EEG EVIDENCE FOR AUDITORY CORTICAL PLASTICITY

ELECTROENCEPHALOGRAPHIC EVIDENCE FOR AUDITORY CORTICAL PLASTICITY IN HUMANS TRAINED ON A FREQUENCY DISCRIMINATION TASK

By

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Abstract

Animal studies have shown that the tonotopic organization of the auditory cortex is not statically fixed, but can be remodeled by experience. The purpose of this study was to investigate whether or not frequency discrimination training can induce changes in the cortical representation of a selected frequency in humans. Six human subjects were trained for approximately 3 weeks to detect a change in pitch between two tones (40 Hz amplitude modulated) using a standard frequency of 2040 Hz. Each subject was tested on his/her discriminative ability before and after training using three different standards (2040 Hz, 1840 Hz, and 2240 Hz). EEG data were recorded both before and after training and changes in transient and steady-state responses were investigated. Behaviourally, every subject improved at the discrimination task using the trained frequency. However, only three subjects demonstrated transfer to both untrained frequencies. In the EEG data, the P2-N1 amplitude increased in five of the six subjects and the N1 latency decreased in all six for the 2040 Hz set. These two findings were statistically significant ($p<0.05$) for the group. There were no statistically significant findings for the side frequencies. The change in the 40 Hz steady-state response was also not significant, increasing in three subjects and decreasing in the other three. These findings indicate that changes are expressed in the secondary auditory cortex. These findings may also be applicable to the treatment of tinnitus.

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Table of Contents

List of Figures

Chapter 1 - Introduction

It was believed for many years that the brain's representation of its sensory world was fixed. In other words, each part of the brain assumed its role early on in life and this role never changed. For example, the auditory cortex was always involved with hearing, the visual cortex always processed information from the eyes, and the motor cortex controlled motor movements.

In the past decade, however, several researchers have demonstrated that in a strict sense, this is not true. That is, the brain is capable of reorganizing itself and a part of the brain which was originally responsible for vision, for example, can be altered so that it plays a role in somatosensory processing. This is what is referred to as cortical plasticity.

Cohen et al. (1997) studied such a phenomenon. They disrupted the function of the visual cortex, using transcranial magnetic stimulation, in both blind and normal-sighted people. It was found that blind people made mistakes in identifying Braille or embossed Roman letters, while visual cortex stimulation had no effects on tactile performance of normal-sighted people. It was concluded that, in blind subjects, the area of the brain normally referred to as the visual cortex was recruited to be used in somatosensory processing. This type of cross-modal plasticity may also be the reason why early-blind humans are better able to localize sounds than normal-sighted humans (Lessard et al., 1998).

The study of cortical plasticity is important. How does the brain internally represent the information it receives from the outside world? How do we learn new tasks, new ideas, or new languages? The cortex plays a role in these things and studies on cortical plasticity will help us in better understanding how.

Most examples of cortical plasticity occur on a smaller scale, within a specific region of the brain, such as the auditory cortex. The auditory system has a tonotopic organization, which starts in the cochlea and continues into the auditory cortex. In the auditory cortex, the tonotopy is such that neurons located deeper within the supratemporal sulcus (farther from the scalp) are tuned to higher frequencies (Romani et al., 1982). However, neurons which at one time represented frequency A, can be altered so that they respond best to frequency B. These plastic changes may be induced by deafferenting the neurons (when neurons lose their sensory input) or by learning a new task.

Robertson and Irvine (1989) examined the effects of cochlear lesions on the topographic mapping of sound frequency in the auditory cortex of adult guinea pigs. A lesion removed the input of a certain frequency range to the auditory cortex. Thirty-five to 81 days after the lesions occurred, neurons in the contralateral auditory cortex, which normally would have represented the lesioned frequency range, responded to tone frequencies adjacent to the frequency range damaged by the lesions. In a second series of experiments, Robertson and Irvine showed that reorganization was also present after a few hours of the making the lesion. Rajan et al. (1993) performed a study on adult cats and found that 2-11 months after the unilateral cochlear lesion, a similar reorganization of

the primary auditory cortex had taken place. Similar map reorganization caused by a removal of input, such as the lesioning of the retinas or the amputation of a finger, also occurs in the visual cortex and the somatosensory cortex (See Buonomano and Merzenich, 1998).

Bakin and Weinberger (1990) were able to induce frequency receptive field plasticity in the auditory cortex of guinea pigs using classical conditioning. The frequency receptive field of a neuron describes how it responds to various frequencies. The guinea pigs were conditioned with trials consisting of a tone of a given frequency (CS) followed by an electrical shock. Following 30 of these trials, the post-conditioning receptive fields were compared with the pre-conditioning receptive fields of primary auditory cortex neurons. It was discovered that, in 70% of the conditioning cases, the responses to the CS frequency increased, whereas there were decreased responses to other frequencies, including the previous best frequency. In 43% of these cases, the CS frequency became the new best frequency. These types of receptive field changes can last up to 8 weeks and possibly longer (Weinberger et al., 1993).

Learning a new task can also produce changes in cortical representations. Recanzone et al. (1993) examined plasticity in the frequency representation of the primary auditory cortex in the adult owl monkey following frequency discrimination training. They trained monkeys to detect a difference in the frequency of sequentially presented tone pips. Following the training period, a craniotomy was performed on each monkey and between 70 and 258 electrodes were inserted into the auditory cortex. Each electrode recorded the activity of neurons near the electrode tip. Tones of different

frequency were presented to each monkey and neurons in different locations in the auditory cortex responded to different frequencies. In this manner, the tonotopic organization of each monkey's auditory cortex was defined.

Five monkeys were trained for frequency discrimination. They were presented with two tone pips (each 150 ms long and a 50 ms pause between the two). If the second tone pip was different from the first, the monkey was to lift its hand off a bar. If the monkey was correct in identifying the second tone pip as different from the first, then it would receive a reward. Two other monkeys also received the same auditory stimuli, but weren't involved in the frequency discrimination training. Instead, these "passively stimulated" monkeys performed a different task. The cortical frequency representations of three other normal monkeys were also examined (untrained controls).

Results showed that the performance of all monkeys, trained on the auditory task, increased with training. However, improvement was only shown at the training frequency. For monkey OM2, training initially began at 2.5 kHz and performance increased for this frequency. However, when OM2 was switched to train at 8 kHz, performance for 2.5 kHz decreased. Thus, training was only shown to be beneficial at one frequency at a time.

If different from the first tone pip, the second would always be higher in frequency. However, even though the monkeys were not trained to detect frequencies lower than the standard tone pip frequency, the monkeys were occasionally tested under such conditions. Interestingly, the performance of the monkeys under these conditions decreased as the amount of training under the normal conditions increased.

When the electrophysiology of each of the ten monkeys was examined, the trained monkeys were shown to have greater cortical representation of their training frequency compared with all other monkeys (including the passively trained monkeys). There was a significant correlation between cortical area of frequency representation and performance. Recanzone et al. (1993) suggested that this increased cortical representation occurred because neurons switched their tuning to the training frequency and away from neighbouring frequencies. Also, since there was no increase in cortical representation in passively trained monkeys, attention to the stimulus appears to have been an important factor.

The reason for the decrease in performance of detecting lower frequencies might also be explained from the cortical reorganization. It is possible that as the cortical representation of the training frequency increases, it must borrow space from neighbouring frequencies. It would be interesting to see whether or not performance would decrease if the monkeys were tested in a situation where the standard (first tone pip) and higher frequency tone pip switched order so that the monkeys were actually hearing a decrease in frequency. If the 'borrowing of cortical representation' hypothesis is correct, we should expect to see a good performance because those two frequencies should be well represented in the auditory cortex, no matter in what order they are presented.

Cortical Plasticity in Humans

Most of the research on cortical plasticity has involved animals, rather than humans. It is easier to look to directly at an animal's brain than it is to try and get

information from a human brain. To work with humans, techniques such as functional magnetic resonance imaging (fMRI), electroencephalography, and magnetoencephalography (MEG) must be used.

Cortical reorganization has been measured in humans with these techniques. Karni et al. (1995) trained human subjects to perform a rapid finger movement task and studied their brain activation using fMRI at various stages of their training. The fMRI data they obtained showed that a greater area of the motor cortex was activated when the subjects performed the trained task, compared to the area that was activated for a control (untrained) task. Elbert et al. (1995) studied string players with magnetencephalography (magnetic counterpart to electroencephalography) and discovered that the cortical representation of the digits of the left hand (but not the right hand) was larger in string players compared with control subjects. As well, the amount of reorganization was correlated with the age at which the musicians starting playing. Studies using MEG have also shown that there is reorganization of the somatosensory cortex in arm amputees, where the representation of the face shifts into the area normally occupied by the hand (Elbert et al. (1994), Yang et al. (1994)). Ciesielski and French (1989) and Krauss et al. (1995) both used EEG to examine human cortical plasticity in the visual system and auditory system, respectively. Cansino and Williamson (1997) used MEG to look for changes in the auditory cortex of subjects trained on a frequency discrimination task (these papers will be discussed later).

Research on humans is important because of the applications that can come out of such studies. Approximately 10% of all people over the age of 60 suffer from tinnitus, a

condition where the person perceives to hear a disturbing noise in the absence of any real sound source (Lockwood et al., 1998). Tinnitus may be an auditory phantom phenomenon, analogous to phantom limb pain where someone with an amputation can have the feeling that the amputated limb is still there. As phantom limb pain has been shown to be associated with the reorganization of the primary somatosensory cortex (Flor et al., 1995), tinnitus may similarly be related to the reorganization of the tonotopic map in the auditory cortex (Muhlnickel et al., 1998).

The process that leads to tinnitus may start with a hearing loss (cochlear lesion) caused by exposure to a loud noise or age-related hair cell loss (Rauschecker, 1999). Such a lesion will restrict certain frequencies from being received by the auditory cortex. The neurons previously tuned to these frequencies may shift their tuning preference and the cortical representation of neighbouring frequencies may expand into these regions. In fact, it has been shown with MEG (Muhlnickel et al., 1998) and positron emission tomography (Lockwood et al., 1998) that, among tinnitus patients, there is an expansion of the cortical representation of the tinnitus frequency into areas adjacent to the expected location. The MEG data also show a strong positive correlation between the subjective strength of the tinnitus and the amount of cortical reorganization.

Not only do frequency ranges neighbouring the lesioned area become over-represented, but they may also lose intracortical inhibitory input from the deafferented part of the auditory cortex. These two things may lead to an increased level of activity for cortical neurons with input from the adjacent frequency range. If the tonotopic

representation of the deafferented frequency could be strengthened, the level of activity of these neurons may decrease.

The Present Experiment

The experiment reported in this thesis addressed the question of whether cortical frequency representations can be modified by training. The experiment was very similar to that of Recanzone et al. (1993). The major differences were that this experiment involved humans, not monkeys, and that electroencephalography (EEG) was used to look for changes that occurred in each subject's brain as a result of the training.

Subjects were trained to discriminate between a standard tone of 2040 Hz (40 Hz amplitude modulated) and other comparison tones of slightly higher frequency. Subjects heard the standard, followed by another tone, which may or may not have been the same frequency as the standard. It was the subject's task to state whether or not the frequencies of the two tones were the same or different. Subjects underwent fifteen training sessions and their pre-training and post-training results were compared to check whether or not they were able to improve at the task. Behaviourally, it was expected that the subjects would improve, just as the monkeys were able to improve in Recanzone et al. (1993).

As for the EEG data, we hypothesized that if indeed a subject's improved performance is related to changes in his/her brain, there also could be changes between the pre-and post-training EEG recordings. A correlation between changes in the EEG data and behavioral performance was examined.

Electroencephalography

Electroencephalography is the recording of electric potentials on the surface of the scalp. These potentials are created by electrical brain activity. More specifically, these scalp potentials arise from the depolarizing and repolarizing of groups of neurons.

The resting membrane potential of a typical neuron is –70 mV. When the membrane potential of a neuron rises above a threshold of approximately –50 mV, sodium channels open up, sodium ions move across the membrane, and an action potential is generated. This action potential propagates along the membrane until it reaches the presynaptic terminal. When an action potential depolarizes the presynaptic terminal, large numbers of calcium ions flow into the terminal. This causes neurotransmitters to be released into the synaptic cleft. These neurotransmitters then act on receptor proteins in the postsynaptic membrane, causing other ion channels to open. If sodium channels open, the postsynaptic neuron is depolarized and a new action potential forms. If potassium and chloride channels open, the membrane potential decreases (it is hyperpolarized) and no action potential is formed (the neuron will be inhibited) (see Guyton, 1987).

The potentials measured from the scalp during an EEG experiment are believed to come from the summation of excitatory and inhibitory postsynaptic potentials. Excitatory postsynaptic potentials (EPSPs) occur when positive ions flow across the membrane surface into the intracellular medium. This can occur when a synapse is activated. However, if positive ions move across the membrane into extracellular space (or if negative ions move into the intracellular region), an inhibitory postsynaptic potential

(IPSP) will be produced. In both cases, current flowing across the membrane at the synapse must be compensated by other currents flowing in the medium. This is shown is figure 1.1. These other currents consist of ions flowing across the membrane at other locations, as well as ions moving along the main axis of the neuron (in both the intra- and extra-cellular mediums).

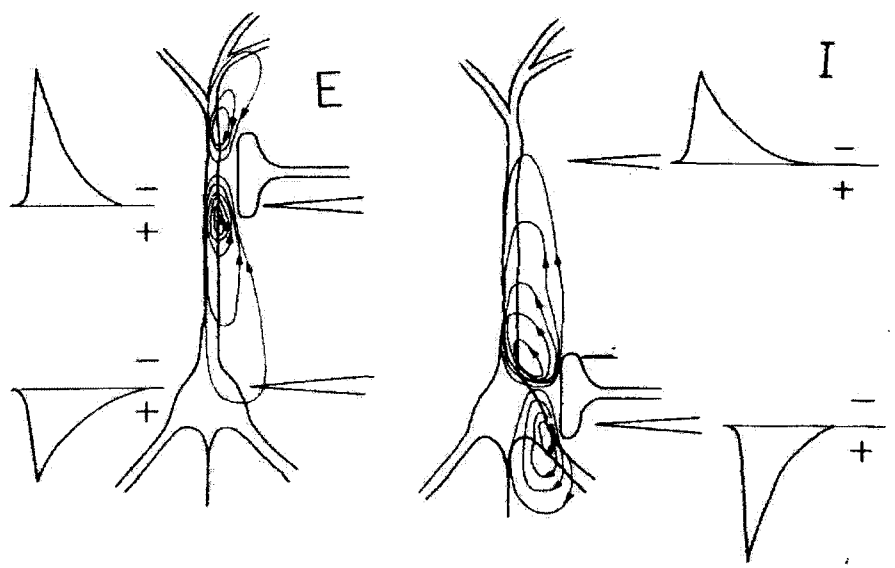


Figure 1.1 – For the excitatory post synaptic potential (E), a negative potential is recorded in the extracellular medium at the synapse. Near the soma, a positive potential is recorded. If the active synapse is inhibitory and near the soma (I), a similar potential will be recorded. (Taken from Niedermayer and Lopes da Silva, 1987).

As seen in figure 1.1, when a neuron is excited, positive ions flow from the soma to the synapse in the extracellular medium. One can state, therefore, that the potential field generated by the neuron in figure 1.1 would resemble that of a dipole. If several of these neurons were aligned together in parallel, they would form a dipole layer. However, only a few postsynaptic potentials will not be strong enough to be recorded at the scalp.

Large numbers of neurons must be involved and must be arranged in such a way so that their respective potentials can summate. An arrangement such as that of the pyramidal neurons in layers II, III, V, and VI of the cerebral cortex is ideal because they are aligned with the main axes of their dendritic trees parallel to one another and perpendicular to the cortical surface. EEG is thus able to 'see' their activity by recording potentials on the scalp. If these neurons were aligned in some other fashion (not parallel), the ionic currents would be able to cancel with one another and this activity would not appear in the electroencephalogram.

The spatial arrangement of neurons is not the only key, however. Timing also plays a crucial role. For an EEG signal to be recorded, neurons must be firing at the same time. If postsynaptic potentials from individual neurons exist at different times, they will not be able to summate to form a potential that would be large enough to be seen on the scalp. Postsynaptic potentials usually last for about 10 to 15 ms, which is much longer than the duration of most action potentials (1-2 ms) (Guyton, 1987). This is one reason why postsynaptic potentials, rather than action potentials, have a better chance of contributing to potentials recorded on the scalp.

Often in EEG, it is desirable to know where the source of the electrical activity lies in the brain. Unfortunately, the problem of figuring out the location of the source, based on a given potential distribution on the scalp, has no unique solution. However, it is possible to compute the potential distribution on the scalp if the source is known. Therefore, one can place a theoretical source (like a dipole) in the brain and compute various potential distributions for various source locations, until a match is found

between the theoretical potential distribution and the one that was measured experimentally. The theoretical source then becomes the best estimate of the location of the actual source.

Transient and Steady-State Responses

A transient response is one in which the brain is in a resting state before each stimulus and returns to a resting state before the next stimulus is presented (Regan, 1989). If the brain does not have time to return to its resting state before the next stimulus is presented, the response will be referred to as a steady-state response.

A transient response to a brief auditory stimulus contains various transient components (potential peaks) (See Picton et al., 1974). Some will have a short latency, appearing less than 10 ms following the onset of the stimulus, while others will take longer than 100 ms to appear. The most prominent components of the auditory evoked potential are the N1, which has a latency of approximately 100 ms, and the P2, which has a latency between 150 and 220 ms.

The neural generators of the N1 and P2 components have been localized using MEG recordings. They are believed to be generated in the secondary auditory cortex, with the N1 generator being approximately 5 mm more lateral and 10 mm more posterior compared to the source of the P2 wave (Pantev et al., 1996a). The N1 and P2 waves thus appear to arise from different populations of cortical cells. Scherg and von Cramon (1986), who localized the source of the N1 generator to the auditory cortex region on the

supratemporal plane, also observed that the dipole source was abolished for patients with lesions of the auditory cortical areas.

As for the steady-state response, the auditory system responds best to stimuli presented at a rate of 40 Hz. That is, the amplitude of the EEG signal recorded from the human scalp will be greatest when auditory stimuli are presented at 40 per second (Galambos et al., 1981). It has been proposed that the 40 Hz auditory response is a sum of overlapping "middle latency responses", which have a latency and wave period of approximately 25 ms and are part of the transient brain response to an auditory stimulus (Galambos et al., 1981; Pantev et al., 1993). Thus, if stimuli are presented every 25 ms (40 Hz), the brain will respond to each stimulus, but these responses will overlap and superimpose on one another. However, Pantev et al. (1996b) reported that the sources of the 40 Hz steady-state response at various carrier frequencies show a medial tonotopy with the sources of the higher frequencies located deeper within the supratemporal sulcus. An earlier study (Pantev et al., 1995) showed that the source of the middle latency response (magnetic Pam) shifts laterally with increasing frequency. These two findings suggest that the 40 Hz response may not be associated with the middle latency responses. It could be that 40 Hz is simply some sort of resonant frequency around which the auditory cortex is tuned. Although the precise mechanism of the 40 Hz response is not entirely known, the response is known to be generated within the primary auditory cortex (Romani and Williamson, 1982; Makela and Hari, 1987; Pantev et al., 1996b).

Recanzone et al. (1993) showed that the auditory cortical representation of the trained frequency in monkeys, following their training, was greater than that of the

control monkeys. If more neurons become tuned to the trained frequency, we might expect to see a greater 40 Hz response when the carrier frequency is the trained frequency. The potentials recorded following training could be bigger for two reasons. The first reason would be because more neurons respond to the stimulus following the training period. If all the neurons are aligned in the correct way (parallel with each other), their individual postsynaptic potentials will sum together. This means the more neurons that are firing, the bigger the potential will be. The second reason would be due to timing. Recall that neurons must fire together, if their postsynaptic potentials are to be able to sum together. If, as a result of training, the neurons learned to fire more synchronously, then the potentials recorded on the scalp could also increase.

Summary

Human subjects were trained at frequency discrimination task for approximately 3 weeks. This was done to answer the question of whether or not training can modify cortical frequency representations in humans. This was determined by measuring EEG from subjects both before and after training. Transient and steady-state responses were used in the analysis.

Chapter 2 – Experimental Methods

Subjects

Six subjects (4 male, 2 female), aged 25 to 30, participated in this experiment. None of subjects had previous musical training. Five of the subjects were right-handed and one (V.L.) was left-handed. All of the subjects agreed to participate after being explained the nature of the study. Four of the subjects were paid for their participation. The other two subjects (A.B. and K.J.) were associated with the lab and not paid.

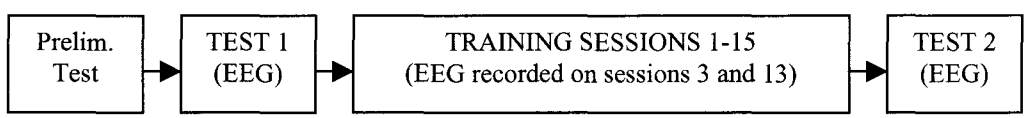
Training Environment

All sessions were carried out in a magnetically shielded room. The room contained ambient noise, mainly from the ventilation system. The subjects were seated in a chair and the stimuli were delivered through Noisebuster® electronic stereo headphones (Noise Cancellation Technologies, Inc., www.nct-active.com). The Noisebuster® feature attenuated background noise between 20 and 1500 Hz. All stimuli were generated with a Tucker-Davis system. All of the tones were 40 Hz amplitude modulated (40 bursts per second, with each burst lasting 10 ms, including a 2 ms rise and fall time). Intensity levels in the experiment were set at approximately 60 dB above each subject's threshold. For subjects A.B. and K.J., no threshold was determined and the volume was set at a level as deemed comfortable by the subjects. The intensity of each

tone was purposely varied randomly by as much as 3 dB (approximately 57-60 dB above threshold). This was done so that the subject could not use intensity to discriminate between tones. Subjects could only base their responses on pitch. Therefore, a subject could only improve at the task by learning to discriminate between different frequencies.

Procedure

The entire experiment lasted 18 sessions, or approximately 20 days (1 session per day, with two days off). The first session was a preliminary test to gauge the ability of the subject to perform a frequency discrimination task. The first session was also used to give the subject a feel for the task. The first test session took place on the second day. Each subject was then trained for 15 sessions, and then retested. The results from test 2 were compared with those of test 1.



One subject (A.B.) went through two additional test sessions, one after the fifth training session and one following the tenth training session. In total, subject A.B. experienced four test sessions.

Four subjects came back for another training session approximately 7 weeks after his/her last test session. This session was used to gauge whether or not the subject was able to retain what he/she had learned during the course of training.

Preliminary Test. A staircase method was used to obtain a rough estimate of the subject's ability to discriminate between two tones with slightly different pitch (Levitt, 1971). Two tones were presented and the subject had to answer "same" or "different". Subjects were told to base their response on frequency, not intensity. The standard was randomly chosen from nine possible different standards, ranging from 1800 Hz to 2280 Hz in increments of 60 Hz. The initial delta F (difference between the standard and the comparison tone) for each standard was 60 Hz. After each measurement, the standard was switched randomly to one of the other nine values. If the standard was switched back to some value at which a measurement had already been taken, the comparison frequency was selected based on the subject's response the last time that particular standard was presented. If the subject had answered correctly the previous time, the delta F would lower. If the subject had responded incorrectly, the delta F would increase. There were forty trials for each standard and the entire test lasted approximately 25 minutes. The results from this preliminary test were used to set the frequencies of the comparison tones used in the actual experiment. Subject R.H. was the only one not to receive this test.

The hearing threshold for each subject was also tested (excluding subjects A.B. and K.J.). The subject listened to a series of 1 second long tones while keeping a button pressed down. The intensity of each successive tone dropped by 1.5 dB. The subject was instructed to release the button when the tone was no longer audible. The intensity of the next tone then dropped by 10 dB and the intensity of each successive tone after that was increased by 1.5 dB. The subject was instructed to press down the button when the tone could be heard. This procedure was repeated six times and the intensity level was

recorded each time for a total of 12 measurements (6 up, 6 down). These measurements were averaged together to obtain an estimate of the subject's hearing threshold.

Testing Sessions. Each testing session consisted of three blocks. For each block, a different standard was used. In the first block, 2040 Hz was used as the standard[1]. This was the same frequency as that used in the training sessions. In the second and third blocks, 1840 Hz and 2240 Hz were the standards, respectively. These two other standards were used to test whether or not any changes in the representation of these side frequencies resulted from the training at 2040 Hz.

For every trial, the subject listened to two 40 Hz amplitude modulated tones. Each tone was one second long and the two tones were separated by an interstimulus interval of 500 ms. The first tone was always the standard frequency. The second tone was either the standard again, or one of 6 different comparison tones which were all higher in frequency than the standard. The probability of the second tone being different was 50%. This method is known as the method of constant stimuli (Dember and Warm, 1979).

After listening to the two tones, the subject pressed the appropriate button to say whether or not the two tones were the 'same' or 'different'. Subjects were instructed to base their response on a change in pitch and not intensity. There was no feedback given during any of the testing sessions. Every trial was initiated 1000 ms after the subject's response to the previous trial. In each test block, there were 360 trials[2]. The standard frequency was repeated 180 times, and each of the six comparison frequencies was

[1] For subjects A.B. and K.J., the order of the test blocks was 1840 Hz, followed by 2040 Hz and 2240 Hz.

presented 30 times. The total time duration of one test block was approximately 30 minutes. The total time duration of one entire test session was approximately 90 minutes.

The comparison frequencies were chosen based on the initial staircase test. The lowest comparison frequency was always 2 Hz higher than the standard. The highest comparison frequency was usually 60 Hz higher than the standard. The other four comparisons were between these two extremes and were chosen by the experimenter on an individual basis. No strict selection method was used, but it was the goal of the experimenter that the subject be able to detect three of the comparisons at least 50 percent of the time and be able to detect the other three less than 50 percent of the time. Every subject could detect a 60 Hz difference, but no subject could detect a 2 Hz difference. The comparison frequencies were identical for test 1 and test 2.

Training Sessions. Training sessions were similar to testing sessions, except for the facts that the standard was always 2040 Hz and feedback was given after each trial. After listening to the two tones, the subject pressed the appropriate button to say whether or not the two tones were the 'same' or 'different'. After responding, the subject was given feedback as to whether or not the response was correct. If correct, a green LED came on; if incorrect, a red LED lit up. The LED stayed on for 500 ms. The next trial was initiated 1200 ms after the button press.

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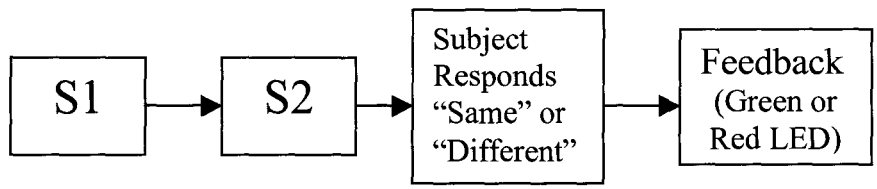
[2] For subjects A.B. and K.J, there were 240 trials per test block (120 standard, 120 comparison trials).



In every session, there were 480 trials. The standard frequency was repeated 240 times, and each of the six comparison frequencies was presented 40 times. The total time duration of one session was approximately 30 minutes.

The comparison frequencies were adjusted if the subject improved to a point where the task became too easy. This was done if the subject was able to detect more than one comparison frequency 100 percent of the time. For example, some subjects were able to detect a delta F of 60 Hz and 36 Hz (100 percent of the time). In this situation, the delta F of 60 Hz was kept constant, but the other delta F of 36 Hz was removed and another smaller delta F was inserted in its place. This was done on an individual basis and the value of the new delta F depended on the subject and the original comparison frequencies. The delta F values of 2 Hz and 60 Hz were constant for all subjects.

Follow-up Session. The follow-up session took place 7 weeks after the last test session. The procedure for this session was identical to that of a training session. Feedback was given. Every subject, except for K.J. and K.D., was able to complete a follow-up session.

EEG Recordings

EEG data were recorded for both of the test sessions, as well training sessions 3 and 13. For two subjects (A.B. and K.J.), a 19-channel cap was used (10/20 system[3]) with tin electrodes. For all of the other subjects, a symmetrical 64-channel montage was used with silver chloride electrodes.

Electro-Gel was inserted into all of the electrode sites to lower the impedance at the scalp. Recording did not begin until all of the electrode impedances were below 10 kΩ. The preparation time for the EEG sessions was approximately 1 hour.

The data were initially recorded with a Cz reference and then re-referenced using a common average. NeuroScan amplifiers were used for all recordings. All data were low-pass filtered from DC to 100 Hz or 200 Hz, depending on the sampling rate (the high frequency cutoff was one fifth of the sampling rate). For subjects A.B. and K.J., the signals were digitally recorded at a rate of 1000 Hz. For the other four subjects, the sampling rate was 500 Hz.

Data Analysis

Behavioural Data. For every training session, there were 240 trials with the standard repeated (S1 = S2) and 240 trials where S2 was a comparison frequency (40 trials for each of the six comparisons).

In a 'standard-repeated' trial, the correct response was 'same'. This was considered a correct rejection. If the subject's response was 'different', then a false alarm

was recorded. In a comparison trial, the correct response was 'different', and this was labeled as a hit. If the subject responded 'same', then a miss was recorded.

The raw hit percentage, P(h), for each comparison frequency was calculated by dividing the number of hits by the number of trials (40). Each raw hit percentage was corrected for the subject's guessing. This done using the false alarm rate (F.A.). The corrected hit rate, P(hit), was calculated as

$$P(hit) = [P(h) - F.A.] / [1 - F.A.]$$

These hit rates were calculated every session for all the comparison tones and tracked over the entire training period. An increase in P(hit) signified an increase in the subject's frequency discriminating ability. Psychophysical functions were constructed for each session by plotting P(hit) versus Delta F (the difference between the comparison frequency and the standard frequency).

Another measure used to gauge to the subject's ability at the task was d'. The d' value is the perceptual index in the theory of signal detection and reflects the subject's ability to discriminate signal from noise (Dember and Warm, 1979). Signal detection theory asserts that every trial contains some degree of noise (for example, the spontaneous firing of neurons) and that the stimulus to be detected always occurs against this noisy background. In any given trial, it is the observer's task to decide whether the sensation experienced in that trial is from noise or from noise plus a signal. The theory

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[3] See Appendix A for how these electrodes are arranged on the head.

assumes that the sensory effects produced by noise vary randomly from moment to moment. These sensory effects are also assumed to follow a normal distribution with unit variance. When a signal is added to the noise, the level of excitation increases, but the nature of the distribution of sensory effects remains the same. The distribution from noise plus signal is simply shifted to a higher level of excitation relative to the distribution from noise alone. But, these two distributions, one from noise and one from noise plus signal, still overlap each other. Therefore, if the magnitude of a sensory excitation lies in the overlapping region of the two distributions, it is a question as to whether or not the sensory excitation was produced by noise or by noise plus a signal. The observer sets a response criterion and all of the excitations exceeding this criterion will be assumed to come from a signal. The greater the separation between the two distributions, the easier it will be for the observer to decide whether or not a signal was present. The separation of the means of these two distributions is known as the perceptual index or d'. The value of d' is independent of how the observer sets the response criterion.

The value of d' was calculated for each comparison tone by subtracting the z-score based on the raw comparison tone hit rate, P(h), from the z-score based on the false alarm rate (Dember and Warm, 1979). (The z-score is the number of standard deviation units that the response probability is away from the mean (0.50) of the normal distribution.)

$$d' = Z(F.A.) - Z(P(h))$$

The d' values were used to check for significant changes between pre- and post-training results. Training sessions 1-3 were grouped together and compared with training sessions 13-15. Paired t-tests (one-tailed) were performed on the two groups of d' values for each comparison frequency that was used in all of the training sessions.

EEG Data. All EEG data were epoched from 200 ms before stimulus onset to 200 ms after stimulus offset. All epochs were baselined, using –20 ms to 0 ms as the baseline (0 ms corresponds to stimulus onset), and linear detrended.

Averages were made for each recording session from all of the epochs of the standards (S1) that were artifact-free. Any trial containing an artifact (in any electrode), that was 75 μV above or below baseline, was rejected from the average. Rejection rates ranged from 5 percent to 50 percent, depending mainly on the amount of blinking the subject did. In the two tests, separate averages were made for each of the three frequency sets (1840, 2040 and 2240 Hz). However, averages were only made for the electrodes from which there were recordings for every subject (i.e. only the 10/20 electrodes). Grand averages were made for the pre- and post-training conditions using the data from all of the subjects.

Two main analyses were performed on the EEG averages. In the first analysis, the data were Fourier transformed and looked at in the frequency domain. The power at 40 Hz was recorded. Comparisons were made between the power at 40 Hz before and after training.

In the second analysis, the averages were digitally low pass filtered under 10 Hz, using a FIR filter with a Hamming window. The amplitude and latency of the N1 and P2 components were determined and the P2-N1 amplitude difference was calculated for every electrode. All of this was done by a computer program (see appendix B) which eliminated human bias from the peak selection process. The latency of each peak was the time at which the data point with the greatest absolute value in that peak occurred. The greatest absolute value was considered the amplitude. An N1 peak was only deemed present if there was a peak in between 80 ms and 140 ms after stimulus onset. If more than one peak was present in this interval, no N1 was selected. The P2 peak had to be located between 150 ms and 220 ms. Again, if more than one peak was present, no peak was selected. In most situations, this method worked quite well as the N1 and P2 waves for most subjects were very well defined. However, occasionally, an N1 or P2 peak was ignored because of noise, which the program interpreted as another peak. On the other hand, an N1 or P2 peak may have been selected, based on the above criteria, without a true N1 or P2 peak being present in the data.

Unless otherwise noted, comparisons were made between the average value of all of the 10/20 electrodes. For example, when looking at changes in the P2-N1 amplitude, the P2-N1 amplitude of every 10/20 electrode was used to calculate an average P2-N1 amplitude for Test 1 and Test 2. However, only those electrodes that showed clear N1 and P2 peaks in both Test 1 and Test 2 were included in the averages.

To better assess each subject's P2-N1 change on an individual basis, a Monte Carlo type simulation was used (Manly et al., 1991). One hundred and twenty trials were

taken at random from the Test 1 data and 120 trials were taken at random from the Test 2 data. These 240 trials were averaged together to form average #1. This same procedure was repeated again to form average #2. The P2-N1 amplitudes for every electrode in average #1 were compared with those of average #2 and the percent change between each pair of values was recorded[4]. The sum of these values was divided by 19 to obtain the average P2-N1 percent change. This constituted one simulation. Five hundred of these simulations were performed and the distribution of P2-N1 changes was plotted. The distribution was centered on zero with some P2-N1 changes being positive and others negative. The actual P2-N1 change between Test 1 and Test 2 was then plotted over the distribution to determine how likely it was to have occurred by random chance and whether or not the observed change was significant.

A similar Monte Carlo simulation was done for the 40 Hz power data. Rather than comparing P2-N1 amplitudes, the 40 Hz power in each electrode in average #1 was compared with the 40 Hz power in the same electrode in average #2. The percent changes for all of the electrodes were averaged to obtain the 40 Hz power change in one simulation. Five hundred of these simulations were done and the true 40 Hz power change was plotted over the simulated distribution.

Statistical Analysis. The training was predicted to cause an increase in 40 Hz power and P2-N1 amplitude. It was also predicted that the subjects would improve at the discrimination task and that d' would increase. To test these predictions, paired, one-

tailed t-tests were used. For the 40 Hz power and P2-N1 amplitude comparisons, the results (from the average of all 19 electrodes) from each of the six subjects in Test 1 were compared with those of Test 2. The d' comparisons were made within subject for each delta F that was used in every training session. The d' values from training sessions 1-3 were paired with sessions 13-15. There was no prediction as to what would happen to the N1 and P2 latencies. Therefore, changes in these variables from Test 1 to Test 2 were tested for statistical significance using a paired, two-tailed t-test.

[4] If an electrode did not contain an N1 wave and P2 wave in both of the simulated averages, the P2-N1 change was recorded as zero for that particular electrode.

Chapter 3 – Results

Behavioural Data

Figure 3.1 demonstrates how the subjects improved across training sessions. The mean P(hit) for each subject was the mean of the P(hit) scores of all of the comparison frequencies that were used in every session. For example, only delta F values of 10 Hz, 18 Hz, and 26 Hz were used in every session for subject A.B. Therefore, only the P(hit) values of those comparison frequencies were used in the calculation of the mean P(hit) for each session for subject A.B. Average P(hit), in figure 3.1, is a grand average of the mean P(hit) scores for every subject. Figure 3.1 shows that most of the improvement occurred in the first four training sessions. However, there was still some improvement in the remaining 11 sessions.

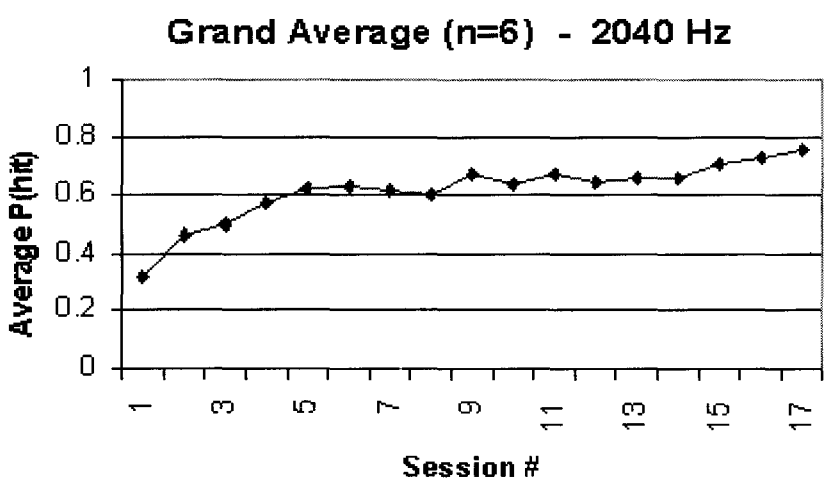


Figure 3.1 – Subjects were able to detect more of the frequency differences as the training went on. Session #1 is test 1 and session #17 is test 2. See test for explanation of "Average P(hit)".

Figure 3.2 shows the psychophysical functions for Test 1 and Test 2 for the 2040 Hz set. The psychophysical functions from Test 2 were shifted upward relative to Test 1 for every subject. An upward shift signified that the subject has improved at the discrimination task. The subjects were able to detect a greater percentage of the frequency differences at every delta F (except for 2 Hz) in Test 2, compared with Test 1.

The psychophysical functions for the 1840 Hz and 2240 Hz sets are shown in figure 3.3 and figure 3.4, respectively. Improvement was still seen in these side frequencies, but to a lesser extent. In other words, the shift in the psychophysical functions was not as great as it was in the 2040 Hz set. In some cases, there was no shift in the psychophysical function, which signified that there was no transfer of ability from the trained frequency set to the untrained side frequencies. For example, on the 1840 Hz set, subjects K.J. and J.K. demonstrated very little transfer. On the 2240 Hz set, subjects K.J. and V.L demonstrated very little transfer. In fact, on the 2240 Hz set, subject K.J. showed a negative transfer (downward shift).

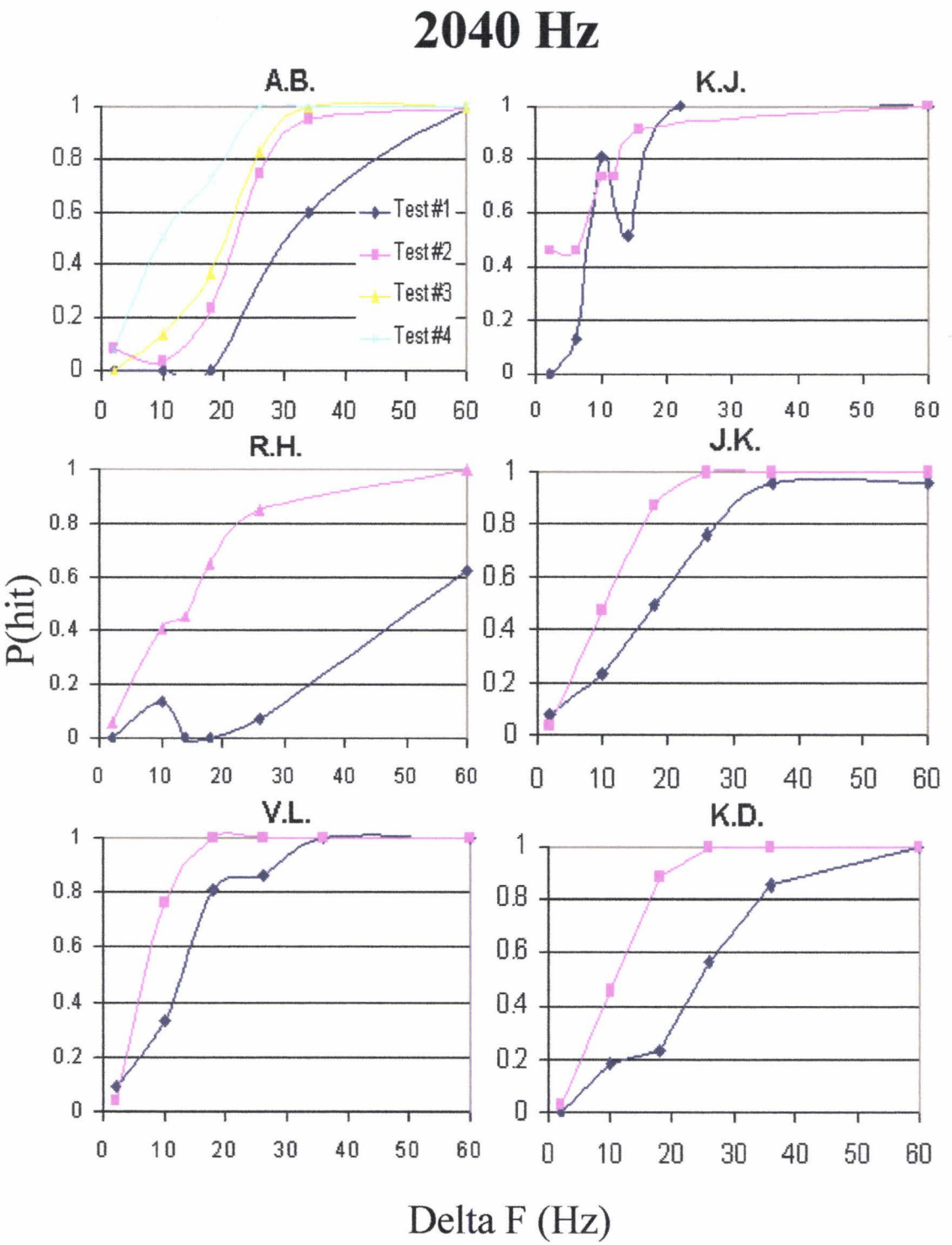


Figure 3.2 - Pre/Post psychophysical functions for each subject for the 2040 Hz test set.

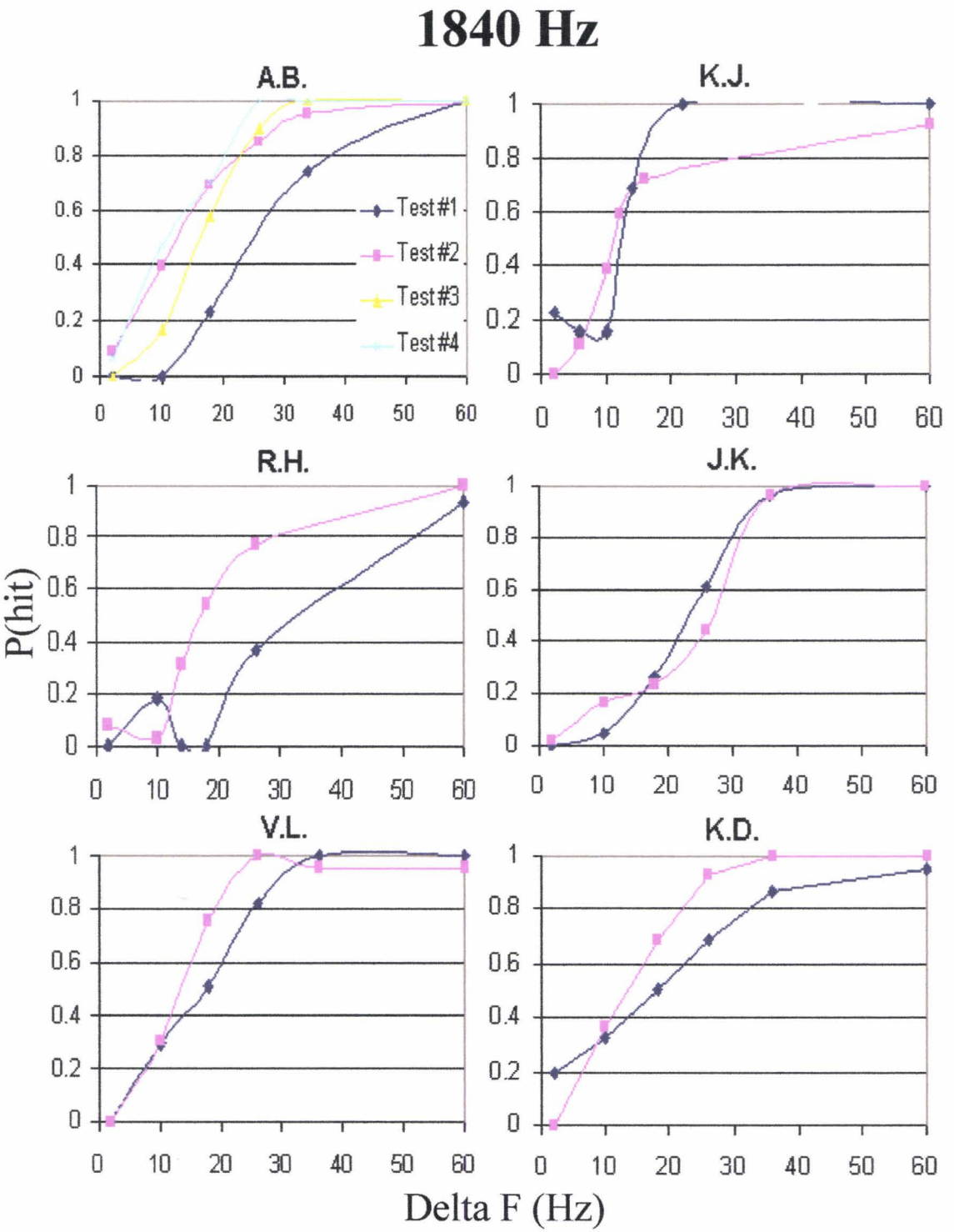


Figure 3.3 - Pre/Post psychophysical functions for each subject for the 1840 Hz test set.

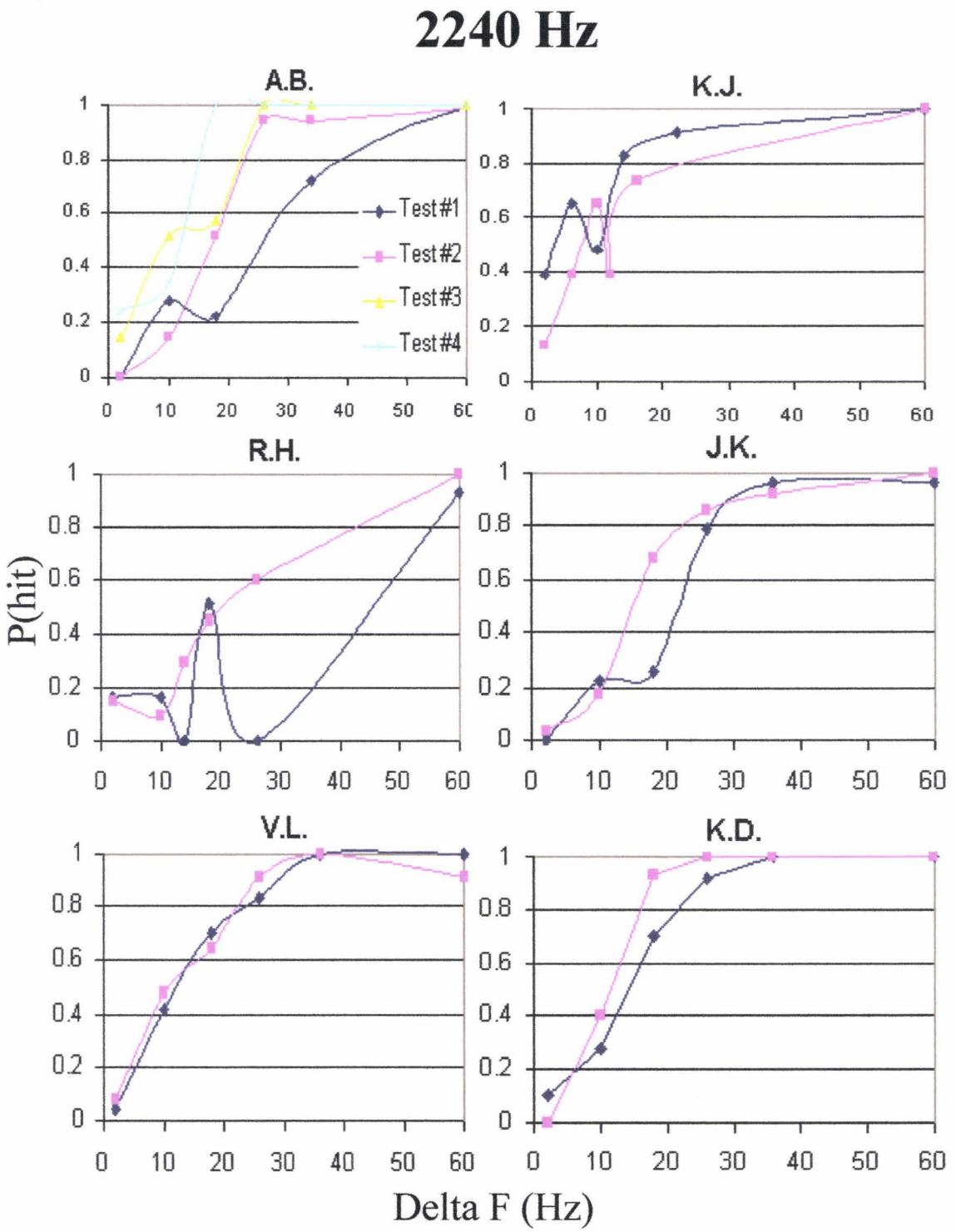


Figure 3.4 - Pre/Post psychophysical functions for each subject for the 2240 Hz test set.

EEG Data

Figure 3.5 presents the grand average EEG recordings (low-pass filtered < 10 Hz) from the Fz and P7 electrodes for Test 1 (blue) and Test 2 (red) (2040 Hz set). The Fz electrode is located near the front of the head, while the P7 electrode is located near the back left of the head (see appendix A). The N1 and P2 peaks are labeled in this figure. In both of these electrodes the N1 and P2 latencies decreased from Test 1 to Test 2. Also, the P2-N1 amplitude increased. Another thing to note in this figure is the polarity reversal between Fz and P7. The N1 peak is negative in Fz, but positive in P7, and the P2 peak is positive in Fz, but negative in P7. This is consistent with a dipole generator located in the auditory cortex. At 100 ms after the stimulus onset, the negative end of the dipole points towards the front of the head and the positive end points towards the back of the head. At approximately 190 ms, the dipole has reversed its orientation.

The grand average EEG traces from all of the 10/20 electrodes (including Fz and P7) for Test 1 and Test 2 are shown in figure 3.6 for the 2040 Hz set. The recordings of 12 of the 19 electrodes contained an N1 and P2 peak in both test sessions. Of these twelve, all twelve demonstrated an increase in P2-N1. As well, all sixteen N1 peaks decreased in latency, and all thirteen repeatable P2 peaks decreased in latency from Test 1 to Test 2.

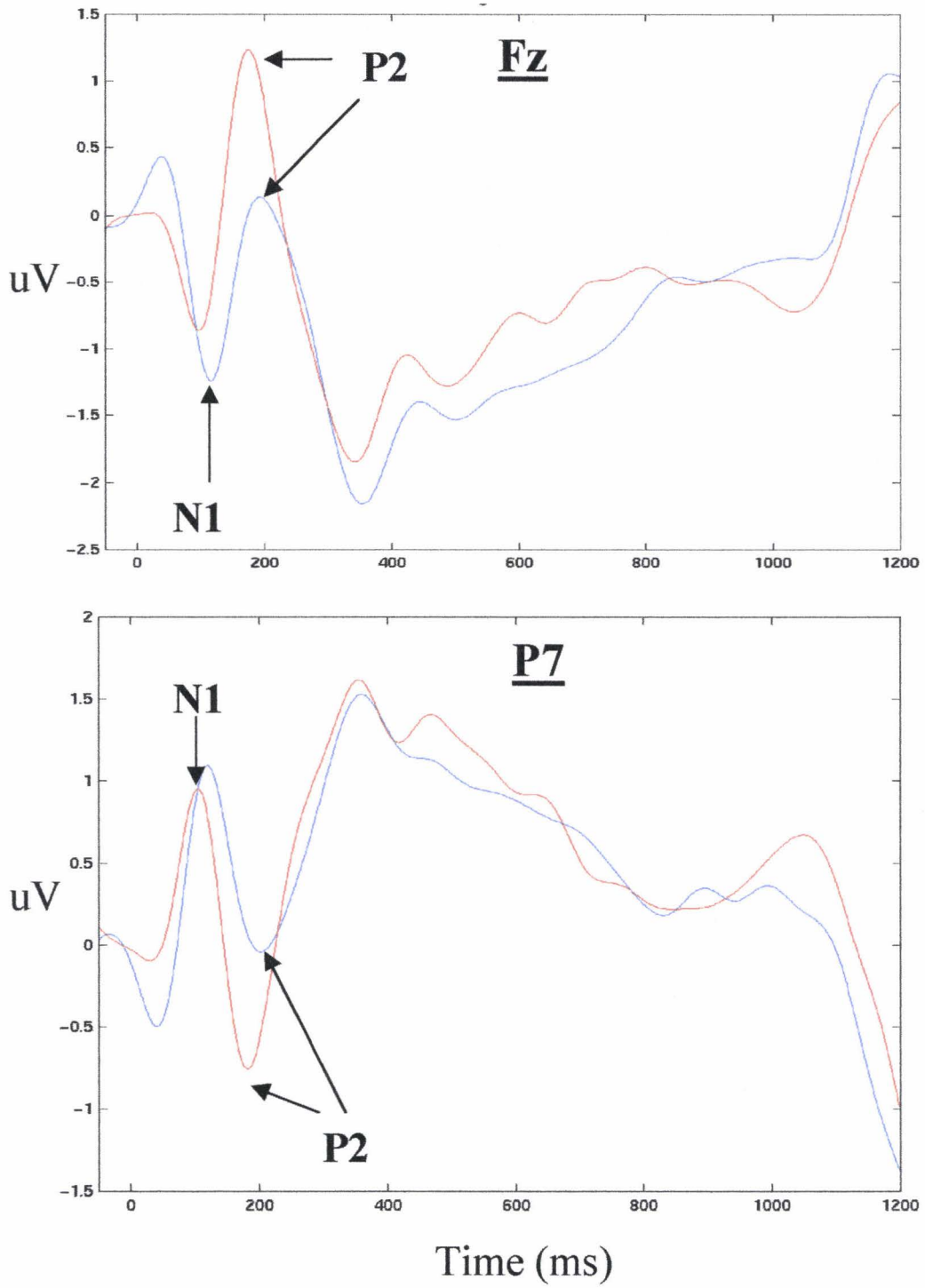


Figure 3.5 - Pre (blue) and post (red) training EEG traces recorded from Fz and P7 (Grand average (n=6), plotted from -50 ms to 1200 ms).

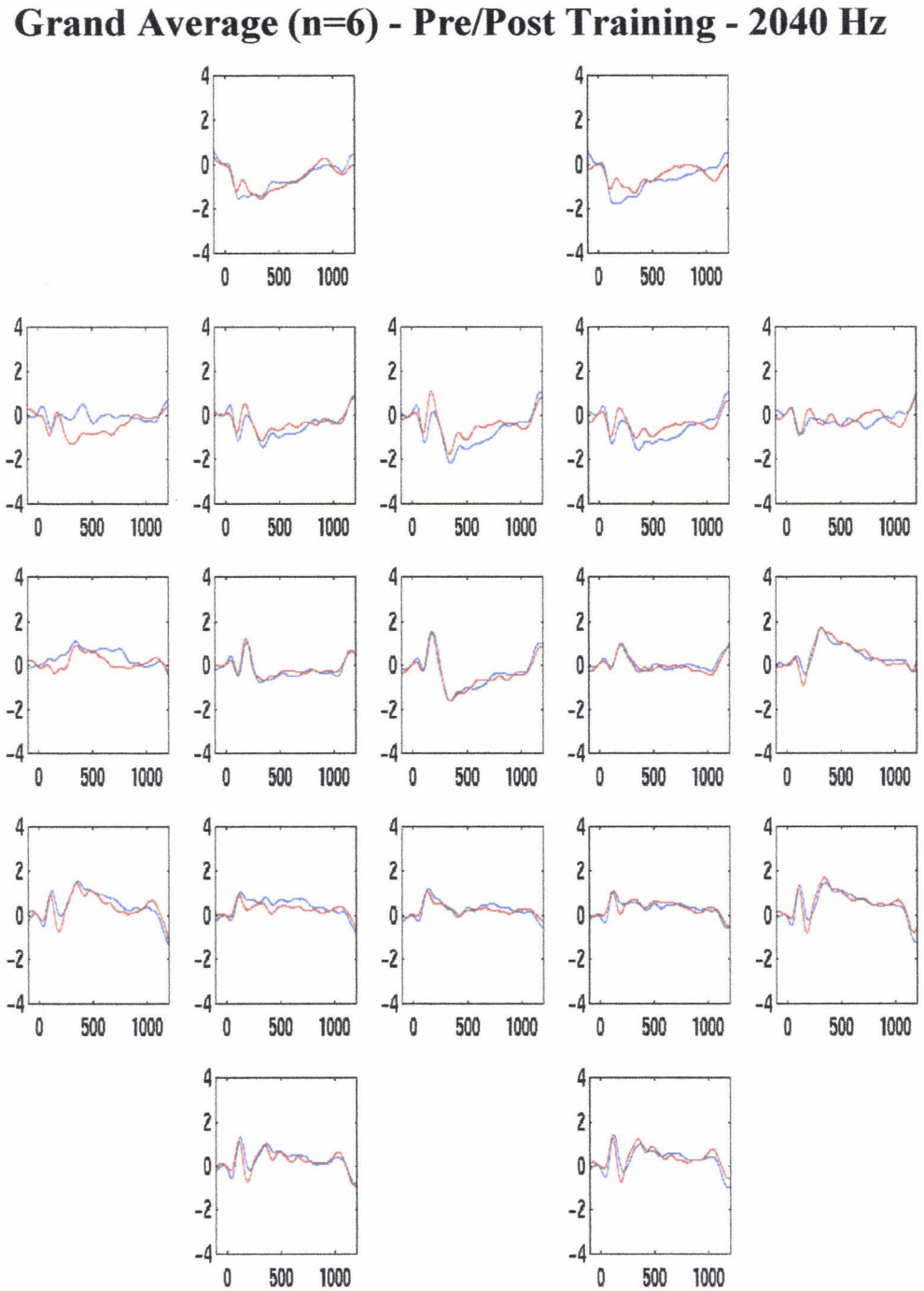


Figure 3.6 - EEG traces from Test 1 (blue) and Test 2 (red). The top two blocks are Fp1 and Fp2. The upper row of five (from left to right) is F7, F3, Fz, F4, and F8. The middle row is T7, C3, Cz, C4, and T8. The lower row of five is P7, P3, Pz, P4, and P8. The bottom two blocks are O1 and O2. The units of the y-axis are microvolts. The x-axis is time, plotted from -100 ms to 1200 ms.

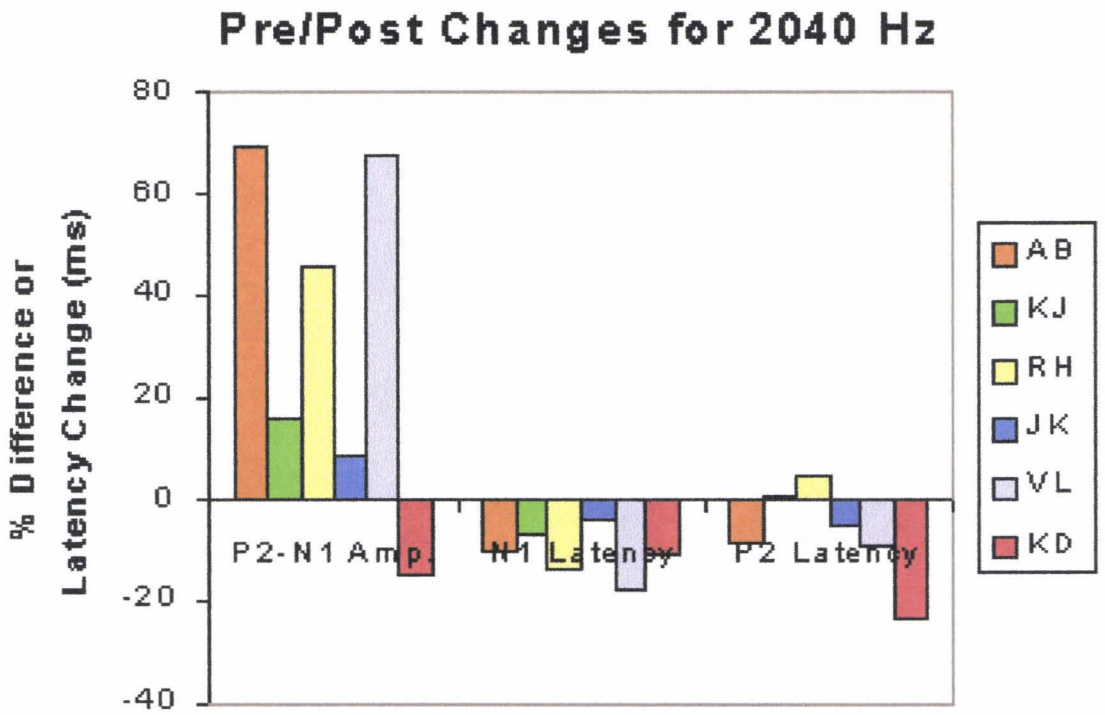


Figure 3.7 – The P2-N1 amplitude increased for 5 of 6 subjects, the N1 latency decreased for all six subjects, and the P2 latency decreased for 4 of 6 subjects.

The results for each subject are demonstrated in figure 3.7. In five of six subjects, the P2-N1 amplitude increased. The post-training P2-N1 amplitudes for this group of six subjects were determined to be significantly greater than the pre-training values using a paired, one-tailed t-test ($p=0.04$, $df = 5$). In all six subjects, the N1 latency decreased. Using a paired two-tailed t-test, the N1 latencies from Test 2 were found to be significantly different from those of Test 1 ($p<0.004$, $df = 5$). In four of six subjects, the P2 latency decreased following training. However, this decrease was not significant ($p=0.14$, $df = 5$).

The three different measures shown in figure 3.7 are shown individually in figures 3.8, 3.9, and 3.10. These three figures include the training set, as well as the side frequencies.

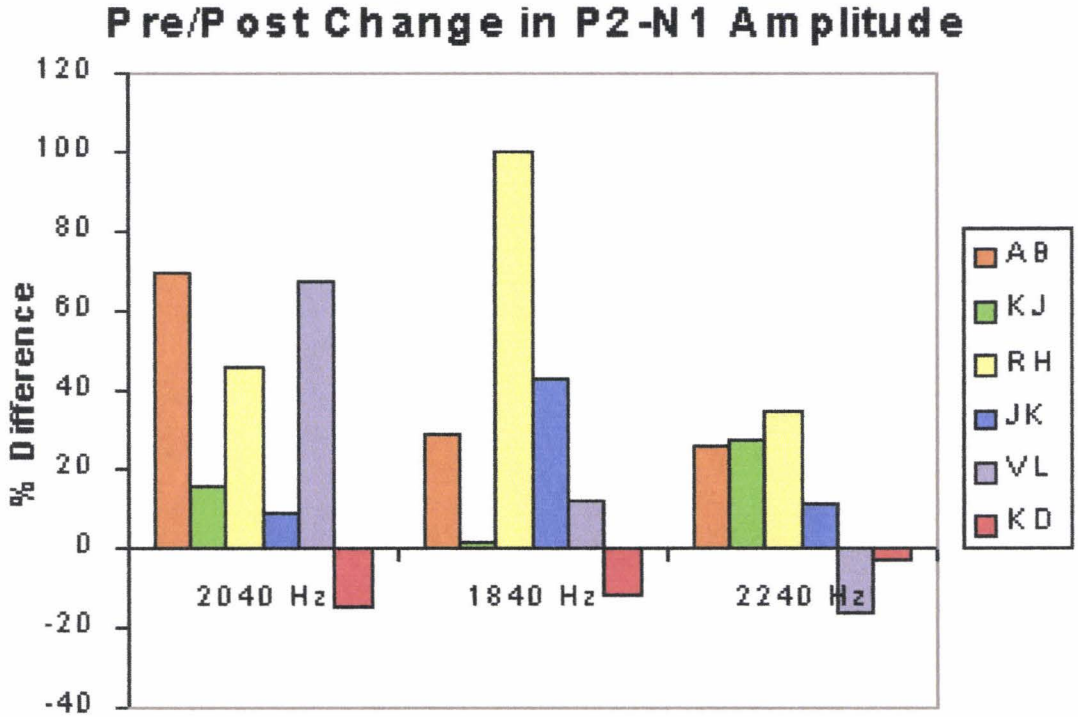


Figure 3.8 – The P2-N1 amplitude increased for most subjects in all three frequency sets.

The P2-N1 amplitude data from all three sets are given in figure 3.8. The trend for all three sets was that P2-N1 increased from Test 1 to Test 2. The data from every frequency set were tested for significance using a paired, one-tailed t-test. As stated above, the effect was significant ($p<0.05$) for the trained frequency set. However, it was not significant for 1840 Hz ($p=0.07$, $df=5$) or 2240 Hz ($p=0.08$, $df=5$). This test was also

performed on the training set data. There were no significant changes between the 3rd and 13th training sessions (p=0.23, df=4).

Figure 3.9 presents the change in N1 latency for each subject in all three frequency sets. The change in N1 latency in all three sets was tested for significance using a paired, two-tailed t-test (comparing pre-training N1 latencies with post-training N1 latencies). The change was significant in the 2040 Hz set (p=0.004, df=5), but not in the 1840 Hz set (p=0.08, df=5) or the 2240 Hz set (p=0.25, df=5). There were also no significant changes between the 3rd and 13th training sessions (p=0.26, df=4).

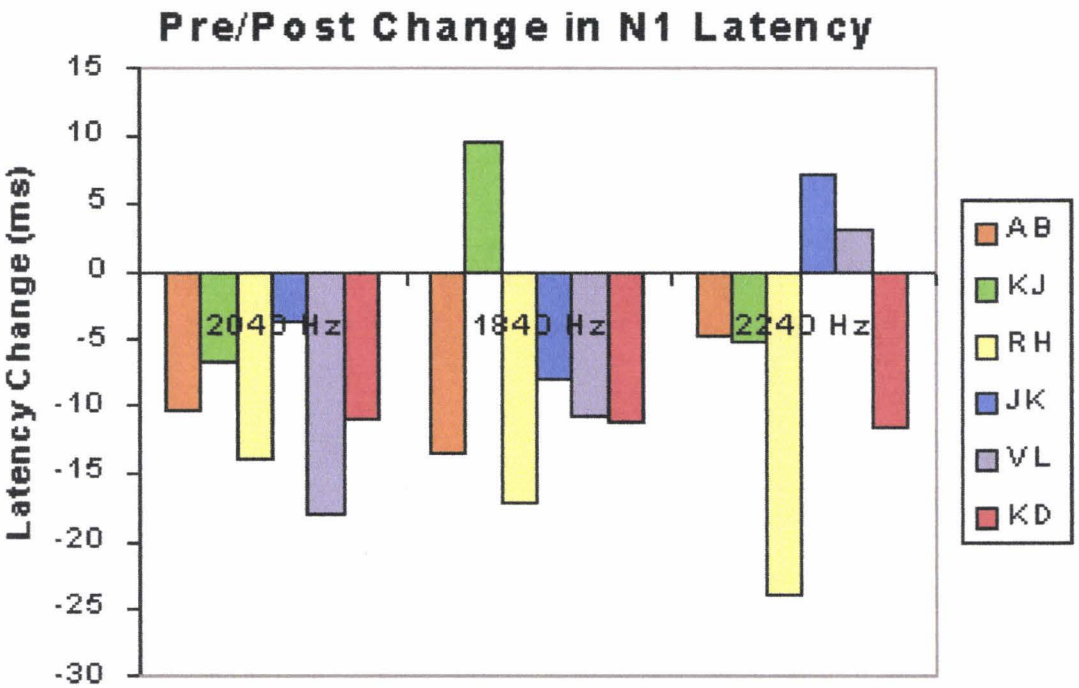


Figure 3.9 – The N1 latency decreased for every subject in the 2040 Hz set, 5 of 6 subjects in the 1840 Hz set, and four or six subjects in the 2240 Hz set.

There were also changes observed for the P2 latency, as shown in figure 3.10. The P2 latencies from Test 2 were compared with those from Test 1 using a paired, two-tailed

t-test. The changes were not significant for 2040 Hz (p=0.14, df=5). They were also not significant for the side frequencies (1840 Hz (p=0.08), 2240 Hz (p=0.23)), or for the comparison of the 3rd and 13th training sessions (p=0.19, df=4).

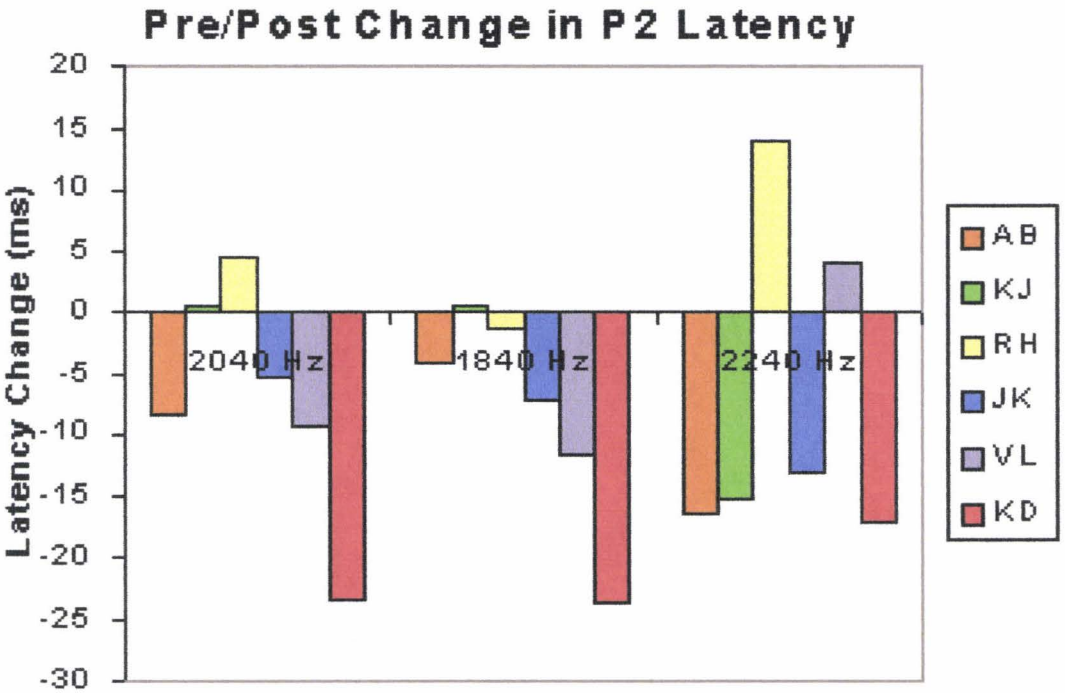


Figure 3.10 – The P2 latency decreased for four of six subjects in the 2040 Hz set, five of six subjects in the 1840 Hz set, and four of six subjects in the 2240 Hz set. The changes were not significant in any set.

The analysis of the 40 Hz power did not produce any conclusive results. Figure 3.11 presents the 40 Hz power recorded in Test 1 and Test 2 (2040 Hz set) for every electrode in the grand average. Of the nineteen electrodes, thirteen recorded an increase in 40 Hz power following training, while six recorded a decrease.

The 40 Hz power results also varied from subject to subject. This is shown in figure 3.12. Three of six subjects had more 40 Hz power in Test 2 than Test 1 in the 2040

Hz set. In the 1840 Hz and 2240 Hz sets, the ratio of increases to decreases was 4 to 2 and 3 to 3, respectively. The 40 Hz power increased in four of five subjects from the 3rd training session to the 13th session. The pre/post changes were tested for significance using a paired, one-tailed t-test. No significant changes were discovered in the 2040 Hz set ($p=0.38$, $df=5$). There also were no significant changes in the 1840 Hz set ($p=0.44$, $df=5$) or the 2240 Hz set ($p=0.43$, $df=5$). The test between the 3rd and 13th training sessions proved not to be significant as well ($p=0.08$, $df=4$).

Figure 3.11 – Analysis of change in 40 Hz power from Test1 (blue) to Test 2 (red). Thirteen electrodes showed a decrease, six showed an increase.

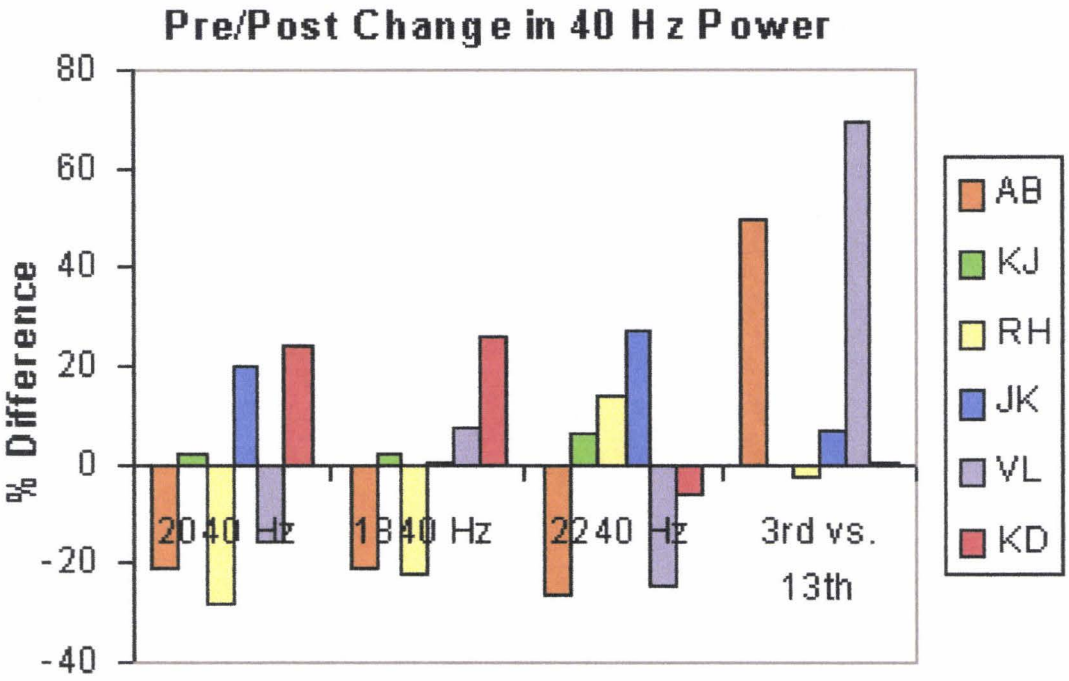


Figure 3.12 – Training did not produce any significant changes in 40 Hz power in the group as a whole.

Individual Subjects

The data for the six individual subjects are shown in figures 3.13 – 3.18. Each of these figures contains six parts (A-F). Parts A-C show the behavioural data and parts D-F give the results of the EEG analysis.

Part A gives the psychophysical functions of the two test sessions for the trained frequency, 2040 Hz, as well as the untrained side frequencies, 1840 Hz and 2240 Hz. Psychophysical functions are also included for some of the training sessions.

Part B shows the change in d' between sessions 1-3 and sessions 13-15. The data are only shown for delta F values that were used in every session. The changes in d' were

tested for statistical significance using a paired, one-tailed t-test (session 1 was paired with 13, 2 with 14, and 3 with 15). Each delta F, for which a statistically significant increase ($p<0.05$) in d' was recorded, is marked with an asterisk.

Part C demonstrates how the subjects improved across training sessions. Performance, on the y-axis, is an average of the p(hit) scores of the comparison frequencies that were used in every session. For example, only delta F values of 10 Hz, 18 Hz, and 26 Hz were used in every session for subject A.B. Therefore, only the p(hit) values of those comparison frequencies were used in the calculation of 'Performance' for each session. All test sessions are in red, all training sessions are in blue, and the 7-week follow-up session is in green.

Part D is the Monte Carlo distribution from the randomized P2-N1 data. The red vertical line shows where the actual pre/post P2-N1 change lies on the distribution. Part E is the Monte Carlo distribution from the randomized 40 Hz power data.

Part F shows the EEG traces from Test 1 and Test 2 for all three standards (subject A.B. had 4 tests). The traces from the 3rd and 13th training sessions are also shown. All of the traces were recorded from the Cz electrode and are plotted from –100 ms to 1200 ms.

Part G is a bar graph demonstrating how the signal from each electrode changed from Test 1 to Test 2, with respect to P2-N1, N1 latency, P2 latency, and 40 Hz power. This data is from the 2040 Hz set only. The order of the electrodes goes from the front of the head to the back of the head (Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz (pink), C4, T4, P7, P3, Pz, P4, P8, O1, O2).

Subject A.B.

The psychophysical functions for subject A.B. shifted to the left for each successive test block, which demonstrates that the subject improved continuously throughout the training period (part A). This occurred for 2040 Hz, but also occurred for the untrained frequencies.

The d' values for sessions 13-15 were significantly higher ($p<0.05$) than those of sessions 1-3 for two of the three comparison frequencies (part B). The change in d', based on the delta F of 26 Hz, was close to being significant ($p=0.05$).

The performance of subject A.B. improved gradually with training (part C). The two dips were from Test 2 and Test 3. Session #20 was the follow-up session, which took place 7 weeks after Test 4. The graph shows that performance was maintained after a 7-week period.

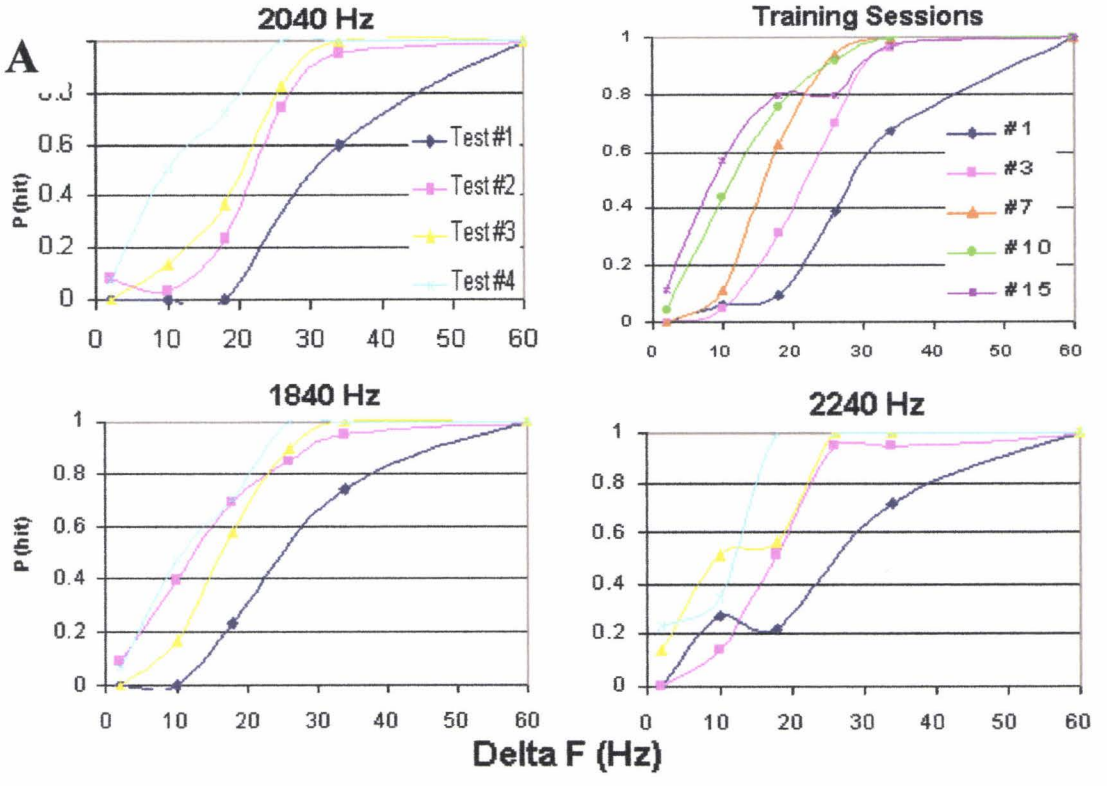
The P2-N1 amplitude was bigger in Test 4 than in Test 1for all frequencies (part F). However, Test 3 produced the smallest P2-N1 difference. The N1 and P2 latencies were shorter for Test 4 compared with those of Test 1 for the 2040 Hz set. However, the data for the other frequencies showed mixed results. The N1 latency actually appeared to be the shortest in Test 1 for the side frequencies.

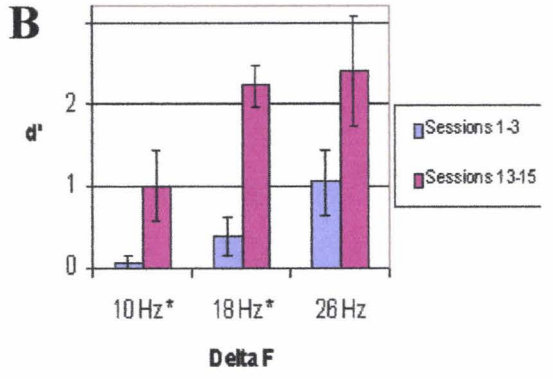
The actual P2-N1 percent change between Test 4 and Test 1 was very close to the edge of the Monte Carlo distribution (part D). Less than 2% of the simulated trials had a greater P2-N1 change than the actual data. Thus, it appears very unlikely that the observed P2-N1 change occurred by chance. On the other hand, the actual change in 40

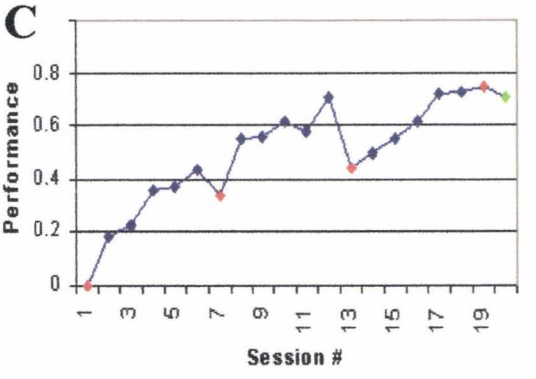
Hz power was close to the middle of the Monte Carlo distribution. This makes this finding not significant.

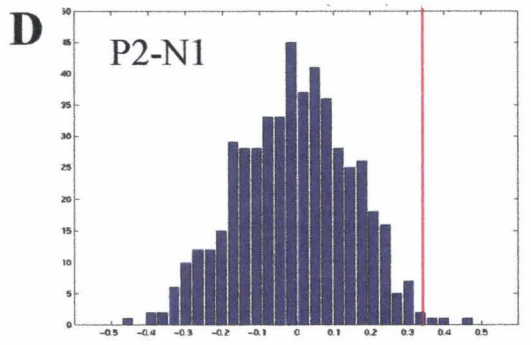
The results from part G show that the positive P2-N1 change for the 2040 Hz set was very uniform across all of the electrodes. Only one electrode (C3) deviated from the norm. Similarly, the number of electrodes with negative N1 and P2 latency shifts outnumbered the electrodes with positive shifts by a margin of 10 to 2 and 11 to 3, respectively. The results from the 40 Hz power analysis were more varied, with 13 electrodes showing a decrease in power, compared to 6 showing an increase.

Figure 3.13 - Subject A.B.









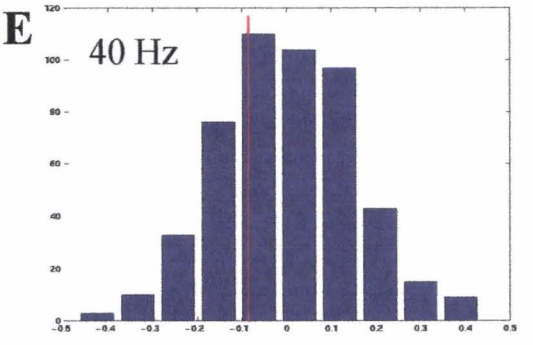
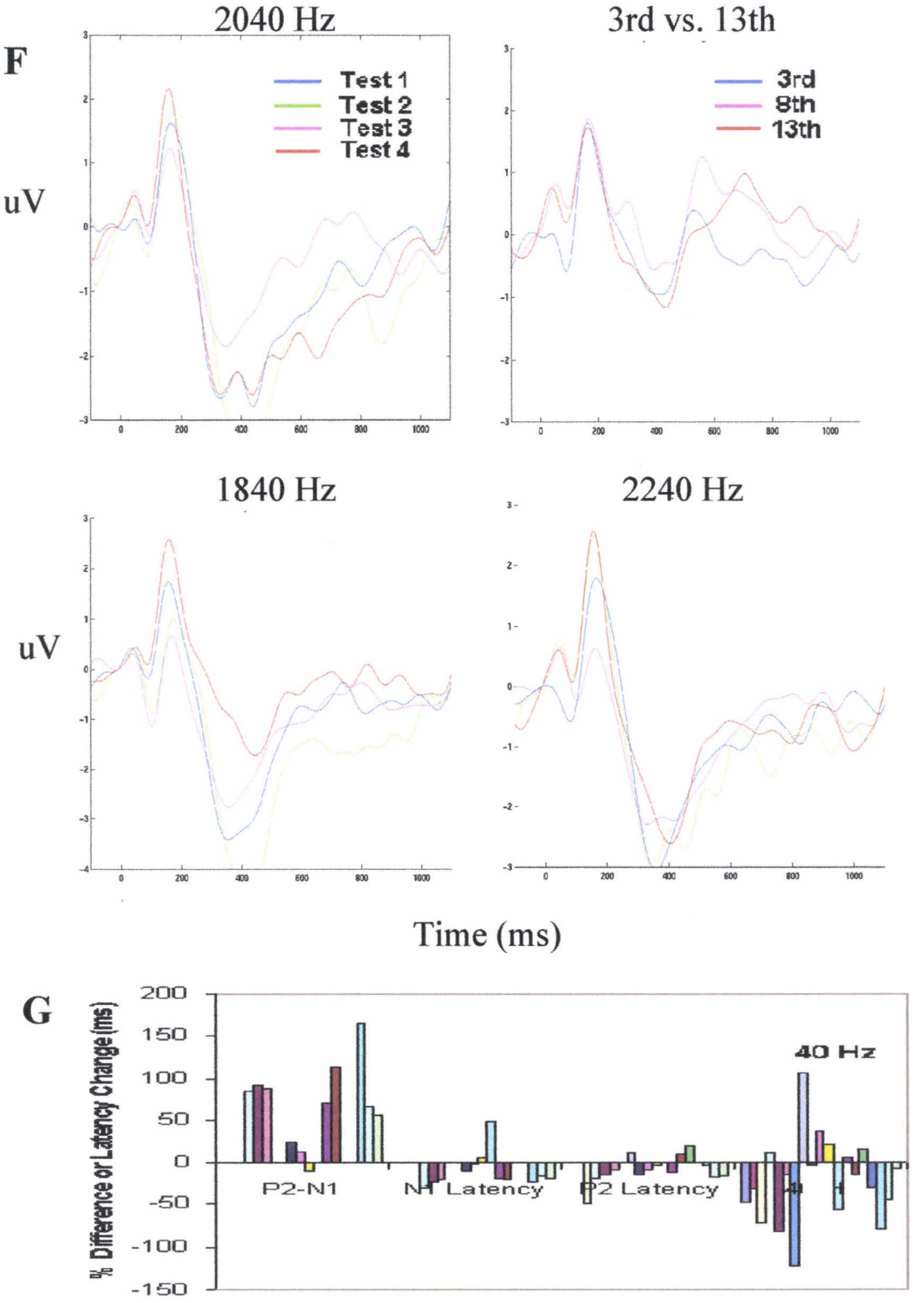


Figure 3.13 - A.B. (cont'd)



Subject K.J.

The psychophysical functions for subject K.J., although somewhat noisy, appear to show that there was improvement at 2040 Hz, and possibly 1840 Hz, but not at 2240 Hz. In fact, the subject appears to have gotten worse at 2240 Hz.

The d' values for sessions 13-15 were significantly higher ($p<0.05$) than those of sessions 1-3 for two of the three comparison frequencies. The change in d', based on the delta F of 6 Hz, was close to being significant ($p=0.05$).

K.J. also demonstrated gradual improvement in his frequency discriminating ability, but initially started at a much higher level than subject A.B, and therefore did not improve nearly as much, in total, from Test 1 to Test 2. This subject was unable to come back for a 7-week follow-up training session.

Interestingly, there was a pre/post training enhancement of P2-N1 for 2040 Hz, and a marginal increase for 1840 Hz, but there was a decrease observed for 2240 Hz. These findings correlate with the psychophysical findings where the subject improved at 2040 Hz, improved marginally at 1840 Hz, but got worse at 2240 Hz. The EEG data from session #3 was damaged for this subject and no comparison could be made between session #3 and #13.

The Monte Carlo analysis (part D) revealed that approximately 7% of the simulated trials had a greater average P2-N1 change than the actual change between Test 2 and Test 1. Therefore, it is possible that the observed P2-N1 change occurred by chance. It is highly likely that the 40 Hz result occurred by chance since it was very close to the middle of the simulated distribution.

There were increases in P2-N1 at six electrode sites for 2040 Hz. These were the only sites to have recorded N1 and P2 peaks in both Test 1 and Test 2. The latency of the N1 decreased in all of the electrode sites containing an N1. The results were more varied, however, for P2 latency and 40 Hz power.

Figure 3.14 - Subject K.J.

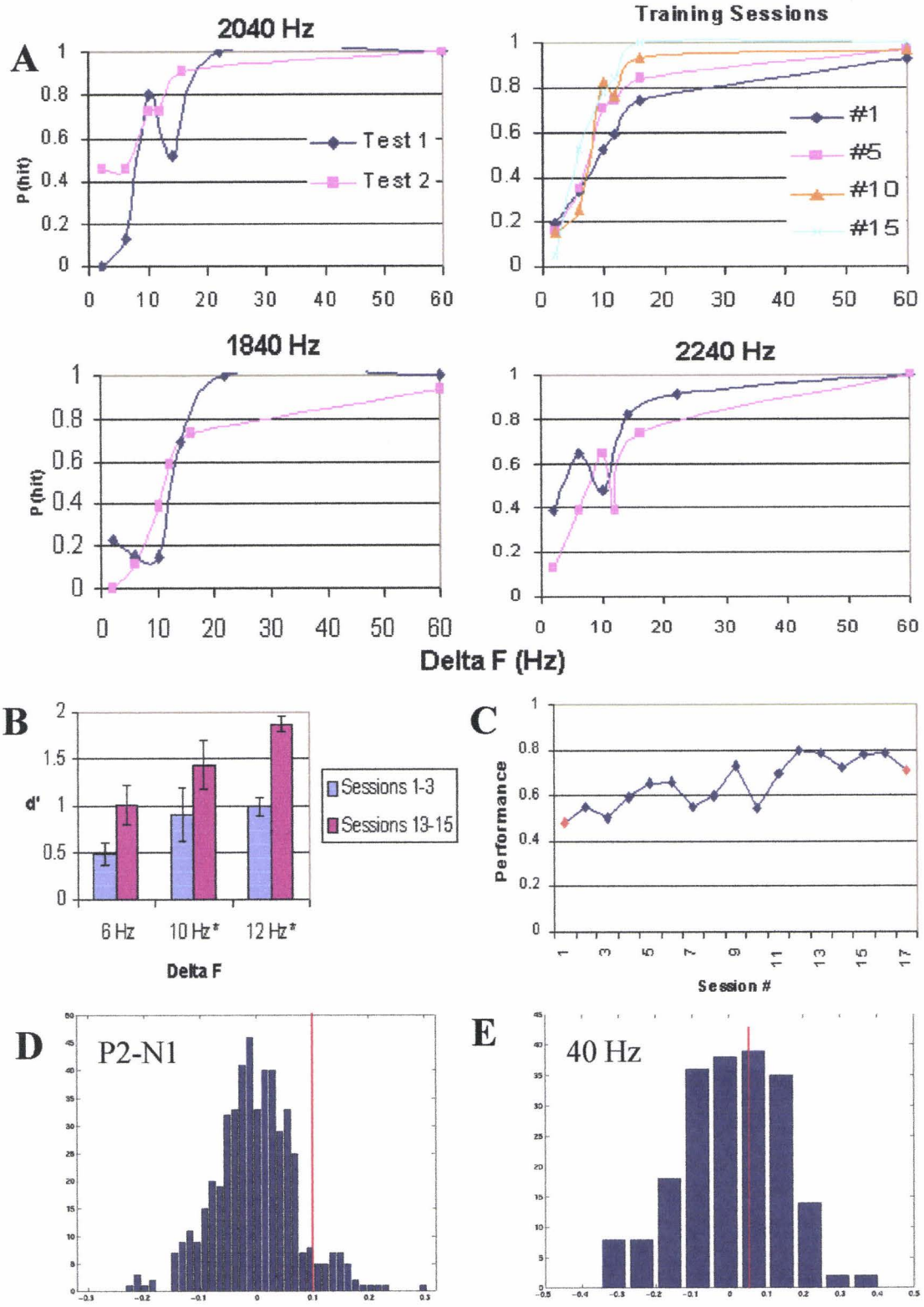
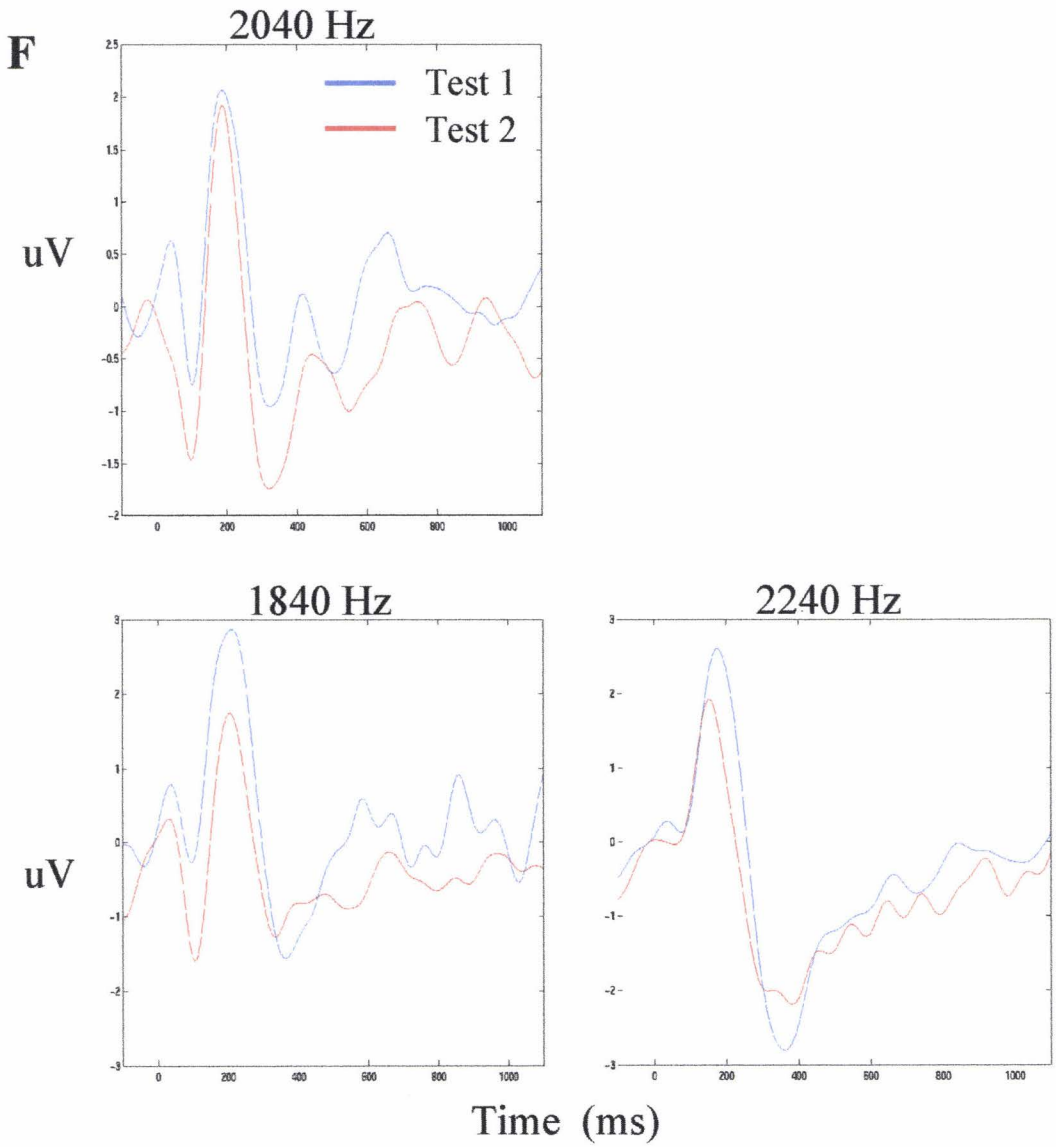


Figure 3.14 - K.J. (cont'd)



Subject R.H.

Subject R.H. improved on each standard frequency set, as shown by his psychophysical functions. The performance in Test 1 may have been affected by not having received a preliminary test. Based on d' values, there was improvement between sessions 13-15 and sessions 1-3. Two of the four d' changes were significant ($p<0.05$).

The performance of subject R.H. was anything but steady, as shown in part C. There was quite a bit of improvement at the beginning of training, but after session #5 performance decreased. R.H. did not regain a performance level comparable to session #5 until session #13. The reasons for this are unknown. The performance of R.H. in the 7-week follow-up session was also much lower than that of Test 2. The erratic performance during the training, however, makes this follow-up result somewhat questionable.

The EEG data of subject R.H. were quite noisy, and it proved very difficult to pick out an N1 and P2 peak. In fact, as shown in part F, only two electrodes contributed to the P2-N1 analysis. It is, thus, very difficult to draw any conclusions from this data set.

The Monte Carlo distribution for P2-N1 had a huge peak at zero. This was because in several of the simulated trials, there were no N1 or P2 peaks that could be detected. The actual P2-N1 change was not significant. Surprisingly, the 40 Hz power change was at the edge of the Monte Carlo distribution, signifying that this result may be significant. Even though this subject did not produce clear N1 and P2 peaks, the recordings still contained 40 Hz power. This 40 Hz power change appeared to decrease from Test 1 to Test 2.

Figure 3.15 - Subject R.H.

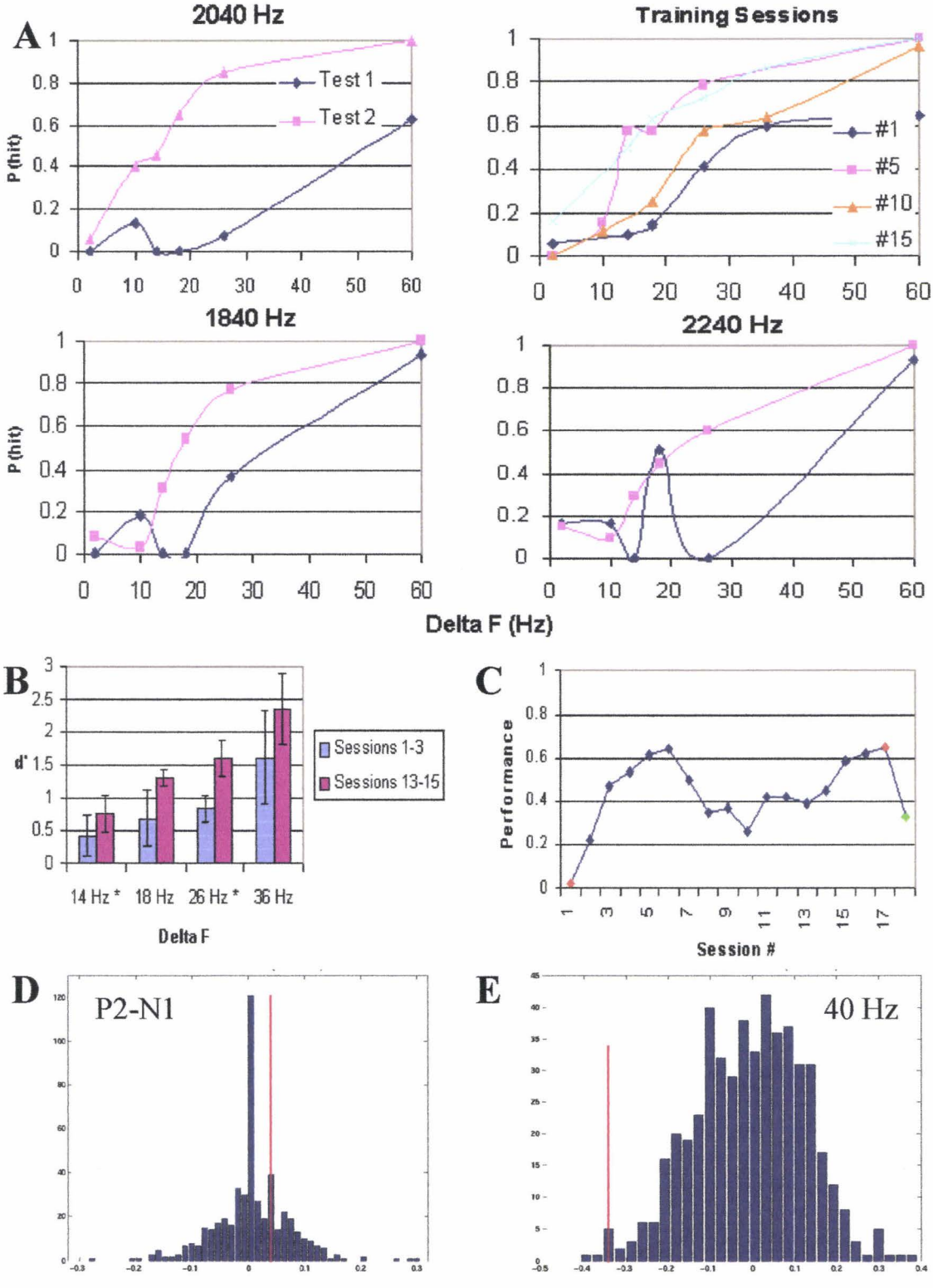
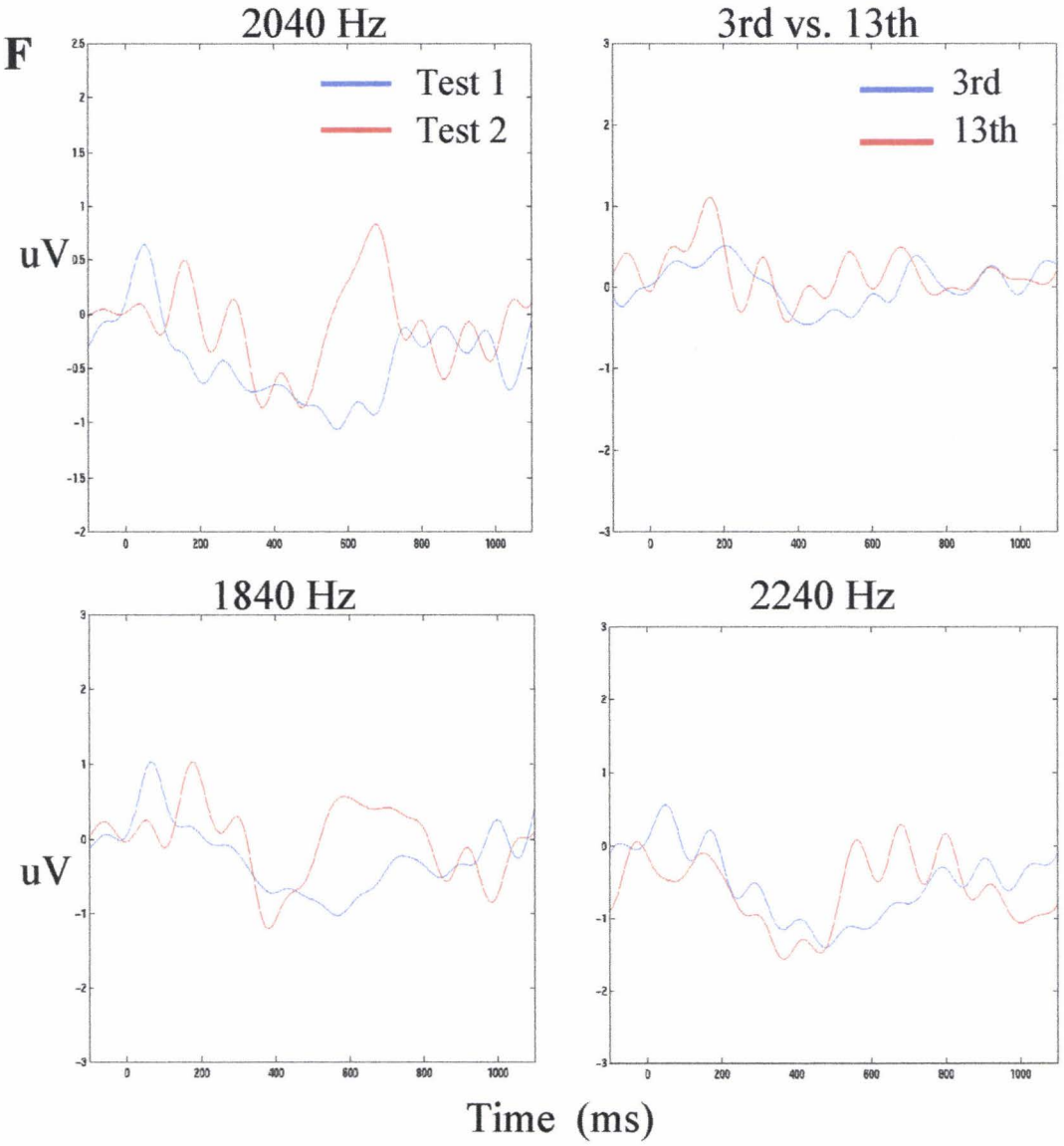
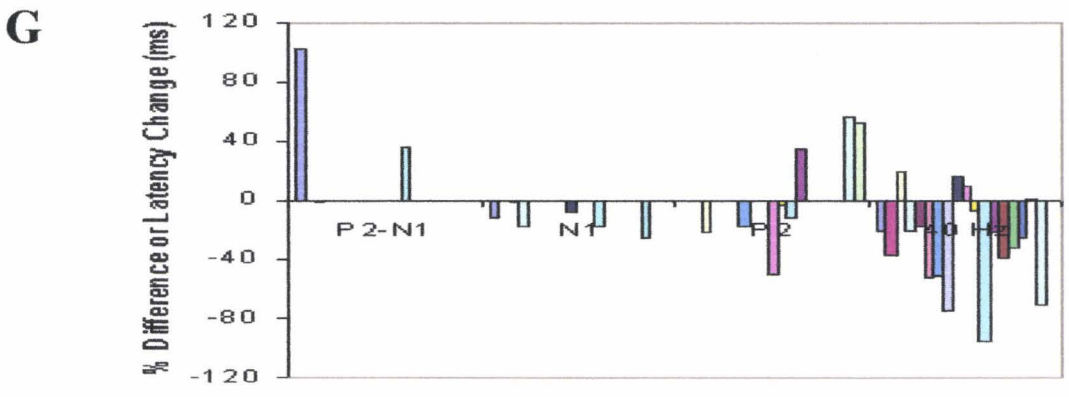


Figure 3.15 - R.H. (cont'd)





Subject J.K.

Subject J.K. improved on the 2040 Hz training set, to a lesser extent on the 2240 Hz set, but showed no improvement on the 1840 Hz set. The d' values were significantly higher ($p<0.05$) in sessions 13-15 compared with sessions 1-3 for three of four comparison frequencies, mainly due to a strong training session #15 (see part C). Overall, the performance did increase with training, but not to the extent seen in some of the other subjects. The 7-week follow-up session indicated that the subject did not retain anything of what had been learned during training.

The EEG traces recorded from the Cz electrode are shown in part F. The P2-N1 amplitude clearly increased in all three frequency sets, but decreased from the third training session to the thirteenth session. As shown in part G, six other electrodes also experienced an increase in P2-N1, while only two electrodes (P4 and P8) recorded a decrease in P2-N1. Using the Monte Carlo technique, this P2-N1 change was found to be significant with less than 2% of the simulated trials having a greater P2-N1 change than the actual change. There also appeared to be an overall decrease in N1 latency, a decrease in P2 latency, and an increase in 40 Hz power. The increase in 40 Hz power was not significant, however, as is shown in the Monte Carlo distribution (part E).

Figure 3.16 - Subject J.K.

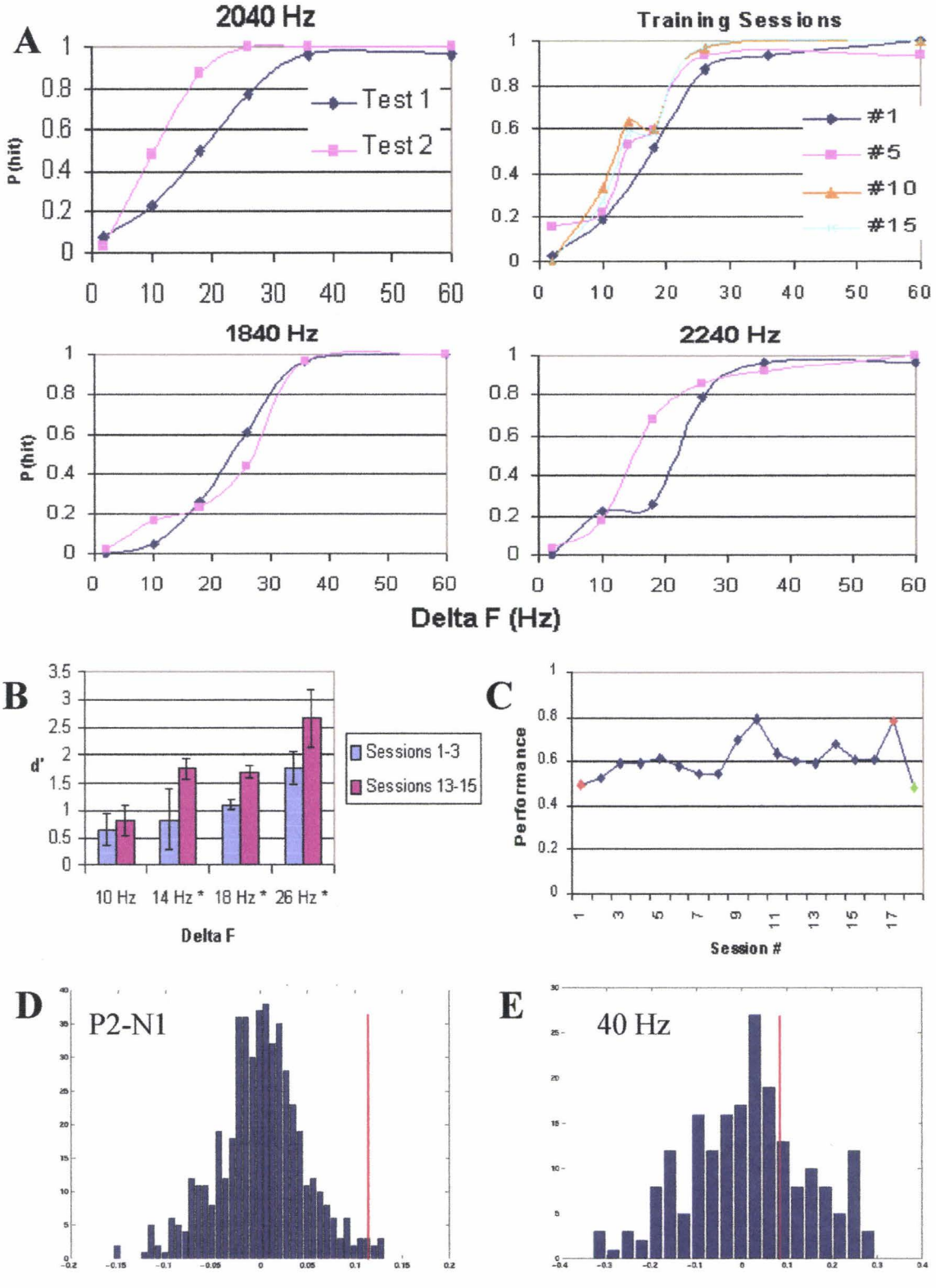
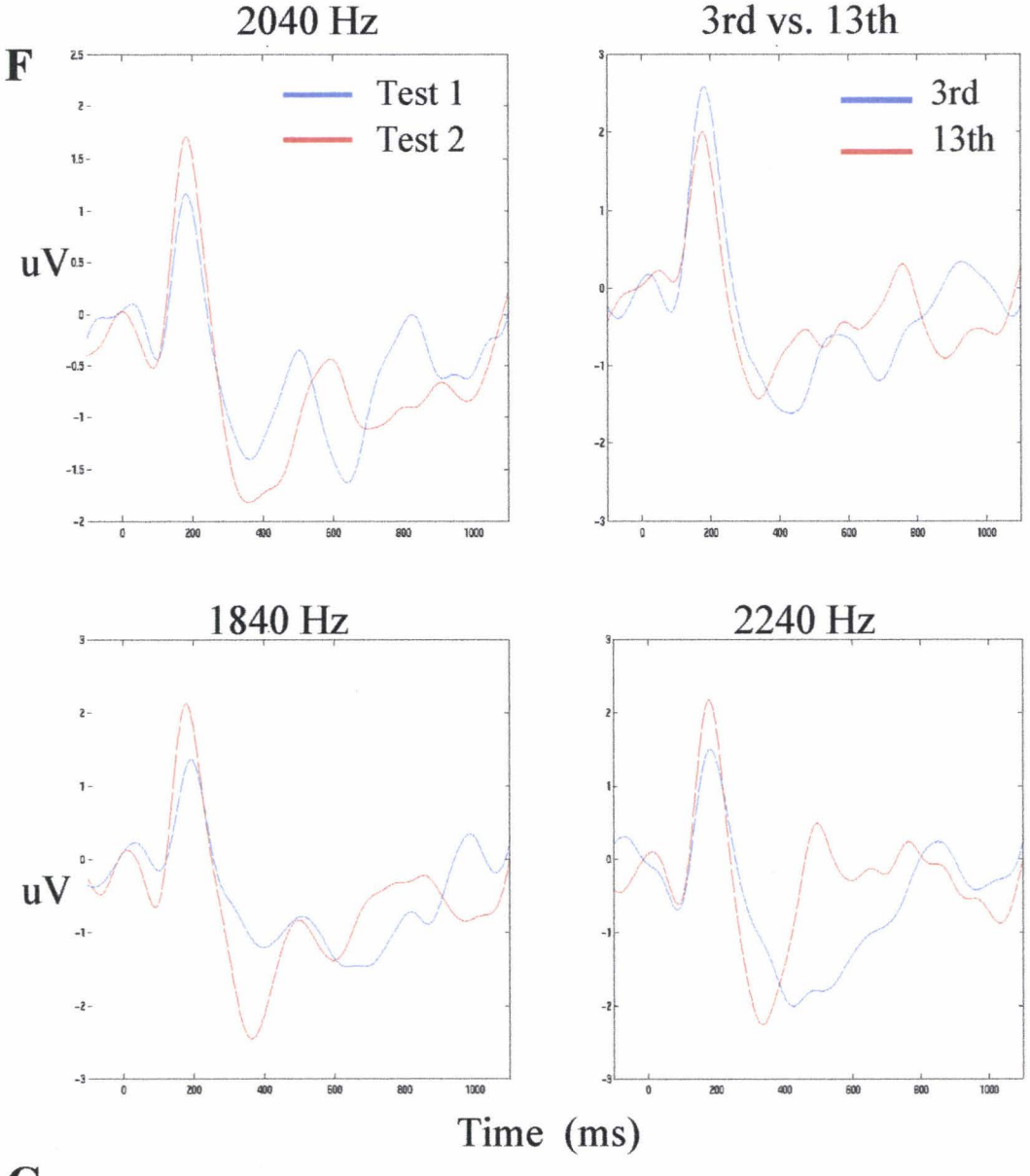
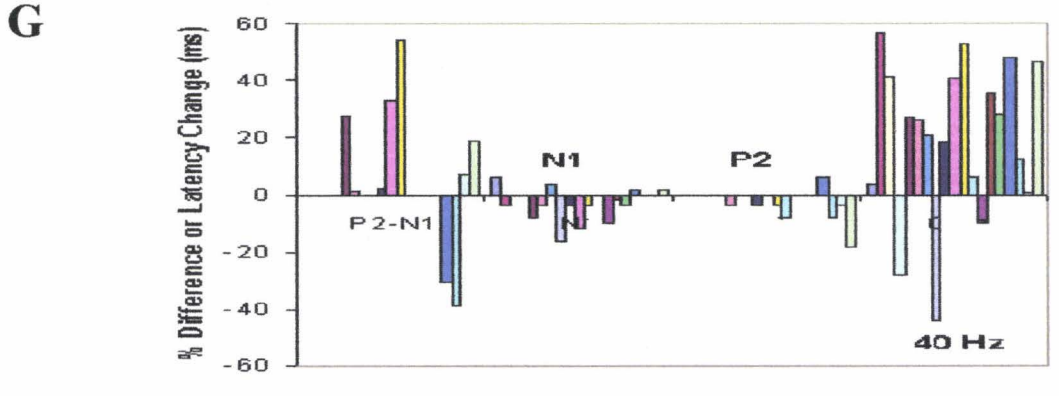


Figure 3.16 - J.K. (cont'd)





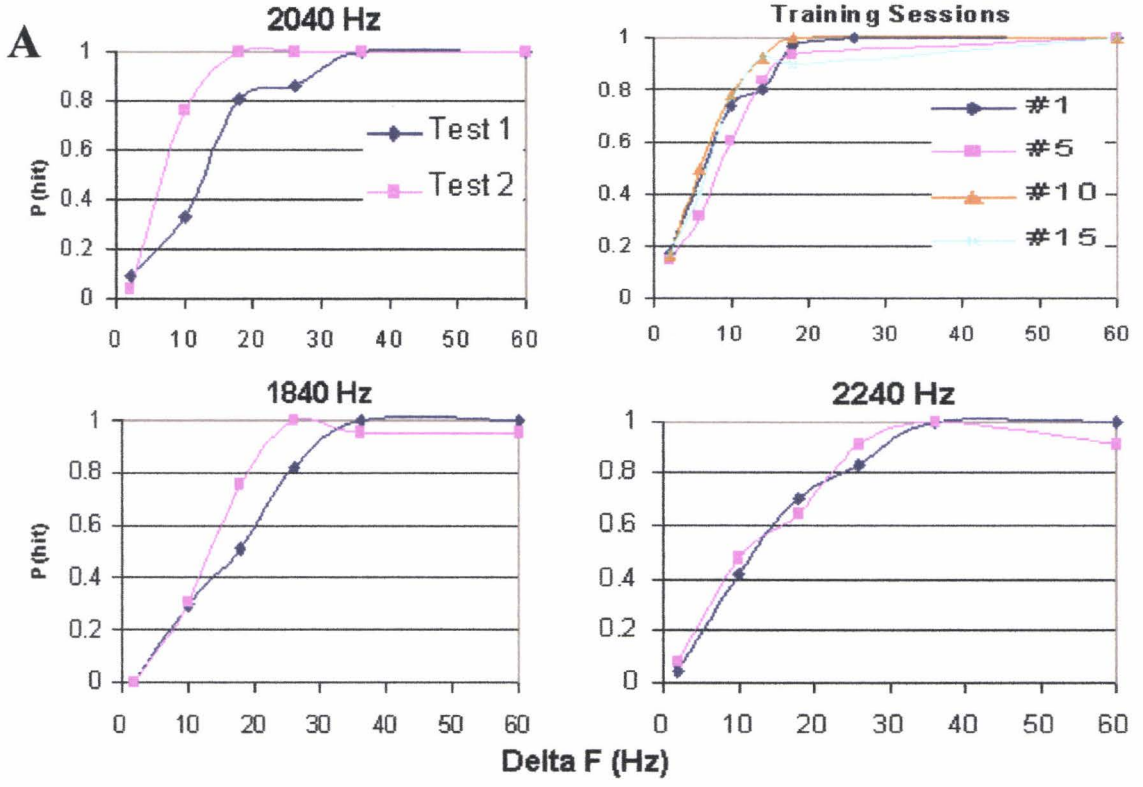
Subject V.L.

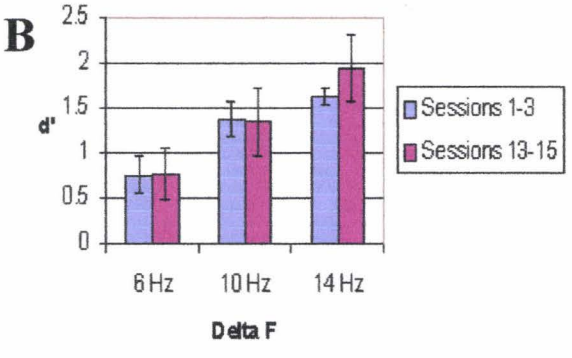
Subject V.L. was very good at the task before training had even started. There was improvement from Test 1 to Test 2 for 2040 Hz and 1840 Hz, but not for 2240 Hz. However, most of the improvement in the 2040 Hz set occurred between Test 1 and training session #1. This subject did not improve much after session #1 and this is shown by comparing the d' values of sessions 13-15 to sessions 1-3. The d' value increased for only one of three comparison frequencies and this change was not significant. The lack of improvement is also indicated in the flatness of the performance curve (part C). Performance in the follow-up session was in line with prior sessions.

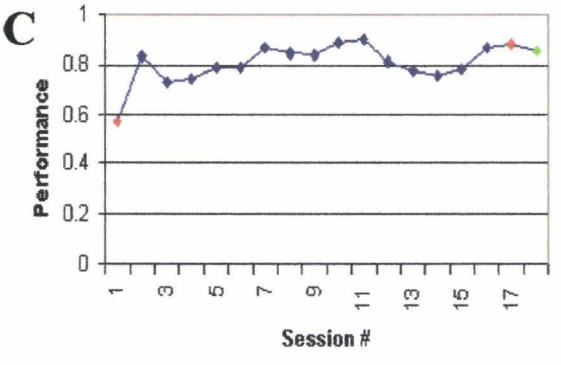
The Cz electrode recorded a decrease in P2-N1 for all three frequency sets, but the decrease was larger for 1840 Hz and 2240 Hz. However, Cz was not a typical electrode for this subject. The recordings from most other electrodes showed an increase in P2-N1 (part G). All of the N1 peaks recorded in Test 2 had a shorter latency than those recorded in Test 1. This was also the case for the P2 peaks for all but one electrode. The change in 40 Hz power was mixed, with 8 electrodes showing an increase and 11 indicating a decrease.

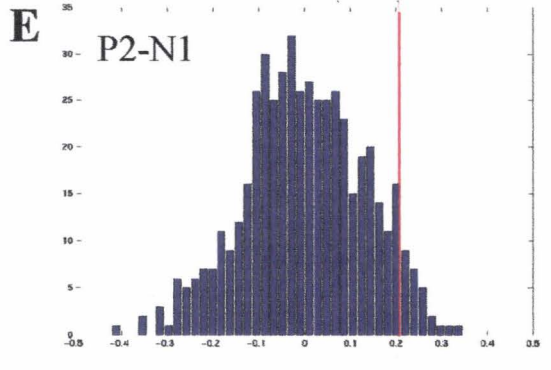
The Monte Carlo analyses indicated that the P2-N1 change and the decrease in 40 Hz power were not significant. Approximately 6% of the simulated post trials contained a greater P2-N1 than the simulated pre trials, indicating that the actual change could have been a result of noise in the data. As well, 5% of the simulated changes in 40 Hz power were more negative than the actual decrease, indicating that this too could have been a result of noise in the data.

Figure 3.17 - Subject V.L.









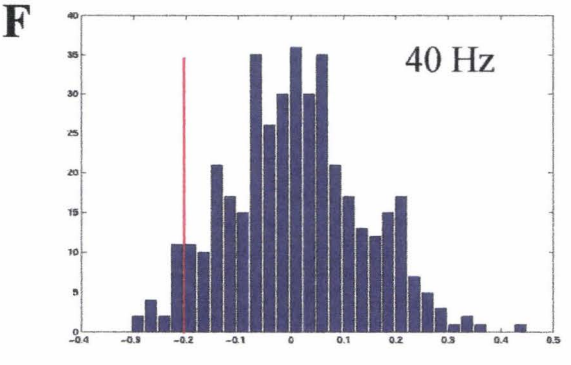
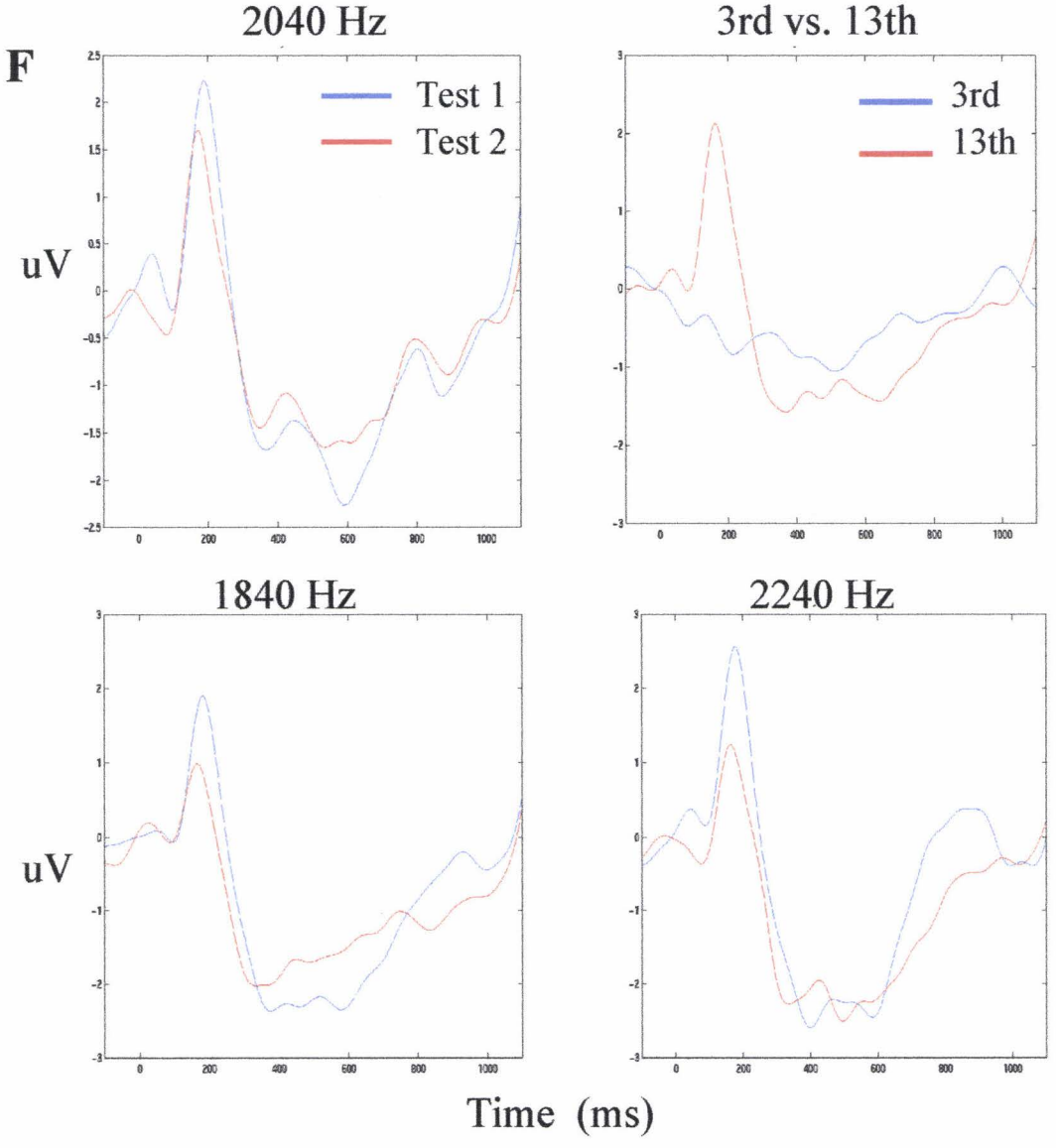
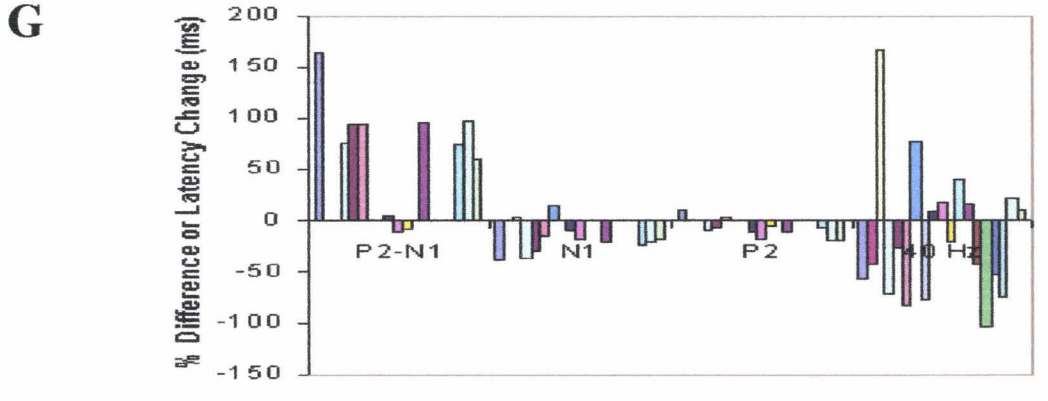


Figure 3.17 - V.L. (cont'd)





Subject K.D.

Subject K.D. improved on all three frequency sets, although the greatest improvement came on the 2040 Hz training set as shown by the psychophysical functions. The d' values were higher in sessions 13-15 compared to the first three sessions for all three frequency differences (10 Hz, 14 Hz, 18 Hz), but none of these proved to be significant. Most of the improvement took place in the first half of training, as performance then leveled off after session #8. This subject was unable to return for a follow-up session.

This was the only subject to show an overall decrease in P2-N1 after training. The decrease in P2-N1 proved not to be significant, however. As shown in part D, the actual change was very close to the middle of the Monte Carlo distribution. This subject was in agreement with the others when it came to the N1 and P2 latencies. The recordings from all but one electrode (Cz) revealed a decrease in N1 latency after training. Every P2 peak had a shorter latency following training. In the 40 Hz power analysis, the number of increases outnumbered the decreases by a margin of 12 to 7. The overall change in 40 Hz was not significant as shown by the Monte Carlo distribution, where 6% of the simulated trials contained a greater increase in 40 Hz power than the actual increase.

Figure 3.18 - Subject K.D.

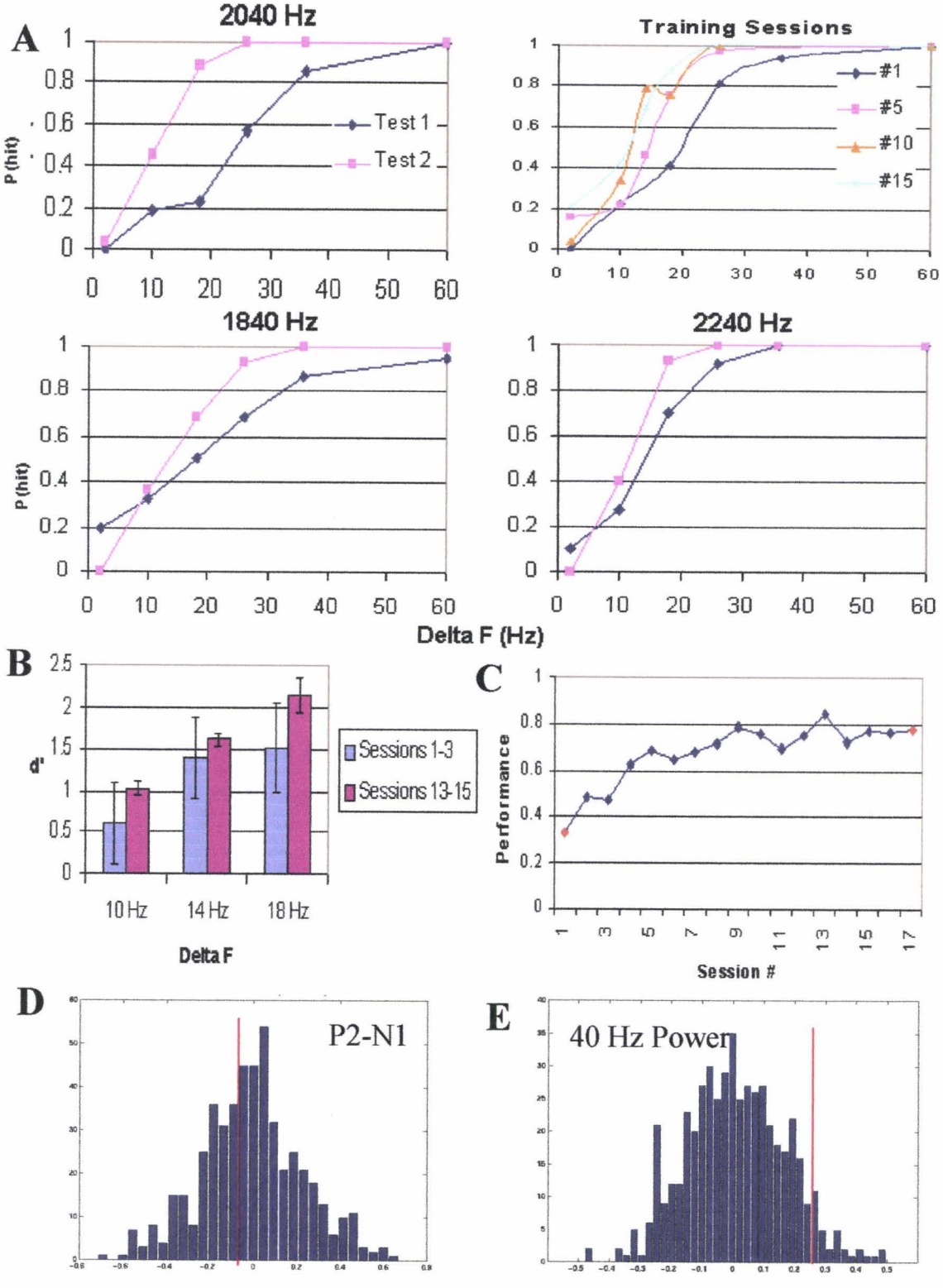
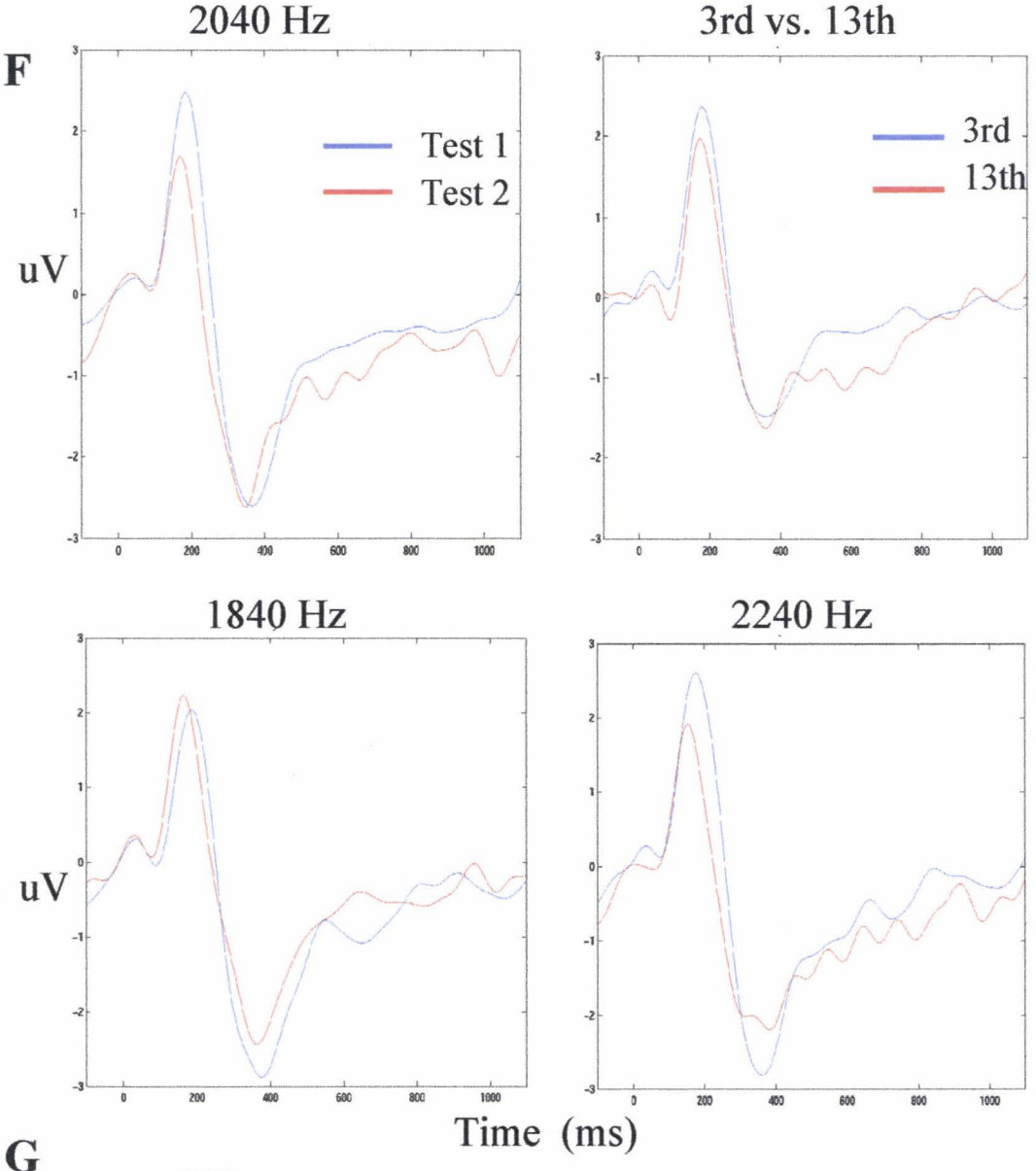


Figure 3.18 - K.D. (cont'd)



SUMMARY

Behavioural Data

All six subjects showed improvement on the training set (2040 Hz standard) from Test 1 to Test 2. Five out of six improved across the training blocks. The other subject (V.L.) showed improved results from the first test session to the first training session, but then did not improve further with more training.

Three of the subjects (A.B., R.H., K.D.) also improved at the side frequencies from Test 1 to Test 2. The other three subjects (K.J., J.K., V.L.) improved very little, if at all, at the side frequencies.

EEG Data

Five out of six subjects, plus the grand average, showed an increase in the P2-N1 amplitude in the trained frequency set. Only one subject (K.D.) demonstrated a decrease in the P2-N1 amplitude. All individual subjects, plus the grand average, showed a decrease in the latency of the N1 peak. Four out of six subjects, plus the grand average, showed a decrease in the latency of the P2 peak. The 40 Hz power increased in three of the subjects and decreased in the other three.

There was a statistically significant increase in P2-N1 and decrease in N1 latency for the group in the 2040 Hz set. The decrease in P2 latency and change in 40 Hz power were not significant. None of these effects were significant in the side frequencies.

Chapter 4 – Discussion

Animal studies have shown that the tonotopic organization of the auditory cortex is not statically fixed, but can be remodeled by experience (Recanzone et al., 1993). There is also some evidence that this remodeling occurs in humans over very long time scales (Pantev et al., 1998). The purpose of this study was to investigate whether the cortical representation for a selected spectral frequency could be enhanced by discrimination training over a 3-week period. The transfer of this training to frequencies adjacent to the trained set was also examined. The behavioural results will be discussed first, followed by the EEG data. Links between the behavioural and EEG data will then be discussed.

Behavioural Data

Subjects improved at detecting all of the comparison frequencies (except for the 2 Hz difference and the 60 Hz difference). This resulted in a shift of the psychophysical function upward. This shift was seen for every subject at 2040 Hz. However, there was less of a shift at the side frequencies, and for some subjects (3 of 6), no shift at all. This indicated that for those three subjects there was very little transfer of the frequency discriminating ability to the side frequencies. It is possible that subjects got tired during the test session, and since the 2040 Hz set was presented first, they performed better at this set. However, the order of the frequency sets was identical for Test 1 and Test 2,

which means that the subject would have to get tired in Test 2 but not Test 1 for this possibility to be true. Also, the order of presentation was different for subjects A.B. and K.J. These two subjects experienced the 1840 Hz set first, followed by the 2040 Hz set, and then the 2240 Hz set. Therefore, the subjects getting tired is an unlikely reason for why no transfer was seen in the side frequencies in some subjects. The effects of training must have been specific to the trained frequency.

Every subject was better at the frequency discrimination task in Test 2 than Test 1. There was only one subject (V.L.) who didn't improve across the training sessions, and that was probably because this subject was very good to begin with. The amount of improvement among the other five subjects varied, but seemed to be dependent on individual starting conditions. In other words, the worse a subject was at the beginning, the more that subject was able to improve. Most of the improvement occurred in the early training sessions, although there was still some improvement at the end of the training period. The 7-week follow-up session produce mixed results. Of the four subjects who received this session, two demonstrated a retention of the discriminating ability, but the other two did not.

The selection of the initial starting conditions was critical for achieving maximum improvement. The effort was made to set the initial (Test 1) comparison frequencies at levels such the subject could understand the task, but still have difficulty with it, thereby leaving lots of room for improvement. The selection of the comparison frequencies was based on each subject's performance in the preliminary session. However, even with these preliminary data, it was still difficult to make these selections.

The preliminary session was also used to give each subject a feel for the task before undergoing Test 1. Subject R.H. was the only subject that did not receive this preliminary session and perhaps this was the reason subject R.H. did not perform well in Test 1. Alternatively, the comparison frequencies may have been such that the task was too difficult.

EEG Data

The P2-N1 amplitude increased in five of six subjects for the trained frequency set, and the group average increase was statistically significant. The N1 latency decreased in all six subjects and the P2 latency decreased in four subjects. The group average change was statistically significant for N1 latency, but not for P2 latency.

So, what does this signify? Does a shorter latency translate into faster brain processing? Is the bigger P2-N1 amplitude the result of a greater cortical representation?

Ciesielski and French (1989) recorded event-related potentials from subjects in a visual-matching task. The subjects' task was to state whether or not the pair of amoeboid patterns presented to them were the same or different. Following 2.5 hours of training on this task, the N2 component increased in amplitude and decreased in latency, while no significant changes were seen in the N1 component[1]. They argued that the decrease in the N2 latency might indicate a reorganization of the mechanisms involved in the information processing of the stimulus. Alternatively, the brain may have learned to

[1] The N1 and N2 components mentioned here are recorded from the visual system. These differ from the components recorded from the auditory cortex.

extract only the information necessary to complete the task and ignore all other features of the stimulus, thereby decreasing the processing time.

Cansino and Williamson (1997) put one subject through an auditory frequency discrimination task and recorded his MEG at various stages. They observed that the amplitude of the 100m component (magnetic counterpart to the N1) decreased with improved discrimination. They hypothesized that "correct discrimination may require a more discrete cortical activation, so inhibitory processes become more forceful with learning." Increased inhibition would translate into less activation, which would give rise to a smaller MEG signal. This result appears contradictory to that of Ciesielski and French (1989) (and to this study), but it should be noted that this result was based on only one subject.

The results from the present study suggest that, based on the shorter N1 and P2 latencies, there may be a reorganization of the information processing mechanisms used to discriminate between sounds of different pitch. The increase in P2-N1 suggests that there may also be an expansion of the cortical representation of the training frequency (2040 Hz), similar to that recorded by Recanzone et al.(1993). Some of the neurons contributing to the N1 wave respond specifically to a narrow range of frequencies (Naatanen and Picton, 1987). These changes may take place in secondary auditory cortical areas, which is where the N1 wave is thought to originate (Pantev et al., 1995).

If there is an expansion of the cortical representation of the training frequency, you might expect to see this in the primary auditory cortex. If this expansion did occur in the primary auditory cortex, you might expect see this change in the steady-state response

since that is where the steady-state response originates. However, the analysis of the 40 Hz power did not produce a clear result. The 40 Hz power increased in three of the subjects and decreased in the other three. It may be the case that more extensive training is required to produce a change in the primary auditory cortex.

Therefore, it is likely that the changes, whatever they may be, are occurring in the secondary auditory cortex. Both the N1 and P2 waves are thought to be generated in the secondary auditory cortex, with the N1 generator being approximately 5 mm more lateral and 10 mm more posterior compared to the source of the P2 wave (Pantev et al., 1996b). EEG data normally reflect sources in the cortex because signals from subcortical generators are much more attenuated when they reach the scalp. As well, cortical lesions abolish this N1/P2 response (Scherg and von Cramen, 1986). Alternatively, the effect seen in the auditory cortex may merely be a reflection of a change occurring some place else in the brain. The site of the remodeling could be subcortical or some other part of the cortex, and this remodeling may then project onto the auditory cortex.

Although the N1 and P2 appear to arise from different populations of cortical cells, they may serve a related purpose. Hillyard and Picton (1978) suggested that the N1/P2 might be a response to change in the acoustic environment. One possibility for this experiment could be that the N1/P2 mechanism alerts, activates, or is a reflection of other processes which may be more directly responsible for frequency discrimination.

Links between EEG and Behavioural Data

In the work of Recanzone et al. (1993), monkeys only improved at the frequency at which they were trained. Also, the performance of monkey 4 decreased in tests where he was supposed to detect decreasing S2 frequencies (he was only trained to detect increasing S2 frequencies). These results were believed to be related to the expansion of cortical representation of the trained frequency (and, possibly, the decrease of the cortical representation of the decreasing S2 frequencies).

We thought we might see similar results in our experiment. We thought that there might be an increase in the representation of the trained frequency, but a decrement in the representation of the two side frequencies. This would be a result of neurons switching their tuning preference from 1840 Hz (or 2240 Hz) to the trained frequency of 2040 Hz. And it was thought that this might translate into improved performance with 2040 Hz, but not with 1840 Hz or 2240 Hz.

The results of our experiment showed that every subject improved using the 2040 Hz standard, but not everyone improved using the two side frequencies (although a few did). Also, in the EEG data, there were differences in the group as a whole between the 2040 Hz set and the side frequencies. These differences were enough to cause the P2-N1 increase and N1 latency decrease to be statistically significant in the 2040 Hz set, but not in the side frequencies. However, at the level of individual subjects, a change (or lack of change) in behavioural performance didn't always correlate with a change in EEG. The reason for this could have been the inappropriate selection of these side frequencies. It may be the case that training on 2040 Hz is detrimental to the cortical representation of

certain side frequencies, but these frequencies may be closer and farther away from 2040 Hz than the frequencies used in this experiment.

So, what is the relationship between behavioural performance and cortical plasticity? How do neuronal changes recorded by electroencephalography relate to behavioural performance?

To get a better idea of the answer to this question, it is helpful to look at the animal literature. Recanzone et al. (1993) showed with monkeys that a significant improvement in the performance of the frequency discrimination task was significantly correlated with the spatial representation of the trained frequency in the primary auditory cortex. This finding suggests that spatial representation may at least contribute in some way to frequency discrimination.

Bakin and Weinberger (1990), on the other hand, demonstrated that neural changes don't always correlate with behavioural performance. As described in the introduction section, they were able to induce frequency receptive field plasticity in the auditory cortex of guinea pigs using classical conditioning. Of the ten guinea pigs, CS frequency-specific receptive field changes developed in seven, while general increases in neural response were observed in three. However, there was no behavioural difference between any of the guinea pigs. The authors indicated that while associative learning may be a necessary condition, it is not always sufficient for inducing frequency-specific receptive field changes.

It has also been shown that behavioural performance on a frequency discrimination task may not be correlated with receptive field plasticity. Edeline and

Weinberger (1993) trained guinea pigs on an easy discriminating task and a more difficult one. The training consisted of trials containing either a postitive conditioned stimulus (CS+) with shock or a negative conditioned stimulus (CS-). For the more difficult task, the frequencies of CS+ and CS- were closer together. The guinea pigs were able to do the easy task, but could not do the harder one. However, receptive field changes occurred in both situations. Response to the frequency of CS+ increased, whereas responses to other frequencies (including CS-) decreased.

If receptive field changes don't necessarily predict behavioural performance, then it is reasonable to say that EEG changes may not always reflect performance either. This could explain the lack of disparity in the EEG data at the level of the individual subject between 2040 Hz and the side frequencies. On the other hand, there does appear to be some sort of relationship between the frequency discrimination training and the EEG data from the trained set. Following training, all six subjects were better at the task, all six had a shorter N1 latency, five of six had an increased P2-N1, and four of six had a shorter P2 latency.

Indeed, the changes taking place in the brain must be complex and the lack of these types of studies using EEG makes it difficult to answer these difficult questions. Needless to say, more research is needed.

Future Work

It has been estimated that 36 million Americans have some form of tinnitus, a ringing in the ears (Vernon, 1998). A strong association exists between tinnitus and cortical reorganization and it has been suggested that if the type of cortical reorganization seen in tinnitus patients could be reversed, the tinnitus may be curable (Muhlnickel et al., 1998). The results from this experiment hint at some sort of reorganization occurring in the brain, although perhaps not the same kind of reorganization of the primary auditory cortex that Recanzone et al. (1993) observed. It may be the case that further training is required to produce changes in the primary auditory cortex.

Although the current findings of this experiment make it difficult to speculate whether frequency discrimination training can help tinnitus patients, the results are nonetheless encouraging from the viewpoint that at least something is being modified in the human brain by this sort of training. But, as far as tinnitus is concerned, we need to be able to better document the effects of discrimination training on auditory representations in normal subjects. This will require more subjects to be trained and tested, and perhaps for longer periods of training. As well, other studies using the same training paradigm but a different imaging technique, such as MEG, would complement the findings of this thesis.

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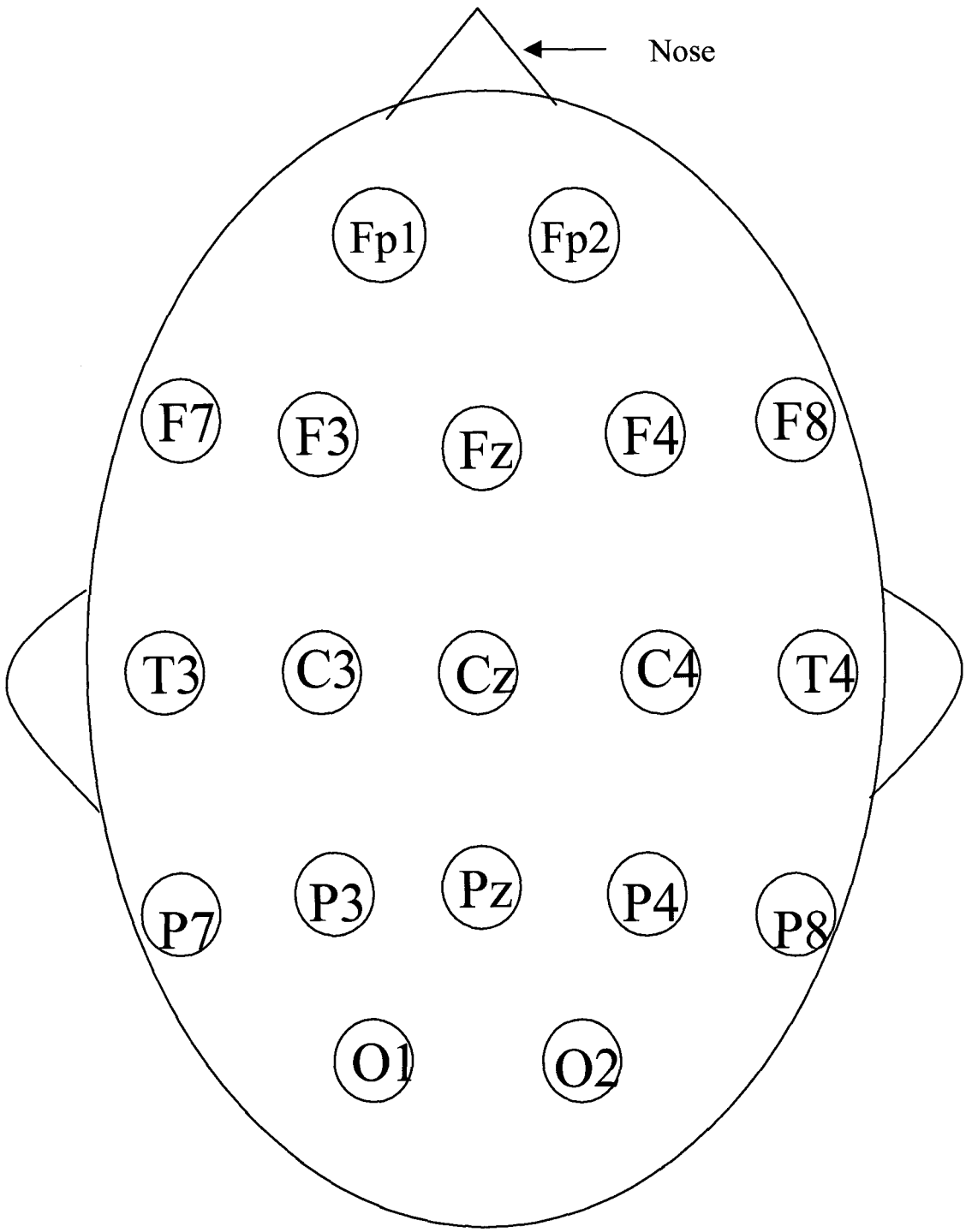
Appendix A

This is the electrode arrangement for the 10/20 system



Appendix B

This is the Matlab computer code used to pick out the amplitude and latency of the N1 and P2 waves in the EEG averaged data.

```
**************************
%Gets peak amplitude and latency of N1 and P2 in data files 'filena' and'filena2'. Finds
%the difference P2-N1. For 19 %channels. A/D must be 500.

function prepost = get64_n1p2(filena,filena2)


for i=1:19


N1=[0 0 0];    %1st element is amplitude, 2nd is latency
P2=[0 0 0];
N12=[0 0 0];
P22=[0 0 0];

        for q=140:170

        %*****this get a minimum peak*************
        if ((filena(q+1,i) > filena(q,i)) & (filena(q-1,i) > filena(q,i)))
        N1(1)=filena(q,i);
        N1(2)=((q*2)-200);
        N1(3)=N1(3)+1;
        end

        %*****this gets a maximum peak************
        if ((filena(q+1,i) < filena(q,i)) & (filena(q-1,i) < filena(q,i)))
        N1(1)=filena(q,i);
        N1(2)=((q*2)-200);
        N1(3)=N1(3)+1;
        end

        end
        %*************************************************************
```

```
for r=175:210

        %*****this get a minimum peak*************
        if ((filena(r+1,i) > filena(r,i)) & (filena(r-1,i) > filena(r,i)))
        P2(1)=filena(r,i);
        P2(2)=((r*2)-200);
        P2(3)=P2(3)+1;
        end

        %*****this gets a maximum peak************
        if ((filena(r+1,i) < filena(r,i)) & (filena(r-1,i) < filena(r,i)))
        P2(1)=filena(r,i);
        P2(2)=((r*2)-200);
        P2(3)=P2(3)+1;
        end

        end
        %*****************************************************************

        N100pre(i,1)= N1(1);
        N100pre(i,2)= N1(2);
        N100pre(i,3)= N1(3);
        P200pre(i,1)= P2(1);
        P200pre(i,2)= P2(2);
        P200pre(i,3)= P2(3);
        diff(i,1)= abs(P2(1)-N1(1));
        diff(i,2)= abs(P2(2)-N1(2));

        if (N1(3) ~= 1)
                diff(i,1)=0;
                diff(i,2)=0;     % if more than one peak is found, set to 0.
        end
        if (P2(3) ~= 1)
                diff(i,1)=0;
                diff(i,2)=0;
        end

        %*filena2*************************************************************

        for q=140:170

        %*****this get a minimum peak*************
        if ((filena2(q+1,i) > filena2(q,i)) & (filena2(q-1,i) > filena2(q,i)))
        N12(1)=filena2(q,i);
```

```
N12(2)=((q*2)-200);
N12(3)=N12(3)+1;
end

%*****this gets a maximum peak************
if ((filena2(q+1,i) < filena2(q,i)) & (filena2(q-1,i) < filena2(q,i)))
N12(1)=filena2(q,i);
N12(2)=((q*2)-200);
N12(3)=N12(3)+1;
end

end
%*****************************************************************

for r=175:210

%*****this get a minimum peak*************
if ((filena2(r+1,i) > filena2(r,i)) & (filena2(r-1,i) > filena2(r,i)))
P22(1)=filena2(r,i);
P22(2)=((r*2)-200);
P22(3)=P22(3)+1;
end

%*****this gets a maximum peak************
if ((filena2(r+1,i) < filena2(r,i)) & (filena2(r-1,i) < filena2(r,i)))
P22(1)=filena2(r,i);
P22(2)=((r*2)-200);
P22(3)=P22(3)+1;
end

end
%*****************************************************************


N100post(i,1)= N12(1);
N100post(i,2)= N12(2);
N100post(i,3)= N12(3);
P200post(i,1)= P22(1);
P200post(i,2)= P22(2);
P200post(i,3)= P22(3);
diff2(i,1)= abs(P22(1)-N12(1));
diff2(i,2)= abs(P22(2)-N12(2));
```

```
        if (N12(3) ~= 1)
                diff2(i,1)=0;
                diff2(i,2)=0;   % if more than one peak is found, set to 0.
        end
        if (P22(3) ~= 1)
                diff2(i,1)=0;
                diff2(i,2)=0;
        end

        if ((diff(i,1)==0) | (diff2(i,1)==0))
                diff(i,1)=0;
                diff(i,2)=0;
                diff2(i,1)=0;   %if one peak doesn't meet the criteria , set them all to 0.
                diff2(i,2)=0;
        end

end

prepost(:,1)=N100pre(:,1);
prepost(:,2)=N100pre(:,2);
prepost(:,3)=N100pre(:,3);
prepost(:,4)=P200pre(:,1);
prepost(:,5)=P200pre(:,2);
prepost(:,6)=P200pre(:,3);
prepost(:,7)=N100post(:,1);
prepost(:,8)=N100post(:,2);
prepost(:,9)=N100post(:,3);
prepost(:,10)=P200post(:,1);
prepost(:,11)=P200post(:,2);
prepost(:,12)=P200post(:,3);
prepost(:,13)=diff2(:,1)-diff(:,1);


for i=1:19
average(i)=((diff2(i,1)+diff(i,1))/2);

        if (average(i)==0)
        average(i)=100;
        end

prepost(i,13)=prepost(i,13)/average(i); %calculates percentage change.

end
prepost
```

Note: If the sampling rate is 1000 Hz, the following code must be used.

```
**************************
%get peak amplitude and latency of N1 and P2. Finds the difference. For 10/20 cap.
%AD must be 1000.

function prepost = get1020_n1p2(filena,filena2)


for i=1:19


N1=[0 0 0];     %1st element is amplitude, 2nd is latency, 3rd is
P2=[0 0 0];     %number of peaks
N12=[0 0 0];
P22=[0 0 0];

        for q=280:340

        %*****this get a minimum peak*************
        if ((filena(q+1,i) > filena(q,i)) & (filena(q-1,i) > filena(q,i)))
        N1(1)=filena(q,i);
        N1(2)=((q)-200);
        N1(3)=N1(3)+1;
        end

        %*****this gets a maximum peak************
        if ((filena(q+1,i) < filena(q,i)) & (filena(q-1,i) < filena(q,i)))
        N1(1)=filena(q,i);
        N1(2)=((q)-200);
        N1(3)=N1(3)+1;
        end

        end
        %*************************************************************

        for r=350:420

        %*****this get a minimum peak*************
        if ((filena(r+1,i) > filena(r,i)) & (filena(r-1,i) > filena(r,i)))
        P2(1)=filena(r,i);
        P2(2)=((r)-200);
        P2(3)=P2(3)+1;
        end
```

```
%*****this gets a maximum peak***********
if ((filena(r+1,i) < filena(r,i)) & (filena(r-1,i) < filena(r,i)))
P2(1)=filena(r,i);
P2(2)=((r)-200);
P2(3)=P2(3)+1;
end

end
%*************************************************************


N100pre(i,1)= N1(1);
N100pre(i,2)= N1(2);
N100pre(i,3)= N1(3);
P200pre(i,1)= P2(1);
P200pre(i,2)= P2(2);
P200pre(i,3)= P2(3);
diff(i,1)= abs(P2(1)-N1(1));
diff(i,2)= abs(P2(2)-N1(2));

if (N1(3) ~= 1)
        diff(i,1)=0;
        diff(i,2)=0;     % if more than one peak is found, set to 0.
end
if (P2(3) ~= 1)
        diff(i,1)=0;
        diff(i,2)=0;
end

%*filena2*****************************************************

for q=280:340

%*****this get a minimum peak*************
if ((filena2(q+1,i) > filena2(q,i)) & (filena2(q-1,i) > filena2(q,i)))
N12(1)=filena2(q,i);
N12(2)=((q)-200);
N12(3)=N12(3)+1;
end

%*****this gets a maximum peak************
if ((filena2(q+1,i) < filena2(q,i)) & (filena2(q-1,i) < filena2(q,i)))
N12(1)=filena2(q,i);
```

```
N12(2)=((q)-200);
N12(3)=N12(3)+1;
end

end
%****************************************************************

for r=350:420

%*****this get a minimum peak*************
if ((filena2(r+1,i) > filena2(r,i)) & (filena2(r-1,i) > filena2(r,i)))
P22(1)=filena2(r,i);
P22(2)=((r)-200);
P22(3)=P22(3)+1;
end

%*****this gets a maximum peak************
if ((filena2(r+1,i) < filena2(r,i)) & (filena2(r-1,i) < filena2(r,i)))
P22(1)=filena2(r,i);
P22(2)=((r)-200);
P22(3)=P22(3)+1;
end

end
%****************************************************************

N100post(i,1)= N12(1);
N100post(i,2)= N12(2);
N100post(i,3)= N12(3);
P200post(i,1)= P22(1);
P200post(i,2)= P22(2);
P200post(i,3)= P22(3);
diff2(i,1)= abs(P22(1)-N12(1));
diff2(i,2)= abs(P22(2)-N12(2));

if (N12(3) ~= 1)
        diff2(i,1)=0;
        diff2(i,2)=0;    % if more than one peak is found, set to 0.
end
if (P22(3) ~= 1)
        diff2(i,1)=0;
        diff2(i,2)=0;
end
```

```
        if ((diff(i,1)==0) | (diff2(i,1)==0))
                diff(i,1)=0;
                diff(i,2)=0;
                diff2(i,1)=0;    %if one peak does not meet the criteria, set them all to 0.
                diff2(i,2)=0;
        end

end

prepost(:,1)=N100pre(:,1);
prepost(:,2)=N100pre(:,2);
prepost(:,3)=N100pre(:,3);
prepost(:,4)=P200pre(:,1);
prepost(:,5)=P200pre(:,2);
prepost(:,6)=P200pre(:,3);
prepost(:,7)=N100post(:,1);
prepost(:,8)=N100post(:,2);
prepost(:,9)=N100post(:,3);
prepost(:,10)=P200post(:,1);
prepost(:,11)=P200post(:,2);
prepost(:,12)=P200post(:,3);
prepost(:,13)=diff2(:,1)-diff(:,1);


for i=1:19
average(i)=((diff2(i,1)+diff(i,1))/2);

        if (average(i)==0)
        average(i)=100;
        end

prepost(i,13)=prepost(i,13)/average(i); %calculates percentage change.

end
prepost
```