (red).

Lower Panel: Following unilateral deafness on the right side, increased responsiveness of central auditory system neurons to input from the left ear will occur, resulting in no contralateral dominance (McAlpine et al., 1997).
2.2.2 Evidence from animal models of unilateral deafness

The effects of unilateral deafness on the responsiveness of the CAS have been extensively studied in animals. Table 2.1 displays a summary of the key studies in this area. In animal models unilateral deafness is usually introduced experimentally via cochlear ablation techniques. Typically performed either surgically or pharmacologically with ototoxic chemicals, such techniques allow fine control of the afferent activity originating from the affected ear since deafness will be abrupt, reliable and complete. On the other hand each technique has its drawbacks. For instance high doses of ototoxic chemicals are often needed to achieve total deafness pharmacologically. These high doses may result in side effects involving the structures or functions of interest (Kral et al., 2006). Mechanical destruction involves extensive invasive surgery although unlike pharmacologically induced deafness it guarantees total deafness.

Initial investigations concentrated on the effect of unilateral deafening induced in the developmental period. Profound changes have been found to occur throughout the CAS following neonatal unilateral deafness compared with normally hearing controls. These changes consist of neural degeneration of first order neurons and afferent projections from the cochlear nucleus on the side of the deafened ear, and an increase in the response of neurons higher up the auditory pathway to stimulation of the intact ear. For example Nordeen et al. (1983) and Kitzes (1984) both reported increases in the number of ipsilaterally excited neurons in gerbils raised with neonatal unilateral deafness after stimulation of the intact ear. Multi-unit and single-unit electrophysiological recordings were made from the ipsilateral inferior colliculus in the brainstem. Compared to binaurally hearing control animals, those with unilateral deafness exhibited neural response thresholds, activity patterns and the proportion of responsive neurons resembling that normally seen on the contralateral side. Similar findings have been reported at other regions of the auditory system (e.g. auditory cortex) and in various species such as ferrets and cats (Reale et al., 1987; Moore et al., 1993; Kitzes and Semple, 1985). In particular, Reale et al. (1987) investigated experience-related plasticity in the auditory cortex of cats who underwent unilateral cochlear ablation as neonates. In controls, the thresholds of neurons in the contralateral hemisphere were significantly lower than those in the ipsilateral hemisphere, with the neural representation of each ear covering a more extensive area of the cortex in the
contralateral hemisphere. However, in the cats with unilateral deafness the response thresholds in the hemisphere ipsilateral to the intact ear were as low as those in the contralateral side, and an expansion in the neural representation over the ipsilateral hemisphere was observed.

Despite these results, initial investigations on the function of the CAS when unilateral deafness occurs after the developmental period did not show such striking changes. For example Nordeen et al. (1983) investigated functional activity in the inferior colliculus in a group of seven gerbils who underwent unilateral cochlear ablation in adulthood. Stimulation of the intact ear did not reveal any marked increase in the number of ipsilateral neural responses compared to control animals, even when recordings were made several months after the onset of deafness. Secondly, although following neonatal cochlear ablation the cochlear nucleus on the affected side (and its afferent projections) was found to undergo substantial degeneration, the same extensive degenerative changes were not seen after ablation in adulthood. One consideration was that the degenerative changes reported after neonatal cochlear ablation may be essential in leading to the observed functional changes in higher levels of the afferent pathway such as the inferior colliculus (Kitzes, 1984), and at the cortex (Reale et al., 1987). If so, then the lack of such severe degenerative changes in first order neurons in adults with unilateral deafness may therefore have been responsible for the lack of any clear functional changes higher up the auditory pathway (e.g. through continued trophic support of these structures via the neurons of the cochlear nucleus).

Moore and Kitzes (1986) investigated this hypothesis further. Electrophysiological responses were again recorded from the inferior colliculus ipsilateral to stimulation of the intact ear of a group of adult gerbils. However, rather than undergoing unilateral cochlear ablation, these animals received unilateral lesioning of the cochlear nucleus instead. The aim was to introduce complete unilateral deafness whilst simultaneously ensuring removal of any trophic support to the inferior colliculus. The study involved two experimental groups. The first group underwent unilateral deafening and subsequent recording of inferior colliculus activity on the same day whereas the recordings from the second group were made several months after deafening. However, once again the results did not reveal the same widespread functional changes in CAS activity as followed neonatal ablation of the cochlea. Both the neural response thresholds and the proportion of neurons excited by stimulation of the intact ear were
not noticeably different from controls. Only the maximum discharge level (the sound level at which the neuron produces the most activity) showed signs of functional changes following unilateral deafness; it was higher than controls in the first group but not in the second. Although this latter finding may suggest unmasking following unilateral deafness, overall these results do not indicate substantial experience-related plasticity when deafness occurs in adulthood. On the other hand, at least the study demonstrated that any changes are not contingent on the neural degeneration of preceding nuclei of the auditory pathway. This suggests that any experience-related plasticity noted following injury may be attributed solely to changes in sensory input.

In another study Reale et al. (1987) investigated the responsiveness of neurons in the auditory cortex of two cats who underwent unilateral cochlear ablation in adulthood. Prior to the onset of unilateral deafness, when binaural input was still present electrophysiological analysis of the left hemisphere demonstrated contralateral dominance of activity characteristic of a normal CAS i.e. a greater proportion of neurons responded to stimulation of the right ear compared with the left. The right cochlea was then ablated and within 24 hours the responsiveness of the left cortex was re-checked via stimulation of the intact left ear. One cat showed virtually no change in cortical activity i.e. there was no evidence for increased responsiveness in the ipsilateral hemisphere to stimulation of the intact ear. However, in the other cat an increase was found, with the proportion of responsive neurons in the ipsilateral hemisphere rising from 22% prior to ablation to 67% afterwards. Although interpretation of results based on only two cats will inevitably be cautious, the findings from the second cat represent preliminary evidence for experience-related plasticity in the mature CAS. The results may also help to shed light on the reasons why the previous studies did not show any effects of unilateral deafness in adult animals. The earlier studies were based on a between-subjects design. It may be that such a design is sufficiently sensitive to demonstrate profound changes following neonatal unilateral deafness but not when changes are potentially less marked. However this may be the case following the onset of deafness in adulthood. On the other hand the study by Reale et al. (1987) was of a within-subjects design and therefore susceptible to fewer sources of error (e.g. through anatomical variation between individuals). Furthermore, the degree of contralateral dominance may be larger in the auditory cortex than in brainstem nuclei (Popelar et al., 1994). Presumably any changes in activity would consequently be easier to detect at the cortex (at least with regard to multi-unit or far-field recording). Whilst the earlier
studies described above concentrated on the brainstem nuclei, Reale et al. (1987) investigated the response of the auditory cortex.

More recent studies concerned with the functionality of the mature CAS following unilateral deafness have adopted a within-subjects design. For example Popelar et al. (1994) aimed to evaluate the effect of unilateral deafness in the CAS of adult guinea pigs. Two groups of guinea pigs were used. In the first group far-field electrophysiological responses were recorded from the auditory cortex over each hemisphere. Activity in response to monaural stimulation was recorded prior and subsequent to unilateral cochlear ablation. In the second group far-field responses were measured from the inferior colliculus instead of the cortex. Another feature of the study was that responses were checked several times over a period of three weeks after the onset of unilateral deafness in order to plot the time course of any changes. The results from the first condition (prior to unilateral deafness) revealed normal CAS activation with characteristic contralateral dominance. Monaural stimulation produced bilateral activity in both the cortex and inferior colliculus, with the activation thresholds on the contralateral side being significantly lower than the ipsilateral side. The difference in thresholds between the contralateral and ipsilateral hemispheres was typically around 20 dB at the cortex and around 4 dB in the inferior colliculus. The differences also varied according to frequency; they were often greater for high frequency stimulation (i.e. above 1 kHz) compared to lower frequencies. Following pharmacologically induced unilateral deafness this pattern of activation changed markedly. Within one day the thresholds in the hemisphere ipsilateral to the intact ear started to decrease in all the guinea pigs. Although initial changes were seen within hours they persisted for several weeks, after which there was almost no difference in thresholds between the two hemispheres. This occurred more rapidly at the cortex than the inferior colliculus, and was proportional across frequencies. In addition to response thresholds the suprathreshold activity, evaluated in terms of response amplitude and latency, was also studied in a subgroup of animals. Once again, the pattern of activity prior to the onset of deafness was characteristic of normally observed contralateral dominance; response amplitudes were greater and latencies shorter over the hemisphere contralateral to the stimulated ear both at the cortex and inferior colliculus. However, following unilateral deafness the response amplitudes increased and latencies decreased in the ipsilateral hemisphere, whilst the contralateral hemisphere responses remained unchanged. These changes were found to occur primarily within the first seven days but persisted over at
least three weeks. The present results therefore support the preliminary findings in adult animals previously reported by Reale et al. (1987). They demonstrate a qualitatively similar pattern of changes in activity within the mature CAS following unilateral deafness as occurs in the developmental period; namely increased ipsilateral excitation causing a reduced degree of contralateral dominance with stimulation of the intact ear. Meanwhile the general stability seen in the responses of neurons in the pathway contralateral to the healthy ear might be due to the removal of the weaker input from the ablated ear having a smaller, less significant effect and/or the activity in that pathway already operating at close to maximum levels.

These changes are a form of representational plasticity that has been described previously (e.g. Buonomano and Merzenich, 1998). The commonly cited example of this representational plasticity in the auditory system is the effect of restricted cochlear lesioning (i.e. introducing cochlear dead regions). This leads to an expansion of the neural representation of adjacent intact epithelia (Robertson and Irvine, 1989). Introducing unilateral deafness is effectively an unrestricted cochlear lesion. However, there is an important distinction between the two types. Following restricted lesioning the characteristic frequencies of the deafferented neurons shift to different frequencies (those of the adjacent, intact input). Following complete unilateral deafness the characteristic frequencies of neurons are not expected to change, only their responsiveness to the unaffected ear. Put another way, in terms of frequency representation in the first case neurons in the cortex begin to perform a different role whereas in the latter case the neurons perform the same role differently. Rajan et al. (1993) reported that while partial unilateral lesioning lead to expansion in neural representation of the intact sensory input on stimulation of the affected ear this was not apparent following stimulation of the opposite, intact ear where normal responses were preserved. Based on the findings by Popelar et al. (1994) it seems that in the absence of any input from the affected side, a subsequent increase in responsiveness to the intact ear can be expected to occur instead. The other key finding from the study by Popelar et al. (1994) was the period of time over which changes in activity were observed (i.e. from one day to at least three weeks). This finding supports a model for multiple physiological mechanisms mediating experience-related plasticity. However, it is difficult to draw firm conclusions as to what these mechanisms may be, based on these results alone. Some mechanisms (as described in the previous section e.g. unmasking) would be expected take hold almost immediately following the onset of deafness and
result in dramatic changes. Others (e.g. modification of existing synapses) may occur gradually over a period of days or longer (Moore et al., 1997). Although the results from a small subgroup of animals studied by Popelar et al. (1994) were made within six hours, most responses were first evaluated over subsequent days following onset of deafness so it is not clear how quickly the observed changes would be expected to take place. Secondly, although most animals were tested for several weeks after the onset of deafness, it also is not clear how long the changes might have persisted beyond this period. Other studies have described changes in neural responses that continued for months or even years after cochlear removal (e.g. Moore et al., 1993), a timescale which is suggestive of anatomical mechanisms of plasticity such as axon sprouting.

The time course of experience-related plasticity following the onset of unilateral deafness was explored further in a series of related studies by McAlpine et al. (1997), Moore et al. (1997) and Mossop et al. (2000). McAlpine et al. (1997) concentrated on the response of the inferior colliculus in ferrets who underwent surgical ablation of the right cochlea in adulthood. This complex study involved two groups; the first were studied using single- and multi-unit electrophysiology immediately after the onset of unilateral deafness. The second were studied three months later. A third, binaural hearing group acted as controls. A range of neural activity measures were carried out including the proportion of neurons responding overall, single-unit discharge patterns, spontaneous activity, response thresholds and maximum discharge rate. Control animals demonstrated a normal pattern of contralateral dominance. For example, a greater proportion of neurons responded in the contralateral hemisphere (94%) compared with the ipsilateral hemisphere (33%) with monaural stimulation. However, after the onset of unilateral deafness, the proportion of excitable ipsilateral neurons increased to 70% in animals studied immediately after surgery and to 92% in those studied three months after surgery. Meanwhile, little or no change was observed in the contralateral hemisphere. Thus, unilateral deafness produced a rapid (within hours) reduction in normally observed contralateral dominance in the brainstem. Similar results were obtained in the ferret auditory cortex (Moore et al., 1997) thereby providing evidence from single-unit data at various levels of the auditory system that is in agreement with the far-field recordings made by Popelar et al. (1994). Once again concentrating on the inferior colliculus, Mossop et al. (2000) aimed to further narrow the time window in which alterations in neural activity first become apparent. A single group of adult ferrets were studied via multi-unit recordings from within the right inferior colliculus to
monaural stimulation. With the recording electrode in-situ the left cochlea was surgically ablated whilst stimulation to the remaining right ear continued. A second group of adult ferrets underwent unilateral cochlear ablation before their inferior colliculi were preserved (by freezing) for later histological examination. Preservation was carried out within hours, days or a year after the onset of deafness. The purpose was to analyse chemical markers for inhibitory neurotransmitter production, hence giving insight into the modification of existing synaptic efficacy. The electrophysiological results demonstrated a dramatic increase in the proportion of excitable neurons ipsilateral to the intact ear within minutes of unilateral deafness. The proportion of excitable neurons increased from around 40% prior to deafness, to between 80% and 90% afterwards. Such a short onset is indicative of unmasking of ipsilateral responses from inhibition previously imposed by the ablated ear. The histological results demonstrated a reduction in inhibitory neurotransmitter substances several days after the onset of unilateral deafness. However they had returned to normal control levels after one year. The range of time over which changes have been seen in these studies, from minutes to days and up to a year, is indicative of some degree of interplay between the possible mechanisms mentioned in the previous section. The evidence supports the emerging concept of multiple substrates and mechanisms explaining the extensive changes seen after injury to sensory input. This concept primarily takes a bottom-up stance. Since sensory information is transmitted from the periphery to the cortex (via sub-cortical nuclei) then peripheral injury will lead to a cascade of widespread functional and structural changes in the CAS, culminating in reorganisation at the cortex that reflects global concurrent changes throughout at least the ascending segment of the neural pathway. Initial changes are known to arise rapidly in the form of alteration of the balance of excitatory and inhibitory responses. A long term imbalance drives any subsequent physiological and ultimately anatomical changes through both the degeneration of sensory axons and their synapses not involved in a task and regeneration / sprouting of new synapses favouring the remaining sensory input (Wall et al., 2002).
Table 2.1 Examples of studies investigating the effect of unilateral deafness on the CAS response in animal models

<table>
<thead>
<tr>
<th>Reference</th>
<th>Design</th>
<th>Species</th>
<th>Recording Location</th>
<th>Result</th>
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<tbody>
<tr>
<td>Kitzes (1984)</td>
<td>Unilateral cochlear ablation</td>
<td>Gerbil</td>
<td>Inferior Colliculus</td>
<td>Increased ipsilateral response</td>
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<td></td>
<td>Induced in neonatal period</td>
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<td>Single-unit recording</td>
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<tr>
<td>Kitzes and Semple (1985)</td>
<td>Unilateral cochlear ablation</td>
<td>Gerbil</td>
<td>Inferior Colliculus</td>
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<td>Single-unit recording</td>
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<tr>
<td>McAlpine et al. (1997)</td>
<td>Unilateral cochlear ablation</td>
<td>Ferret</td>
<td>Inferior Colliculus</td>
<td>Increased ipsilateral response</td>
</tr>
<tr>
<td></td>
<td>Induced in adulthood</td>
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<td>Single + multi-unit recording</td>
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</tr>
<tr>
<td>Moore and Kitzes (1986)</td>
<td>Unilateral Cochlear Nucleus lesion</td>
<td>Gerbil</td>
<td>Inferior Colliculus</td>
<td>Increased ipsilateral response</td>
</tr>
<tr>
<td></td>
<td>Induced in neonatal period</td>
<td></td>
<td>Single-unit recording</td>
<td></td>
</tr>
<tr>
<td>Moore et al. (1993)</td>
<td>Unilateral cochlear ablation</td>
<td>Gerbil</td>
<td>Inferior Colliculus</td>
<td>Increased ipsilateral response</td>
</tr>
<tr>
<td></td>
<td>Induced in neonatal period</td>
<td></td>
<td>Single-unit recording</td>
<td></td>
</tr>
<tr>
<td>Moore et al. (1997)</td>
<td>Unilateral cochlear ablation</td>
<td>Ferret</td>
<td>Auditory Cortex</td>
<td>Increased ipsilateral response</td>
</tr>
<tr>
<td></td>
<td>Induced in adulthood</td>
<td></td>
<td>Single + multi-unit recording</td>
<td></td>
</tr>
<tr>
<td>Reference</td>
<td>Design</td>
<td>Species</td>
<td>Recording Location</td>
<td>Result</td>
</tr>
<tr>
<td>------------</td>
<td>--------------------------------------------</td>
<td>----------</td>
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<td>----------------------------------------------------------------------</td>
</tr>
</tbody>
</table>
| Mossop et al. (2000) | Unilateral cochlear ablation  
Induced in adulthood | Gerbil   | Inferior Colliculus  
Single + multi-unit recording | Increased ipsilateral response                                      |
| Nordeen et al. (1983) | Unilateral cochlear ablation  
Induced in neonatal period, and a separate group in adulthood | Gerbil   | Inferior Colliculus  
Single-unit recording | Increased ipsilateral response in animals with deafness induced as neonates but not as adults. |
| Popelar et al. (1994) | Unilateral cochlear ablation  
Induced in adulthood | Guinea Pig | Inferior Colliculus and Auditory Cortex  
Far-field recording | Increased ipsilateral response                                      |
| Reale et al. (1987) | Unilateral cochlear ablation  
Induced in neonatal period, and a separate group in adulthood | Cat      | Auditory Cortex  
Single-unit recording | Increased ipsilateral response in animals with deafness induced as neonates. Preliminary findings of plasticity in one adult cat. |
2.2.3 Evidence of experience-related plasticity in adult humans with late onset unilateral deafness

An increasingly substantial body of research has focused on unilateral deafness as a means for investigating physiological changes in the human CAS. This is summarised in Table 2.2. Some key questions that have been addressed so far, but with varying degrees of success are:

1. what evidence exists for experience-related plasticity in humans with unilateral deafness?
2. is the evidence consistent with predictions based on findings with animal models?
3. what is the time course of events?
4. what are the perceptual consequences of such experience-related plasticity?

Most experiments involving human participants have focused on activity arising from the auditory cortex. They generally mirror the experimental designs that are used in animal studies i.e. measuring the strength of activation in each hemisphere to stimulation of the healthy ear in individuals with unilateral deafness. The key differences are first the use of non-invasive measurement techniques and the associated technical challenges that each one brings. Secondly, unilateral deafness in humans will not be experimentally induced via cochlear ablation as in studies involving animal models. Instead it could be due to various causes such as injury, infection or following surgery. It may therefore vary in severity, speed of onset and site of lesion. As a result, studies involving humans are often less well controlled than those on animal models and careful consideration of these differences on the pattern of results is important. To relate the findings from non-invasive measurements in humans to electrophysiological measurements in animals, where near-field and intra-cellular recordings provide detailed information on firing patterns of neurons combined with fine spatial resolution, consideration of the basic information provided by each technique is necessary.

Functional Magnetic Resonance Imaging (fMRI) provides an indirect measure of neural activity. It is based on the blood-oxygen-level-dependent (BOLD) signal, where changes in the amount of oxygenated blood due to the increased metabolic demands of the active neurons causes a localised change in the MRI signal. The BOLD signal is an
indirect measure of the gross neural activity, comprising excitatory and inhibitory synaptic activity as well as neural spiking activity (Arthurs and Boniface, 2002). Temporal resolution is limited by the slow time course of the haemodynamic changes and is of the order of several seconds. However, the high spatial resolution offered by fMRI is particularly useful in differentiating activity arising from each hemisphere, and in more recent studies, sub-regions of the auditory cortex in each hemisphere. Results are usually given in terms of either the volume of activation or the level of activation. When given in volume this refers to the number of voxels (the minimum units of volume) in each hemisphere that are considered active (i.e. when the BOLD signal exceeds a certain threshold) normalised to the total number of voxels in the region of interest. Level of activation usually refers to the average BOLD signal change (i.e. the magnitude of activity). The level of activation may be better suited to describing hemisphere lateralisation since merely comparing the extent of activity in each hemisphere could lead to errors, for instance due to differences in the volume of each hemisphere.

On the other hand electroencephalography (EEG) and magnetoencephalography (MEG) allow direct measures of neural activity. Whereas EEG signals reflect the electrical potentials, the MEG signal reflects the magnetic field activity that is associated with the current flow arising from neural activity. These techniques offer high temporal resolution, with the timing of activity described on a millisecond scale. Increased strength of activity is characterised by larger amplitudes and shorter latencies of evoked responses which reflects involvement of more synchronously firing neurons. However, because the recordings are far-field in nature the output is influenced by several factors other than neural activity. These include the degree of synchrony of neural activity and the orientation of active neural populations with respect both to each other and to the sensors located on (or near) the scalp. In addition, the inability to differentiate specific anatomical structures makes it difficult to know the exact areas of the brain that are involved. Studies that have investigated the effect of unilateral deafness using these techniques have typically focused on the N1 wave of the human auditory evoked response (or the magnetic homolog, N1m). This is a prominent component with a latency of around 100 ms and it consists of at least three sources in each hemisphere. It is thought to reflect the sum of neural activity arising from the auditory cortex on the supra-temporal plane (Naatanen and Picton, 1987). Specific interest in the N1 wave derives from its potential use as a clinical tool to monitor changes associated with
auditory rehabilitation of hearing impaired individuals (Purdy, 2001). It is also relatively easy and inexpensive to measure, reflects cortical neural activity to a wide range of stimulus types and shows close association with CAS maturation (Ponton et al., 2000) and perceptual performance, for example with speech perception (Rance et al., 2002). Furthermore it is strongly associated with the plastic behaviour of neurons following new auditory experience or training (Ponton et al., 2001; Tremblay et al., 2001).

With respect to the first two key questions posed in the previous section (i.e. what evidence exists for plasticity in humans with unilateral deafness and is the evidence consistent with predictions from animal models?), despite the number of studies noted in Table 2.2, a surprisingly small proportion have clearly demonstrated plasticity in the human CAS with stimulation of the remaining, intact ear. However, close inspection of Table 2.2 reveals that generally the most consistent findings have been reported in studies that used fMRI.

Scheffler et al. (1998) were the first to report on the effects of unilateral deafness in humans using fMRI. Activity was measured from the cortex in each hemisphere in response to a sequence of pulsed 1 kHz tones presented at 95 dB SPL. The results for stimuli presented to the intact ear of five adult individuals with unilateral deafness were compared with a control group of 10 normally hearing listeners. The causes of the unilateral deafness varied considerably; of the five participants two had congenital and three acquired deafness either as a result of infection, surgery or idiopathic causes. The duration of deafness also varied, ranging from a matter of weeks to several years. In addition, two participants had left ear deafness and three had right ear deafness. Despite these variations, a clear difference in the pattern of CAS activity between the experimental participants and controls was observed. Monaural stimulation of either ear in controls produced the normal pattern of contralateral dominance i.e. activity in both hemispheres with a greater volume of activation in the contralateral hemisphere. On a group basis, the activation volumes were, on average, 70-80% greater in the contralateral hemisphere for left and right ear stimulation. However the responses from the unilaterally deafened listeners showed a much reduced contralateral dominance of around 20%.
Table 2.2 Examples of studies investigating the effect of unilateral deafness on the CAS response in humans

<table>
<thead>
<tr>
<th>Name</th>
<th>Design</th>
<th>Participants</th>
<th>Stimuli</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilecen et al. (2000)</td>
<td>fMRI</td>
<td>1 (right)</td>
<td>1 kHz tone bursts 95 dB SPL</td>
<td>Gradual increase in ipsilateral activity resulting in reduced contralateral dominance</td>
</tr>
<tr>
<td></td>
<td>Longitudinal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Firszt et al. (2006)</td>
<td>fMRI</td>
<td>7 (left)</td>
<td>/ba/ speech token 80 dB HL</td>
<td>Increase in ipsilateral and decrease contralateral activity resulting in reduced contralateral dominance</td>
</tr>
<tr>
<td></td>
<td>Retrospective</td>
<td>9 controls</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fujiki et al. (1998)</td>
<td>MEG</td>
<td>17 (3 right / 14 left)</td>
<td>1 kHz tone bursts &amp; /a/ speech token 80 dB HL</td>
<td>No clear evidence of plasticity</td>
</tr>
<tr>
<td></td>
<td>Retrospective</td>
<td>14 controls</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hanss et al. (2009)</td>
<td>EEG</td>
<td>18 (10 right / 8 left)</td>
<td>1 kHz tone bursts and /pa/ speech token 50 dB SL</td>
<td>No clear evidence of plasticity</td>
</tr>
<tr>
<td></td>
<td>Retrospective</td>
<td>16 controls</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hine et al. (2008)</td>
<td>EEG</td>
<td>6 (2 right / 4 left)</td>
<td>1 kHz tone bursts/ BBN noise 60 dB SL</td>
<td>No clear evidence of plasticity</td>
</tr>
<tr>
<td></td>
<td>Retrospective</td>
<td>6 audiogram matched controls</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Name</td>
<td>Design</td>
<td>Participants</td>
<td>Stimuli</td>
<td>Result</td>
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<tr>
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</tr>
<tr>
<td>Khosla et al. (2003)</td>
<td>EEG</td>
<td>19 (10 right / 9 left)</td>
<td>Click train</td>
<td>Increase in ipsilateral activity resulting in reduced contralateral dominance. However, only observed in individuals with left ear deafness</td>
</tr>
<tr>
<td></td>
<td>Retrospective</td>
<td>8 controls</td>
<td>70 dB nHL</td>
<td></td>
</tr>
<tr>
<td>Langers et al. (2005)</td>
<td>fMRI</td>
<td>5 (1 right / 4 left)</td>
<td>BBN</td>
<td>Increase in ipsilateral and decrease contralateral activity resulting in reduced contralateral dominance</td>
</tr>
<tr>
<td></td>
<td>Retrospective</td>
<td>8 controls</td>
<td>0, 40, 70 dB SL</td>
<td></td>
</tr>
<tr>
<td>Po-Hung Li et al. (2003)</td>
<td>MEG</td>
<td>9 (4 right / 5 left)</td>
<td>1 kHz tone burst</td>
<td>Apparent unmasking of ipsilateral excitability shortly after idiopathic unilateral hearing loss which was reversed upon recovery of hearing function</td>
</tr>
<tr>
<td></td>
<td>Retrospective</td>
<td>70 dB SPL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Li et al. (2006)</td>
<td>MEG</td>
<td>16 (8 right / 8 left)</td>
<td>1 kHz tone bursts</td>
<td>Apparent unmasking of ipsilateral excitability shortly after idiopathic unilateral hearing loss which was reversed upon recovery of hearing function</td>
</tr>
<tr>
<td></td>
<td>Retrospective</td>
<td>16 controls</td>
<td>70 dB SPL</td>
<td></td>
</tr>
<tr>
<td>Name</td>
<td>Design</td>
<td>Participants</td>
<td>Stimuli</td>
<td>Result</td>
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<tr>
<td>Moore et al. (2005)</td>
<td>fMRI</td>
<td>11 (6 right / 5 left)</td>
<td>4-kHz / 0.25 kHz</td>
<td>No clear evidence of plasticity</td>
</tr>
<tr>
<td></td>
<td>Retrospective</td>
<td>12 controls</td>
<td>90 dB SPL</td>
<td></td>
</tr>
<tr>
<td>Morita et al. (2007)</td>
<td>MEG</td>
<td>2 (1 right / 1 left)</td>
<td>1 kHz tone bursts</td>
<td>Apparent unmasking of ipsilateral excitability shortly after idiopathic unilateral hearing loss which was reversed upon recovery of hearing function</td>
</tr>
<tr>
<td></td>
<td>Retrospective</td>
<td></td>
<td>40, 50, 60, 70 dB HL</td>
<td></td>
</tr>
<tr>
<td>Ponton et al. (2001)</td>
<td>EEG</td>
<td>15 (7 right / 8 left)</td>
<td>Click train</td>
<td>Increase in ipsilateral activity resulting in reduced contralateral dominance</td>
</tr>
<tr>
<td></td>
<td>Retrospective</td>
<td>9 controls</td>
<td>65 dB SL</td>
<td></td>
</tr>
<tr>
<td>Scheffler et al. (1998)</td>
<td>fMRI</td>
<td>5 (2 right/ 3 left)</td>
<td>1 kHz tone bursts</td>
<td>Increased symmetry between hemispheres in participants with unilateral deafness</td>
</tr>
<tr>
<td></td>
<td>Retrospective</td>
<td>10 controls</td>
<td>95 dB SPL</td>
<td></td>
</tr>
<tr>
<td>Suzuki et al. (2002b)</td>
<td>fMRI</td>
<td>11 (right)</td>
<td>Monosyllable speech tokens</td>
<td>Apparent unmasking of ipsilateral excitability shortly after idiopathic unilateral hearing loss which was reversed upon recovery of hearing function</td>
</tr>
<tr>
<td></td>
<td>Retrospective</td>
<td>10 controls</td>
<td>95 dB SPL</td>
<td></td>
</tr>
<tr>
<td>Name</td>
<td>Design</td>
<td>Participants</td>
<td>Stimuli</td>
<td>Result</td>
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<tr>
<td>Vasama et al. (1994)</td>
<td>MEG</td>
<td>6 (4 right / 2 left)</td>
<td>1 kHz tone bursts</td>
<td>Participants had a unilateral conductive hearing disorder. No clear evidence of plasticity.</td>
</tr>
<tr>
<td></td>
<td>Retrospective</td>
<td>9 controls</td>
<td>50 and 70 dB HL</td>
<td></td>
</tr>
<tr>
<td>Vasama and Makela (1997)</td>
<td>MEG</td>
<td>5 (3 right / 2 left)</td>
<td>1 kHz tone bursts</td>
<td>Participants had unilateral deafness from early childhood. No clear evidence of plasticity</td>
</tr>
<tr>
<td></td>
<td>Retrospective</td>
<td>5 controls</td>
<td>80 dB SPL</td>
<td></td>
</tr>
<tr>
<td>Vasama and Makela (1995)</td>
<td>MEG</td>
<td>8 (4 right / 4 left)</td>
<td>1 kHz tone bursts</td>
<td>No clear evidence of plasticity</td>
</tr>
<tr>
<td></td>
<td>Retrospective</td>
<td>8 controls</td>
<td>60 dB HL</td>
<td></td>
</tr>
<tr>
<td>Vasama et al. (1995)</td>
<td>MEG</td>
<td>9 (5 right / 4 left)</td>
<td>1 kHz tone bursts</td>
<td>No clear evidence of plasticity</td>
</tr>
<tr>
<td></td>
<td>Retrospective</td>
<td>9 controls</td>
<td>60 dB HL</td>
<td></td>
</tr>
<tr>
<td>Vasama et al. (2001)</td>
<td>MEG</td>
<td>7 (side unspecified)</td>
<td>1 kHz tone bursts</td>
<td>No clear evidence of plasticity</td>
</tr>
<tr>
<td></td>
<td>Longitudinal</td>
<td>10 controls</td>
<td>80 dB SPL</td>
<td></td>
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</tbody>
</table>
These results are important as they provide a clear demonstration of the ability of the human CAS to exhibit experience-related plasticity. Furthermore the pattern of reduced contralateral dominance after unilateral deafness is in line with predictions from animal models. This pattern was much the same irrespective of whether deafness was congenital or acquired, affecting either the right or left ear, and whether deafness was of short or long duration. On the other hand it is not clear from the study whether the differences between groups are due to increased activity in the ipsilateral hemisphere of the experimental group, reduced contralateral activity, or a combination of the two. In addition to the potential for errors associated with comparing activation volume in each hemisphere (particularly with between-groups designs such as this) early fMRI studies of auditory evoked activity also suffered from methodological limitations related to the intrusion of noise produced by the MRI scanner. Potential problems in early auditory fMRI experiments arose due to the masking effect of the noise on the experimental stimuli. The auditory activity and/or the attentional demands on the participants may be altered due to this masking effect (Hall et al., 1999). However, a more important consideration in the study by Scheffler et al. (1998) was the extent to which monaural stimulation was achieved in control participants as they would have heard the scanner noise in both ears. Potentially the differences between the two groups were even greater than observed since binaural stimulation would be expected to result in a more symmetrical pattern of activity between the hemispheres in the control group.

Later fMRI studies such as those by Firszt et al. (2006) and Langers et al. (2005) have extended these initial findings by using a sparse scanning sequence. This technique separates the BOLD response in relation to the auditory stimulus from that of the scanner noise, unlike the conventional scan sequences as used previously by Scheffler et al. (1998). In the study by Firszt et al. (2006) cortical activity in response to complex speech-like stimuli presented at 80 dB HL was measured. The BOLD responses from seven individuals with unilateral deafness of the left ear were recorded and compared to those of a control group. Monaural stimulation of the right ear in nine normally hearing control participants resulted in responses from both hemispheres, with around 40% greater volume of activity recorded in the contralateral hemisphere. However similar stimulation in the unilateral deaf group produced more symmetrical activation between the hemispheres, with contralateral dominance reduced to around 20%. This pattern occurred as a result of both slightly decreased contralateral and markedly increased ipsilateral hemisphere activity compared with the controls. Langers et al. (2005) carried
out a similar study but included analysis of the activity in sub-cortical nuclei such as the inferior colliculi and medial geniculate nuclei as well as the auditory cortex. Another slight difference was in the stimulus type and level of presentation. Two types of broad band noise stimuli were used; steady state and amplitude modulated pink noise. These were presented at levels of 0, 40 or 70 dB SL, varied in a pseudo-randomised manner. The broad band stimuli were selected to evoke a robust BOLD signal. Varying the stimulus type and intensity was employed to help maintain a constant passive attention, although no distinction between the different conditions was made in the subsequent analysis. A sparse scanning sequence was used and the activity was reported in terms of both the volume and magnitude of the BOLD signal in each hemisphere. The responses from five individuals with unilateral deafness were measured. Three of these listeners had acquired deafness from a young age whereas two experienced late onset unilateral deafness but all had several years’ experience. Four participants had left and one had right ear deafness. Eight normally hearing participants served as controls. In terms of both volume and strength of the BOLD signal, activation was consistently stronger in the contralateral hemisphere to stimulation of either ear in the controls. In the auditory cortex the contralateral hemisphere produced around 60% greater volume of activation whereas in the medial geniculate nuclei and inferior colliculi this was around 70% to 80%, with similar asymmetries observed in terms of the response magnitude. However in unilaterally deaf participants activation was shifted towards a more symmetrical pattern in the cortex, with only around 30% contralateral dominance observed. Similarly to the results of Firszt et al. (2006) this was apparently due to a combination of decreasing contralateral and increasing ipsilateral activity. Conversely, no such differences were apparent in the sub-cortical nuclei compared with the controls.

These studies provide consistent evidence for reorganisation in humans with unilateral deafness. Furthermore, reduced hemispheric asymmetry does not seem to differ amongst participants despite the heterogeneous samples, with similar types of changes seen following congenital or acquired deafness affecting either ear. However, in contrast to the studies on animals described earlier, where the activity on the contralateral side to the healthy ear generally remained stable after the onset of unilateral deafness (e.g. Popelar et al., 1994), the results described by Firszt et al. (2006) and Langers et al. (2005) indicate that the reduction in asymmetrical activity results from both increased ipsilateral and reduced contralateral hemisphere activity. The discrepancy may be due, at least in part, to the source of the signal being detected using
fMRI. The BOLD response primarily reflects synaptic activity whilst electrophysiological measures reflect neural discharge rates. Once afferent activity from one ear is removed following deafness then the initial unmasking effect is thought to be followed by longer term structural changes (e.g. synaptogenesis). Presumably any such structural changes will be most apparent in individuals with several years experience as is generally the case in these studies on humans. This not only implies increased activity on the hemisphere ipsilateral to the healthy ear due to the anatomy of the ascending auditory pathway described earlier, but also reduced contralateral activity compared with controls as measured with fMRI. The cessation of input from the deafened ear would be expected to lead to reduced activity in the neural circuitry of the ascending pathway previously driven by the deafened ear. These changes may not be reflected in the discharge rates of neurons primarily influenced by activity from the healthy ear (when studied using electrophysiology), however they may be apparent with fMRI since this provides a measure of gross neural activity. The other interesting discrepancy relates to the apparent absence of evidence for sub-cortical plasticity in the study by Langers et al. (2005) despite the evidence from animal models of unilateral deafness which have consistently demonstrated experience-related plasticity of sub-cortical nuclei (e.g. Popelar et al., 1994; McAlpine et al., 1997). The authors suggest this may also be explained by fMRI measures primarily reflecting synaptic activity. Experience-related reorganisation in these structures may only be detectable at higher levels in the CAS due to the magnifying effect further along the ascending pathway, as more neurons become active.

In contrast to these findings, there are examples of studies using fMRI that do not indicate experience-related plasticity in adults with unilateral deafness. Moore et al. (2005) used fMRI to compare the central auditory function of seven individuals with unilateral deafness to that of twelve normally hearing controls. The participants with unilateral deafness consisted of four individuals with right-sided and three with left ear deafness, all of whom had several years’ experience. The stimuli consisted of high (4-kHz) and low (500-Hz) frequency tones that were presented at 90 dB SPL. The participants were asked to discriminate between the two tones via button presses, and the resulting BOLD signal was recorded using a sparse sampling procedure. The purpose of the discrimination task was to maintain active attention to the stimuli rather than the passive attention exhibited in the previously described studies. Another difference in the study design relates to the analysis, which distinguished the primary
and non-primary auditory cortex in particular. The results revealed two interesting points. Rather than the normally observed contralateral dominance in controls, monaural stimulation of either ear produced stronger activity in the left primary auditory cortex. When stimuli were presented to the right ear the left primary auditory cortex showed 60% greater activation than the right whereas when stimuli were presented to the left ear this value fell to around 20%. The second interesting result was that none of the participants with unilateral deafness exhibited a pattern of activity that was clearly different to that of controls. However, these two results may be attributed to the same cause. The asymmetries observed between each hemisphere may be related to other factors in addition to differences in the input from each ear (contralateral dominance). One example is a difference in the amount of auditory processing occurring in each hemisphere. Substantial differences in the activity of each hemisphere have been reported that depend on the nature of the auditory task and these are known as functional hemispheric asymmetries (Zatorre and Belin, 2001). The studies by Scheffler et al. (1998), Firszt et al. (2006) and Langers et al. (2005) employed passive listening whereas the participants in the present study actively performed a frequency discrimination task. The dominance of left hemisphere activation in controls, irrespective of the ear of stimulation, is probably due to this task emphasising the functional differences between the auditory cortices in each hemisphere (Devlin et al., 2003). Not only did this produce complex and novel results in the control participants but any changes in the contralateral dominance of subjects with unilateral deafness may have been masked by the emphasis on the functional differences between each hemisphere in auditory processing.

Regardless of this anomalous finding, the main area of confusion in the literature lies with the evidence from studies that used either auditory evoked potentials or fields (AEPs or AEFs) to study CAS activity following unilateral deafness. The findings from these studies have been far less consistent than those using fMRI. To date there have only been isolated instances where results have clearly demonstrated experience-related reorganisation following unilateral deafness. The clearest demonstration was reported by Ponton et al. (2001). Auditory evoked potentials were recorded in response to click stimuli (broad band) presented at 65 dB SL. Responses were recorded from a group of 15 adults with unilateral deafness and compared with those from nine normally hearing controls. The causes of deafness varied from idiopathic and disease related to abrupt deafness following surgery. The duration also varied from a matter of months to years.
Eight had left ear deafness and seven had right ear deafness, although no distinction between the sides of deafness were made in the subsequent analysis. The results from each group were compared in two ways. Initial comparisons were based on the RMS amplitudes across the entire recording window (400 ms). The mean RMS amplitude, measured in microvolts (µV) provides a summary of activity in each hemisphere. Monaural stimulation produced asymmetrical activity with a mean contralateral dominance of around 8% in controls. This value is much less than typically observed in fMRI studies, most likely due to volume conducted currents hindering the ability to clearly discriminate activity at the scalp arising from each hemisphere. However this value is in agreement with several other AEP studies (for a review see Naatanen and Picton, 1987). Participants with unilateral deafness showed significantly greater activity over the ipsilateral hemisphere and no significant difference in contralateral hemisphere activity, resulting in reduced contralateral dominance of 2%. Further analysis focusing on individual waveforms suggests these gross hemisphere differences were also reflected specifically by changes in the N1 wave.

In contrast, the majority of AEP and AEF studies have either reported unexpected findings that are difficult to interpret simply in terms of a shift in contralateral dominance or have not shown any evidence for experience-related plasticity. For example Khosla et al. (2003), using AEPs to study N1 activity, noted experience-related changes in participants with left but not right ear deafness. A series of studies carried out by Vasama et al. (e.g. Vasama and Makela, 1995; Vasama et al., 1995; Vasama et al., 2001; Vasama et al., 1994) using AEFs to study N1m activity reported experience-related changes in some individuals but not others. Hine et al. (2008) and Fujiki et al. (1998), using AEPs and AEFs respectively, showed no difference in N1 or N1m related activity compared with normally hearing controls. The varied nature of these findings has lead to the suggestion that experience-related plasticity does not necessarily occur as a result of acquired unilateral deafness, or at least depends on factors such as cause and duration of deafness. On the other hand, given the previously described evidence from fMRI studies an alternative hypothesis is that the discrepancies are related to methodological issues that apply specifically to AEP and AEF techniques. A number of studies have reported differences in the degree of contralateral dominance in normally hearing participants depending on whether the left or right ear is stimulated (e.g. Hine and Debener, 2007). This is not typically the case in fMRI and may be a result of sensitivity of the N1 response to anatomical and/or functional differences between the
hemispheres. This may also complicate the interpretation of any changes in contralateral dominance following acquired deafness. These discrepancies in the literature form one of the main motivations for the study reported in Chapter 4 therefore the issues relating to this subject area are described in more detail here.

Regardless of these discrepancies there is converging evidence, mainly from fMRI studies but also from some studies using AEPs, for experience-related plasticity following unilateral deafness in adult humans that is consistent with the findings in animals. However a major limitation in all of the above mentioned studies is the lack of control over the onset of deafness. Experiments therefore adopt a between-subjects retrospective design that makes comparisons with a normally hearing control group. Unfortunately, not only does this design introduce inter-subject variability but it also makes tracking the time course of any subsequent reorganisation very difficult. Knowledge of the time course of events following the onset of unilateral deafness is currently the least well understood area in humans; consequently little is known about the neurophysiological mechanisms that underlie the plasticity seen in these individuals.

Some progress has been made by using a cross-sectional approach which differentiates participants according to the duration of deafness. For example Ponton et al. (2001) compared the patterns of N1 activity from individuals with a long duration of deafness (greater than two years) with those from individuals with a short duration of deafness (less than two years). The reduced contralateral dominance in terms of N1 activity from each hemisphere was more marked in individuals with a longer duration of deafness, suggesting that reorganisation may continue over at least a two year period. This would imply that structural changes, for instance axonal sprouting, can take place in the mature human auditory system. On the other hand the study does not provide any information about the events shortly after the onset of deafness or the rate of changes post onset. Furthermore, as the authors noted, those with less experience of unilateral deafness were also older on average and the findings may in fact merely reflect a possible reduced capacity for reorganisation with age (Kleim and Jones, 2008).

One way to overcome this limitation is to obtain measurements from individuals in the acute phases of sensory deprivation, shortly after onset. This allows subsequent tracking of the sequence of events. However, since pre-onset measures will not be available, comparison with a separate control group is still necessary. Several studies investigating
Suzuki et al. (2002b) used fMRI to study individuals with sudden onset idiopathic unilateral deafness. With this condition hearing is typically normal prior to onset and, although the deafness may vary in severity, recovery often occurs with treatment. The stimuli consisted of speech-like monosyllables presented at 95 dB SPL and the activity in 11 individuals with right ear deafness was studied on two occasions. The first was within seven days of onset and the second was around one month later, after which some recovery of hearing was noted in 10 of the 11 participants. The results from each recording session were compared with those of a normally hearing control group of 10 individuals. Monaural stimulation in controls produced the normal pattern of contralateral dominance in terms of volume of activation. An average contralateral dominance of around 50% to 70% to respective stimulation of the left and right ears was seen. However, stimulation of the intact left ear in individuals with unilateral deafness showed a change to this pattern. In the acute phase ipsilateral dominance of around 50% was observed. Subsequent stimulation one month later showed the same pattern of ipsilateral dominance, however the extent was much less on average (down to around 30%), suggestive of a return towards the normal pattern of activation.

Li et al. (2006) performed a study on a similar group of individuals but this time using AEFs. 16 participants with idiopathic unilateral deafness were studied, eight affected in the left ear and eight in the right. The participants were tested within three weeks of onset, whilst nine normal bilateral hearing listeners served as controls. N1m activity was recorded in response to 1 kHz tones presented at 70 dB SPL. With respect to both source strength and latency of N1m a normal pattern of contralateral dominance was observed in controls. Stimulation of the left ear produced an average contralateral dominance of 28% whereas stimulation of the right ear showed 11% contralateral dominance. Latencies were also shorter in the contralateral hemisphere by around 10 ms. On the other hand those with unilateral deafness had significantly increased ipsilateral response amplitudes producing a pattern of ipsilateral dominance of around 13% irrespective of the side of stimulation, although the latencies were unaffected.

Morita et al. (2007) carried out an AEF study on individuals with idiopathic unilateral deafness. Two participants were studied; participant 1 had right ear deafness and
participant 2 had left ear deafness. Stimuli consisted of 1 kHz tone bursts presented at 70 dB HL. Three measures were carried out on each participant. The first was in the acute phase and took place between eight and 10 days after onset. Subsequent measures were made after partial and complete recovery of hearing in the affected ear following treatment. For participant 1 these sessions took place approximately one and three months later, when hearing had improved from a moderate severity to mild and finally returned to within the normal range. For participant 2 the recovery was much quicker, with partial and complete recovery at approximately two and three weeks post onset respectively. Despite these differences in time course the same basic pattern of results emerged in both individuals. Stimulation of the intact ear revealed a marked increase in ipsilateral hemisphere activity during the acute phase. The activation strength was significantly greater than the 14 normally hearing controls studied previously (Morita et al., 2003). However, no differences were observed in contralateral hemisphere activity. This lead to a slight ipsilateral dominance of around 4% in participant 1, but was around 55% in participant 2. During the recovery phases this pattern began to revert to the normally observed contralateral dominance and this was due to reduced ipsilateral activation. Interestingly this was more apparent in participant 1, who experienced a more gradual recovery period. During the recovery phases participant 1 demonstrated a normal pattern of contralateral dominance (~27%). Participant 2 still exhibited ipsilateral dominance after partial recovery, but the degree of asymmetry had fallen to around 40%.

The results from all of these studies are therefore qualitatively similar. Shortly after unilateral deafness the activation strength in the ipsilateral hemisphere increases markedly in response to stimulation of the intact ear. However, following recovery of hearing in the deafened ear the activation strength reduces again. Although it is impossible to tell how soon these changes occur after the onset of deafness, the results are consistent with the loss and recovery of inhibitory effects exerted by the affected ear as described by Mossop et al. (2000). One major limitation of these studies is that it is not clear how the ipsilateral dominance patterns translate to the symmetrical activity seen in the studies described previously where participants had permanent unilateral deafness. The enhancement of ipsilateral activity alongside general stability in the contralateral hemisphere would suggest that some subsequent modulation of ipsilateral activity occurs in a manner not described in animal studies (Mossop et al., 2000; Popelar et al., 1994). However, further longitudinal analysis was not carried out. It is
also not clear whether this effect is generalisable to other causes of deafness, where longer lasting mechanisms of experience-related plasticity are expected to take hold subsequently to disinhibition. It is also noteworthy that the same effect of ipsilateral dominance described in these studies is consistent in both fMRI and AEFs. However, this is not the case in studies of retrospective design described in the previous section. These questions constitute key areas with respect to question 3 posed earlier, relating to the time course of events, where understanding currently remains most limited. Clarification of the long term time course of events will be addressed in Chapter 5. Despite these discrepancies the limited evidence in humans to date indicates a clear ability for the mature CAS to exhibit experience-related plasticity following unilateral deafness.

2.2.5 Perceptual consequences of plasticity

Some of the clearest insights into the behavioural consequences of experience-related plasticity originate from human amputees who report phantom limb sensations. In some (although not all) individuals, somatosensory perception of the missing limb can occur following stimulation of other parts of the body such as the face, that are represented in adjacent regions of the cortex. This suggests that the part of the somatosensory system that would ordinarily be responsive to the missing limb has become responsive to the adjacent regions. This has been demonstrated empirically in humans using non-invasive imaging techniques (Yang et al., 1994).

In the auditory modality certain forms of tinnitus, particularly accompanied by hearing loss, have been described as an auditory sensation analogous to phantom limbs. Muhlackel et al. (1998) demonstrated similar links to physiological changes in humans in the auditory domain by showing that some tinnitus sufferers also show a change in the tonotopic neural representation at the cortex, with more severe subjective tinnitus accompanied by more extreme reorganisation. Some individuals experience gaze- or cutaneous-evoked tinnitus following cochlear deafferentation (e.g. following surgery) that is especially interesting as this also demonstrates cross-modal plasticity; presumably this form of reorganisation has lead to over-representation of somatosensory input in the auditory cortex (Cacace et al., 1999a; Cacace et al., 1999b; Cullington, 2001). Other perceptual abilities may be improved by such over representation. For example individuals with cochlear dead regions have been shown to demonstrate enhanced frequency discrimination to stimuli at the edge frequency, where
increased neural representation of those edge frequencies have been found (Kluk and Moore, 2006; McDermott et al., 1998). Another line of evidence has emerged from the study of acclimatisation effects in monaural hearing aid users. Improvements in perceptual measures such as speech perception, intensity discrimination and loudness perception occur after a period of hearing aid use (Munro, 2008). However the improvements are only apparent in the normal aided listening environment, as apparent by the relative performance between the aided and unaided ears in monaural hearing aid users. This suggests that experience-related plasticity has occurred, causing the behavioural cues available in the aided condition to become the most favourable, since these are the ones utilised under normal everyday circumstances and as such become most relevant. Although little information demonstrating any causal relationship between these and physiological changes is available, some studies have shown both perceptual and physiological changes in monaural hearing aid users (Munro et al., 2007; Gatehouse and Robinson, 1996).

This evidence, although sparse and inconclusive with respect to demonstrating a causal link between perceptual and physiological phenomena, supports the notion that experience-related plasticity is likely to occur simply as a result of the normal capacity of the CNS to favour the most relevant input. As a result, sometimes the functional outcomes are not desirable (e.g. phantom limb or gaze-evoked tinnitus) whereas other times the outcomes may be considered positive (e.g. hearing aid acclimatisation).

In the case of unilateral deafness there are only a few examples of the perceptual consequences potentially related to plasticity, although the disabilities following unilateral deafness have been well described. Unsurprisingly these disabilities are mainly a reflection of the loss of binaural hearing. This leads to difficulties in understanding speech in background noise, loss of binaural summation, increased head shadow effect and difficulties localising sound (Bess et al., 1986; Douglas et al., 2007). Since unilateral deafness alters the binaural input to the listener it may be that behavioural performance on tasks relying on binaural hearing are most influenced following experience-related plasticity. Enhancement of localisation abilities using the remaining monaural listening cues is one possibility. For example Slattery and Middlebrooks (1994) compared localisation abilities using monaural cues in a group of five individuals with long standing deafness in one ear with a group of seven normally hearing controls. Subjective accuracy of localisation was measured in controls under
two conditions, binaural and monaural after wearing an ear plug in the left ear. Under binaural listening conditions the controls produced a consistently accurate localisation performance that showed marked disruption following the introduction of the ear plug. The greatest localisation errors were seen in the horizontal plane, performance in which relies mainly on the inter-aural difference cues disrupted by the ear plug. However three of the five deaf participants showed lateralisation accuracy that, although still worse than controls in the binaural condition, was much better than controls in the monaural condition suggesting that these individuals had learned to use monaural cues only. Other tasks relying on binaural cues such as masking level difference tasks have also been used to demonstrate functional improvements that may be associated with plasticity. For example Hall and Grose (1993) noted an improvement in masking level difference tasks in individuals with unilateral conductive hearing loss who had their hearing restored with corrective surgery. However, work combining both behavioural and physiological approaches to studying plasticity remains sparse and future studies are needed to clarify the precise relationship between plasticity and function.

2.3 Conclusions and research aims

At present, it is clear that the adult human CAS is capable of reorganisation following a change in the sensory input. The evidence from humans with unilateral deafness measured using fMRI mirrors the evidence obtained from animals. The normal pattern of contralateral dominance to stimulation of the healthy ear reduces, mainly due to increased activation from the ipsilateral hemisphere relative to the healthy ear. Nevertheless several other studies observing the N1 response using either AEPs or AEFs have provided contradictory evidence. Given that attention is increasingly directed towards using the N1 response as a means to measure plasticity in humans clinically, one priority is to clarify and extend the current findings. Furthermore, despite around 15 years of research involving humans there is very little information on the time course of events.

The three studies described in this thesis therefore aim to investigate the pattern and time course of experience-related plasticity in humans with late onset unilateral deafness using the N1 auditory evoked potential.
The specific aims of the studies in each subsequent chapter are as follows:

**Chapter 3: Auditory evoked potentials and contralateral dominance in adult humans with normally hearing**

Aim: To verify the validity of an AEP technique used to measure hemispheric asymmetries by replicating previous findings in normally hearing individuals. A second aim was to investigate the effects of both level and frequency of stimulation on measures of hemispheric asymmetries.

**Chapter 4: Effects of late onset unilateral deafness on contralateral dominance in adult humans**

Aim: To compare hemispheric asymmetries between unilaterally deaf and normally hearing individuals.

**Chapter 5: The time course of experience-related plasticity in adult humans with late onset unilateral deafness**

Aim: To investigate the time course of changes in AEPs following unilateral deafness in humans.

The work described in this thesis has relevance to the understanding of experience-related plasticity in humans, to future studies investigating the perceptual consequences of plasticity, and ultimately for the rehabilitation of hearing impaired individuals.
Chapter 3: Auditory evoked potentials and contralateral dominance in adult humans with normally hearing

3.1 Introduction

The ability of the N1 cortical auditory evoked potential, and its magnetic homolog (N1m) to demonstrate contralateral dominance in response to monaural sounds has been established for many years (for a review of early work see Naatanen and Picton, 1987). As described in the previous chapter, this contralateral dominance is attributed to the anatomical asymmetries in the ascending CAS, with the majority of afferent projections from each ear crossing the midline and projecting to the cortex on the contralateral side. This has lead to studies utilising the N1 response as a means of investigating experience-related plasticity non-invasively in humans with unilateral deafness.

To date, the findings from such studies have been variable. While Ponton et al. (2001) demonstrated an increase in activity in the ipsilateral hemisphere; other studies have differed in the type of changes that have been reported. Some report changes to be apparent following left ear deafness only (e.g. Khosla et al., 2003; Hanss et al., 2009) or they have not demonstrated any clear or consistent evidence for reorganisation following long term unilateral deafness (Fujiki et al., 1998; Vasama and Makela, 1997; Vasama et al., 1995; Hine et al., 2008). To some extent these conflicting results may be related to variation in the inherent ‘adaptability’ within the CAS between individuals (Makela, 2006). Furthermore, differences between individuals in the duration of deafness, speed of onset or other aspects of the disease process have also been suggested as possible explanations (Makela, 2006; Hine et al., 2008). However, whilst it will be helpful to study individuals with a common cause, onset and duration of deafness (addressed in subsequent chapters) these aspects do not fully explain the inconsistencies in the literature. For instance some studies have found clear evidence of plasticity despite studying samples with mixed aetiologies and durations of deafness (e.g. Ponton et al., 2001) whereas others with homogeneous samples have reported no evidence of plasticity (e.g. Hine et al., 2008). A number of methodological factors also vary across studies. For example, little is known about the effect of stimulus parameters such as frequency and level on the degree of contralateral dominance measured in control conditions. A lack of understanding of factors such as these is likely to impact on the interpretation of evidence for plasticity following unilateral deafness. As a first
step, future studies looking to extend the current understanding of plasticity in humans using N1 will therefore need to verify the validity of their approach in terms of measuring contralateral dominance in normally hearing individuals.

3.1.1 Methodological issues when measuring hemispheric asymmetries

Early studies describing contralateral dominance using AEP and AEF techniques described the scalp distribution of N1 activity in terms of the raw output at each sensor. The asymmetries in scalp distribution were measured simply by comparing the N1 amplitude at homologous locations over each hemisphere. Contralateral dominance is characterised by higher amplitudes (and earlier latencies) at sensors located over the hemisphere on the opposite side to the ear of stimulation. For example Vaughan and Ritter (1970) compared the N1 amplitude between sensors located over the central scalp regions on either side of the midline. Four normally hearing individuals took part in the study and they received monaural stimulation using 1 kHz tone burst stimuli. The subsequent N1 responses were consistently higher in amplitude over the contralateral hemisphere. Following stimulation of the right ear the response over left hemisphere was 7.5% greater whereas following left ear stimulation the response over the right hemisphere was 3.8% greater. Many other studies have demonstrated similar findings using both AEPs and AEFs (Price et al., 1966; Reite et al., 1981; Elberling et al., 1981; Pantev et al., 1986). Furthermore, asymmetries between responses recorded over temporal regions are typically greater than central regions (Connolly et al., 1985; Wolpaw and Penry, 1975; Cacace et al., 1988). Based on evidence from a number of AEP studies, Naatanen and Picton (1987) concluded that the N1 amplitude is around 10% greater over the contralateral hemisphere.

However, quantifying contralateral dominance using N1 is complicated by two factors: functional differences between the hemispheres (i.e. differences in the amount of auditory processing occurring in each hemisphere) and anatomical differences between the hemispheres. Anatomical differences may refer to issues such as the skull thickness (which affects volume conduction in AEP studies) and differences in the location, size and orientation of the neural generators underlying the evoked response.
Functional hemispheric asymmetries seem to depend at least partly on the way in which individuals attend to a given stimulus. The differences in processing between the hemispheres under different experimental conditions can affect the degree to which the underlying contralateral dominance is apparent. This was demonstrated by Devlin et al. (2003). The purpose of the study was to investigate functional hemispheric asymmetries in auditory processing. Brain activity in response to pure tones presented monaurally was recorded using fMRI. A high and low frequency pure tone was used and participants actively attended to these stimuli by performing a frequency discrimination task. The response in the left hemisphere was greater irrespective of the ear of stimulation, therefore obscuring the underlying contralateral dominance. A similar effect occurred in a subsequent study by Moore et al. (2005) where participants also actively attended to the stimuli. However studies investigating contralateral dominance that employ passive listening tasks do not show this effect (e.g. Langers et al., 2005).

Anatomical variations can also affect the degree to which contralateral dominance is apparent in any given individual, particularly with N1 or N1m measurements. This was illustrated in a study by Makela et al. (1993). The study investigated contralateral dominance in humans using AEFs. Nine normally hearing participants were presented with pure tone stimuli (1 kHz) monaurally to the right and left ears. The resulting N1m response was recorded over both hemispheres using a whole-head magnetometer. On average the strength of activity was 22% greater over the hemisphere contralateral to the ear of stimulation. However the results varied considerably on an individual basis. One participant showed normal activity over the left hemisphere in terms of N1m amplitude and latency, but little or no discernable N1m response over the right hemisphere. The resulting pattern of hemispheric asymmetry therefore clearly differed from those of the other participants. An MRI scan subsequently showed the individual to have an unusually convoluted cortical surface on the right temporal lobe where the neural generators of the N1m are located. This suggests that the apparent lack of right hemisphere activity was due to phase cancellation of the response, for example through neural generators that are in opposing orientations.

Accounting for the effects of anatomical variations between participants is not a straightforward task. The raw sensor output used in early studies describing contralateral dominance will vary considerably depending on which pair of sensors is used for comparison and depending on the spatial relation of the underlying neural
generators to each other and with respect to the sensors on the scalp. This warrants caution when interpreting differences in contralateral dominance between individuals (Makela, 2006).

A related difficulty is the variation amongst studies using AEPs in the reference position. A basic principle of AEP measures is that activity recorded at each scalp sensor represents a difference in potentials between one scalp position and another, known as the reference position. The activity described at any given position is in reality a reflection of the sum of activity at the recording and reference positions. Since the activity varies across the scalp, then activity at a given recording position can vary considerably depending on the position of the reference (or, in the case of the ‘average reference’ technique, the spatial electrode density and extent of head coverage). Unfortunately there is no standardisation in reference position or electrode density and this makes comparisons across studies particularly difficult (Hagemann et al., 2001).

It has become clear that to overcome these difficulties source modelling must be employed and the strengths of the sources in each hemisphere be compared instead (Scherg and Von Cramon, 1986; Hine and Debener, 2007). Source modelling bypasses the variations that may be present at the scalp sensors by calculating the location, orientation, and strengths of the underlying neural generators. The simplest and most popular model is the single current dipole. A dipole is an entity with physical properties that resemble a battery. That is, the dipole is a power source with an internal current (called the primary current) and an external current (the volume current). These properties are conceptually the same as the internal neural current and the external volume conducted current that are present in the brain. A dipole can therefore be used to represent the neurons in a simplified way. The scalp distribution resulting from dipoles in a given position, orientation and strength can be predicted using established mathematical equations (Lutkenhoner and Mosher, 2006). This is known as the forward solution. Conversely the reverse solution is the prediction of the properties of the dipole (i.e. the strength, location and orientation) based on the pattern of the electric or magnetic fields recorded on the scalp. There is no unique reverse solution to a given pattern of scalp activity. However, it is possible to produce a plausible model by applying a series of constraints based on a priori knowledge such as specifying one dipole in the temporal regions to represent the neurons of the auditory cortex in each hemisphere. The properties of each dipole are then varied in order to minimise the
deviation between the measured and forward modelled data. In practice one of the most common approaches to finding the reverse solution is by spatio-temporal source modelling (Scherg and Von Cramon, 1986). In the auditory domain one or more dipoles are used in each hemisphere and the parameters of each dipole are adjusted iteratively to explain the scalp recorded activity as closely as possible over a given latency window. Once this is done, calculating contralateral dominance becomes a case of comparing the strength, location and orientation of the dipoles in each hemisphere. Thus the purpose of source modelling in this context is to provide a way in which to represent the activity in each hemisphere of the brain in a simplified manner that does not rely solely on the activity at a homologous pair of discrete positions on the scalp.

Several studies using source modelling have been concerned with understanding the behaviour of the intracerebral sources of the N1 wave to various stimulus manipulations. Considerable progress has been made to date. For example, it is clear that multiple neural components which become active simultaneously contribute to N1 (Picton et al., 1999). The principle component appears to be a tangentially orientated source that is located in the supratemporal plane in each hemisphere. It is known that dipoles representing these sources tend to orientate more anteriorly for higher frequency stimuli (Picton et al., 1999; Woods, 1995), and are typically located more posteriorly in the left hemisphere than the right (Makela et al., 1993). The earlier components contributing to N1 (N1a, typically active around 90 ms) are more sensitive to physical stimulus parameters such as frequency and duration than the later sources (N1b, activation around 120 ms) (Alain et al., 1997). For a review see Picton et al. (1999). Despite this progress, relatively few studies have described contralateral dominance in detail using source modelling, or specifically examined the effect of various stimulus manipulations on the degree of contralateral dominance. The studies that have made such examinations are summarised in Table 3.1.
<table>
<thead>
<tr>
<th>Name</th>
<th>Method</th>
<th>Stimulus type</th>
<th>Level</th>
<th>n</th>
<th>Result</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hine and Debener (2007)</td>
<td>AEP</td>
<td>1 kHz tone burst (&amp; WBN)</td>
<td>60 dB SL</td>
<td>16</td>
<td>L ear: ~22% C&gt;I</td>
<td>Right hemisphere dominance in most participants</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>R ear: ~8% C&gt;I</td>
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</tr>
<tr>
<td>Khosla et al. (2003)</td>
<td>AEP</td>
<td>Click</td>
<td>65 dB SL</td>
<td>8</td>
<td>~30% C&gt;I</td>
<td>No R/L hemisphere dominance noted</td>
</tr>
<tr>
<td>Li et al. (2006)</td>
<td>AEF</td>
<td>1 kHz</td>
<td>70 dB SPL</td>
<td>16</td>
<td>L ear: ~27% C&gt;I</td>
<td>Right hemisphere dominance in most participants</td>
</tr>
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<td></td>
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<td></td>
<td>R ear: ~12% C&gt;I</td>
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<tr>
<td>Makela et al. (1993)</td>
<td>AEF</td>
<td>1 kHz tone burst</td>
<td>85 dB HL</td>
<td>9</td>
<td>~12 % C&gt;I</td>
<td></td>
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<tr>
<td>Nakasato et al. (1995)</td>
<td>AEF</td>
<td>2 kHz tone burst</td>
<td>80 dB SPL</td>
<td>20</td>
<td>~6% C&gt;I</td>
<td></td>
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<tr>
<td>Pantev et al. (1998)</td>
<td>AEF</td>
<td>0.25, 0.5, 1, 2, 4-kHz tone burst</td>
<td>60 dB SL</td>
<td>6</td>
<td>~10% C&gt;I</td>
<td>No R/L hemisphere dominance noted</td>
</tr>
<tr>
<td>Scherg and Von Cramen (1986)</td>
<td>AEP</td>
<td>Click</td>
<td>70 dB HL</td>
<td>15</td>
<td>~11% C&gt;I</td>
<td>No ear specific information</td>
</tr>
<tr>
<td>Vasama and Makela (1995)</td>
<td>AEF</td>
<td>1 kHz</td>
<td>60 dB HL</td>
<td>8</td>
<td>L ear: ~16% C&gt;I</td>
<td>Right hemisphere dominance in most participants</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>R ear: ~4% C&gt;I</td>
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<tr>
<td>Name</td>
<td>Method</td>
<td>Stimulus type</td>
<td>Level</td>
<td>n</td>
<td>Result</td>
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<tr>
<td>Vasama and Makela (1997)</td>
<td>AEF</td>
<td>1 kHz</td>
<td>80 dB SPL</td>
<td>5</td>
<td>L ear: ~30% C&gt;I</td>
<td>Right hemisphere dominance in most participants</td>
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<td></td>
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<td>R ear: ~16% I&gt;C</td>
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<tr>
<td>Vasama et al. (1994)</td>
<td>AEF</td>
<td>1 kHz tone burst</td>
<td>70 dB HL</td>
<td>9</td>
<td>L ear: ~37% C&gt;I</td>
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<td>R ear: C=I</td>
<td>Right hemisphere dominance in most participants</td>
</tr>
<tr>
<td>Vasama et al. (2001)</td>
<td>AEF</td>
<td>1 kHz</td>
<td>80 dB SPL</td>
<td>10</td>
<td>~15% C&gt;I</td>
<td></td>
</tr>
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<td>Woldorff et al. (1999)</td>
<td>AEF</td>
<td>0.5 – 4-kHz pure tone sweep</td>
<td>73 dB SPL</td>
<td>9</td>
<td>C&gt;I</td>
<td>LI not available</td>
</tr>
<tr>
<td>Yu et al. (2007)</td>
<td>AEF</td>
<td>1 kHz tone burst</td>
<td>70 dB SPL</td>
<td>21</td>
<td>L ear: ~31% C&gt;I</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>R ear: ~11% I&gt;C</td>
<td>Right hemisphere dominance in most participants</td>
</tr>
</tbody>
</table>
The first study to report contralateral dominance based on source modelling of the N1 AEP was by Sherg and Von Cramen (1986). The evoked responses of 15 normally hearing individuals were recorded using an 11-channel recording montage. Stimuli consisted of 1 kHz tone bursts presented monaurally at 70 dB HL. One radial and one tangentially orientated dipole in each hemisphere were used to represent the resulting scalp recorded activity between 45 and 200 ms after the onset of the stimulus (i.e. encompassing the N1 latency range). The tangentially orientated sources were located in the superior temporal cortex on each hemisphere and angled anteriorly towards the fronto-central regions of the scalp. When the responses from each ear were averaged together the tangentially orientated source in the contralateral hemisphere was 11% stronger than the ipsilateral source. However the effect of left versus right ear stimulation was not examined separately.

The results of other studies listed in Table 3.1 corroborate these findings. An interesting result is that when studying the effect of stimulating each ear, substantially greater asymmetries occur when stimuli are presented to the left ear compared with the right. Close inspection of Table 3.1 reveals that several studies providing ear specific results report this effect, although it is not new to the literature. Previous studies that relied on sensor level data have also shown greater contralateral dominance with stimulation of the left ear (Cacace et al., 1988; Wolpaw and Penry, 1977; Wolpaw and Penry, 1975; Connolly, 1985). The effect is due to greater activity apparent over the right hemisphere and this is known here as hemisphere dominance. This hemisphere dominance has been attributed to functional differences in the way stimuli are processed (Hine and Debener, 2007). In particular the radial sub-component (known as N1c), which is most prominent in the temporal scalp regions, seems to display hemisphere dominance. The differences in contralateral dominance, depending on the ear of stimulation, occur as a result of interaction with this hemisphere dominance. The combined effect of contralateral dominance and right hemisphere dominance tends to give large asymmetries with stimulation of the left ear. When the right ear is stimulated smaller asymmetries occur, since the effect of contralateral dominance is counteracted somewhat by the larger response of the right hemisphere.

Despite this progress, there are two areas where further investigation would be beneficial to understanding the relative activity of sources in each hemisphere following monaural stimulation: investigating the effect of stimulus presentation level and
stimulus frequency on contralateral dominance of N1. These are two key stimulus parameters that have received surprisingly little attention in the existing literature. The reason why it would be beneficial in the present context is because there are reasons to suspect that these parameters could have an effect on measures of contralateral dominance and therefore interpretation of any changes following the onset of unilateral deafness.

The level of stimulus presentation has varied considerably both in studies describing the nature of contralateral dominance in the N1 response and in studies investigating plasticity following unilateral deafness. For example, in studies that have used a 1 kHz pure tone, presentation levels have ranged from 50 dB SL up to around 90 dB SL (Hine and Debener, 2007; Picton et al., 1999; Connolly, 1985; Vaughan and Ritter, 1970; Hanss et al., 2009; Hine et al., 2008). Sufficiently robust source modelling, in terms of low residual variance, relies on an adequate signal-to-noise ratio. This would suggest that high presentation levels are most desirable because the N1 response amplitude increases with level. However, the response also saturates at sufficiently high presentation levels, where further increases in level results in relatively smaller increases or even reductions in response amplitude (Beagley and Knight, 1967). Existing evidence suggests that in normally hearing individuals response saturation occurs at levels above 70 dB SL (Adler and Adler, 1989). It may be that the degree of asymmetry becomes attenuated with increasing level due to this saturation behaviour. One explanation for this is that with monaural stimulation the contralateral sources may be expected to begin to saturate earlier than ipsilateral sources. This differential saturation between the hemispheres would presumably lead to reduced asymmetries with increasing stimulus level; the ipsilateral activity would increase relatively more than contralateral activity. Some evidence of this has been seen previously (Cacace et al., 1988) where on examination of the t-complex, one component of the N1 wave that is typically recorded over temporal regions of the scalp, the degree of hemispheric asymmetry seemed to decrease with increasing stimulus intensity. To the author’s knowledge this has not previously been systematically investigated. However, clarification may allow identification of an optimum level of stimulus presentation in plasticity studies involving contralateral dominance, where sufficiently robust source analysis is achieved without any saturation of the N1 response.
Studies investigating shifts in N1 hemispheric asymmetries following unilateral deafness will also benefit from clarification of the effect of frequency of stimulation. To date, the AEP and AEF plasticity studies have used either broad band stimuli (Khosla et al., 2003; Ponton et al., 2001) or single frequency (1 kHz) tones (Hine et al., 2008; Hanss et al., 2009; Vasama et al., 2001). However, the clearest evidence for plasticity seems to come from studies that have used broad band click stimuli. The low frequency emphasis in the N1 response to such stimuli has raised questions relating to the effect of unilateral deafness on neurons with high frequency sensitivity (Khosla et al., 2003), differences in which could contribute to the variability in findings elsewhere. This is based on two observations. On the one hand, Khosla et al. (2003) speculated that different patterns of reorganisation may be observed as a result of the different patterns of input to binaurally sensitive neurons in the cortex. Areas of cortex that represent low frequency stimuli have been shown to possess mainly excitatory inputs from contralateral and ipsilateral ears (EE) whereas high frequency areas are dominated by excitatory inputs from the contralateral ear, but inhibitory units from the ipsilateral ear (EI) (Reser et al., 2000). If this is the case then a greater increase in ipsilateral hemisphere response might be expected with high frequency stimulation, based on the unmasking of excitatory inputs following unilateral deafness discussed in Chapter 2. On the other hand, experience-related reorganisation due to age related gradually reducing hearing thresholds in the intact (test) ear may also influence the observation of any changes associated with unilateral deafness. Topographical reorganisation following presbyacusis has been noted previously (Frisina and Rajan, 2005) whereby expansion of low frequency representation has been seen in animals with sloping high frequency hearing loss. This is possibly as a result of low frequency input becoming behaviourally more relevant (Recanzone et al., 1993). In plasticity studies involving humans, if some individuals with unilateral deafness exhibit age related hearing loss in the intact ear (which is often the case) then the interaction between the two effects may also produce different patterns of reorganisation across frequencies. Presumably greater effects will be apparent with low frequency stimulation in this case. This represents an extension of the general expectation that experience-related plasticity should be greatest in frequency regions most affected by the hearing loss. In any case, it seems important to consider frequency specific responses when investigating reorganisation following unilateral deafness, but in terms of measuring contralateral dominance this relies on knowledge of what to expect under normal circumstances. Although several studies have demonstrated varying locations and orientations of sources in each hemisphere.
according to the frequency of stimulation (e.g. Picton et al., 1999; Pantev et al., 1998) the effect on contralateral dominance to monaural stimulation has not been reported previously. Furthermore, there are reasons to suspect that greater N1 asymmetries may result from high frequency stimulation compared with low. For example, Woods (1995) found evidence for N1 sources in the contralateral hemisphere that were responsive to some frequencies but not others. Twelve subjects received monaural tone bursts of 250-Hz and 4-kHz to each ear. Upon stimulation using the 4-kHz stimuli an additional positive component at 90 ms latency was observed at posterior temporal recording sites on the contralateral side. The latency range and the fact that the vertex negative N1 response undergoes polarity reversal at these posterior sites suggests that contralateral N1 amplitudes may be boosted for high frequencies compared to low due to the additional component. Alternatively the overall N1 activity is known to be of lower amplitude in general for high-frequency stimuli compared to low. A weaker response to high frequencies is commonly seen in other imaging techniques as well, for instance in fMRI, and has been attributed to the tonotopic arrangement of the cochlea; low frequency tones activate a broader region of the basilar membrane, at least with high levels of stimulation. Secondly generators of low frequency responses are located closer to the surface of the cortex, resulting in larger amplitudes apparent at the scalp (Dimitrijevic et al., 2008). Therefore in the same way that high level stimuli may be expected to cause reduced contralateral dominance due to relatively greater ipsilateral activity, high-frequency stimuli may be expected to cause greater contralateral dominance due to relatively weaker (or more labile) ipsilateral activity.

The aim of the study described in this chapter is to verify the validity of the present technique used to measure hemispheric asymmetries by replicating previous findings in normally hearing individuals. A second aim was to investigate the effects of both level and frequency of stimulation on measures of hemispheric asymmetries.

It was hypothesised that hemispheric asymmetry will reduce with increasing level due to saturation of the response; specifically, as level of presentation increases the contralateral hemisphere will saturate before the ipsilateral hemisphere.

A second hypothesis is that high-frequency stimuli will produce greater contralateral dominance compared with low. This could be due to greater activity in the contralateral hemisphere as a result of additional sources sensitive to high-frequency stimuli, and/or
relatively less activity in the ipsilateral hemisphere as a result of the overall weaker response typically seen from high-frequency stimuli.

3.2 Methods

3.2.1 Participants

Twenty-four participants (15 female, 9 male; 21 – 30 years old) took part in the study. All had normally hearing thresholds (≤ 20 dB HL at octave intervals between 250-Hz and 8- kHz), were right handed according to the Edinburgh Handedness Inventory (Oldfield, 1971) and reported no history of ear related or neurological illness or injury.

The number of participants was determined by statistical power analysis. The estimated mean of the differences between contralateral and ipsilateral dipole strengths was 1.3 nAm (± 0.55 nAm), based on the results from normal bilateral hearing controls reported by Khosla et al. (2003). On a two tailed parametric significance test, the number of participants required to give a statistical power in excess of 80% (at \( p < 0.05 \)) was 12. Participants were randomly split into one of two groups according to the frequency of stimulation (low and high), and each group comprised 12 individuals. Two groups were used to ensure the duration of testing in a single session (2.5 hours) was manageable for each participant seen.

The experiment was approved by the School of Psychological Sciences research ethics committee, University of Manchester (261/06D) and all participants gave written informed consent.

3.2.2 Paradigm

Two pure tones (500-Hz and 4-kHz) were selected to represent low- and high-frequency stimuli. These were of 80 ms duration including 10 ms onset and offset ramps, defined using the Blackmann windowing algorithm. The stimuli were generated digitally and presented monaurally via a 44.1 kHz digital-analogue converter. Presentations were made in a pseudo randomly interleaved fashion to each ear via ER-3A insert earphones. Interleaving the ear of presentation was carried out in order to minimise response habituation and allow a valid comparison of activity in each hemisphere (Hine and Debener, 2007). The inter-stimulus interval varied pseudo randomly between 900 and 1300 ms, which is long enough to produce a good signal-to-noise ratio without
requiring an excessively long recording time. Randomly varying the inter-stimulus interval was done in order to minimise response habituation. Stimuli were presented in three blocks of 500 repetitions per ear. Each block contained stimuli at a different level (40, 60 or 80 dB SL), the order of which was counterbalanced across participants. The levels were selected in order to produce activity over a range of signal-to-noise ratios, with the highest level expected to result in response saturation (Adler and Adler, 1989) whilst remaining within the comfortable listening range of participants and without causing significant interaural cross-over (Munro and Agnew, 1999). Employing a fixed sensation level normalises the stimuli for variations in the pure tone thresholds between participants, with the absolute levels varying by up to 10 dB between participants. Passive attention to the stimuli was maintained throughout testing by watching a silent closed-caption movie for the duration of each session. The potential for any auditory evoked activity occurring as a result of watching these videos (e.g. through references to sound within the closed-captioning) was ignored as any such activity would not be time-locked to the EEG recording, hence would not produce any systematic effect on the results.

### 3.2.3 EEG recording

Participants were seated comfortably in a reclining chair with head support in a sound attenuating room. A Neuroscan data acquisition system (Acquire v4.3) was used to record EEG data from 30 sintered Ag/AgCl electrode sensors arranged in a standard 10-20 montage over the scalp. There were four midline electrodes and 13 located over each hemisphere. A separate bi-polar channel was used to record vertical electro-oculographic (EOG) activity, with an electrode placed above and below the right eye. Data was recorded online with a sampling rate of 1 kHz, analog filtered from 0.05 to 200 Hz (6 dB/Oct) and referenced to the AFz (midline) position. Electrode impedances (measured at 30 Hz) were below 5 kΩ and inter-electrode impedances were below 2 kΩ.

### 3.2.4 Data processing

Subsequent processing was carried out offline using Neuroscan’s Edit software (v4.3.1). Ocular artefact reduction was carried out first. The procedure involves a computational method developed by Semlitsch et al. (1986) and uses a regression analysis in combination with artefact averaging to correct for eye blinks. Initially the maximum overall voltage in the EOG channel for each block is determined and 10% of this value.
is taken arbitrarily as the threshold defining the beginning of each eye blink. On every occasion where activity exceeds this threshold then a blink is assumed to have occurred. When 60 presumed blinks are identified an average is constructed based on a time window extending 400 ms after the starting point of the blink (the 10% point in the EOG channel). Transmission co-efficients are then computed by estimating the co-variance of the average EOG blink activity with the activity in EEG channels at the same point in time. The EOG activity is then subtracted from the EEG channels on a point by point basis.

EOG corrected data were then low pass filtered (30 Hz, 24 dB/Octave), baseline corrected and epoched from 200 ms prior to the stimulus onset, to 600 ms post stimulus onset. Any epochs still containing activity exceeding +/- 150 µV (value set arbitrarily) were excluded from further analysis, with an average of 474 (s.d. = 37) epochs accepted in each block. Accepted epochs were averaged to reveal the N1 AEP. Finally, the data were re-referenced to the common average. Independent component analysis was used to selectively remove 50 Hz components in some cases (n=2).

3.2.5 Dipole source modelling

Source modelling was performed using Neuroscan’s Source software (v2.0). Modelling was performed on grand average waveforms from the 12 participants in each condition, and on the participant’s individual averaged data from each condition. A symmetrical 2-dipole fit (one dipole in each hemisphere) was applied according to convention using a classical 3-shell spherical head model. Source activity was allowed to vary in location, orientation and strength in a latency window of +/- 10 ms around N1, with the peak latency of N1 identified in global field power.

Dipole locations (Neuroscan Source native format) are given in \((x, y, z)\) coordinates measured in millimetres, where \(x\) extends from left (negative values) to right (positive values) and 0 is on the midline. The \(y\) axis extends anterior (positive values) to posterior (negative value) and 0 is on the midline. The \(z\) axis extends superior (positive values) to inferior (positive values) and 0 is at the base of the brain in the same plane as the bottom of the cerebellum.

Dipole orientations in Neuroscan Source native format are given in \((x,y,z)\) axes as unit vectors (i.e. a geometric entity in a normed vector space whose length is 1). For analysis
these values were converted to degrees relative to the three orthogonal planes (coronal, sagittal and axial) using a standard trigonometric function (i.e. arctangent, which finds the angle when given the ratio of the two sides of a right-angle triangle). The coronal plane is found by arctangent \((x/z)\), the sagittal plane by arctangent \((-y/z)\) and the axial plane by arctangent \((x/y)\).

Current dipole strengths are given in nanoAmperemeters (nAm).

### 3.2.6 Analysis

Differences in dipole location between the groups were assessed using independent samples \(t\)-tests. Differences in dipole orientation were assessed using the Watson-Williams test (Zar, 1984). This test is designed to evaluate circular distributions such as two or more vectors, where no true zero point exists and high and low values are designated arbitrarily. The test utilises the F distribution and takes the form:

\[
F = \frac{K (N-2) (R_1 + R_2 - R) / (N - R_1 - R_2)}{(R_1 + R_2)}
\]

\(N\) is the combined sample size under comparison \((n_1 + n_2)\), \(R_1\) and \(R_2\) are the Rayleigh values for each group (Rayleigh values are related to the distribution of the data around a circle), \(R\) is a weighted average of \(R_1\) and \(R_2\) and \(K\) is a factor that corrects for bias in the \(F\) calculation. Dipole orientations were compared between hemispheres (contralateral and ipsilateral in all three planes), for stimulation of left and right ears at all levels and between 500-Hz and 4-kHz data.

The mean dipole strengths in the latency window around N1 (+/- 10ms identified in global field power) were also compared. Laterality indices (LIs) are percentage values used to quantify the asymmetry in each condition by comparing source strengths in each hemisphere. LI was calculated as follows:

\[
LI = \frac{(\text{contralateral activity} - \text{ipsilateral activity})}{(\text{contralateral activity} + \text{ipsilateral activity})} \times 100
\]

The LI values range from -100% to +100%. Positive values indicate contralateral dominance, negative values indicate ipsilateral dominance and a value of zero indicates
symmetrical activity. This technique allows normalisation of inter-hemisphere activity (dipole strength only) although since it is a difference measure, it does not allow determination of ipsilaterial and contralateral activity patterns alone. Therefore, additional measures of source strength were performed separately for contralateral and ipsilateral hemispheres. The Shapiro-Wilks test was used to ensure the assumption of normality of distribution. Levene’s test for equality of variance (and Mauchly’s test of sphericity for within-subject comparisons) was also used. In all cases where assumptions of normality of distribution and equality of variance were met, parametric tests were used to compare means. Analysis of variance (ANOVA) was used, with ear [2] and level of presentation [3] specified as within-subjects factors, and frequency of stimulation [2] specified as a between-subjects factor.

3.3 Results

As an example, Figures 3.1 and 3.2 show the grand average AEP waveforms for 500-Hz and 4-kHz tone burst stimulation in the 60 dB SL condition, respectively. The most prominent response is N1, which is present in all conditions. It occurs with maximal amplitude at the vertex and fronto-central positions and with inverted polarity at the inferior positions. Additional peaks are apparent at temporal sites, particularly over the right hemisphere where a negative peak between 140 and 150 ms can be observed. This has sometimes been termed N1c to differentiate it from the vertex-negative N1 (otherwise known as N1b). A prior negativity termed N1a (typically occurring around 70ms) is also apparent in the frontal and fronto-temporal regions of some individuals.

3.3.1 Effect of stimulus level and frequency

The effect of stimulus level was assessed initially using global field power (GFP). This is a convenient way to summarise activity across all of the sensors and is sensitive to both latency and amplitude of activity. The N1 response was objectively identified in GFP using a peak detection algorithm sensitive to the maximum amplitude in the latency range of 70 to 130 ms. Results were also checked by the experimenter to ensure no anomalous peak labelling had occurred. Both the latency of the peak and mean amplitude over a latency range +/- 10ms about the peak were then compared. An expanded view of the grand average GFP for each frequency is displayed in Figure 3.3. As stimulus level increases the N1 peak increases in amplitude and decreases in latency following right and left ear stimulation, consistent with results reported repeatedly in the
past. Group data expressed as amplitude- and latency-intensity functions are displayed separately for 500-Hz and 4-kHz stimuli in Figures 3.4 and 3.5, respectively. No clear signs of saturation are apparent in either frequency condition. Separate 2-factor repeated-measures ANOVA were performed for each stimulus frequency (ear [2] and level [3]), both for measures of N1 amplitude and latency.

For amplitude measures, statistically significant main effects for level were observed in the 500-Hz condition ($F_{(2,22)} = 7.99, p<0.01$), but no statistically significant differences were observed for ear of stimulation ($F_{(1,11)} = 0.55, p>0.05$), nor any interaction effects ($F_{(2,22)} = 0.22, p>0.05$), indicating the effect of level was the same for both ears. Similar findings were obtained in the 4-kHz condition. Statistically significant main effects for level were observed ($F_{(2,22)} = 10.08, p<0.01$), but no statistically significant differences were observed for ear of stimulation ($F_{(1,11)} = 0.36, p>0.05$), nor any interaction effects ($F_{(2,22)} = 0.84, p>0.05$).

For latency measures, statistically significant main effects for level were observed in the 500-Hz condition ($F_{(2,22)} = 13.35, p<0.01$), but no statistically significant differences were observed for ear of stimulation ($F_{(1,11)} = 1.35, p>0.05$), nor any interaction effects ($F_{(2,22)} = 0.61, p>0.05$), indicating the effect of level was the same for both ears. Again, similar effects were noted in the 4-kHz condition. Statistically significant main effects for level were observed ($F_{(2,22)} = 12.50, p<0.01$), but no statistically significant differences were observed for ear of stimulation ($F_{(1,11)} = 0.46, p>0.05$), nor any interaction effects ($F_{(2,22)} = 0.29, p>0.05$).

Post-hoc pairwise comparisons are displayed in Table 3.2. The post-hoc tests showed 5 out of 8 comparisons between 60 and 80 dB SL presentation levels produced significant differences. The P2 response that is most prominent in the 500-Hz condition (see Figure 3.3, upper panel) does seem to show signs of saturation. However, no clear asymmetries were observed in this latency range and the P2 response was much less prominent in the 4-kHz condition.
Table 3.2 Results of Bonferroni corrected post-hoc testing for GFP amplitude and latency. One asterisk corresponds to significance at the 0.05 level, whereas two asterisks corresponds to significance at the 0.01 level

<table>
<thead>
<tr>
<th></th>
<th>Amplitude</th>
<th>Latency</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>40-60 dB SL</td>
<td>60-80 dB SL</td>
</tr>
<tr>
<td>500-Hz</td>
<td>Left ear</td>
<td>n.s.</td>
</tr>
<tr>
<td></td>
<td>Right ear</td>
<td>n.s.</td>
</tr>
<tr>
<td>4-kHz</td>
<td>Left ear</td>
<td>**</td>
</tr>
<tr>
<td></td>
<td>Right ear</td>
<td>**</td>
</tr>
</tbody>
</table>

3.3.2 Source modelling of AEPs

Satisfactory fits between measured and modelled data were obtained in the majority of participants. The residual variance is an estimation of the error in the model (i.e. the amount of signal that remains unexplained by the model in the given latency window), and is a ratio of the measured and modelled scalp potentials calculated as follows:

$$\text{Residual Variance} = \left(\frac{\text{Voltage}_{\text{measured}} - \text{Voltage}_{\text{modelled}}}{\text{Voltage}_{\text{measured}}}\right) \times 100$$

For the grand average AEPs the residual variance ranged from 5.8% to 7.1% across all conditions for the 4-kHz stimuli. This corresponds to a goodness-of-fit (an estimation of the amount of signal that is explained by the model) of between 99.5% and 99.7%.

$$\text{Goodness-of-fit} = (100 - ((\text{Residual Variance}^2)/100))$$

Residual variances were slightly greater in the 500-Hz condition, ranging from 5.7% to 11.4% for the grand average AEPs, corresponding to between 98.7% and 99.7% goodness-of-fit. Source modelling for individual AEPs were also performed and the variances were typically greater accordingly. These are summarised in Table 3.3.
Table 3.3 Goodness-of-fit values (%) for source modelling of individual participants data

<table>
<thead>
<tr>
<th></th>
<th>500-Hz</th>
<th>4-kHz</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left ear</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40 dB SL</td>
<td>93.5 - 99.2</td>
<td>93.3-99.4</td>
</tr>
<tr>
<td>60 dB SL</td>
<td>94.6 - 99.1</td>
<td>96.6-99.0</td>
</tr>
<tr>
<td>80 dB SL</td>
<td>91.5 - 99.2</td>
<td>98.1-99.1</td>
</tr>
<tr>
<td>Right ear</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40 dB SL</td>
<td>89 - 99.6</td>
<td>98.2-99.5</td>
</tr>
<tr>
<td>60 dB SL</td>
<td>88.8 - 99.3</td>
<td>98.7-99.4</td>
</tr>
<tr>
<td>80 dB SL</td>
<td>95.4 - 99.6</td>
<td>98.1-99.6</td>
</tr>
</tbody>
</table>

3.3.3 Contralateral dominance

Grand average source modelled scalp topographies are shown in Figures 3.6 and 3.7 for 500-Hz and 4-kHz, respectively. The topographies relate to activity at the peak latency of the N1 wave (identified in GFP). The greatest amplitude occurs in the fronto-central regions contralateral to the ear of stimulation. Contralateral dominance is apparent in all of the conditions with the exception of presentation to the right ear in the 500-Hz condition. Here, contralateral dominance is only apparent at the 40 dB SL presentation level. As the level increases to 60 and 80 dB SL the activation shifts first towards a more symmetrical and subsequently towards an ipsilaterally dominant pattern.

The locations, orientations and strengths of the dipoles in each hemisphere reflect the contralateral dominance apparent in these scalp topographies. Table A1 in Appendix A summarises the results of the grand average dipole source analysis, whereas Table A2 in Appendix A provides a summary of the group data obtained from dipole source analysis of the individuals averaged waveforms.

**Location:** The grand average results are displayed in Figure 3.8. The majority of dipoles in the 4-kHz condition are located more laterally (>50 mm from the origin on the x-axis; top panel of Figure 3.8), whereas the majority of dipoles in the 500-Hz condition are more medial (< 50 mm from the origin). These differences were statistically significant ($t_{(142)} = 3.88$, $p < 0.01$). In addition, the dipoles of individuals in the 4-kHz condition were located significantly more frontally in each hemisphere than those of the 500-Hz condition ($t_{(142)} = 2.96$, $p < 0.01$). This is clear from the lower panel of Figure 3.8, where dipoles are consistently further forward on the y-axis in the 4 k Hz condition compared with the 500-Hz condition. The more frontal negativity of the
N1 associated with the 4-kHz stimuli is also apparent from the topographies of the grand averages shown in Figures 3.7 compared with those in Figure 3.6. Finally, although there is a trend for dipoles in the 4-kHz condition to be located deeper below the surface of the cortex (Figure 3.8, middle panel), there was no statistically significant difference (t_{(142)} = 1.49, p > 0.05).
Figure 3.1 Grand average auditory evoked potentials from 12 subjects receiving 500-Hz tone bursts monaurally at 60 dB SL. Blue lines show responses to left ear stimulation and red lines to right ear stimulation. N1 (and P2) are labelled at the Cz position. Polarity reversal of N1 response is apparent at inferior positions compared to the fronto-central positions.
Figure 3.2 As Figure 3.1 but for 4-kHz tone burst stimulation. N1c (see T8 recording position) is apparent at temporal sites over the right hemisphere.
Figure 3.3 GFP for grand average AEPs to 500-Hz stimuli (top panel) and 4-kHz stimuli (lower panel). Red lines indicate right ear stimulation and blue lines indicate left ear stimulation. Dotted lines depict the 40 dB SL condition, solid lines depict the 60 dB SL condition and dashed lines depict the 80 dB SL condition.
Figure 3.4 Amplitude- and latency-intensity input/output functions in the 500-Hz stimulus condition based on global field power measurements. Red points indicate results for right ear stimulation and blue lines for left ear stimulation. Error bars indicate +/- 1s.d.
Figure 3.5 as Figure 3.4 for 4-kHz condition.
**Orientation**: The orientations of the dipoles are described in terms of their angles in the coronal ($z/x$), sagittal ($z/y$) and axial planes ($y/x$). In each plane the angles range from 0° to -180°. In the coronal plane an orientation of -90° would indicate a vertical orientation. Angles between 0° and -90° indicate dipoles which are orientated to the right (with 0° being perpendicular with the vertical) whereas angles between -90° and -180° indicate dipoles which are orientated to the left (with -180° being perpendicular with the vertical). The 500-Hz data showed dipoles that were consistently orientated near vertically in both hemispheres when stimuli were presented to the left ear (Figure 3.9, top left panel). As such there were no orientation differences between contralateral and ipsilateral hemispheres. When stimuli were presented to the right ear the dipole orientations shifted in both hemispheres from lateral to more vertical orientations as the level of presentation increased (Figure 3.9, top right panel). This reflects the changes in scalp topographies noted in Figure 3.6 (lower panel). However, these changes were not statistically significant in the group data where variability was considerable (see Table 2, Appendix A). The orientation pattern from the 4-kHz data was more consistent. Following left ear stimulation the dipoles are orientated medially, which is similar in both hemispheres therefore no statistically significant differences were observed. However, with right ear stimulation the dipoles in the contralateral hemisphere are vertical whilst those in the ipsilateral hemisphere are more medially orientated i.e. towards the contralateral hemisphere (Fig 3.10, top right panel). These differences were statistically significant in both the 60 dB SL ($F_{(1,22)} = 14.47; p<0.01$) and 80 dB SL ($F_{(1,22)} = 10.80; p<0.01$) conditions.

In the sagittal plane an angle of -90° indicates a vertical orientation. Angles between 0° and -90° show dipoles orientated anteriorly (with 0° being perpendicular with the vertical) whereas angles between -90° and -180° show dipoles orientated posteriorly (with -180° being perpendicular with the vertical). The contralateral and ipsilateral dipoles showed similar anterior orientations in the majority of conditions, hence no differences were observed statistically. However, in one condition (500-Hz, 80 dB SL) statistically significant differences were observed. With stimulation of the left ear the contralateral dipole was significantly more anterior than the ipsilateral dipole ($F_{(1,22)} = 4.40 \; p<0.05$). However, with stimulation of the right ear the opposite occurred; the contralateral dipole was significantly more vertical than the ipsilateral dipole ($F_{(1,22)} = 5.27 \; p<0.05$). These differences are illustrated in the middle panel of Figure 3.9.
In the axial plane an angle of -90° indicates a tangential orientation. Angles between 0° and -90° show dipoles orientated radially to the left (with 0° being perpendicular) whereas angles between -90° and -180° show dipoles orientated radially to the right (with -180° being perpendicular). As such the patterns of orientations in the axial plane (Figures 3.9 and 3.10, lower panel) closely reflect those already described in the coronal plane. No significant differences were observed in the 500-Hz data. However following right ear stimulation in the 4-kHz condition the dipoles in the contralateral hemisphere were tangential whilst those in the ipsilateral hemisphere were more radially orientated (Figure 3.10, bottom right panel). These differences were statistically significant in both the 60 dB SL ($F_{(1,22)} = 13.53; p<0.01$) and 80 dB SL ($F_{(1,22)} = 12.32; p<0.01$) conditions.

Comparisons between the 500-Hz and 4-kHz dipoles orientations in both contralateral and ipsilateral hemispheres were also carried out. The results of the analysis are shown in Table 3.4. Generally the orientations in each plane were similar across frequencies. However, there were some differences. On presentation to the left ear in the 60 dB SL condition, dipoles in the contralateral hemisphere were significantly more laterally orientated with the 500-Hz stimuli compared with the 4-kHz stimuli. Ipsilateral dipoles were also significantly more anterior with stimulation of the left ear in the 80 dB SL. The most consistent differences were in the coronal and axial planes. In the coronal plane dipoles in the 500-Hz condition were generally more lateral and radial in both hemispheres than those in the 4-kHz condition. In the axial plane dipoles in the contralateral hemisphere were generally more vertical in the 500-Hz condition compared to those in the 4-kHz condition.

Source Strengths: The amplitude of the sources in the contralateral and ipsilateral hemispheres, with corresponding LI values, is displayed in Figures 3.11 and 3.12 for the 500-Hz and 4-kHz stimulus conditions, respectively. These results refer to the grand average dipole source analysis. The source strengths increase in both hemispheres with increasing stimulus level. LI values range from 9% to 32% in the 500-Hz condition and from 19% to 44% in the 4-kHz condition.
Figure 3.6 Top-down view of source modelled grand average scalp topographies for 500-Hz stimuli. Upper row denotes left ear stimulation. Lower row denotes right ear stimulation. Blue contours show negative activity and red contours show positive activity. Each contour represents a 2 µV amplitude increment.
There is a consistent trend for reduced LI with right ear stimulation in both the 500-Hz and 4-kHz conditions. In particular, in the 500-Hz condition the strength of the ipsilateral hemisphere increases markedly with increasing level, whilst the strength of contralateral hemisphere does not. As a result, LI falls from 25% in the 40 dB SL condition to 9% in the 80 dB SL condition. However, despite showing a lower LI value with increasing level, the contralateral dipole remains stronger than the ipsilateral dipole (despite the topographies depicted in the lower panel of Figure 3.6 which suggest ipsilateral dominance in this condition).

The dipole source amplitudes from the individual data were also compared. This was done in two ways; first by comparing the LI values (collapsed across ears and then separately for left and right ears) and secondly by comparing the contralateral and ipsilateral activity separately.

The results of the first comparison (collapsed across ears) are displayed in Figure 3.13. The degree of asymmetry is around 15% in the 500-Hz condition and around 25% in
the 4-kHz condition. Although there is a trend for reduced contralateral dominance with level in the 500-Hz condition, a mixed design (frequency [2] x level [3]) ANOVA conducted on the LI results did not reveal any significant main effect of level ($F_{(2,44)} = 0.62, p>0.05$). This is consistent with the lack of any saturation effects. A main effect of frequency was observed ($F_{(1,22)} = 7.87, p<0.01$) indicating a statistically significantly greater degree of asymmetry with high frequency stimulation. No significant frequency x level interaction was observed ($F_{(2,44)} = 0.17, p>0.05$), therefore the effect of frequency was consistent across all levels of stimulation.

Analyses of LIs according to the ear of stimulation are displayed in Figure 3.14. The mean data shows clear contralateral dominance to stimulation of the left ear, which was around 20% in the 500-Hz condition and around 30% in the 4-kHz condition. However, stimulation of the right ear produced a lower mean contralateral dominance (around 10% contralateral dominance for 500-Hz and around 17% for 4-kHz) with a greater tendency for some individuals to show symmetrical activity or even ipsilateral dominance. Despite the trend, repeated-measures (ear [2] x level [3]) ANOVA did not reveal any significant effects of ear of stimulation either in the 500-Hz condition ($F_{(1,11)} = 1.20, p>0.05$) or the 4-kHz condition ($F_{(1,11)} = 1.41, p>0.05$). The trend for greater LI with stimulation of the left ear was due to right hemisphere dominance. On a group level, a slight asymmetry was found in the 500-Hz condition, with right hemisphere activity between approximately 2% and 5% greater across levels of stimulation. Greater differences of approximately 7% to 12% were observed in the 4-kHz condition, also in favour of the right hemisphere. However, some individuals showed left hemisphere dominance (n=9). Consequently, the pattern of ear specific asymmetry was reversed in these individuals, with greater contralateral dominance apparent following right ear stimulation. As can be seen in Figure 3.14, this has lead to an increased standard deviation across the group, which may explain the lack of significance in the above comparisons.
The strengths of activation in the contralateral and ipsilateral hemispheres are shown in Figures 3.15 and 3.16 for the 500 and 4-kHz stimuli respectively. The strengths of the sources in each hemisphere increase with level. However, the relation between the hemispheres is maintained, giving rise to the results shown in Figure 3.14. The source strengths were further analysed separately using a mixed design (hemisphere [2] x ear [2] x level [3] x frequency [2]) ANOVA, with frequency specified as a between subjects factor. As expected, a significant main effect of hemisphere was observed (F (1,22) = 47.75 p < 0.001), highlighting the greater activity in the contralateral hemisphere. Furthermore, a significant main effect of level was also to be expected as a result of the increasing amplitude with level of stimulation (F (2,44) = 15.00 p < 0.001). However, no significant main effect of ear (F (1,22) = 0.59 p > 0.05) or frequency of stimulation (F (1,22) = 0.29 p > 0.05) was observed. A significant frequency x hemisphere interaction was observed (F (1,22) = 4.42 p < 0.05) indicating that there is a difference in response amplitudes according to frequency when the contralateral and/or ipsilateral hemispheres are considered separately. Bonferroni corrected post-hoc pairwise comparisons revealed that the main effect of level was because amplitudes to stimulation at 40dB SL were significantly lower than those to both 60 dB SL (p < 0.05) and 80 dB SL (p < 0.01). Post-hoc pairwise analysis of the frequency x hemisphere interaction revealed no difference in contralateral amplitudes across frequency, however ipsilateral amplitudes were
significantly lower for high frequency stimulation than for low ($p<0.05$). This gives rise to the significantly greater asymmetries seen for high frequency stimulation.

Figure 3.8 Summary of dipole locations in three orthogonal planes from the grand average data. 500-Hz data are given by filled symbols and 4-kHz data are given by open symbols. Squares denote 40 dB SL data, circles denote 60 dB SL data and triangles denote 80 dB SL data. Red symbols denote stimulation of the right ear and blue symbols denote stimulation of the left ear. Locations displayed for left dipole only.
Figure 3.9 Summary of dipole orientations in three orthogonal planes from the grand average data for 500-Hz stimuli. The dipoles are displayed on a standard fMRI image. The column on the left shows data from stimulation of the left ear and the column on the right shows data from stimulation of the right ear. 40 dB SL data are denoted by yellow and red dipoles; 60 dB SL data are denoted by dark blue and light blue dipoles; 80 dB SL data are denoted by dark green and light green symbols. n.b. fMRI images are reversed by convention, such that the left hemisphere is displayed on the right and the right hemisphere is displayed on the left.
Figure 3.10 Summary of dipole orientations in three orthogonal planes from the grand average data for 4-kHz stimuli. Details as Figure 3.9.
Figure 3.11 Contralateral and ipsilateral source strengths for 500-Hz stimuli based on grand average data. The upper panel shows results of stimuli presented to the left ear. Lower panel shows results of stimuli presented to the right ear. The numbers above each pair of columns are the corresponding LI values for each condition.
Figure 3.12 Contralateral and ipsilateral source strengths for 4-kHz stimuli based on grand average data. Details as for Figure 3.11.
Figure 3.13 Chart showing laterality indices for 500-Hz and 4-kHz conditions, averaged across stimulation of left and right ears. Error bars indicate +/- 1s.d. Laterality Index was statistically significantly greater in the 4 kHz condition across all levels of stimulation. Note that this and subsequent bar charts present the data from a within-, rather than a between-subjects experimental design. Consequently the variability shown here is not that associated with the statistical tests carried out.
Figure 3.14 Chart showing laterality indices for 500-Hz and 4-kHz conditions, separated according to ear of stimulation. Error bars indicate +/- 1s.d.
Figure 3.15 Contralateral and ipsilateral source strengths for 500-Hz stimuli. The upper panel shows results of stimuli presented to the left ear and the lower panel shows results of stimuli presented to the right ear. Error bars indicate +/- 1 s.d. Contralateral source strengths were statistically significantly higher than ipsilateral sources to both ears of stimulation.
Figure 3.16 Contralateral and ipsilateral source strengths for 4-kHz stimuli. The upper panel shows results of stimuli presented to the left ear and the lower panel shows results of stimuli presented to the right ear. Error bars indicate +/- 1 s.d. Contralateral source strengths were statistically significantly higher than ipsilateral sources to both ears of stimulation.
3.4 Discussion

The study aimed to replicate previous findings regarding measuring hemispheric asymmetries using AEPs. A second aim was to investigate the effect of level and frequency of stimulation on contralateral dominance measured using N1 AEPs. The key results of the study are as follows:

- The pattern of ear specific hemispheric asymmetry in the present study was similar to previous findings.
- No clear reduction in the degree of contralateral dominance occurred with increasing level of stimulation in general.
- In one condition (500-Hz stimuli presented to the right ear) a change in contralateral dominance patterns according to scalp topographies was apparent with increasing level; higher levels produced reduced contralateral dominance.
- Greater contralateral dominance was observed with high frequency stimulation compared with low frequency stimulation.

These results do not support the hypothesis that the level of stimulation affects the degree of contralateral dominance, but they do support the hypothesis that hemispheric asymmetries will be different according to the frequency of stimulation. Three particular areas will be discussed in relation to these findings. First, the general behaviour of the N1 AEP waveforms and dipoles will be discussed and compared with previous findings relating to contralateral dominance. Secondly, possible explanations for the lack of effect of changing the level of stimulation and thirdly possible explanations for the greater effect with higher stimulus frequency will be discussed.

3.4.1 Behaviour of N1 AEP waveforms and contralateral dominance

The AEP waveforms and scalp topographies measured in the present study are consistent with previous findings (e.g. Picton et al., 1999). The N1 amplitude increases and latency decreases with level of stimulation. Variations in the response according to frequency of stimulation are also consistent with expectations; from the scalp topographies displayed in Figures 3.6 and 3.7 it is apparent that high-frequency stimuli produced activity that is maximal more anteriorly than was the case for low frequency stimuli. The scalp topographies also show N1 activity to be maximal over the
hemisphere contralateral to the ear of stimulation, which is consistent with the results of the studies summarised in Table 3.1. The results of the source modelling analysis reflect this contralateral dominance, with dipole strengths showing that source activity is greater in the contralateral hemisphere.

The degree of asymmetry in dipole strength has previously been found to depend on the side of stimulation; greater asymmetries are typically seen when stimulating the left ear as a result of greater N1 activity in the right hemisphere compared with the left. Studies analysing sensor level data such as Connolly (1985) and Wolpaw and Penry (1977), as well as those employing source modelling such as Hine and Debener (2007) using AEPs and Yu et al.(2007) using AEFs have all reported this ear specific effect. The trends noted in the present study corroborate these reports.

Comparison of responses from each hemisphere demonstrates right hemisphere dominance on average. This has also been reported previously (e.g. Hine and Debener, 2007; Yu et al., 2007). On a group level this leads to an interaction effect; greater lateralisation of responses occurs with stimulation of the left ear due to a combination of greater contralateral activity following left ear stimulation, and greater ipsilateral activity following right ear stimulation. Therefore the larger response from the right hemisphere leads to the trend for ear specific pattern of contralateral dominance. There could be several causes of right hemisphere dominance such as functional and/or anatomical differences between the hemispheres. A prominent line of evidence based on studies employing dichotic listening tests has revealed functional differences between auditory processing in the left and right hemispheres. Functional specialisation in humans was first demonstrated by Broca (1861). By studying the site of lesions, Broca found that language was almost always disturbed by damage to the left hemisphere, but not by damage to the right. Subsequently these functional differences have been examined in great detail. The left auditory cortex is thought to be more sensitive to the processing of rapidly changing sounds whereas the right auditory cortex is sensitive towards the tonal aspects of stimuli such as the melodic aspects of music (for a review see Zatorre et al., 2002). With this in mind, the right hemisphere dominance has previously been attributed to its greater sensitivity towards tonal stimuli, leading to the interaction effects when stimuli are presented to the left and right ears separately (Hine and Debener, 2007).
On the other hand not all studies have clearly demonstrated right hemisphere dominance. The control participants in the study reported by Khosla et al. (2003) gave the same degree of contralateral dominance irrespective of the ear of stimulation. One suggestion in the literature attributes this finding to the use of click stimuli (i.e. a train of clicks presented in rapid succession). Due to their short duration, clicks do not produce a favourable signal-to-noise ratio for source modelling purposes (Hine and Debener, 2007). However this does not seem to adequately explain why equal contralateral dominance was observed following stimulation of either ear; if anything more erratic results may be expected. None the less, the stimuli used by Khosla et al. (2003) might be expected to produce left hemisphere dominance if it is the case that tonal stimuli produce right hemisphere dominance, yet this was not found either. The functional differences between hemispheres therefore do not seem to fully explain the findings.

It is notable that results from the present study show a more complicated pattern of hemisphere dominance on an individual basis than was suggested on a group level, or indeed than has been reported previously. Although the mean results show right hemisphere dominance, some individuals (n=9) were apparently left hemisphere dominant. In these individuals the pattern of ear specific contralateral dominance reversed i.e. stimulation of the left ear lead to a reduced hemispheric asymmetry and stimulation of the right ear lead to greater asymmetry. This finding may explain why the trends did not reach statistical significance, but is not easily explained in terms of possible interactions of the contralateral pathway asymmetry with functional specialisations in each hemisphere, given that all participants were right handed. However, it is important to note that individual variations in functional hemisphere specialisations are likely to exist (Davidson, 1988). Some individuals will show less right hemisphere dominance than others, and some individuals will show left hemisphere dominance. Alternatively it may be that anatomical differences between hemispheres account for differences in the amount of activity apparent from each hemisphere. Discussions by Naatenan and Picton (1987) and Cacace et al. (1988) indicate that hemispheric asymmetries that persist through various experimental manipulations are in fact more likely to be a reflection of the size and geometry differences between the auditory cortices in the left and right hemispheres such as reported by Geschwind and Levitsky (1968), rather than differences in the amount of processing occurring in each hemisphere. Naatenan and Picton (1987) argue that
functional differences between the hemispheres are likely to explain different patterns of ear specific asymmetries only when the same stimulus is perceived in different ways and under different conditions. However this is not typically the case in studies investigating contralateral dominance, including the present one. Future studies which compare hemisphere dominance measured using AEPs or AEFs with anatomical information, for instance via MRI scans, would provide the answer more definitively.

Moreover, with respect to investigating experience-related plasticity following unilateral deafness, the implications of the present findings may go some way towards explaining the variability in the existing AEP and AEF literature. There is no way to identify whether an individual with unilateral deafness is right or left hemisphere dominant when attempting to compare with control samples, which means matching for this variable is impossible. Furthermore, when left and right hemisphere dominant groups are combined in control samples the variability will increase, reducing statistical power accordingly, which implies that matching for hemisphere dominance is important. At the very least future studies investigating plasticity will benefit from qualifying laterality measures with separate estimations of contralateral and ipsilateral hemisphere activity to minimise the effect of this potential problem.

### 3.4.2 Effect of stimulus level

The motivation for investigating the effect of level of stimulation on the degree of contralateral dominance lies with the possibility that asymmetries may become attenuated at high levels. This concept is based on the tendency for the auditory evoked potentials to saturate with level. Since the contralateral response is greater in amplitude following monaural simulation then it would also be expected to saturate before the ipsilateral response. As a result, high level stimuli were hypothesised to lead to a reduced contralateral dominance which would make choosing the correct stimulus level important in studies using measures of hemispheric asymmetry to investigate experience-related plasticity. No clear evidence for N1 response saturation was seen in the present study and the relation between contralateral and ipsilateral hemispheres was maintained at all levels of stimulation.

Despite the majority of studies involving normally hearing individuals reporting saturation to occur at around 70 dB SL, other instances where no evidence for saturation at levels well above this mark have previously been reported (Billings et al., 2007).
that study an inter-stimulus interval of 1919 ms was used when presenting sound field stimuli in order to investigate the effects of level on aided cortical evoked potentials. The authors attributed the lack of saturation effects to the length of the inter-stimulus interval, since intensity asymptotes are more apparent with short inter-stimulus intervals (Picton et al., 1970). The present study employed an overall average inter-stimulus interval of 1100ms. However, as opposed to a blocked design, stimuli were presented to each ear in a pseudorandom fashion in order to minimise response habituation and to allow a valid comparison of activity in each hemisphere. Clearly, comparing activity from each hemisphere was an important component of the methodology, although this approach effectively doubles the inter-stimulus interval at each ear. This is the most likely cause of the lack of any clear saturation effects. Nevertheless the N1 response will still ultimately saturate. Therefore, although the hypothesis was not tested adequately in the present study, at least the results show that over the range of levels used, it is possible to rule out any influence of stimulus level. This is important for interpretation of the results of future studies investigating plasticity following unilateral deafness. It is noteworthy that the results from one condition did show evidence of a shift in asymmetry with increasing level. Stimuli presented to the right ear in the 500-Hz condition seemed to evoke a contralateral dominant response at 40 dB SL, but a more symmetrical activation in the 60 dB SL condition and an ipsilateral dominant pattern in the 80 dB SL condition. This is based on the grand mean scalp topographies in Figure 3.6. The changes in topography were reflected by reduced LI values through increased ipsilateral source activity, and altered dipole orientations. Despite observing no clear saturation effects overall, it may be argued that this condition is the most susceptible to the effect of level for two reasons. First, low frequency stimuli evoke a more robust N1 due to basalward extension of excitation on the basilar membrane recruiting more neurons. Second, greater activity was typically seen in the right hemisphere, which would be expected to boost the ipsilateral response when presenting to the right ear. Another outcome from this finding is that even though the scalp topographies showed activity to be maximal over the ipsilateral hemisphere at the highest presentation level, the dipole sources still showed contralateral dominance, albeit of reduced magnitude. This is because the scalp topographies were reflected in the source model by a change in orientation and location of the dipoles as well as strength. This could be a useful clue in explaining some of the variability in studies investigating plasticity following unilateral deafness. It might be that changes in activity patterns across the scalp are not necessarily reflected simply by altered dipole strengths, but also
by orientation and location parameters. Not all studies have controlled for these variables and the issue will be discussed further in Chapter 4. It does mean, however, that LI values used to normalise activation strengths between hemispheres are therefore of limited value because in source modelling procedures they only provide a summary of one variable (dipole strength) out of a possible three (dipole strength, orientation and location).

The decision to choose a particular level of presentation in future studies can be informed by these results. As mentioned earlier, higher level stimuli produce greater signal-to-noise ratios, which is particularly important for accurate source modelling. However this must also be balanced against the need to minimise any potential level effects on contralateral dominance, minimise interaural cross talk and maintain comfortable listening levels for participants. Whilst the participants in the present study could all comfortably tolerate sounds presented at 80 dB SL, this will not always be the case in individuals with reduced hearing sensitivity in the test ear (for example due to presbyacousis) where, depending on the degree of sensory impairment, achieving sound levels of 80 dB above absolute threshold is more likely to lead to loudness discomfort. On this basis 60 dB SL is a more appropriate level with which to present sounds to such individuals. However, these findings show that variation in absolute level in either direction (due to differences in thresholds between individuals) is unlikely to have a dramatic effect on contralateral dominance, at least over the range of levels and inter-stimulus intervals used here.

3.4.3 Frequency of stimulation

Previous studies have shown changes in scalp distribution as a function of frequency of stimulation, indicating that some or all of the underlying N1 generators are tonotopically organised (Woods, 1995; Alain et al., 1997). The results of the present study reflect these findings; higher frequency stimuli produced more frontally located negativity than for lower frequencies. The dipoles were also located more laterally and anteriorly for high frequency stimulation compared with low.

In line with the experimental hypothesis, high-frequency stimuli were found to produce significantly more lateralised activation than low frequency stimuli. This is consistent with findings elsewhere, for example in animal models studied electrophysiologically (Popelar et al., 1994; Gross et al., 1967) and humans when studied via functional MRI.
(Hall, D.A., personal communication, 2007). Based on evidence from animals using implantable electrodes it appears that frequency specific hemispheric asymmetries arise from anatomical asymmetries and can vary between subdivisions of the cortex (Tunturi, 1952). This implies that binaural interactions and/or the degree of functional hemisphere specialisation also vary in this manner. The present study does not provide detailed anatomical information, which limits detailed discussion and conclusions. However, analysis of activation strengths in each hemisphere revealed that contralateral hemisphere activity was comparable for both high and low frequencies whereas significantly weaker ipsilateral responses to high-frequency stimuli were seen compared with low frequencies. In other words, high-frequency stimuli give a strong contralateral and relatively weaker ipsilateral response. Such a finding is consistent with the generally weaker response that is commonly seen to high frequency stimulation when presented at constant levels of either stimulus intensity or loudness (Woods, 1995). This suggests the frequency specific difference is due to a sensitivity issue; generally the high frequency responses are weaker than the low frequencies, but this is more apparent in the ipsilateral hemisphere. This leads to a larger asymmetry for high-frequency stimuli. However, such an explanation cannot fully explain the finding since if it was purely a sensitivity issue then an interaction effect should occur with level; frequency specific differences in hemispheric asymmetries should be less with higher levels of stimulation, yet no clear differences were seen with level. The full explanation is unclear at present but could involve a combination of both sensitivity issues and anatomical asymmetries across frequencies. It would be interesting to learn whether or not the level of presentation has an effect in fMRI measures that are not subject to the same types of difficulties in differentiating responses from sub-cortical areas as are AEP (and AEF) measures.

The finding of frequency dependent contralateral dominance has implications for the interpretation of any shifts in hemispheric asymmetries following unilateral deafness. It is unclear whether the pattern of any reorganisation following unilateral deafness is different across frequencies (Khosla et al., 2003). If so, it will be important to consider whether or not, with all other aspects considered, changes are simply more readily apparent to high-frequency stimuli or whether there are underlying frequency specific differences.
3.5 Conclusions

An important observation with respect to the aims of the present thesis is that the approach used here to measure contralateral dominance produced results that are consistent with previous findings. In particular, the degree of contralateral dominance varied according to the ear of stimulation; it was more apparent following stimulation of the left ear. The variability in the present results suggests that the reasons for these ear specific differences are more complex than previously thought i.e. there may be additional or alternative explanations than merely interactions with functional differences between the hemispheres. In any case, on this basis it seems reasonable to conclude that the source modelling techniques used in this study are suitable for measuring hemispheric asymmetries in individuals with unilateral deafness. This study also investigated two further hypotheses, the understanding of which will inform the subsequent studies in this thesis. They also make incremental contributions to the existing knowledge. With respect to the level of presentation, the present study shows that, at least given sufficient inter-stimulus interval to minimise saturation of the N1 response, contralateral dominance is consistent over a range of stimulus levels. Not only can more practical considerations such as loudness discomfort be made more readily, but in studies where hearing impairment in the test ear forces an adjustment to the level of presentation (such as with sloping high frequency sensory losses that are common in individuals with unilateral deafness) these results indicate that the measures of hemispheric asymmetry will not be affected. Nevertheless, the influence of level on the somewhat mixed outcomes of previous studies that have used shorter inter-stimulus intervals can not be ruled out. Finally, hemispheric asymmetry is greater following high frequency stimulation. Although the reasons for this are as yet unclear, at least the present results indicate that the effects of stimulus level are the same at low and high-frequency stimuli.
Chapter 4: Effects of late onset unilateral deafness on contralateral dominance in adult humans

4.1 Introduction

In the previous two chapters it has been explained that whilst the results from studies using fMRI to investigate experience-related plasticity after unilateral deafness are consistent with findings from animal models, results from studies using AEPs and AEFs are not. Although the explanation for this discrepancy is unclear at present, there are likely to be several contributory factors. These can be divided broadly into two categories; participant factors and methodological factors.

Participant factors refer to issues such as differences between individuals in the cause, duration and/or severity of deafness, and/or simply individual differences in ‘adaptability’ to changes in sensory input (Makela, 2006; Hine et al., 2008). This ‘adaptability’ is a rather vague term that has been used by others to refer to differences between individuals, the origins of which are as yet unclear. For example there are several reports of reduced hemispheric asymmetries in some individuals that were not reflected on a group level even though other participant factors such as cause of deafness were common between individuals (Vasama and Makela, 1997; Vasama and Makela, 1995; Fujiki et al., 1998). It is known that the extent (and variability in measures) of contralateral dominance in N1 activity depends on the ear of stimulation. In normally hearing listeners monaural presentation to the left ear produces activity that is more asymmetrical and less variable between individuals than presentation to the right ear (Hine and Debener, 2007; Yu et al., 2007; Wolpaw and Penry, 1977). Similar findings were obtained in study 1 of this thesis. This suggests that showing changes in normal contralateral dominance using a between-groups approach may be problematic, at least with limited numbers of participants, when individuals present with deafness on the left side (and hence receive stimuli via the right ear). Due to the greater variability with stimulation of the right ear, the N1 activity may not show hemispheric asymmetries that are noticeably different from normally hearing individuals when analysed on a group level, even when changes may have taken place amongst individuals. The results reported by both Fujiki et al. (1998) and Hine et al. (2008) may have been affected by this issue. Of the 17 unilateral deaf individuals described by Fujiki et al (1998), 14 were affected on the left side. More recently Hine et al. (2008)
studied the N1 AEP. Pure tone (1 kHz) and broad band noise burst stimuli were presented to six individuals with unilateral deafness. All participants had several years’ experience, four of whom had left ear deafness and two with right ear deafness as a result of surgery for the removal of an acoustic neuroma. Six matched control participants were also used, with bilateral sensitivity thresholds equivalent to those of the healthy ear of the unilaterally deaf participants. The matched controls (and a third group of 16 normally hearing controls that were not matched) showed clear contralateral dominance to stimulation of the left ear and more variable responses to stimulation of the right ear in line with expectations. However the hemispheric asymmetries in those with unilateral deafness showed no clear differences; thus, no evidence of experience-related plasticity was observed.

Furthermore, there is speculation that some form of recovery of N1 activity may mask any initial changes when individuals are studied at a much later date after the onset of unilateral deafness. If true this would help to explain much of the confusion to date, since all but one of the AEP and AEF studies described in the literature so far are retrospective in design and often the participants have a history of deafness spanning several years. There is some supporting evidence for recovery of N1 function. For example an early study into the effects of unilateral deafness on human CAS activity was carried out by Vasama et al. (1995) using AEFs. Eight individuals with permanent unilateral deafness took part in the study. Their deafness was caused by surgery for the removal of an acoustic neuroma. Four were affected on the left and four on the right. Each individual was seen post-operatively and the response to stimulation by 1 kHz tones was compared with that of nine normally hearing individuals acting as controls. Most of the deafened individuals were examined several years post-operatively and no differences in the N1m response amplitudes (or latencies) compared to the control group were apparent. However, two participants were seen shortly after the onset of deafness and on several occasions during the following year. Around two months after onset the N1m responses were both weak and delayed compared with controls. These results suggest possible disruption to the synchrony of neural firing immediately after surgery. However over the following year the subsequent measures showed the N1m activity to have recovered to the levels seen in control participants, with normal patterns of hemispheric asymmetries. The authors speculate that any changes in activity patterns through mechanisms of plasticity may have been counter-acted by the removal of the tumour and the disruption to auditory processing that this entails, with the effect of
spontaneous activity arising from the deafened ear presumably thought to influence binaurally responsive neurons.

Although all of these issues could be clarified by carrying out a longitudinal study of individuals with the same aetiology from prior to the onset of deafness (addressed in Chapter 5), they cannot fully explain the contradictory findings. There is already clear evidence for experience-related plasticity in individuals irrespective of the aetiology and duration of deafness, and the ear of deafness (Bilecen et al., 2000; Firszt et al., 2006; Langers et al., 2005; Scheffler et al., 1998; Ponton et al., 2001), and irrespective of any short term disruption to the synchrony of neural firing (Ponton et al., 2001; Morita et al., 2007). Therefore, although controlling for participant factors is important, there must be an additional explanation for the mixed AEP and AEF results. The most likely explanation lies with methodological factors affecting previous studies.

Methodological factors refer to differences between or limitations of studies regarding the way in which hemispheric asymmetries are measured. The principle limitation in existing AEP and AEF studies of plasticity following unilateral deafness is the lack of consideration of the dipole orientation and location in each hemisphere. It is clear from some of the findings described in Chapter 3 that substantial changes in the pattern of activity across the scalp may be reflected by two dipoles with asymmetrical source strength in favour of the contralateral hemisphere. The altered pattern of activity is simply reflected in the model by altered dipole location and orientations in each hemisphere (with the stronger dipole having the most influence). Therefore consideration of asymmetries in dipole strength alone may lead to the impression that no experience-related plasticity has occurred in individuals with unilateral deafness when compared with controls. One way to determine whether or not this is the case in the AEP and AEF studies to date would be to compare the overall response strengths between groups (e.g. using global field power measures) as this measure is independent of hemispheric asymmetries. Increased responsiveness of CAS neurons to stimulation of the intact ear should result in increased N1 amplitude in global field power.

Unfortunately, no study has made any such comparisons to date. However, it is clear that the few studies involving AEPs and AEFs to have reported altered hemispheric asymmetries in line with evidence from fMRI studies would not have been affected by dipole location or orientation variables (Ponton et al., 2001; Morita et al., 2007; Li et al., 2006). Morita et al. (2007) seeded a dipole in the contralateral and ipsilateral
hemisphere and the locations and orientations of each dipole were then fixed. Subsequently, only the strength of activation in each hemisphere was allowed to vary in order to explain the activity patterns recorded at the scalp. In individuals with unilateral deafness this resulted in a dramatic increase in ipsilateral source strength in order to reflect any altered activity patterns. Although a similar result was reported by Li et al. (2006), there was insufficient information provided in the methodology to confirm whether or not the dipole location and orientations were also fixed a priori. However, the key example demonstrating reduced contralateral dominance using AEPs was reported by Ponton et al. (2001). The details of this study were provided in Chapter 2. N1 activity from 15 individuals with unilateral deafness was compared with nine normally hearing controls. A key aspect of the methodology was that the analysis was based on sensor level data. In order to avoid the complications associated with comparing activity at discrete sensor positions, the average activation across groups of sensors was compared. The analysis was performed in two stages. In the first stage, the average activity across all of the sensors over each hemisphere (13 sites on each hemisphere) was compared. In the second stage, the activity across a subset of several sensors at various scalp regions (i.e. central, frontal, temporal and parietal) was compared. Results from the first analysis showed that while the response amplitude over the contralateral hemisphere was similar between the groups, the ipsilateral amplitude was significantly greater in those with unilateral deafness compared with controls. These changes were subsequently found to be reflected primarily by sensors in the central scalp regions. This change is consistent with a reduction in contralateral dominance of N1 activity. The tendency for these changes to occur in central regions is consistent with N1 activity with a low frequency emphasis, as per the nature of the click stimuli, which produces maximal activity in those regions.

This study is the only example to demonstrate experience-related reorganisation in humans with long term unilateral deafness that is consistent with findings from animal studies and from fMRI studies involving humans. As such, it is important to confirm these findings, taking into account the participant and methodological factors described above.

There are a number of limitations to the study of Ponton et al. (2001) which have not been addressed adequately. First, although the sensor level approach to comparing activity over each hemisphere requires a straightforward comparison of response
amplitudes, the analysis is restricted to the sensor positions that are chosen beforehand. On the other hand dipole modelling techniques have the advantage that they can be used to analyse the scalp potential waveforms that are maximal at any location. This may be particularly useful when different stimulus types produce activity that is maximal at different scalp locations (e.g. high frequency versus low frequency stimuli). Secondly, unlike most studies that typically use either pure tone or broad band noise bursts, the stimuli in the study of Ponton et al. (2001) consisted of a series of broad-band clicks presented in rapid succession. These were intended to emulate the auditory nerve input produced by applying a current to the electrode array of cochlear implant patients, although the exact relevance given the present context is unclear. In any case, the N1 activity recorded at the scalp is likely to be dominated by the low-frequency content of the click stimuli. This has been attributed to phenomena such as basal-ward extension of excitation on the basilar membrane and the more shallow position of low frequency neural generators in the auditory cortex compared with high frequency generators. However, although experience-related plasticity following unilateral deafness would be expected across the frequency range, it seems important to use frequency specific stimuli at both high and low frequencies. The basis for this was detailed in Chapter 3 and is related to two opposing hypotheses. On the one hand, there is reason to suspect that the balance of excitatory and inhibitory synaptic activity (the physiological mechanisms implicated in driving experience-related plasticity) changes according to frequency. Disinhibition, and potentially the pattern of changes following this, may have a greater effect (at least initially) in high frequency regions (Reser et al., 2000). On the other hand, the gradually sloping high frequency hearing loss that is typical of the intact ear in most adults with unilateral deafness might lead to greater cortical representation of low frequency input (Frisina and Rajan, 2005). Subsequent reorganisation following unilateral deafness might therefore be more apparent with low frequency stimuli. To date this issue has not been investigated in humans. A third limitation of the study by Ponton et al. (2001) was that it did not differentiate between left and right ear deafness. Although fMRI studies have shown reorganisation to occur in humans following unilateral deafness in either ear, given the apparent sensitivity of the N1 response to functional hemispheric asymmetries this can be regarded as an important area where current understanding is limited. In order to address this limitation the data from the study by Ponton et al. (2001) was re-analysed and re-published by Khosla et al. (2003). As well as considering each ear separately the data was analysed using source modelling procedures instead of the sensor level analysis. A spatio-
temporal source modelling procedure was used where the strengths and orientations of dipoles in each hemisphere were allowed to vary within a defined latency window around the peak of N1 activity. Importantly however, only the dipole strengths were subsequently compared between the experimental and control groups. Two analyses were performed on the source strengths in each hemisphere of each group. First, an initial group analysis of dipole strengths for both overall activity (RMS of the activity in each epoch) and the N1-P2 activity was carried out. In order to demonstrate congruence with the findings of Ponton et al. (2001) following the addition of the source analysis step, the initial analysis did not differentiate between left and right ear deafness. The control group showed amplitudes around 25-30% larger in the contralateral hemisphere compared to the ipsilateral hemisphere, whilst the unilaterally deaf group showed significantly reduced differences of approximately 15%. These results are consistent with the original study. However whilst in the original study the ipsilateral hemisphere amplitude was found to be greater in those with unilateral deafness compared with controls (as may be expected based on an increase in CAS response), the dipole strengths were consistently weaker in those with unilateral deafness; i.e. although the hemispheric asymmetries were reduced in those with unilateral deafness, the overall strength was also reduced.

A subsequent analysis was carried out according to the ear of stimulation. Two further intriguing findings were reported in this analysis. The first was that the degree of contralateral dominance in normally hearing controls did not differ according to ear of stimulation. Second, in terms of amplitudes, reduced contralateral dominance was only observed in individuals with left ear deafness following stimulation of the right ear. Those participants with right ear deafness showed hemispheric asymmetries that were no different from the control participants. However, latency differences in responses from each hemisphere were reduced following right and left ear deafness. The results from the first analysis are hard to explain given that the expectation is for increased overall activity following unilateral deafness and given that the same data, when described previously by Ponton et al. (2001), did show such an increase. The finding that experience-related plasticity only occurs following left ear deafness is also difficult to explain since other studies have clearly demonstrated plasticity subsequent to both right and left ear deafness in humans (e.g. Scheffler et al., 1998; Bilecen et al., 2000; Firszt et al., 2006). The obvious area for scrutiny is with the methodology surrounding
the additional source modelling procedures that were carried out, in particular regarding the effect of any differences in dipole orientations between the groups.

A more recent study has also considered the effect of left and right ear deafness (Hanss et al., 2009). Eighteen individuals, eight with left-sided and 10 with right-sided acquired unilateral deafness were studied. N1 activity in response to stimulation using tones and speech like signals were compared with 16 normally hearing controls. Contralateral dominance estimates were based on N1 (and P2) amplitudes measured directly from a pair of sensors located at posterior-temporal locations on each side of the head. Monaural stimulation in controls produced conventional patterns of contralateral dominance. Eight control participants receiving stimulation of the left ear showed clear contralateral dominance to both stimulus types whereas the remaining eight who received right ear stimulation produced more symmetrical activity on average, but with greater variability. Individuals with right ear deafness receiving stimulation in the left ear also showed contralateral dominance that was not significantly different to controls. The overall activity in deaf individuals was not significantly stronger compared with controls either, thus no evidence of increased activity or reduced hemispheric asymmetries was apparent. The same was true of individuals with left ear deafness receiving tonal stimuli to the right ear. However, the speech-like stimuli did produce enhanced ipsilateral activity, causing a shift towards ipsilateral dominance in terms of both amplitude and latency in those with left ear deafness. These findings appear to corroborate those of Khosla et al. (2003), at least with respect to broad band stimuli. However, the results should be treated with caution since the validity of comparing hemispheric asymmetries between groups based on sensor level data from discrete positions on the scalp has already been called into question. This may explain why differences between groups were observed using one stimulus type and not the other, and upon presentation to the right ear but not the left, since the auditory cortices are known to be located asymmetrically between the hemispheres (Pantev et al., 1993). Due to the potential methodological issues of these reports the ear specific nature of experience-related plasticity in humans remains inconclusive, at least with respect to N1 activity.

The study described in this chapter had two main aims. The first was to compare the strength of activation between unilaterally deaf and normally hearing individuals. It was hypothesised that an overall increase in response amplitude will be apparent in those
with unilateral deafness reflecting an increased responsiveness of CAS neurons to stimulation of the intact ear. The second aim was to compare contralateral and ipsilateral hemisphere activation between unilaterally deaf and normally hearing individuals. It was hypothesised that a reduction in the normally observed contralateral dominance will occur in conjunction with the increased overall response amplitude. This is because increased neural activity is expected to occur primarily in the ipsilateral hemisphere. An opportunity was also taken to investigate any frequency- or ear-specific differences in the results. Although any changes should occur across the frequency range, the pattern of changes might be different for high-frequency stimuli compared to low. Further, although some evidence exists to suggest there are ear specific differences in experience-related plasticity in the N1 response, this is not consistent with fMRI findings in humans and may be related to the methodological issues discussed above. It was therefore predicted that any apparent experience-related plasticity would occur irrespective of the ear of deafness.

4.2 Methods

4.2.1 Participants

Nineteen unilaterally deaf participants took part in the study. This number was determined by statistical power analysis based on the results presented by Ponton et al. al. (2001). A “large” effect size, described by Cohen (1992) of at least 0.80 provides a known benchmark from which to judge statistical power. The effect size in the study by Ponton et al. (2001), based on the F statistic of 4.62 and the first degree of freedom equal to 1, which signified a difference in AEP amplitude between groups, was 0.94. On this basis, for a two-tailed parametric significance test the number of participants required to give a statistical power in excess of 80% (at p < 0.05) was 17. Nineteen were therefore recruited to allow for attrition.

To minimise variation between participants the unilateral deafness was due to surgery for the removal of a unilateral acoustic neuroma. In all participants, the acoustic neuroma was accessed via the translabyrinthine surgical approach. When removing an acoustic neuroma there are a number of options available to the surgeon in order to access the lesion, the choice of which depends on its size and location amongst other considerations. The main advantage of the translabyrinthine approach is that the potential for damage to the facial nerve, which runs along the internal auditory meatus,
is minimised. However, the inner ear is removed which results in complete abrupt deafness that is similar in nature to experimentally induced deafness in animal studies using cochlear ablation. The participants in this study (6 female, 13 male; 43 – 75 years old; mean = 60 years) had between 6 months and 7 years history of deafness post-surgery and all were right handed according to the EHI (Oldfield, 1971). Matched to each was a control participant whose hearing thresholds in both ears matched the participant’s intact ear to within 10 dB at 500-Hz and 4-kHz. The mean audiogram for participants with right ear deafness (n=12) is shown in Figure 4.1. Independent samples t-tests showed that there were no statistically significances differences in pure tone thresholds of each group at either 500-Hz ($t_{22} = 0.84, p>0.05$) or 4-kHz ($t_{22} = 1.60, p>0.05$). The mean audiogram for participants with left ear deafness (n=7) is shown in Figure 4.2. Independent samples t-tests showed that there were no statistically significances differences in pure tone thresholds of each group at either 500-Hz ($t_{12} = 0.44, p>0.05$) or 4-kHz ($t_{12} = 1.39, p>0.05$). Detailed audiometric information for each participant is displayed in Table A7 in Appendix A. The participants were also matched for sex, handedness and age (controls: 42 – 74 years old; mean = 58 years). They were not matched for hemisphere dominance as it is not possible to obtain this information from individuals with unilateral deafness, since it requires comparison of responses from each hemisphere to stimulation of each ear. The study was approved by the Cumbria and Lancashire NHS Research Ethics Committee (08/H1016/66) and all participants gave written, informed consent.
Figure 4.1 Mean pure tone thresholds of the intact ear for participants with right ear deafness and matched controls. Error bars denote +/- 1 s.d.

Figure 4.2 Mean pure tone thresholds of the intact ear for participants with left ear deafness and matched controls. Error bars denote +/- 1 s.d.
4.2.2 Paradigm

As in the previous study two pure tones (500-Hz and 4-kHz) were selected to represent low and high-frequency stimuli. These were of 80 ms duration including 10 ms onset and offset ramps, defined using the Blackmann windowing algorithm. The stimuli were generated digitally and presented via a 44.1 kHz digital-analogue converter monaurally to the intact ear of participants with unilateral deafness, and the corresponding ear in control participants. Stimuli were presented in a pseudo randomly interleaved fashion via ER-3A insert earphones. The inter-stimulus interval varied pseudo randomly between 900 and 1300 ms. Each stimulus was presented in blocks of 500 repetitions and the order of frequency of presentation was counterbalanced across participants. Level was fixed at 60 dB SL, although several participants and their matched controls received reduced levels of 40 dB SL in the 4-kHz condition due to subjective loudness discomfort. In light of the lack of level effects on hemispheric asymmetries described previously no distinction was made between any responses evoked at a lower sensation level. The absolute presentation levels varied by up to 30 dB between participants. Passive attention to the stimuli was maintained through watching a silent closed-caption movie for the duration of each session.

4.2.3 EEG recording

The details of this aspect of the study were the same as described in section 3.2.3 in the previous chapter.

4.2.4 Data processing

The details of this aspect of the study were the same as described in section 3.2.4 in the previous chapter. Following EOG correction and artefact rejection procedures an average of 470 (1 s.d. = 36) epochs were accepted in each run.

4.2.5 Dipole source analysis

The details of this aspect of the study were the same as described in section 3.2.5 in the previous chapter.

4.2.6 Analysis

The analysis was carried out in two stages. The first compared overall response amplitudes using GFP. The N1 response was objectively identified in GFP using a peak
detection algorithm sensitive to the maximum amplitude in the latency range of 70 to 130 ms. The mean amplitude over a latency range +/- 10ms about this peak was then obtained for comparison between groups. In all cases where assumptions of normality of distribution and equality of variance were met, parametric tests were used to compare means between matched groups. Within subjects t-tests and multi-factor ANOVA were used because matched pairs are treated as if the measures were repeated on the same subject. In both cases, the variance that the two members of the pair have in common is effectively removed (assuming they are matched appropriately). If there is substantial variance in common (i.e. the variable on which the matching was done does have an effect on the dependent variable) then sensitivity is validly increased by treating them as matched. If there is no variance in common then the paired test will still be valid; it will just have no advantage in sensitivity over the non-matched between groups ANOVA (Bland and Altman, 1994). The second analysis stage involved dipole source modelling and the details of this aspect of the analysis were the same as described in section 3.2.6 in the previous chapter.

4.3 Results

Figures 4.3 and 4.4 show the grand average waveforms to 500-Hz and 4-kHz stimuli presented to individuals with right ear deafness and the matched control group. Similar information is displayed in Figures 4.5 and 4.6 for those with left ear deafness and the respective matched control group. The vertex-maximal N1 response is the most prominent component and was present in all conditions. In general the response characteristics in both participant groups were similar to those described in Chapter 3.

Figure 4.7 displays the topographic maps corresponding to the grand average waveforms displayed in Figures 4.3 to 4.6. In controls the response from each hemisphere is asymmetrical. The regions of maximal N1 activity are centred over the contralateral hemisphere relative to the ear of stimulation. This is apparent in all conditions. The amplitude of maximal activity is also generally greater for the 500-Hz stimuli compared to the 4-kHz. In unilateral deaf participants the response from each hemisphere appears less asymmetrical. Similar differences seem to occur between participants and controls for both left and right ear deafness and with 500-Hz and 4-kHz stimuli (although this is less obvious in the 4 kHz condition for individuals with left sided deafness than for the other conditions).
Figure 4.3 Grand average waveforms from twelve participants with right ear deafness receiving 500-Hz stimuli in the left ear. The blue lines denote responses to participants whereas green lines show equivalent responses from twelve matched controls.
Figure 4.4 As Figure 4.3 but for 4-kHz stimulation.
Figure 4.5 Grand average waveforms from seven participants with left ear deafness receiving 500-Hz stimuli in the right ear. The red lines denote responses to participants whereas green lines show equivalent responses from seven matched controls.
Figure 4.6 As Figure 4.5 but for 4-kHz stimulation.
Figure 4.7 Top-down views of sensor level topographic maps. Each map is compiled from the corresponding grand average waveform displayed in Figures 4.3 to 4.6. The top two rows display the results from left ear stimulation to participants with right ear deafness. The bottom two rows display the results from right ear stimulation to participants with left ear deafness. The black dots represent each sensor position.
4.3.1 Global field power analysis

The overall amplitude of activity based on GFP was compared between individuals with unilateral deafness and the matched controls. The results are displayed in Figure 4.8. There is a trend for greater response amplitudes in those with unilateral deafness to stimulation of the intact ear. The response is larger by around 16% for both types of stimuli. However, these results did not reach statistical significance at either 500-Hz ($t_{(18)} = 1.71; p > 0.05$) or 4-kHz ($t_{(18)} = 1.24; p > 0.05$).

Figure 4.8 GFP results for participants and matched controls collapsed across ear of stimulation. Error bars denote +/- 1 s.d.

A further analysis was carried out according to the ear of stimulation. The results are displayed in Figure 4.9. A similar trend for greater response amplitudes was observed following unilateral deafness compared with controls irrespective of the ear of deafness. For those with right unilateral deafness, a 2-factor (group [2] x frequency [2]) repeated-measures ANOVA did not reveal any statistically significant main effect of group ($F_{(2,6)} = 0.37; p > 0.05$), frequency ($F_{(2,6)} = 0.52; p > 0.05$) or any interaction effects ($F_{(2,6)} = 1.09; p > 0.05$). For those with left unilateral deafness, a 2-factor (group [2] x frequency [2]) repeated-measures ANOVA again did not reveal any statistically significant main effect of group ($F_{(2,11)} = 1.93; p > 0.05$), frequency ($F_{(2,11)} = 0.03; p > 0.05$) or any interaction effects ($F_{(2,11)} = 0.34; p > 0.05$).
Figure 4.9 GFP results separated according to the ear of stimulation. Top panel shows results for individuals with right ear deafness and stimulation of the left ear (n=7) along with matched controls. The bottom panel shows the equivalent results for individuals with left ear deafness and stimulation of the right ear (n=12). Error bars denote +/- 1s.d.
4.3.2 Source modelling of AEPs

In response to 500-Hz stimuli the residual variance for grand average AEPs ranged between 5.4% and 7.7% across all groups. In the 4-kHz condition the residual variance of grand average AEPs was between 5.6% and 7.7% across all groups. These values correspond to goodness-of-fit values between 99.4% and 99.7%. For individual data, satisfactory fits between measured and modelled data were obtained in the majority of participants. The average variance (1 s.d.) for individual data across all conditions was 12.06 (4.12) corresponding to an average goodness-of-fit of 98.55%. The data from all but one participant (highlighted in red, Table 4.1) achieved a goodness-of-fit above 92%, and these values are summarised in Table 4.1.

Table 4.1 Goodness-of-fit values (%) for source modelling of individual AEPs

<table>
<thead>
<tr>
<th>Participants</th>
<th>500-Hz</th>
<th>4-kHz</th>
</tr>
</thead>
<tbody>
<tr>
<td>RED</td>
<td>95.1 – 99.6</td>
<td>97.0 – 99.7</td>
</tr>
<tr>
<td>LED</td>
<td>92.9 – 99.4</td>
<td>77.9 – 99.6</td>
</tr>
<tr>
<td>Controls</td>
<td>95.4 – 99.6</td>
<td>96.6 – 99.7</td>
</tr>
<tr>
<td>Left ear</td>
<td>95.1 – 99.6</td>
<td>95.0 – 99.5</td>
</tr>
<tr>
<td>Right ear</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

4.3.3 Contralateral dominance

Figure 4.10 displays source modelled scalp topographies for individuals with right ear deafness alongside those from matched controls. The topographies depict activity at the peak latency of N1 identified in GFP. Topographies from the control data show maximal activity over the contralateral hemisphere in response to both low- and high-frequency stimuli. The activity is centred more frontally for high-frequency stimuli. In contrast, the pattern of activation from individuals with unilateral deafness appears more symmetrical. Although still maximal over the contralateral hemisphere, the region of maximal activity is centred closer to the midline for both low and high-frequency stimuli. However, the area of maximal activity is still located more frontally for high-frequency stimuli. These topographies are consistent with the sensor level scalp topographies shown in Figure 4.7.

Figure 4.11 shows the corresponding scalp topographies for individuals with left ear deafness along with matched controls. The results from matched controls again show
maximal activity centred over the contralateral hemisphere. The results from individuals with unilateral deafness are more symmetrical although the differences appear less marked than with right ear deafness. In particular, the 4-kHz condition produced activity that clearly remained centred over the contralateral hemisphere based on the grand average data.

The locations, orientations and strengths of the dipoles in each hemisphere quantify the activity reflected by these scalp topographies. Table A3 of Appendix A summarises the results of the grand average dipole source analysis and Table A4 summarises the results of analysis of individual data.

**Location:** Figure 4.12 displays the locations of dipoles from the grand average analysis in the three orthogonal planes (coronal, axial and sagittal). Similarly to the previous study a constraint of symmetry was applied, meaning the dipole locations in the right hemisphere will have an equivalent value to the left hemisphere. For simplicity, only the locations for dipoles in the left hemisphere are displayed.

The top panel of Figure 4.12 shows locations in the coronal plane. The dipoles in the 500-Hz condition were located significantly more medially than the 4-kHz condition in the control group ($t_{(18)} = 2.8; p<0.05$) However there were no clear differences for participants with unilateral deafness ($t_{(18)} = 0.94; p>0.05$), which reflects the more symmetrical activity evident in the scalp topographies. Although the dipoles for individuals with right ear deafness are located more medially for both frequencies than the matched controls, the locations for those with left ear deafness are very similar to controls. As such no statistical differences were observed on a group level between unilaterally deaf participants and controls at 500-Hz ($t_{(18)} = 0.24; p>0.05$), although differences were approaching significance in the 4-kHz condition ($t_{(18)} = 1.88; p=0.07$).

The middle panel of Figure 4.12 shows dipole locations in the axial plane. There are no clear differences according to frequency. However in general the dipoles for individuals with unilateral deafness are located more deeply below the surface of the cortex than matched controls, reflecting the increased dipole strengths. This is particularly apparent for individuals with right ear deafness. The differences were significant in both the 500-Hz condition ($t_{18} = 3.32; p<0.01$) and the 4-kHz condition ($t_{18} = 2.88; p<0.01$).
The lower panel of Figure 4.12 shows dipole locations in the sagittal plane. Generally the 4-kHz locations are further forward than the 500-Hz locations reflecting the tonotopicity of the auditory cortex. However, there were no statistically significant differences between unilaterally deaf participants and controls.

**Orientation**: The orientation of the dipoles is described in terms of their angles with the coronal, sagittal and axial planes. An angle of -90° indicates vertical orientations in each plane. Angles between 0° and -90° indicate orientations to the left in the coronal and axial planes, and more anterior in the sagittal plane. Angles between -90° and -180° indicate orientations to the right in coronal and axial planes, and more posterior in sagittal planes (a more detailed description is provided in Chapter 3).

Figure 4.13 (top panel) shows the orientations of dipoles in the coronal plane for individuals with right unilateral deafness and the corresponding matched control group. The display is based on the grand average data. The dipoles in both hemispheres are orientated medially for both low and high-frequency stimuli in individuals with unilateral deafness (i.e. they are orientated towards the vertex). This reflects the centralised area of maximal activity that is apparent in the scalp topographies displayed in Figure 4.10. The variability in dipole orientations within the individual data was substantial and no statistically significant differences between contralateral and ipsilateral orientations were observed at either 500-Hz ($F_{(1,6)} = 0.05; p>0.05$) or 4-kHz ($F_{(1,6)} = 3.91; p>0.05$). The dipoles in the matched control group are orientated more vertically on the contralateral hemisphere and more laterally on the ipsilateral hemisphere. This reflects the contralateral dominance apparent from the scalp topographies. The orientations were more consistent within the individual data in this group and the differences between contralateral and ipsilateral orientations were statistically significant in the 500-Hz condition ($F_{(1,6)} = 9.19; p<0.05$), but not for the 4-kHz condition ($F_{(1,6)} = 0.92; p>0.05$).

Figure 4.14 (top panel) shows the same information (coronal plane) for individuals with left unilateral deafness and the matched control group. The orientations are similar for participants and matched controls, with dipoles in both contralateral and ipsilateral hemispheres generally slanted towards the contralateral (left) hemisphere. However, the contralateral dipole in unilateral deaf participants is more vertical, reflecting the slight shift towards more centralised activity that is apparent in the topographies displayed in
Figure 4.11. However, there were significant differences between contralateral and ipsilateral orientations for the 500-Hz stimuli in both unilaterally deaf ($F_{(1,11)} = 6.23; p<0.05$) and control ($F_{(1,6)} = 31.9; p<0.01$) groups. In the 4-kHz condition the differences approached significance in the unilaterally deaf group ($F_{(1,11)} = 4.04; p=0.057$), but were not statistically significant in the control group ($F_{(1,11)} = 2.28; p>0.05$).

Contralateral and ipsilateral dipole orientations were compared directly between participants with unilateral deafness and matched controls. The contralateral dipoles were generally shifted more medially for individuals with unilateral deafness, reflecting the more centralised regions of maximal activity shown in the scalp topographies. In the majority of cases these differences were not statistically significant. However, in the 4-kHz condition the differences approached significance for right ear deafness ($F_{(1,6)} = 3.43; p=0.08$) and were statistically significant between individuals with left ear deafness and matched controls ($F_{(1,11)} = 5.43; p<0.05$). Comparisons between the 500-Hz and 4-kHz conditions were also carried out. For those with right ear deafness the orientations were very similar across frequencies and no significant differences were observed (since the topographies were also very similar across frequency). For those with left ear deafness differences were observed; although the grand average data show the contralateral dipoles to be orientated vertically, group comparisons show the contralateral dipole orientation to be shifted to the left in the 500-Hz condition compared with the 4-kHz condition ($F_{(1,11)} = 4.43; p<0.05$). A similar effect occurred with the ipsilateral dipole in the opposite direction; dipoles were further to the right in the 500-Hz condition compared with the 4-kHz condition ($F_{(1,11)} = 5.99; p<0.05$), which is reflected in the grand average data in Figure 4.14.

Figures 4.13 and 4.14 (middle panels) show orientations in the sagittal plane for right and left ear deafness, respectively. Dipole orientations in this plane were similar between contralateral and ipsilateral hemispheres in the majority of cases. However, in the 500-Hz condition the contralateral dipole was more vertical than the ipsilateral dipole for the matched controls of individuals with right ear deafness ($F_{(1,6)} = 9.19; p<0.05$), yet more anterior in the matched controls of individuals with left ear deafness ($F_{(1,11)} = 31.9; p<0.01$). No comparisons between contralateral or ipsilateral hemisphere across frequency or groups were statistically significant although there was a consistent
trend for more anterior orientations in the 4-kHz condition compared with the 500-Hz condition, as seen in Chapter 3.

Figures 4.13 and 4.14 (lower panels) show dipole orientations from grand average data in the axial plane for right and left ear deafness, respectively. The orientations in the axial plane generally reflect those of the coronal plane. Hence the dipoles in each hemisphere of participants with right ear deafness are generally orientated medially whereas those of the matched controls are more tangentially orientated (and are more parallel with each other) in the grand average results. Statistically significant differences were observed in two conditions; individuals with right ear deafness receiving 4-kHz stimuli ($F_{(1,6)} = 6.23; p<0.05$), and matched controls receiving 500-Hz stimuli ($F_{(1,6)} = 9.09; p<0.05$). A more consistent pattern was seen in the grand average results between participants and matched controls with left ear deafness, with the contralateral dipole more tangential in unilaterally deaf participants and more radial in controls. Statistically significant differences between contralateral and ipsilateral orientations were found in the 500-Hz condition in both unilaterally deaf participants ($F_{(1,11)} = 6.99; p<0.05$) and matched controls ($F_{(1,11)} = 23.9; p<0.01$). There were also differences between the ipsilateral dipole orientations in the 500-Hz and 4-kHz conditions in both individuals with left ear deafness ($F_{(1,11)} = 5.56; p<0.05$) and matched controls ($F_{(1,6)} = 5.27; p<0.05$), where dipoles were more radial to low frequency stimuli.

**Source Strengths:** Figure 4.15 shows the source strengths for dipoles in the contralateral and ipsilateral hemispheres in each condition based on the grand average data. The dipole strengths are greater in both hemispheres of individuals with unilateral deafness compared with matched controls. This occurs irrespective of the frequency and ear of stimulation. Consequently the hemispheric asymmetry between dipole strengths in each condition is generally preserved i.e. the contralateral dipole is stronger than the ipsilateral dipole. The corresponding LIs are provided in Table 4.2. LIs in the 500-Hz condition are somewhat reduced with both left and right ear deafness compared with matched controls. However the LI values in the 4-kHz condition are very similar between participants and controls. Neither the matched controls nor participants showed any increase in LI with frequency.
Figure 4.10 Top-down view of source modelled grand average scalp topographies for individuals with right ear deafness and corresponding matched controls. Upper row depicts the results from matched controls and lower row depicts results from individuals with unilateral deafness. Blue contours show negative activity and red contours show positive activity (in 0.2 µV contour increments).
Figure 4.11 As Figure 4.10 but for individuals with left ear deafness and the corresponding matched control group.
Figure 4.12 Summary of dipole locations in three orthogonal planes from the grand average data. Squares denote participants with unilateral deafness and triangles denote matched controls. Filled symbols show data for the 500-Hz condition and open symbols show data for the 4-kHz condition. Blue symbols show stimuli to the left ear (i.e. individuals with right ear deafness) and red symbols show stimuli to the right ear (i.e. individuals with left ear deafness).
Figure 4.13 Summary of dipole orientations in three orthogonal planes from grand average data of individuals with right ear deafness. The dipoles are displayed on a standard fMRI image with data from the 500-Hz condition in the left column and from the 4-kHz condition in the right column. Data from participants with unilateral deafness are shown with red and yellow symbols. Matched controls are shown with light blue and dark blue symbols. n.b. fMRI images are reversed by convention, such that the left hemisphere is displayed on the right and the right hemisphere is displayed on the left.
Figure 4.14 Summary of dipole orientations in three orthogonal planes from the grand average data of individuals with left ear deafness. Details as Figure 4.13.
Figure 4.15 Source strengths of dipoles modelling the grand average data.

Table 4.2 LI (%) values for the results displayed in Figure 4.14.

<table>
<thead>
<tr>
<th></th>
<th>500-Hz</th>
<th>4-kHz</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right unilateral deafness</td>
<td>23</td>
<td>24</td>
</tr>
<tr>
<td>Matched control</td>
<td>31</td>
<td>23</td>
</tr>
<tr>
<td>Left unilateral deafness</td>
<td>13</td>
<td>17</td>
</tr>
<tr>
<td>Matched control</td>
<td>20</td>
<td>19</td>
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</table>
Figure 4.16 Source strengths of dipoles modelling the individual data. Error bars indicate +/- 1 s.d.
Figure 4.16 shows the magnitude of contralateral and ipsilateral hemisphere activation based on the source analysis of individual data. As with the GFP analysis, there is a trend for greater dipole strength in participants with unilateral deafness compared with matched controls. The effect is apparent in both contralateral and ipsilateral hemispheres, at both 500-Hz and 4-kHz and for both left and right ear deafness. For 500-Hz the dipoles are around 20% stronger and for 4-kHz the dipoles are around 33% stronger in participants with unilateral deafness. Separate within-subjects ANOVAs were performed for those with right and left ear deafness (hemisphere [2] x frequency [2] x group [2]). For individuals with right ear deafness a statistically significant main effect of hemisphere was observed ($F(1,6) = 10.46; p<0.05$). The contralateral dipole strengths were therefore significantly greater than ipsilateral strengths. Furthermore, a statistically significant main effect of group was also observed ($F(1,6) = 16.23; p<0.01$), demonstrating that the trend for increased amplitudes in those with right ear deafness over matched controls was significant. However, no statistically significant main effect for frequency nor any interaction effects were found. The second ANOVA for individuals with left ear deafness produced a similar result. Statistically significant main effects of both hemisphere ($F(1,11) = 15.51; p<0.01$) and group ($F(1,11) = 5.11; p<0.05$) were observed. Again no statistically significant main effect for frequency nor any interaction effects were found.

For unilateral deaf participants the average LI was 25% for 500-Hz and 17% for 4-kHz stimuli. However, the variability amongst participants was considerably higher than controls. Two participants showed clearly reduced contralateral dominance/ipsilateral dominance in both stimulus conditions (participants 18 & 19) whereas several showed contralaterality that was greater than the mean control value plus one standard deviation. A within-subjects (LI [2] x frequency [2]) ANOVA did not reveal any statistically significant differences between groups ($F(1,6) = 0.48; p>0.05$), across frequency ($F(1,6) = 0.3; p>0.05$) nor were there any statistically significant interaction effects ($F(1,6) = 0.59; p>0.05$). On average the LI in participants with left ear deafness is around 15% across frequencies. The LI values from these participants are not noticeably different from controls. However, one participant did show ipsilateral dominance that was smaller than the mean minus one standard deviation in the 4-kHz condition (participant 03), as did another whose LI was greater than the mean plus one standard deviation (participant 10). A similar within-subjects ANOVA as described above (LI [2] x frequency [2]) did not reveal any statistically significant main effects for LI between the groups ($F(1,11) = \ldots$)
1.54; \( p > 0.05 \), across frequency (\( F_{(1,11)} = 0.38; p > 0.05 \)) or any significant interaction effects (\( F_{(1,11)} = 0.02; p > 0.05 \)).

4.4 Discussion

This study had two main aims; the first was to compare the strengths of N1 activity between a group of adult humans with late onset unilateral deafness and a control group. The second was to compare contralateral and ipsilateral hemisphere activity between these two groups. The results show that there is a difference in cortical auditory evoked potentials between the groups. The differences include increased source strengths of N1 AEPs and more centralised regions of maximal activity across the scalp. These differences are consistent with the presence of experience-related plasticity within the adult CAS. The study therefore corroborates the only previous evidence for such plasticity measured via AEPs. The results also extend the previous findings by demonstrating that differences occur irrespective of the ear of deafness and are apparent to both low and high frequency stimulation. Two types of analyses were carried out. Global field power analysis was used to address the first main aim and source modelling the second. The results of the two analyses will be discussed in turn:

4.4.1 Global field power

A trend for greater N1 amplitudes in GFP was observed in individuals with unilateral deafness compared with matched controls. Although the differences at neither stimulus frequency reached statistical significance, a similar sized increase was seen in the N1 amplitudes to both high and low frequencies. Evoked response amplitude increases have been reported previously in association with other forms of experience-related plasticity. For example, Salvi et al. (2000) described increased amplitude of activity in the inferior colliculus of animal models with high frequency hearing loss at frequencies below the region of the hearing loss. Dietrich et al. (2001) reported a similar increase in the N1m amplitude to stimulation at the edge frequency in adult humans with steeply sloping high frequency hearing losses compared to other, much lower frequencies. Tremblay et al. (2001) described an increase in N1 amplitude in normally hearing adult humans after speech sound training and Ponton et al. (2001) described an increase in N1 amplitude over the ipsilateral hemisphere in adults with unilateral deafness. Two phenomena could explain an increase in amplitude in response to stimulation of the intact ear; an increase in the number of responsive neurons and/or an increase in the
synchrony of neural firing. However it seems plausible that the explanation could involve a combination of both. First, reorganization resulting in an increase in neural representation must entail more neurons responding to stimulation of the intact ear, in line with the predictions made earlier. With respect to synchrony of firing, although GFP is not sensitive to activity from each hemisphere separately, the expectation is that this form of representational plasticity will be most apparent on the hemisphere ipsilateral to the intact ear. Any subsequent enhancement of neural activity to stimulation of the intact ear will therefore also result in an increase in the synchrony of firing between neural populations in the contralateral and ipsilateral hemispheres.

Indeed, the sensor level topographic maps which are directly related to the GFP data suggest reduced asymmetry in the activity across the hemispheres in individuals with unilateral deafness. The reduced asymmetry apparent in these maps derives from an increase in regions of maximal N1 activity over the ipsilateral hemisphere.

There are two additional aspects of the GFP analysis which extend existing knowledge. These are the effect of stimulus frequency and the effect of ear of deafness. Previous evidence indicates that under normal circumstances the overall amplitude should be less for high-frequency stimuli. The GFP data did not show any frequency specific differences in the amplitude of responses in controls. Two phenomena could explain this; one is that the gently sloping pure tone thresholds apparent in most participants caused an increase in the absolute levels of the high-frequency stimuli relative to the lower frequency stimuli, and a corresponding increase in the response amplitude. Secondly, GFP takes into account the activity across all recording sites. Differences in N1 amplitude most apparent at central recording sites may have therefore been diluted by the responses at more distant recording sites near the areas where the polarity of the N1 reverses, and consequently where activity is minimal (Vaughan and Ritter, 1970). In any case, until now the only studies to have investigated experience-related plasticity following unilateral deafness in adults used stimuli of one frequency (i.e. 1 kHz pure tones) or broad band stimuli, the response to which has a low frequency emphasis in cortical AEPs. It has been suggested that the nature of any changes might be different according to frequency (Khosla et al., 2003). However, based on the present findings this is not the case. The results therefore tie in with the findings of Popelar et al. (1994) where proportional changes in AEPs were observed across the frequency range in animal models with unilateral deafness. It is plausible however, that observation of any differences in the degree of reorganisation across frequencies was obscured by age
related changes that might already have taken place. For example if lower frequency stimuli may (at least in some cases) have an expanded neural representation due to high frequency hearing loss (Frisina and Rajan, 2005), and therefore evoke responses from higher frequency neurons. Alternatively, any frequency specific differences in plasticity attributed to differences in the excitatory/inhibitory balance, as had been suggested, might only be apparent in the early stages after deafferentation, where disinhibition is thought to underlie the enhanced neural responses (McAlpine et al., 1997). Therefore the retrospective design of the present study would not be sensitive to any such differences should they be present.

The second item of additional information from the GFP analysis is that the same trend for enhanced neural activity was observed in individuals with both left and right ear deafness. This is consistent with expectations based on previous evidence from studies on humans using either fMRI or AEFs after deafness of either ear (e.g. Scheffler et al., 1998; Morita et al., 2007) but it has not been shown previously using AEPs. Some ear specific evidence using AEPs has shown altered activity following left-sided unilateral deafness only (Khosla et al., 2003). However, this effect was noted in the absence of corresponding enhanced overall activity, at least when carried out using source modelling techniques. This suggests some methodological aspect of that study, perhaps related to the modelling, masked subtle changes following right ear deafness. The present results demonstrate congruence between the various non-invasive techniques available in the study of humans. The result also highlights potential methodological difficulties when using source modelling to demonstrate altered hemispheric asymmetries. Interpretation of source modelling in this context may be more reliable when considered in combination with sensor level data because of the difficulties in measuring hemispheric asymmetries using AEPs. That is, the GFP analysis and the topographic maps can provide a simple but useful guide. If there are apparent differences in responses at the sensor level that do not seem to be reflected in the asymmetries calculated from the model then they must be reflected in some other parameter such as the location or orientation of the dipoles. In previous AEP and AEF studies investigating the effect of unilateral deafness, important sensor level information has not been provided.
4.4.2 Source modelling

Although the GFP analysis provides a convenient summary of the overall activity the simplicity of the approach does have several limitations. Primarily it does not differentiate between contralateral and ipsilateral hemisphere activity. In addition it does not provide any impression of the regions where any changes over each hemisphere are most apparent. For example, Ponton et al. (2001) noted the greatest changes at sensors located centrally over either hemisphere. The biggest differences between hemispheres in the present study are also most notable at central and temporal recording sites either side of the midline. However, response amplitudes at more distant recording sites such as in the parietal and occipital regions near to where polarity reversal occurs are often similar between groups. This may explain why the trends observed in the GFP analysis did not reach statistical significance; differences in N1 amplitude most apparent at central recording sites may have been diluted by responses at distal recording sites where activity was minimal, reducing statistical power accordingly. On the other hand, the source modelling procedures do allow comparison of contralateral and ipsilateral hemispheres separately, and the dipoles will gravitate towards the locations on the scalp with the strongest activity. Consequently, a statistically significantly greater response in terms of source strength was observed in individuals with unilateral deafness affecting either ear.

The expected reduction in contralateral dominance was not observed, at least with respect to the dipole strengths alone. Instead, the overall increase in amplitude was reflected by an increase in both contralateral and ipsilateral dipole strengths. Nonetheless, the source derived topographies did suggest a reduction in contralateral dominance in individuals with unilateral deafness. Based on these topographies, the region of maximal N1 activity appeared to shift from the contralateral hemisphere towards more central regions, especially following right ear deafness. If the activity really did increase similarly in both contralateral and ipsilateral hemispheres as the dipole strengths suggest, then no shift in the scalp topographies would have occurred. This unexpected and apparently conflicting finding can be explained by the use of a rotating dipole model, and consideration of the interplay between dipole strength and the remaining parameters; dipole location and orientation. First, the persistence of contralateral dominance with respect to dipole strength is not necessarily surprising since close inspection of the waveforms and sensor level topographies (shown in section...
4.3) do show strong activity in the temporal regions on the contralateral hemisphere. This persistence of some degree of contralateral dominance after unilateral deafness has been noted in fMRI studies as well, where hemispheric asymmetries were merely reduced as a result of the enhanced ipsilateral activity, but did not disappear completely (Scheffler et al., 1998; Langers et al., 2005). In the present study the altered scalp topographies are reflected by a shift in both the orientations and locations of each dipole. Following unilateral deafness, both dipoles tend to orientate towards the vertex, where the activity was maximal. They are also located generally more medially and deeper below the surface, this latter effect reflecting the increased strength of activation.

There is considerable variability in dipole orientation and location amongst the individually modelled data although this could be attributable to factors such as EEG noise and distortions introduced by the head model. This finding may help to explain some of the lack of evidence for experience-related plasticity in the existing literature (e.g. Fujiki et al., 1998; Vasama et al., 2001; Hine et al., 2008) where reduced asymmetries in dipole strength were not apparent either. It is also possible that future studies using a higher number of recording sensors and producing a more refined source model would also be able to demonstrate the effect more clearly.

The increase in both contralateral and ipsilateral hemisphere activation in individuals with unilateral deafness explains the outcome of the LI analysis. The control participants demonstrated the normal pattern of ear specific asymmetries as described in Chapter 3 (reduced LI and increased variability in results following stimulation of the right ear), and the results from participants with unilateral deafness were not different. These LI results are still worth mentioning from the perspective that this type of analysis has been commonly used in previous fMRI studies (e.g. Langers et al., 2005; Scheffler et al., 1998; Bilecen et al., 2000). The technique is useful for this type of analysis in that it controls for differences across individuals in the absolute levels of activation (and, for test-retest differences for the same individual). Results from these studies suggest a reduction in LI should occur after the onset of unilateral deafness. However, in the present context the LI only summarises one parameter of the model (dipole strength). The variability in LI due to the interplay between all three modelling parameters limits its usefulness in AEP studies. This is particularly true when overall activity is small, meaning that differences between hemisphere activities are disproportionately large compared to the overall activity. Furthermore, LI is not sensitive to changes affecting both hemispheres similarly, as was noted here in the
dipole strengths. Future studies using dipole modelling to quantify activity in each hemisphere may therefore take one of two approaches. The first is to summarise activity based on all parameters of the model, as was done here. The second is to fix *a-priori* two of the three parameters, which was the approach taken in the study by Morita et al. (2007). With this approach LI would be more useful since it will summarise the only dependent variable. Important differences in AEPs between the hemispheres may otherwise be masked by not accounting for all parameters. However, fitting the location and orientation parameters to the topography of each individual and then fixing them and comparing dipole strengths, as done by Khosla et al (2003), may also lead to errors. The choice between these two options poses an interesting conceptual problem. Both options will allow one to demonstrate the normal pattern of contralateral dominance in individuals with binaural hearing. However, they can differ in the way in which they reflect changes in this pattern following unilateral deafness. On the one hand, constraining the model so that strength of the dipoles is the only parameter allowed to vary is the only way in which to reliably quantify increases in ipsilateral hemisphere response in terms of strength alone. In any other case the changes could be demonstrated in a number of different ways such as changes in contralateral or ipsilateral dipole orientations, strengths and locations or complex combinations of all of these parameters. However, in choosing to constrain the model in this way one is forced into making an assumption about causality relating to the results before the results have been obtained, and then producing a model that can only adhere to these assumptions. Furthermore, using a highly constrained model leads to other difficulties. For example, there is no definitive argument as to whether dipole orientation and/or location should be constrained at angle ‘x’ and position ‘x’, or angle ‘y’ and position ‘y’. The information could be obtained from control data but this will introduce inter-subject variability and so is not necessarily a valid option. A rotating dipole model bypasses these assumptions and simply fits the data in the most appropriate way on a case-by-case basis. The difficulty with this approach is in the fact that there are three dependent variables needed to quantify the response from each hemisphere instead of one. These variables interact in ways that are not predicted based on the animal models and fMRI data in humans discussed in Chapter 2. The predictions are that the ipsilateral hemisphere will increase in response, not that neurons in the contralateral and ipsilateral hemisphere sources will change in their orientation as well as strength. However, this is what may be suggested in the rotating dipole model.
The rotating dipole model can be revived for the present purposes when considered in combination with the GFP data. For instance, it is clear that no shift in neural orientation alone could explain the change in scalp topography. If such a shift really did occur then no net change in amplitude would occur and the trend for increased GFP amplitude would not have been recorded. It is also clear that the same increase in both contralateral and ipsilateral source strengths could not have occurred in isolation. If this were the case no change in the scalp topography would occur. One plausible explanation for the combination of results that were seen in the present study is the increase in response amplitude from the ipsilateral hemisphere, as is indicated by the sensor level topographies.

4.5 Conclusions

The study reported in this chapter had two main aims: to compare the overall strength of AEPs and to compare the contralateral and ipsilateral hemisphere activation strengths in humans with and without unilateral deafness. Additional aims were to note the effects of frequency of stimulation and ear of deafness on any differences between the groups.

The results showed enhanced mean amplitude of responses in unilaterally deaf individuals. One explanation for this is an increased responsiveness of neurons to stimulation of the intact ear as a result of experience-related plasticity. This study is the first to corroborate the only previously published dataset to demonstrate this finding in humans using AEPs (Ponton et al., 2001). This is important because a number of other studies with similar aims have not consistently done so, in particular where dipole modelling has been used to quantify the activity arising in each hemisphere. It is apparent that AEPs are sensitive to experience-related plasticity due to unilateral deafness and the mixed findings reported previously are probably due to limitations in methodology. In addition, the present results clarify and extend previous findings by demonstrating a similar pattern of changes irrespective of the ear of deafness or the frequency of stimulation.

The results help to address the first two questions that were posed in Chapter 2; question one asked what evidence exists for experience-related plasticity in humans with unilateral deafness and question two asked whether or not this is consistent with findings in animal models. Converging evidence from various forms of non-invasive measurement techniques suggest that changes occur in humans with late onset unilateral
deafness and that the pattern is consistent with findings in animals. The next step is to address the third question posed in Chapter 2, which asks about the time course of events in humans. AEPs are particularly well suited to addressing this question because, in addition to ease of stimulus manipulation, the fine temporal resolution and good test-retest reliability, they are relatively easy and inexpensive to measure, which is important for making multiple measurements over time.
Chapter 5: Time course of experience-related plasticity in adult humans with late onset unilateral deafness

5.1 Introduction

One of the main motivations for studying experience-related plasticity is to optimize rehabilitation strategies for individuals with sensory impairments such as deafness. Progress in this regard requires knowledge of the mechanisms that underlie plasticity in humans, the rate and extent of changes, and for how long they may continue (Wall et al., 2002).

A lot of information on the physiological mechanisms of plasticity has been revealed by plotting the time course of events in studies on animals with sensory deafferentation. There are at least three mechanisms by which plasticity may occur after deafferentation; unmasking of existing connections, changes in the efficacy of existing connections, and growth of new synapses and/or axons (McAlpine et al., 1997; Salvi et al., 2000).

Much attention has been paid to the mechanisms governing the early stages after deafferentation in animal models. For example, there are several lines of evidence in the visual and somatosensory domains demonstrating a rapid expansion (within minutes) in the neural representation of the neighbouring intact sensory input following peripheral deafferentation (Calford and Tweedale, 1991; Chino et al., 1992). Similarly rapid increases in the responsiveness (i.e. within minutes to hours) of the auditory cortex following complete unilateral deafening have been described upon stimulation of the intact ear (McAlpine et al., 1997; Reale et al., 1987; Popelar et al., 1994; Mossop et al., 2000). Essentially, initial changes in the neural representation of the intact sensory input can be observed as soon as the experimental conditions allow (Calford, 2002). The speed of these initial changes has been attributed to disruption in the excitatory-inhibitory interactions that are thought to be necessary for normal cortical function. Many neurons in the cortex possess a receptive field with a central excitatory zone surrounded by a ring of inhibition. This is thought to be a basic arrangement underlying processes such as feature extraction in the visual cortex (e.g. discerning the orientation of objects) (Gilbert and Wiesel, 1992), or in the auditory cortex; (Calford and Semple, 1995). The only plausible explanation for such rapid changes following deafferentation is the unmasking of neural connections that are already present, but are normally
ineffective in producing excitation due to the inhibition. The basic neural arrangement
and the rapid changes following deafferentation can be summarised as follows: 1) Afferent projections from the sensory epithelium diverge progressively through each
stage of the ascending neural pathway. 2) This leads to a centre-surround pattern of
organisation at the cortex. Centre afferent connections to a given cortical region are
excited by the corresponding region of the sensory epithelium. However, divergent
connections terminating in surrounding regions of cortex are inhibited. 3) The inhibitory
drive is normally provided by neighbouring sensory input, which in turn will exhibit a
centre-surround pattern of projection at its own cortical region. 4) When this
neighbouring sensory input is removed (i.e. following deafferentation) then the
divergent connections of the intact afferent input become disinhibited. 5) Stimulation of
the intact sensory input subsequently produces excitability at both the centre and
surrounding cortical regions. This effectively increases the neural representation at the
cortex to the remaining input. Stimulation of the intact sensory epithelium therefore
produces hyper excitability of the cortex (Salvi et al., 2000).

When deafferentation involves complete unilateral deafness it is worth remembering
that most neurons in the CAS are binaurally sensitive and the onset of deafness disrupts
the binaural interactions. The disinhibition noted in animal models of unilateral
defauness refers to the removal of the inhibitory effect of one ear on the responsiveness
of CAS neurons to input from the opposite ear. Subsequently, the neuron’s
responsiveness to the intact ear is increased. Removal of the dominant afferent input
(i.e. on the side ipsilateral to the intact ear) produces a marked increase in activity to the
intact ear. Removal of the normally weaker, inhibitory input (i.e. on the side
contralateral to the intact ear) produces much less marked changes (McAlpine et al.,
1997).

After the immediate changes associated with disinhibition a prolonged series of further
changes have been reported in the months following deafferentation. Changes over this
time course may be attributed to alterations in the efficacy of the existing synaptic
connections. Such alterations may involve uprating (for example this may be mediated
by long term potentiation) or downrating (long term depression) the strengths of these
connections. In the somatosensory cortex an expansion in cortical representation of the
dorsal surface of the hand occurs in primates undergoing ventral hand surface
deafferentation (Merzenich et al., 1983). However, the initial expansion mediated by
disinhibition described above only produces what may be described as a vague
topographical representation of the emergent sensory input. In that study, individual
regions of the somatosensory cortex had wide receptive fields, responding to
stimulation of wide regions of the dorsal skin. Over the ensuing weeks and months this
vague representation underwent refinement into a more precise topographic map of the
intact input over the deafferentated region of cortex. This is consistent with initial
cortical activation reflecting the availability of all of the unmasked connections.
Subsequent refined activation reflects the long term expression of only a relevant subset
of these connections, which is determined in an experience dependent manner
(Churchill et al., 1998). Stimulation of a given point on the sensory epithelium would
therefore be expected to lead to a decline in the initial over-representation seen
immediately after deafferentation through consolidation of the unmasked connections,
and a reduction in the initial hyper excitability. On the other hand McAlpine et al.
(1997) noted a further increase in the number of excitable neurons in the ipsilateral
inferior colliculus of adult ferrets 3 months after unilateral deafness, in addition to the
initial increase seen immediately after the onset. This suggests the prolonged imbalance
in input lead to a general strengthening of the gain in the unmasked connections with
this form of experience-related plasticity.

The emergence of new synaptic and/or axonal projections supporting experience-related
plasticity has also been discussed (Cusick et al., 1990; Elliott et al., 1996; Moore, 1994;
Darian-Smith and Gilbert, 1994; Trachtenberg et al., 2002). Following unilateral
deafness in infant animals an exuberance of afferent projections from the intact ear has
been noted on the ipsilateral side of the brain (Kitzes, 1984). In another example Moore
(1994) noted continuing changes in CAS activity several years after unilateral deafening
in infancy or adolescence, which is too long a period to be attributed to functional
reorganisation alone. There is no clear evidence for this in adults with unilateral
deafness but Pons et al. (1991) noted somatotopic reorganisation several years after
sensory deafferentation of the hand in adult primates. The extent of cortex that changed
was greater than the extent of the surrounding inhibitory receptive fields thus could not
be explained merely through disinhibition or alterations in existing synaptic efficacy.

Thus, experience-related plasticity observed over the short term may be associated with
physiological mechanisms involving existing neural connections whereas changes that
take place over the long term (i.e. months or even years) following deafferentation may be associated with structural reorganisation.

Plotting the time course of events is relatively straightforward in animal studies since the onset of deafferentation is under the control of the experimenter. However in humans this is not the case. Instead, with respect to unilateral deafness, one approach has involved the study of individuals with sudden onset idiopathic unilateral deafness. The results are simply collected as quickly as possible after the onset. Several studies have reported results that were collected within days or weeks after onset (Suzuki et al., 2002b; Li et al., 2006; Morita et al., 2007). As described in Chapter 2, all have described a dramatic increase in activity on the hemisphere ipsilateral to the intact ear. The normally observed contralateral dominance following monaural stimulation shifts to ipsilateral dominance as a result. An advantage of studying these populations is that often, following medical treatment, recovery of hearing occurs. In these cases a restoration of the contralateral dominance has been reported with subsequent stimulation of the intact (unaffected) ear. Both the rapid onset of the initial change and the return to normal CAS activity following hearing recovery can be explained by functional switching. This means unmasking of latent afferent connections, possibly through disinhibition, occurs following the onset of unilateral deafness. However, following the recovery of hearing the normal inhibitory activity mediated by the affected ear is also restored, which would be expected to suppress the hyper-excitability once more.

Although this finding is consistent with the evidence described in animal models, little is known in humans about the time course of events beyond these initial stages. For example the rate and extent of changes are unclear, as are the pattern of changes. In particular, it is unclear how the ipsilateral dominance that occurs immediately following the onset of unilateral deafness translates to more symmetrical hemisphere activity reported elsewhere after long term deafness.

One patient group offers the opportunity to study CAS activity both before and after the onset of unilateral deafness and over a long period after the onset. These are individuals due to undergo surgery for the removal of an acoustic neuroma. Pre onset measures can be obtained in advance of the surgery. To date there have been only two longitudinal
studies of this nature that provide any insight into the time course of experience-related plasticity beyond the short term changes already described.

The first was a case study involving a single individual with a right-sided acoustic neuroma (Bilecen et al., 2000). Prior to surgery the hearing thresholds in both ears were normal. The circumstances surrounding the case therefore closely resemble the experimental conditions which are possible in animal studies. (The main difference is that there is a delay in obtaining the initial post-onset recordings from humans to allow for recovery from the effects of surgery.) FMRI was used to measure the brain’s activity according to the same methodology previously reported by Scheffler et al. (1998) and described in Chapter 2. Prior to surgery, stimulation of either ear produced a pattern of contralateral dominance of around 80%, which is in line with the results from normally hearing individuals reported by Scheffler et al (1998). Subsequent recordings following stimulation of the intact ear were made one week, five weeks and 12 months after the onset of deafness. These results revealed a very different pattern of activation. After one week a striking increase in contralateral dominance was observed, with an LI approaching 100%. This was due primarily to an almost complete absence of a BOLD signal apparent on the ipsilateral hemisphere. However, over subsequent sessions a progressively more symmetrical response was observed (after one year the LI reached around 20%). This was largely due to a gradual increase in activation of the ipsilateral hemisphere with little or no changes in the response on the contralateral hemisphere.

These results are interesting for several reasons. First, the initial changes occurred over a timescale that is consistent with that observed following idiopathic unilateral deafness. Furthermore, subsequent changes culminating in the end-point of symmetrical hemisphere activity are consistent with previously described data from retrospective studies (e.g. Scheffler et al., 1998; Langers et al., 2005; Ponton et al., 2001) and with the results reported in Chapter 4. The end-point, showing increased ipsilateral hemisphere activity can be explained by an over-representation of the intact ear at the cortex. However, two aspects of the results are difficult to explain in terms of the principles described above. First, no dramatic increase in ipsilateral hemisphere activity was seen shortly after the onset of deafness, as per expectations. Instead, a decrease in ipsilateral hemisphere activity was reported. It could be that the deafferented region of cortex became temporarily ‘silent’ after the surgery. This is something reported initially by Merzenich et al. (1983) in areas of somatosensory cortex deep within the
The deafferented region, beyond the unmasked receptive field of the remaining, intact input. It has also been suggested that fMRI may be blind to any initial changes in neural spiking activity expected immediately following deafferentation (Calford et al., 2005). However, even if true, or alternatively if no reorganisation had occurred, a BOLD response would still be expected in the ipsilateral hemisphere due to the original CAS organisation, with each ear producing neural activity on both hemispheres to some degree (albeit asymmetrically) normally. The second confusing aspect of the results was that when increased ipsilateral activity was observed it was not until several weeks or months later, rather than the minutes and hours reported in animal models. It would be tempting to attribute this to some methodological aspect related to BOLD signal changes following deafferentation, however the problem of lack of the normal BOLD signal to stimulation of the intact ear remains unexplained. Unfortunately the study involved just one individual and it would be important to learn whether or not this pattern is generalizable.

In the second study, Vasama et al. (2001) used AEFs to study CAS activity in humans before and after surgery. Seven individuals were monitored once prior to surgery and at one, three and six months post surgery. A control group of ten normally hearing individuals were also tested on one occasion. N1m activity was recorded in response to 1-kHz tone bursts presented to the intact ear at 80 dB SPL. The results revealed a normal pattern of contralateral dominance in controls. The peak latency of N1m was earlier and the dipole source strengths were greater by an average of 15% over the contralateral hemisphere. A similar hemispheric asymmetry was observed in participants when they were studied prior to surgery. One month after the surgery the dipole strengths were seen to increase markedly in both hemispheres. Over the course of subsequent measurements a progressive reduction was observed such that dipole strengths returned to the pre-operative levels after six months. No changes in hemispheric asymmetry were seen throughout. These results are complex and difficult to interpret. First, the absence of any change in hemispheric asymmetry following surgery when described according to dipole strength is not necessarily surprising in light of the findings described in the previous chapter. It may be that any changes in the scalp topographies were reflected primarily by changes in the dipole location or/and orientation of the dipoles although these parameters were not reported. Any changes would therefore have been missed. Furthermore, the initial increase in dipole strengths does support the notion of unmasking and hyper-excitability. However, the subsequent
return to normal levels of activity does not seem consistent with a persistent (or increasing) responsiveness of neurons to the intact ear seen in animals (McAlpine et al., 1997; Moore et al., 1997), attributed over-representation of the intact ear at the cortex. It was notable that of the seven participants one was already completely deaf in the affected ear prior to surgery, presumably due to the presence of the acoustic neuroma itself. Furthermore, three of the remaining six participants did not undergo translabyrinthine surgery and benefited from preserved hearing in the affected ear after surgery. Thus, four of the seven participants exhibited no change in sensory input to the CAS after surgery compared with beforehand. In the participant who was already deaf it may be that substantial reorganisation had already taken place, whereas in the three with preserved hearing no actual deafferentation could have occurred even though this is the very driver of the experience-related plasticity under investigation. No distinction was made between these individuals in the analysis so it is not possible to consider separately the results of the remaining three participants who did go deaf. Intriguingly, despite this drawback no differences in the pattern of results were reported between the individuals either; i.e. hyper-excitability was reported even in individuals with preserved hearing after surgery. Rather than experience-related plasticity, the authors therefore suggest that the results must be explained by events during the surgical intervention disrupting synchrony of firing or/and producing temporary hearing loss in the healthy ear due to the surgery (Barratt and Prasher, 1988). However, if true, both explanations would presumably lead to an apparent decrease in activity immediately after surgery rather than the reported increase. Alternatively, re-organisation prior to surgery due to the presence of the acoustic neuroma and subsequent asymmetry in hearing sensitivity could have occurred. For example it is known that adaptive plasticity can occur following attenuation of sensory input in the absence of deafferentation (Munro and Blount, 2009) and this has been attributed to changes in central gain mechanisms. The changes observed after surgery in some individuals with preserved hearing may in fact have been secondary plasticity in response to the removal of the tumour.

In any case, both existing lines of evidence into the time course of changes are not consistent with predictions based on animal models, and both studies seem to have technical flaws that make a clear interpretation of the findings difficult. The only other insight into the long term effects of unilateral deafness in humans was provided by a cross-sectional analysis of the results reported by Ponton et al. (2001). The results of
this analysis have already been described in Chapters 2 and 4. For the present discussion
the important aspect is that following the initial analysis, participants were divided into
two sub-groups according to the duration of deafness (less than or greater than two
years deafness). The changes in N1 activity described earlier were found to be greater in
the longer duration group, suggesting that experience-related reorganisation continues
for at least two years after the onset of deafness. However, the participants with longer
duration of deafness were also younger. Although age related factors are often
considered most important when discriminating between the developing and mature
CNS, the possibility of age-related differences between groups could not be ruled out as
an explanation for the result. In addition, it is not possible to describe the rate of
changes or the pattern of changes over time based on this type of cross-sectional
analysis.

The study described in this chapter aimed to investigate the time course of changes in
AEPs following unilateral deafness in humans. This was motivated by the lack of clear
evidence in the literature to date and may help to shed light on the mechanisms of
experience-related plasticity in humans. The aims were addressed in two ways. First, a
longitudinal study was carried out on a group of individuals before and on several
occasions after surgery for removal of an acoustic neuroma. This provided information
on the sequence of events up to six months following the onset of deafness. Information
on the extent of changes over subsequent years was provided by further analysing the
data presented in Chapter 4 using a cross-sectional design. If different mechanisms of
plasticity drive changes in CAS responsiveness, it was hypothesised that changes would
be seen over a short and longer term. Immediately following the onset of deafness the
response amplitudes were expected to increase and contralateral dominance was
expected to reduce. Further increases in response amplitudes as the duration of deafness
increased were predicted.

5.2 Methods

5.2.1 Participants

Nine participants were recruited to the study. At the time of recruitment all participants
were scheduled to undergo translabyrinthine surgery for the removal of an acoustic
neuroma. This surgery results in complete, abrupt deafness of the affected ear.
No suitable within-groups data was available to allow a formal sample size calculation. However, the number of participants was based on achieving a “large effect size” for analysis of variance as described in Cohen (1992), based on the effect size of 0.94 noted in the results from Ponton et al. (2001). This assumes an effect size of 0.80, an error probability of 0.05 and power in excess of 0.80 with 4 repetitions and an assumed correlation amongst repetitions of 0.5, based on conservative estimates of test-retest variability in measures of N1 activity (Virtanen et al., 1998). This gives a required sample size of 6.

Participants were tested once prior to surgery and at 1, 3 and 6 months post surgery. Following surgery one participant experienced medical complications and was unable to continue. Two others were unable to tolerate the EEG recording procedure, which involves wearing a tight fitting head cap, due to the surgical wound (s03, with left ear deafness and s04 with right ear deafness). Six participants (4 female, 2 male; 40 to 69 years old at time of surgery; mean = 52 years) therefore completed the study. Of these 4 had right and 2 had left-sided acoustic neuromas. Matched to each individual was a control participant whose hearing thresholds in both ears corresponded to the participant’s intact ear to within 10 dB at 500-Hz and 4-kHz. Participants were also matched for age and handedness (42 to 79 years old; mean = 60 years). The matched controls were tested on one occasion only.

The mean pure tone thresholds for participants with right ear deafness are shown in Figure 5.1 and for participants with left ear deafness in Figure 5.2. These results refer to measures made prior to surgery. Post surgical audiograms relating to the test ear are displayed in Figure 5.3 for both right and left ear deafness respectively. Detailed audiometric information for each participant is displayed in Table A8 in Appendix A. The study was approved by the Wigan NHS Research Ethics Committee (08/H1014/27) and all participants gave written, informed consent.

5.2.2 Paradigm

As in the previous studies two pure tones (500-Hz and 4-kHz) were selected to represent low and high-frequency stimuli. These were of 80 ms duration including 10 ms onset and offset ramps, defined using the Blackmann windowing algorithm. The stimuli were generated digitally and presented via a 44.1 kHz digital-analogue converter.
monaurally to the intact ear of unilateral deaf participants, and the corresponding ear in controls. Stimuli were presented in a pseudo randomly interleaved fashion via ER-3A insert earphones. The inter-stimulus interval varied pseudo randomly between 900 ms and 1300 ms. Each stimulus was presented in blocks of 500 repetitions per ear and the order of frequency of presentation was counterbalanced across participants. Level was fixed at 60 dB SL, although several participants and their matched controls received reduced levels of 40 dB SL in the 4-kHz condition due to subjective loudness discomfort. In light of the lack of level effects described in Chapter 3 no distinction was made between any responses evoked at a lower sensation level. Employing a fixed sensation level normalises the stimuli for variations in the audiogram between participants, with the absolute presentation levels varying by up to 30 dB between participants. Passive attention to the stimuli was maintained through watching a silent closed-caption movie for the duration of each session.

5.2.3 EEG recording, data processing and source analysis

The details of this aspect of the study were the same as described in section 3.2.3 and 3.2.4 in Chapter 3. Following EOG correction and artefact rejection procedures an average of 458 (1 s.d. = 49) epochs were accepted in each run of the longitudinal study. The details of the source analysis procedure were the same as described in section 3.2.5 in Chapter 3.

5.2.4 Analysis

The longitudinal data were analysed in two stages as in the previous study. The first involved comparison of N1 amplitudes, identified in GFP, between unilaterally deaf participants prior to surgery and matched controls (t-test). In all cases where assumptions of normality of distribution and sphericity were met, parametric tests were used to compare means. The results of unilaterally deaf participants pre and post surgery were compared using repeated measures ANOVA. In the second analysis dipole source modelling was employed as in the previous studies. The dipole location and orientation parameters were analysed descriptively because the numbers of participants with left and right ear deafness were insufficient for statistical comparisons and it is invalid to combine these parameters across ears of stimulation. For the cross-sectional analysis the results obtained from study 2, described in Chapter 4 were reconsidered according to the duration of deafness of participants. The ear of deafness was not considered as a factor.
for this analysis, since the previous results already study show changes in the CAS response irrespective of the ear of deafness.

Participants were divided into two groups according to the duration of deafness (short duration and long duration). The first group contained 9 participants who were deaf for less than two years. (RED = 4, LED = 5; 3 female, 6 male; 43 – 75 years old; mean age = 60 years). The second group contained 10 participants who were deaf for greater than two years (RED = 3, LED = 7; 3 female, 7 male; 50 – 75 years old; mean age = 61 years). There were no differences between the age of participants in each group ($t_{(17)} = 0.91; p > 0.05$). Comparisons of N1 amplitudes identified in GFP were carried out between the two groups of participants and the matched control group. Further source modelling was not necessary as this would not provide any new information over and above that which is described in Chapter 4.
Figure 5.1 Mean pure tone thresholds for participants with a right-sided acoustic neuroma (n=4) prior to surgery and matched controls. Solid line and filled symbols = participant. Dashed line and open symbols = controls. Error bars denote +/-1 s.d.
Figure 5.2 As Figure 5.1 with respect to participants with a left-sided acoustic neuroma (n=2). Error bars denote +/- 1 s.d.
Figure 5.3 Mean pure tone thresholds of the test (intact) ear before and after surgery for participants with left and right ear deafness. The solid lines denote pre-surgery thresholds of the test ear whilst the broken lines denote the post surgery thresholds of the test ear. Error bars denote +/- 1 s.d.
5.3 Results

Figures 5.4 and 5.5 show the grand average waveforms to 500-Hz and 4-kHz stimuli presented to the left ear of individuals with right ear deafness in the pre surgery and post surgery conditions. Equivalent information is displayed in Figures 5.6 and 5.7 for those with left ear deafness. The vertex-maximal N1 response is the most prominent component and was present in all conditions. In the post surgery conditions a greater N1 response amplitude is apparent compared with the pre surgery responses, particularly at the temporal sensor positions on the side contralateral to the ear of stimulation.

Figure 5.8 shows the sensor level topographic maps to the corresponding waveforms in Figures 5.4 and 5.5. The topographic maps in Figure 5.9 correspond to the waveforms in Figures 5.6 and 5.7. The control results in all conditions show maximal activity over the contralateral hemisphere. In the pre-surgery conditions a similar pattern emerges in participants. One exception is the 4-kHz condition in Figure 5.8. Compared with controls the response already appears less asymmetrical. Another important observation is that the response magnitudes appear consistently higher in unilaterally deaf participants compared with controls.

In the post-surgery conditions the responses are greater in magnitude in general. The regions of maximal activity tend to cover a wider area, with the biggest increases appearing over the ipsilateral hemisphere.
Figure 5.4 Grand average waveforms from 4 participants with right ear deafness receiving 500-Hz stimuli in the left ear. Blue lines denote responses prior to surgery. Red, black and orange lines denote responses at 1, 3 and 6 months post surgery respectively.
Figure 5.5 As Figure 5.4 but for 4-kHz stimulation.
Figure 5.6 Grand average waveforms from 2 participants with left ear deafness receiving 500-Hz stimuli in the right ear. Red lines denote responses prior to surgery. Blue, black and orange lines denote responses at 1, 3 and 6 months post surgery respectively.
Figure 5.7 As figure 5.6 but for 4-kHz stimulation.
Figure 5.8 Top-down views of sensor level topographic maps. Each map is compiled from the corresponding grand average waveform displayed in Figures 5.5 and 5.6 relating to participants with right ear deafness and stimulation of the left ear. The top row displays the results from the 500-Hz condition and the bottom row displays results from the 4-kHz condition. The black dots represent each sensor position.
Figure 5.9 As Figure 5.8 for participants with left ear deafness and stimulation of the right ear. Corresponding waveforms are displayed in Figures 5.7 and 5.8.
5.3.1 Global field power: Longitudinal data

Figure 5.10 shows the GFP analysis for both 500-Hz and 4-kHz. In the 500-Hz condition (shown in the top panel) the amplitude of N1 for unilaterally deaf participants appears greater than controls in the pre-operative condition. However, there were no statistically significant differences between the groups ($t_{(6)} = 1.49, p > 0.05$). Following surgery and the onset of deafness an increase in response amplitude appears to occur after 1 month compared to the pre-operative condition. There is a trend for a slight decline in the response amplitude at 3 and 6 months post-onset, compared with amplitudes at 1 month post-onset. However, a 1-way repeated measures ANOVA did not show any significant difference in amplitude across the four time intervals ($F_{(3,18)} = 2.16, p > 0.05$).

A similar pattern occurs in the 4-kHz condition, which is shown in the bottom panel of Figure 5.10. Again there were no statistically significant differences between the presurgical condition and the control sample ($t_{(6)} = 1.39, p > 0.05$). Although the trend for increased responsiveness 1 month after the onset of deafness was again followed by an apparent decline over the subsequent measures, a 1-way repeated measures ANOVA also shows that there are no statistically significant differences in amplitude across the four time intervals ($F_{(3,18)} = 1.85, p >0.05$).
Figure 5.10 GFP results for longitudinal data. Open bars denote control participants and filled bars denote participants with unilateral deafness prior to onset (-1) and at 1 month (+1), 3 months (+3) and 6 months (+6) post onset. Error bars denote +/- 1 s.d.
5.3.2 Source modelling AEPs: Longitudinal data

The residual variance for models of the grand average AEPs ranged from 5.5 to 12.2 across all conditions, corresponding to a goodness-of-fit of between 98.5% and 99.7%. For the individual data the average residual variance (1 s.d.) was 12.53 (5.65). The corresponding goodness-of-fit values are summarised in Table 5.1.

Table 5.1 Goodness-of-fit values (%) for source modelling of individual AEPs

<table>
<thead>
<tr>
<th></th>
<th>500-Hz</th>
<th>4-kHz</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>92 - 99.6</td>
<td>90.2 – 99.7</td>
</tr>
<tr>
<td>Controls</td>
<td>98.7 – 99.6</td>
<td>98.5 – 99.7</td>
</tr>
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</table>

The source modelled scalp topographies are displayed in Figure 5.11 and 5.12 for participants with right and left ear deafness respectively. They generally reflect the sensor level topographies shown previously, although they have been smoothed by the interpolation of activity between sensor positions.

The locations, orientations and strengths of the dipoles in each hemisphere reflect these differences between the scalp topographies. Table A5 in Appendix A summarises the results of the grand average dipole source analysis for those with right ear deafness. Table A6 in Appendix A provides the same information for those with left ear deafness.

**Location:** Figure 5.13 shows the location of dipoles for all conditions in the three orthogonal planes (coronal, axial and sagittal). Since the constraint of symmetry was applied the dipoles in the right hemisphere will have the equivalent values to those in the left hemisphere (the values of which are displayed).

The top panel shows the dipole locations in the coronal plane. The dipoles in the 500-Hz condition in each recording session are located more medially than those of the 4-kHz condition. The middle panel shows the orientations in the axial plane. There are no frequency specific trends. However, the dipoles are located more deeply below the surface of the cortex in all conditions post-surgery after the onset of deafness compared to the pre-surgery condition. The lower panel shows orientations in the sagittal plane. The locations in this plane were similar between frequencies and across conditions.
**Orientation**: The orientation of the dipoles in the grand average data is displayed in Figures 5.14 and 5.15 for right and left ear deafness respectively.

The top panel in each figure shows orientations in the coronal plane, the middle panel shows the axial plane and the lower panel shows the sagittal plane. The left columns represent the orientations to the 500-Hz stimuli and the right columns show the 4-kHz condition. Based on the orientations in the coronal and axial planes, prior to surgery the dipoles in each hemisphere are orientated laterally and tangentially reflecting the contralateral dominance apparent in the scalp topographies. However, in the 4-kHz condition in those with right ear deafness where the topographies were not clearly lateralised, the dipoles in each hemisphere were parallel with each other and more radial. There were no clear frequency specific trends in either the coronal or axial planes, however in the sagittal plane (bottom panel) dipoles in the 4-kHz condition show more anterior orientations reflecting the more frontal maximal N1 activity with increasing stimulus frequency.

Post surgery the orientations of the dipoles in both hemispheres shift towards a more radial and medial orientation at both stimulus frequencies. This is particularly apparent for dipoles in the left hemisphere irrespective of the ear of stimulation.

**Source Strengths**: Figure 5.16 shows the source strengths for contralateral and ipsilateral hemisphere dipoles in the grand average data. The results reflect the individually modelled data, displayed in Figure 5.17 and a similar pattern of results was obtained for 500-Hz and 4-kHz stimuli.

**500-Hz**: In controls the contralateral dipole is stronger than the ipsilateral dipole. In unilaterally deaf participants a similar effect occurs in both the pre-surgery condition and all of the post-surgery measures. Initial comparisons were made between controls and unilaterally deaf participants in the pre-surgical condition. A 2-factor (hemisphere [2] x group [2]) repeated measures ANOVA showed a statistically significantly main effect of hemisphere ($F_{(1,5)} = 7.6, p<0.05$). There were no significant main effects of group ($F_{(1,5)} = 0.66, p>0.05$) or interaction effects ($F_{(1,5)} = 0.41, p>0.05$) demonstrating no statistical differences in the dipole strengths between controls and unilaterally deaf participants prior to surgery. The contralateral and ipsilateral dipole strengths for
participants were then compared across the recording conditions using a 1-way repeated measure ANOVA. The contralateral dipole strengths increase markedly 1 month after the onset of deafness compared to before. However, as with the GFP analysis there is a progressive reduction at 3 and 6 months compared to the 1 month condition. The ipsilateral dipole strengths remain relatively stable across all the conditions. After employing the Huyn-Feldt correction for violation of the assumption of sphericity, differences approached significance in the contralateral dipole comparison ($F_{(2.81,14.03)} = 3.18, p = 0.07$). However no statistically significant differences were found in the ipsilateral dipole comparison ($F_{(3,15)} = 0.83, p > 0.05$).

4-kHz: Equivalent comparisons were made for data obtained in response to 4-kHz stimuli. Again, the contralateral hemisphere dipoles were significantly stronger than the ipsilateral dipoles ($F_{(1,5)} = 12.57, p < 0.05$), although there were no statistically significant differences between controls and unilaterally deaf participants in the pre-surgery condition ($F_{(1,5)} = 1.287, p > 0.05$), or any interaction effects ($F_{(1,5)} = 0.10, p > 0.05$). An increase in contralateral dipole strengths was found 1 month after surgery compared with prior, again followed by a systematic reduction in source strengths over the successive measures. A 1-way repeated measures ANOVA showed statistically significant differences between contralateral hemisphere source strengths ($F_{(3,15)} = 6.64, p < 0.01$) but not between ipsilateral source strengths ($F_{(3,15)} = 1.39, p > 0.05$). Bonferroni corrected pairwise comparisons of the contralateral source strengths did not reveal any significant differences despite the ANOVA. However, the smallest overlap in the data spread occurs between the pre and 1 month post surgery conditions, which is clearest in response to the 4-kHz stimuli (Figure 5.17, lower panel).
Figure 5.11 Top-down view of grand average scalp topographies for individuals with right ear deafness and corresponding matched controls. The upper row depicts results from 500-Hz stimulation and the lower row from 4-kHz stimulation. Blue contours show negative activity and red contours show positive activity (0.2 µV increments).
Figure 5.12 As Figure 5.11 with respect to individuals with left ear deafness and matched controls.
Figure 5.13 Summary of dipole locations in three orthogonal planes based on grand average data. Circles show results from pre-surgery, triangles from 1 month, squares from 3 months and diamonds from 6 months after surgery. Closed symbols show data for the 500-Hz condition and open symbols for the 4-kHz condition. Blue symbols show results from individuals with right ear deafness and red symbols show results from individuals with left ear deafness.
Figure 5.14 Summary of dipole orientations in three orthogonal planes from grand average data of individuals with right ear deafness. The dipoles are displayed on a standard fMRI image with data from the 500-Hz condition in the left column and from the 4-kHz condition in the right column. Red/yellow dipoles show pre-surgery results. Dark/light blue dipoles show +1 month post-surgery. Dark/light green dipoles show +3 months post-surgery. Dark/light purple show results +6 months post surgery. n.b. fMRI images are reversed by convention, such that the left hemisphere is displayed on the right and the right hemisphere is displayed on the left.
Figure 5.15 Summary of dipole orientations in three orthogonal planes from grand average data of individuals with left ear deafness. Details as Figure 5.14.
Figure 5.16 Source strengths of dipoles modelling the grand average data. Open symbols show results from matched controls and closed symbols show results from unilaterally deaf participants (collapsed across ears). C = contralateral hemisphere I = ipsilateral hemisphere.
Figure 5.17 Source strengths of dipoles modelling the individual data. C = contralateral hemisphere I = ipsilateral hemisphere. Error bars denote +/-1.s.d.

5.3.3 Global field power analysis: Cross-sectional data

Figure 5.18 shows the GFP results for the cross-sectional analysis. In both the 500-Hz condition (top panel) and 4-kHz condition (lower panel) the average amplitudes appear to increase progressively with duration of deafness compared with controls. The variance also increases with duration of deafness (indicated by wider error bars).
However, statistical comparisons using one-way ANOVA did not reveal any significant differences between groups in the 500-Hz condition ($F_{(2,37)} = 2.09, p > 0.05$), or in the 4-kHz condition ($F_{(2,37)} = 2.74, p > 0.05$).

In order to ascertain the relevance of the apparent increase in variance with duration of deafness, the individual GFP data are displayed in Figure 5.19. According to the Shapiro-Wilk test the data from control participants came from a normally distributed population (500-Hz: $W_{(19)} = 0.97, p = 0.72$; 4kHz: $W_{(19)} = 0.96, p = 0.50$). It can be seen that a number of participants exhibit response amplitudes greater than the mean of the control group plus two standard deviations. Of those, the greatest increases occur in participants in the long duration group. Thus, although the group data does not show clear evidence of increased response amplitudes with increasing duration of deafness, increases are apparent in at least some individuals. However, one participant showed response amplitudes that were smaller than the control data by more than two standard deviations. Subject 13, who was in the long duration group, showed reduced amplitudes in both stimulus conditions, leading to a weak signal-to-noise ratio in both conditions (500-Hz = 2.06; 4kHz = 1.57). It is important to note that this is the same subject who gave particularly low goodness-of-fit values in the source modelling results reported in the previous chapter (92.9 in the 500-Hz condition and 77.9% in the 4-kHz condition).

The variance of the data in the prestimulus interval (giving an estimation of overall noise) for this participant was 0.16 µV in the 500-Hz condition and 0.17 µV in the 4-kHz condition, which is lower than the average variance of the group (500-Hz = 0.22 µV; 4-kHz = 0.19 µV). This suggests that the reduced SNR was as a result of low signal amplitude and not other factors such as poor recording conditions leading to excessive noise.
Figure 5.18 GFP results for cross-sectional data. Open bars denote control results and filled bars denote data points for participants with unilateral deafness. The numbers on the x-axis show duration of deafness in years. Error bars denote +/- 1.s.d.
Figure 5.19 GFP results for cross-sectional data. Open bars denote mean control results (Error bars denote +/- 2 s.d.). Filled bars denote individual GFP results for participants with unilateral deafness. The brackets on the x-axis show duration of deafness in years.
5.4 Discussion

This study aimed to investigate the pattern and time course of the changes in N1 AEPs that occur following unilateral deafness in humans. The patterns of changes were similar to those reported in the previous chapter. They include increased dipole source strengths and a less asymmetrical pattern of N1 activity across the scalp after the onset of deafness. These changes begin within one month of the onset and then persist. The data also suggests that subsequent increases in overall activation may occur over periods of greater than two years in some individuals. These changes are consistent with experience-related plasticity in the CAS. Furthermore, the suggestion that changes continue over a wide range of time periods is consistent with the presence of different physiological mechanisms giving rise to the changes. As in the previous chapter, these changes were apparent after both left and right ear deafness, and to both high and low frequency stimuli. The results of the two analyses, longitudinal and cross-sectional, will be discussed in turn.

5.4.1 Longitudinal data

The pattern of mean activity following monaural stimulation was examined in two ways; according to GFP and using source modelling. The first issue is to consider the N1 activity in participants prior to the onset of unilateral deafness, along with the matched controls. In terms of both the response amplitudes and dipole strengths, the study did not reveal any statistically significant differences in N1 amplitude between the two groups. In addition, on the basis of both sensor and source level topographies, the patterns of activity across the scalp were also similar. In both groups and for both high and low frequency stimuli, the areas of maximal activity were generally centred over the hemisphere contralateral to the ear of stimulation. This is consistent with expectations and is attributed to the underlying organisation of the CAS leading to contralateral dominance. The results demonstrate that prior to surgery and the onset of profound unilateral deafness the N1 responses in participants correspond with normal CAS activation.

None the less it was interesting to note that even prior to surgery the mean GFP amplitudes and dipole strengths were slightly greater in unilaterally deaf participants compared with controls. As is often the case in individuals with an acoustic neuroma, the participants in this study exhibited asymmetrical hearing sensitivity thresholds prior to surgery. Based on previous evidence it seems plausible to expect some degree of
change in the CAS response as a result of a prolonged asymmetry between the thresholds of each ear (and/or suprathreshold audibility), even prior to deafferentation of the non-test cochlea. For example, Vasama et al. (1998) studied the modification of CAS responses as a result of improvement in thresholds after unilateral middle ear surgery. Individuals with middle ear disorders will exhibit reduced thresholds in the affected ear, e.g. due to otosclerosis. Hence, in these individuals an asymmetry in hearing sensitivity will be apparent prior to surgery that shifts to a more symmetrical configuration after corrective surgery. The CAS responses to stimulation of the healthy ears of seven such individuals were compared with normally hearing controls. A number of changes were noted after the surgery such as increased N1m response amplitudes and decreased latencies to stimulation of the healthy ear. The results were interpreted as an indication of the ability of the CAS to modify its function so as to maintain a balance of neural input between the two ears. However, the relevance here is that any modifications were as a result of attenuation of the sound level in one ear only, and must have taken place without sensory deafferentation. The modifications that were reported are therefore a result of asymmetrical input alone. More recently, similar physiological changes have been noted after a temporary elevation of thresholds in one ear (Munro and Blount, 2009). In this study a group of 11 adult participants with normal hearing wore an ear plug monaurally for one week. Immediately after removal, the acoustic reflex thresholds of the previously plugged ear were found to have reduced compared with pre-plug measures, whereas the thresholds in the not-plugged ear were found to have increased. However, one week after removal of the ear plug, the thresholds in both ears changed in the opposite direction; i.e. they reverted to their pre-plug levels. These findings were also attributed to a central gain mechanism which apparently acts to restore the balance in input between the ears. The increase in suprathreshold response amplitude with stimulation of the healthy ear noted by Vasama et al. (1998) after the corrective middle ear surgery (and hence restoration of symmetrical input) is consistent with the reduction in reflex thresholds in the not-plugged ear after the removal of the ear plug noted by Munro and Blount (2009). The presence of such a central gain mechanism might also be expected to cause changes to the N1 response to stimulation of the intact ear in individuals with an acoustic neuroma as well. However, based on the above discussion the prediction would be for higher thresholds and reduced response amplitudes evident in the intact ear prior to surgery. Whilst speculative, if anything, the present results suggest the opposite. Furthermore, a slight increase in response amplitudes prior to surgery compared with controls was also
indicated in the study by Vasama et al. (2001), where the hearing threshold asymmetries were also due to the presence of an acoustic neuroma. The discrepancy could be related to the origin of the asymmetry; changes exhibited after wearing an ear plug or following middle ear disorders are effectively examples of training-induced plasticity. The precise effects of this form of plasticity might be different from that due to the presence of an acoustic neuroma, which constitutes a trauma on the CAS and is therefore an example of injury-induced plasticity. For example, the acoustic neuroma might cause a reduced spontaneous firing rate of afferent projections from the affected side (Lenarz et al., 1993), or an alteration in the synchrony of neural firing on the affected side, which is not thought to occur through training e.g. after wearing an ear plug. In any case, whatever their origin, if any differences in the N1 response between participants prior to surgery and the controls were present, they could only have been slight. This means that once all other factors are considered, any subsequent differences must be attributed to the effect of the onset of unilateral deafness after the surgery.

The next issue is to consider the effect of unilateral deafness and the time course of any changes. The results show a trend for increased N1 amplitudes after the onset of deafness according to the GFP analysis with both low and high frequency stimulation. The differences in contralateral dipole source strengths did reach statistical significance in the 4-kHz condition, and approached significance in the 500-Hz condition. Furthermore, these changes were accompanied by altered sensor and source modelled scalp topographies. After the onset of deafness the pattern of N1 activity appeared more symmetrical across the scalp. As argued in the previous chapter, this combination of results must be due to an increased response primarily from the ipsilateral hemisphere, with the altered scalp topographies reflected by altered dipole location and orientations and not necessarily ipsilateral dipole strengths. Although following the significant differences noted in the 4-kHz condition, the post-hoc pairwise comparisons did not reveal any significant differences, this is probably due to use of a more stringent alpha value, to minimise the chance of a type 1 statistical error. However, in both the 500-Hz and 4-kHz stimulus conditions the biggest differences between groups occurred between the pre- and 1 month post-operative conditions. Thus, changes are likely to have commenced by the time of the first post-operative recording session, which was one month after the onset of deafness, and persisted over at least the ensuing six months. The difference in N1 responses between pre- and post-deafness measures indicates experience-related plasticity. The timescale of the changes would implicate
physiological mechanisms that can occur rapidly i.e. within one month. Unfortunately, it is not possible to establish from the present data exactly when the changes first commenced, but changes over this time scale in adults have typically been attributed to the functional mechanisms discussed previously, such as the unmasking through disinhibition and/or increases in gain of existing synapses and hence increased excitatory influence of the intact ear (McAlpine et al., 1997).

It is important to rule out alternative explanations for these findings. One possible issue is the variability of N1 measured on multiple occasions in the same individuals. However, test-retest variability is unlikely to fully explain the present findings. First, AEPs in general have shown good test-retest replicability in the short term. For example Tremblay et al. (2003) showed that speech evoked cortical potentials recorded at the vertex were highly stable in a group of seven individuals tested twice over an eight-day period. Intra-class correlations between waveforms of up to 0.94 were seen in some individuals, where a value of 1 would indicate identical waveforms obtained over the two sessions. Virtanen et al. (1998) used standard deviation as a measure of replicability in MEG and EEG measures of N1 activity. The study reported a variance of up to 14% in relation to the mean amplitude values of N1 AEPs measured twice over a two day period in five individuals. However, the variance was different depending on the reference position used, which emphasises the dependence of signal-to-noise ratio on the particular methods used in a given study. In particular, AEPs lend themselves well to longitudinal studies because, whilst systematic errors due to factors such as reference position will remain constant across conditions, AEPs do not suffer acutely from random errors associated with head position or movement as do fMRI or MEG studies. For instance, Virtanen et al. (1998) reported amplitude variances in MEG data recorded at the same time as the AEPs mentioned above of almost twice as much across conditions as within conditions. The stability of the N1 response recorded at the scalp suggests that source analysis will also produce reliable results across sessions. Indeed Virtanen et al. (1998) reported variances of around 20% in source strengths across conditions, whilst Atcherson et al. (2006) found no significant differences in either source strengths or locations across sessions in 10 individuals tested 3 times over a 28 day period.

Second, Connolly (1985) noted that measures of contralateral dominance were highly replicable over a six week period on a group level, meaning that there is no reason to
suspect that the systematic changes in scalp topographies shown in the present findings occurs across different measurements under normal circumstances. A third reason that argues against test-retest variability being able to explain the present findings relates to the robustness of the GFP analysis against showing changes. The lack of statistical findings in the GFP component of the analysis in spite of differences in the source modelling analysis is probably due to the same issue that arose in Chapter 4. GFP takes into account the activity across all of the sensors yet the data from a number of these (e.g. those in occipital regions, frontal and fronto-temporal regions ipsilateral to the stimulus ear) is not likely to be markedly different across conditions, whilst any experience-related changes might be most apparent at only a subset of these (those located around the central scalp regions). The effect of this will be to dilute somewhat any differences that are apparent at a subset of recording positions. This overcomes the difficulties of comparing amplitudes at discrete recording sites on either hemisphere. Whilst this makes it difficult to show changes statistically without either very large sample sizes or effect sizes, this attribute does make GFP measures robust to test-retest variability as well. In order to demonstrate this, an opportunity was taken to study the replicability of N1 according to GFP over a period of 6 months. Eight normally hearing participants from the study described in Chapter 3 (four receiving 500-Hz and four receiving 4-kHz stimuli) agreed to return six months later and were tested on a second occasion. The results are shown in Appendix B. The grand mean waveforms from the first and second recording sessions are shown in Figures B1-4. Although the waveforms at most recording sites are similar, a number of differences are apparent. Despite this the waveforms demonstrated intra-class correlations ranging from 0.83 to 0.92, which is consistent with the results of Tremblay et al. (2003). The mean N1 amplitudes according to GFP analysis (displayed in figure B7) were within 2% when collapsed across ears for both frequencies (and were within 12% when each ear was considered separately), and neither was statistically significant. In addition, the pattern of contralateral dominance was also similar across the two recording sessions, as shown by the scalp topographies displayed in Figures B5 and B6. However, compared with the pre-operative condition, the GFP amplitudes collapsed across ears from the longitudinal study were 11.3% greater after 1 month in the 500-Hz condition and 8% greater in the 4-kHz condition. Smaller differences were apparent at 3 and 6 months post onset, but these were still higher than the biggest differences seen in the control sample.
One observation from the present study is the tendency for response amplitudes to decrease in measurements made 3 and 6 months post onset of deafness compared with the measures made 1 month post onset. There were no statistical differences between amplitudes across the post onset data from either the GFP or source modelled data from the present study, thus any conclusions will be tentative. However, the reduction was no lower than 3% across the conditions according to the GFP measures. Although small, this is still greater than the test-retest differences demonstrated in Appendix B and the differences always ran in the same direction. Vasama et al. (2001) also reported a subsequent reduction in source strengths after the initial post-surgery increase. In that study the source strengths at 6 months post surgery were no different from the pre-surgery measures, whereas in the present study the GFP amplitudes and source strengths remained higher. Still, it would be very interesting to ascertain the results after even longer periods such as 9 or 12 months post surgery, in order to determine whether the trend continued. It would also have been interesting to note whether the amplitudes recorded at one month post surgery would have been the same or different from those at an earlier point. It may be hypothesised that N1 amplitudes would be higher still. There are reasons to suspect that the hyperactivity occurring due to deafferentation might subsequently reduce over time as the results tentatively suggest. One hypothesis relates to the concept of homeostatic plasticity (Turrigiano, 1999). If the changes noted by 1 month post surgery in the present study are attributed to Hebbian based experience-related plasticity, then antagonistic mechanisms must also be present to maintain selectivity in the neural network. It has been recognised that without such mechanisms, Hebbian based plasticity alone would be insufficient for maintaining a stable neural network. Potentiation of some inputs would lead to increased correlation of firing between pre- and post-synaptic neurons, which would potentiate those inputs further and so on, ultimately increasing the correlation in firing to the limit. The opposite would happen to inputs with a negative correlation, with the end result being a destabilised neural network that would not be able to respond differently to different inputs. Suggestions for physiological mechanisms underlying homeostatic plasticity include changes in the intrinsic excitability of neurons and cellular mechanisms regulating the rate and extent of synapse formation (Turrigiano, 1999). Another possibility is an increase in inhibitory input that is presumed to have been disrupted due to the deafferentation (Calford, 2002). For example Calford and Tweedale (1988) noted an enlarged somatosensory representation of adjacent input following digit amputation in the flying fox. The changes occurred rapidly but were followed in subsequent weeks by
a reduction of the enlarged representation. This reduction was associated with the re-establishment of inhibitory balance. The source of such inhibitory input is unclear given the deafferentation, although ultimately it must either derive from the remaining sensory input from the periphery, or from tonic input mediated by central nervous system structures. Indeed Clarey et al. (1996) showed modulation of activity within the primate somatosensory cortex in one hemisphere after inducing, via freezing, a temporary cessation of tonic activity derived from the contralateral hemisphere and mediated via interhemispheric callosal connections. In any case, whether or not the present findings reflect the presence of homeostatic plasticity within the CAS of adult humans remains an open question.

5.4.2 Cross-sectional data

For simplicity, the GFP results in this study were compared in the absence of source modelled data. This is because in each group there was a mixture of individuals with left and right ear deafness. The source modelled data depends on stimulation of the same ear for a valid comparison of the activity in each hemisphere. Subdividing each group according to the ear of deafness in order to do this would lead to small sample sizes, making comparisons difficult. On the other hand, GFP is not sensitive to hemispheric asymmetries meaning that it is not necessary to subdivide the groups. When organised according to the duration of deafness, the results show a trend for greater mean amplitude in the group with longer duration of deafness, compared with the normally hearing control group. The trend did not reach statistical significance in either stimulus condition therefore any conclusions to be drawn from this trend are purely speculative. However, none of the previous comparisons involving GFP reached statistical significance either, even though comparison of source strengths did. Thus, it may be that this aspect of the study was simply underpowered in statistical terms.

Another finding that seems to lend strength to any speculation based on the trend was that the GFP amplitudes of a number of individuals fell above the mean amplitude of control participants plus two standard deviations. On a normal distribution, 2.5% of the population will fall above this range by chance. Furthermore, the majority of the individuals in the present example were in the long duration group. This would be consistent with the findings reported by Ponton et al. (2001), in which evidence of reorganisation was also reported to occur over a period of two years or more. In that
study, the possibility that the smaller changes noted in individuals with a lower duration of deafness was merely reflecting less extensive changes later in life could not be ruled out. This is because those with a smaller duration of deafness were also significantly older. In the present study however, there was no difference in age between participants with either a short or long duration of deafness, or indeed any other noticeable differences between variables such as sex or hearing thresholds in the intact ear.

On the other hand, one subject gave noticeably small amplitude responses under normal recording conditions. Although a possible outlier, the pattern of results (e.g. scalp topographies, GFP and source modelled data) do not change systematically when the data of this individual were removed. The reasons for the small amplitude responses are unclear but similar results have been reported previously and have been attributed to an exceptionally convoluted supratemporal surface, as revealed by MRI scanning (Makela et al., 1993). The folding of the perisylvian regions where the auditory cortex is located, the length of the planum temporale and the size of cytoarchitectural areas will show individual variation. This can, in extreme circumstances, lead to an inability to record evoked potentials at the scalp, since the dipoles from the neural populations giving rise to the evoked potentials must be appropriately spatially aligned in order to summate. If their orientation is opposing then cancellation will occur. Thus, even if plasticity resulting in hyperactivity had occurred, it would be missed by far-field EEG recordings in such individuals. It is precisely this issue that lead to past criticism of between-subjects comparisons of inter-hemisphere amplitudes at the sensor level. Unfortunately MRI data of the supratemporal cortex of participants in the present study was not available and so other explanations cannot be ruled out.

Another issue is why, if changes were continuing over a time course of two years or more in some participants, were they not apparent in the others. Inter-subject variability may have contributed to the confusion to some extent, for example due to the same dipole orientation issues described above. Further, it is plausible that some individuals exhibit the ability for CNS reorganisation more than others. For example, although Reale et al. (1987) demonstrated dramatic changes in the ipsilateral response of one adult cat after receiving unilateral cochlear ablation, the responses of another remained unchanged over the recording period. Considerable variability between animal models of representational plasticity has also been reported following somatosensory deafferentation (Merzenich et al., 1987). This is consistent with individual differences in
sensory experience (and possibly genetic factors) and is perhaps only to be expected with dynamically maintained cortical maps, or in the present example, binaural interactions. Finally, pre-surgery data was not available, but it is possible that some individuals exhibited asymmetries in hearing sensitivity for different durations prior to the removal of the acoustic neuroma. Factors such as rate of growth and location of the tumour, residual hearing in the affected ear and general health issues are used to decide when a tumour should be removed. Although the groups were divided according to the period of time after surgery, it might be that the true duration of deafness varied more markedly between individuals than was recorded. On the other hand if this were the case then one might have expected a greater proportion of individuals with apparently increased response amplitudes to fall into the short duration group than was observed. Issues to do with inter- and intra-subject variability need to be addressed further by a longitudinal study that spans at least two or three year’s post-onset of unilateral deafness.

5.4.3 Conclusions

The study described in this chapter aimed to investigate the pattern and time course of changes in AEPs following unilateral deafness in humans. The results show enhanced amplitudes of N1 AEPs following unilateral deafness, with the greatest increases occurring over the hemisphere ipsilateral to the ear of stimulation. The changes appear to commence within one month. This is consistent with experience-related plasticity within the CAS that is driven by changes in the existing connections between neurons within the CAS. The pattern and rate of changes is similar for both low and high-frequency stimuli, and no differences were apparent for either left or right ear deafness. There is also tentative evidence for changes over a period of at least two years, and this may represent preliminary evidence in humans for experience-related plasticity that is driven by other physiological mechanisms such as the emergence of new projections in the auditory pathway.

These results are important because they help to address the third research question posed in Chapter 1, which asked what is the time course of experience-related plasticity in adult humans? Until now there has been a lack of evidence describing this in the literature. One of the main motivations for studying experience-related plasticity is to optimize rehabilitation strategies for individuals with deafness. Whilst further progress
in this regard will inevitably involve establishing what, if any, perceptual consequences result from physiological changes, the present results may also highlight another issue. At least on the basis of the cross-sectional study it appears that some individuals may show a greater capacity for reorganisation than others. The relevance of this may be apparent, for example when designing rehabilitation strategies for individuals with sensory impairment.
Chapter 6: Summary and Conclusions

This final chapter summarises the main findings and conclusions of the studies in this thesis, and goes on to discuss possible areas for future investigation. There were two general aims of the thesis. The first was to clarify the pattern of experience-related plasticity within the CAS of humans with late onset unilateral deafness when measured using AEPs. The second was to study the time course of the changes.

Under normal circumstances, monaural stimulation results in bilateral and asymmetrical activity between the hemispheres of the brain; the contralateral hemisphere responds more strongly than the ipsilateral hemisphere, known here as contralateral dominance. This occurs because there are more ascending nerve fibres in the contralateral pathway than the ipsilateral pathway that respond to each ear. Based on evidence obtained from animal models (using electrophysiological techniques) and from fMRI data in humans, the expectation is that individuals with unilateral deafness will exhibit a reduction in the normal pattern of contralateral dominance with stimulation of the intact ear. The activity from the ipsilateral hemisphere should increase, causing a more symmetrical pattern of activation between the hemispheres. This is thought to be as a result of a disruption to the binaural interactions within the CAS that occurs following unilateral deafness, after which more nerve fibres in the ipsilateral pathway become responsive to the intact ear. This is one example of experience-related plasticity and it is a useful one to study in humans due to the large scale changes that occur. In addition, certain categories of patients with unilateral deafness lend themselves well to longitudinal studies (i.e. acoustic neuroma patients), since pre-onset data may also be available. Longitudinal studies of experience-related plasticity are important because they reveal the time course of changes. Such information is crucial in elucidating the physiological mechanisms that may underlie the changes in humans.

The aims of this thesis were addressed using cortical AEPs. In particular, the N1 cortical AEP, as it can be used to demonstrate contralateral dominance in humans, and is known to reflect neuroplasticity. AEPs are also non-invasive and inexpensive to measure, and have good test-retest reliability which is useful for conducting longitudinal studies in humans. Unfortunately, despite clear evidence in studies using fMRI, studies that have investigated plasticity in individuals with unilateral deafness
using N1, measured using either AEPs or AEFs, have not consistently demonstrated a similar reduction in hemispheric asymmetries, even when controlling for what are thought to be important inter-subject variables (e.g. cause of unilateral deafness and sensitivity of hearing in intact ear).

The discrepancy may be due to methodological issues related to measuring changes in hemispheric asymmetries using AEPs and AEFs. It is thought that one can-not simply compare the amplitude of activity between homologous locations on the scalp in the sensor space. This is because the amplitude may be affected by a number of factors other than magnitude of activity e.g. it could also be affected by source geometry. One way to overcome this issue is to move into the source space. The aim of the first study was to measure hemispheric asymmetries in the source space in normally hearing individuals. A second aim was to investigate the effect of level and frequency of stimulation on hemispheric asymmetries. The purpose of the study was to verify the validity of the methodology to be used in the later studies in this thesis. This was necessary to address the methodological issues that may have affected previous studies, and inform the design and interpretation of the results of the subsequent studies. In addition, until now the effect of varying these stimulus parameters has not been systematically investigated in humans using AEPs. It was hypothesised that hemispheric asymmetry will reduce with increasing level due to saturation of the response; specifically, as level of presentation increases the contralateral hemisphere will saturate before the ipsilateral hemisphere. A second hypothesis is that high-frequency stimuli will produce greater contralateral dominance compared with low. This could be due to greater activity in the contralateral hemisphere as a result of additional sources sensitive to high-frequency stimuli, and/or relatively less activity in the ipsilateral hemisphere as a result of the overall weaker response typically seen for high-frequency stimuli.

**Study 1: Auditory evoked potentials and contralateral dominance in adult humans with normally hearing**

Findings and conclusions:

- The results in this study were consistent with previous measures of hemispheric asymmetries in normally hearing individuals using AEPs. The ear specific pattern of contralateral dominance was similar to other studies also using source modelling. This lead to the conclusion that the technique used was valid.
With respect to presentation level, the study showed that, at least given a sufficient inter-stimulus interval to minimise saturation of the N1 response, contralateral dominance is consistent over a range of stimulus levels.

In terms of stimulus frequency, measures of hemispheric asymmetry are greater following high frequency stimulation. Although the reasons for this latter finding are unclear as yet, it could be as a result of frequency specific differences in the process of transduction in the cochlea, and anatomical differences in the frequency representation in the central auditory system.

These latter two findings provide an incremental contribution to existing knowledge and inform the interpretation of subsequent studies in this thesis by demonstrating the effect of variation in stimulus levels, at least over the range of stimulus levels tested here. This is important as level will vary in late-onset plasticity studies due to hearing threshold variation at both high and low frequencies.

The second study in the thesis involved comparing the AEPs measured from individuals with late onset unilateral deafness to those of matched controls. The purpose was to study experience-related plasticity in humans using AEPs. It was hypothesised that an overall increase in response amplitude will be apparent in those with unilateral deafness reflecting an increased responsiveness of CAS neurons to stimulation of the intact ear. In addition, it was hypothesised that a reduction in the normally observed contralateral dominance will occur in conjunction with the increased overall response amplitude. This is because increased neural activity is expected to occur primarily in the ipsilateral hemisphere. Two further aims were to investigate any frequency- or ear-specific differences in the results. Although any changes should occur across the frequency range, the pattern of changes might be different for high-frequency stimuli compared to low. It was predicted that any apparent experience-related plasticity would occur irrespective of the ear of deafness.

**Study 2: Effects of unilateral deafness on contralateral dominance in adult humans**

Findings and conclusions:

- A number of differences in AEPs are apparent between individuals with unilateral deafness and matched controls. The differences include trends for increased response amplitudes in GFP, increased source strengths bilaterally, and more symmetrical topographies.
The dipole strengths in the source space did not reflect the scalp topographies. The contralateral dipole remained stronger than the ipsilateral.

This discrepancy can be explained by considering that in the source space there are three dependent variables (i.e. dipole orientation, location and strength). Thus, reduction in hemispheric asymmetry can be reflected in the source space in more than one way. It could be reflected by an increase in ipsilateral dipole strength, a shift in orientation and/or location of contralateral and/or ipsilateral dipoles, and/or a complex combination of the above. It is possible that this explains the mixed findings reported earlier. Indeed the only clear demonstration in the AEP literature previously compared amplitudes in the sensor space hence would not have been subject to this issue (as the only dependent variable was amplitude; Ponton et al., 2001). However, the information provided by the GFP analysis and scalp topographies in the present results suggests that the explanation is an increase in ipsilateral response amplitude, since any change in orientation without increased amplitude would result in no net increase in amplitude according to GFP, and the topography would not change as it did.

The most important conclusion from these results is therefore that although the model is able to reflect changes in AEPs due to experience-related plasticity, it does not show these changes in the way one would expect based on fMRI data and animal models.

Two additional novel findings from the study were that the differences in AEPs measured from individuals with unilateral deafness occur irrespective of the ear of deafness and are apparent to both low and high-frequency stimuli.

Previous evidence in AEPs for ear specific experience-related plasticity may therefore be attributed to other factors such as methodological factors.

The finding that changes occur across frequencies is consistent with findings from animal models, where changes are also proportional across the frequency range. This demonstrates congruence between evidence for plasticity in animal models and humans.

The time course of the changes in AEPs following unilateral deafness in humans is reported in the final study for the first time. This information helps to shed light on the physiological mechanisms driving experience-related plasticity in humans. The aims were addressed in two ways. First, a longitudinal study was carried out on a group of
individuals before and on several occasions after surgery for removal of an acoustic neuroma. This provided information on the sequence of events up to six months following the onset of deafness. Information on the extent of changes over subsequent years was provided by further analysing the data presented in Chapter 4 using a cross-sectional design. The data was split into two groups, those with <2 years deafness and with ≥2 years deafness. If different mechanisms of plasticity drive changes in CAS responsiveness, it was hypothesised that changes would be seen over a short and longer term. Immediately following the onset of deafness the response amplitudes were expected to increase and contralateral dominance was expected to reduce. Further increases in response amplitudes as the duration of deafness increased were predicted.

**Study 3: The time course of experience-related plasticity in adult humans with late onset unilateral deafness**

Findings and conclusions:

- The results from the longitudinal data reveal evidence of an increase in AEP amplitude after surgery, with the biggest increases occurring within one month. This would be consistent with physiological changes within the CAS such as unmasking through disinhibition.

- The increase in amplitude seen after one month was coupled with a shift towards more symmetrical scalp topographies, indicative of increased ipsilateral hemisphere response. These changes were shown using the same source model as in study 2 and consequently the same issues arose; i.e. that the reduction in asymmetry apparent from topographies was not reflected by dipole strength alone, but also orientation and location.

- The changes noted after one month persist over at least the ensuing six months, although there is a non-significant trend for a gradual decline in AEP amplitude in the ensuing months. Whether or not this decline is due to homeostatic plasticity is an open question.

- From the cross-sectional data there is also evidence for changes in some individuals with ≥2 years deafness. This is consistent with physiological mechanisms driving plasticity that take a longer period of time than unmasking, for example synapse growth.

For around the past thirty years, research involving animal models of unilateral deafness to study experience-related plasticity in the CAS has progressed steadily and has
followed a clear pattern. Early studies focused on the effects of neonatal deafness and typically adopted a between-groups design whereas later studies interested in the effect of late onset deafness and the time course of events adopted within-groups and longitudinal designs.

Progress in research involving humans with unilateral deafness has followed a similar pattern. Initial studies approximately fifteen years ago utilised a between groups design such as the one described in Chapter 4. However, until now there have been conflicting findings, and no previous studies have provided adequate within-groups longitudinal data to describe the time course of events following late onset unilateral deafness. The studies in this thesis therefore contribute new knowledge. However, there are still areas which require further clarification. For example there is little or no evidence for sub-cortical plasticity in humans with unilateral deafness. This could be investigated using AEPs, since due to volume conduction they lend themselves well to detecting the responses of sub-cortical nuclei. Resolving the response from the contralateral and ipsilateral hemispheres in sub-cortical regions may be technically challenging using AEPs. However, overall greater amplitudes and shorter latencies would be expected to stimulation of the intact ear of individuals with unilateral deafness compared with controls. Second, it will be important to ascertain why some individuals appear to exhibit changes over a period of two years or more, whereas others do not. A longitudinal study which spans a period of greater than two years post onset would help to address this issue, since inter-subject variability in the present data may be one explanation.

Information relating to the perceptual consequences of experience-related plasticity remains sparse. Further studies should therefore look to improve understanding in this area. One possibility is that the experience-related plasticity described here results in changes in perceptual abilities such as frequency discrimination to stimuli presented to the intact ear. This would be analogous to the perceptual correlates of changes in frequency representation seen following the introduction of cochlear dead regions. Frequency discrimination abilities typically improve to stimuli around the edge frequency (McDermott et al., 1998). The improvements are associated with an over-representation of edge-frequencies at the cortical level, allowing more effective processing of these frequency cues (Kluk and Moore, 2006). Similar over-representation of the intact ear following unilateral deafness might result in similar improvements in
frequency processing. This could be investigated by comparing the difference limens for frequency of a group of individuals with unilateral deafness with a normally hearing control group. Alternatively, it may be that any perceptual correlates of plasticity following unilateral deafness are as a consequence of the disruption to binaural cues such as those required for accurate localisation. It is well known that localisation abilities are severely disrupted following the introduction of a unilateral earplug, but that over time a partial recovery of performance can be observed with training (Wright and Zhang, 2006). Furthermore, some evidence has already been described relating to improvements in monaural localisation tasks in individuals with long standing unilateral deafness (Slattery and Middlebrooks, 1994). This could be tested further by monitoring the performance of individuals with unilateral deafness in a free-field localisation task alongside physiological measurements made longitudinally. It may be expected that improvements in localisation abilities occur concurrently with changes in CAS activity. Other changes as a result of the disruption in binaural cues, such as intensity discrimination to stimuli presented in the intact ear, or speech recognition abilities in noise, might also be used to quantify the perceptual correlates of plasticity. As briefly mentioned in chapter 2, evidence of such changes has already been noted in the ear receiving amplification in monaural hearing aid users (Munro, 2008). Here, it is argued that the asymmetry in input is the important factor driving such functional changes, since differences according to ear of stimulation are not seen in binaural hearing aid users. The profound asymmetries in sensory input in those with unilateral deafness might lead to similar changes i.e. improvements in intensity discrimination and/or speech recognition in noise. Intensity discrimination abilities could be investigated by comparing the difference limens for intensity in a group of individuals with unilateral deafness with a normally hearing control group. Similarly, speech recognition in noise could be tested by comparing performance against a control group tested in two conditions, binaural and simulated monaural (e.g. via an ear plug), which would mirror the design used by Slattery and Middlebrooks (1994). However, it should be noted that monaural hearing aid users provide an example of training-induced plasticity rather than injury-induced plasticity under consideration here, and it is currently unclear as to how closely the two drivers of plasticity may be compared.
References


Appendix A
Table A1 Summary of dipole source analysis for grand average data from study 1, described in Chapter 3

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<th>Strength (nAm)</th>
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Table A2 Summary of dipole source analysis for individual data from study 1, described in Chapter 3. (Numbers in parentheses show 1 s.d.)

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Table A3 Summary of dipole source analysis for grand average data from study 2, described in Chapter 4

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Table A5 Summary of dipole source analysis for grand average data from participants with right ear deafness from study 3, described in Chapter 5.

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500-Hz: Session 1, Session 2, Session 3, Session 4, Control
4-kHz: Session 1, Session 2, Session 3, Session 4, Control
Table A6 Summary of dipole source analysis for grand average data from participants with left ear deafness from study 3, described in Chapter 5.

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Table A7 Audiometric and demographic information for participants from study 2, described in Chapter 4. Thresholds displayed in dB HL. Age and durations of deafness are displayed in years.

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Table A8 Audiometric and demographic information for participants from study 3, described in Chapter 5. Thresholds displayed in dB HL. Age is displayed in years.

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Appendix B
Figure B1 Grand average waveforms for four normally hearing participants receiving 500-Hz pure tone stimuli in the left ear. The waveforms shown in red and blue were recorded in separate sessions 6 months apart.
Figure B2 As Figure B1, but for participants receiving stimuli in the right ear.
Figure B3 Grand average waveforms for four normally hearing participants receiving 4 k Hz pure tone stimuli in the left ear. The waveforms shown in red and blue were recorded in separate sessions 6 months apart.
Figure B4 As Figure B3, but for participants receiving stimuli in the right ear.
Figure B5 Top-down views of sensor level topographic maps of the waveforms displayed in Figures B1 and B2.
Figure B6 Top-down views of sensor level topographic maps of the waveforms displayed in Figures B3 and B4.
Figure B7 GFP results from the waveforms shown in figures B1-4. Column 1 depicts the data from session 1, and column 2 depicts the data from session 2 which took place 6 months later. Error bars denote +/- 1s.d.