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Plastic Effect of Tetanic Stimulation on Auditory Evoked Potentials

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PLASTIC EFFECT OF TETANIC STIMULATION ON AUDITORY EVOKED
POTENTIALS

Monograph

by

Rajesh <u>Tripathy</u>

Graduate Program in Health and Rehabilitation Sciences

A thesis submitted in partial fulfillment
of the requirements for the degree of
Masters of Science

The School of Graduate and Postdoctoral Studies
The University of Western Ontario
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Abstract

The goal of this thesis was to investigate tetanic acoustic stimulation (TS) and its effects on the human auditory system. Two experiments were completed to study the effects of a 2 minute duration 1 kHz TS on the auditory brainstem and cortex using auditory evoked potentials. At the cortical level the auditory long latency response (ALLR) was recorded and the P1, N1, and P2 components were measured; in the brainstem the amplitude of the 80 Hz auditory steady state response (ASSR) was measured. TS induced significant changes in ALLR component latencies, and a significant reduction in ASSR amplitude, but these changes were not specific to the TS acoustic frequency of 1 kHz.

Keywords

Table of Contents

List of Tables

List of Figures

List of Aberrations

μV: Micro volt

AAF: Anterior auditory field

AEP: Auditory evoked potential

AI: Primary auditory cortex

ALLR: Auditory long latency response

AMPA: alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid

AMT: Active motor threshold

ASSR: Auditory steady state responses

cTBS: Transcranial magnetic continuous theta burst stimulation

dB: Decibel

ERD: Event related desynchronization

ERP: Event related potentials

fm: Frequency modulation

fMRI: Functional Magnetic resonance imaging

HC: Healthy adults

HFS: High frequency stimulation

IHS: Intelligent hearing system

iTBS: Transcranial magnetic intermittent theta burst stimulation

kHz: Kilohertz

kΩ: Kilo ohm

LTP: Long-term potentiation

M1: Motor cortex

MEP: Motor evoked potential

msec: Millisecond

NA: Not available.

NB: Nucleus Basalis

NMDA: N-methyl-D-aspartate

rTMS: Transcranial magnetic stimulation

RF: Receptive field

RMT: Resting motor threshold

S1: Sensory cortex

SEP: Somatosensory evoked potentials

SPL: Sound pressure level

SZ: Schizophrenia patients

SSP: Stimulus specific plasticity

TEOAE: Transient oto-acoustic emissions

TMS: Transcranial magnetic stimulation

TS: Tetanic stimulation

VEP: Visual evoked potential

Chapter 1

1 Introduction

Neuroplasticity is a term used to describe a variety of physiological and structural changes in the central nervous system in response to altered patterns of stimulation. In sensory and motor systems, demands for transmitting sensory or motor information within these systems can change when there (1) are altered patterns of stimulation (peripheral or central) and/or (2) is a loss of sensory cells, neurons or nerve fibres (e.g., deafferentation). That is, the brain modifies as a function of the stimulation it receives, changes which may or may not be a positive adaptation to the external environment.

Neuroplasticity can involve changes in the physiological, biochemical, and/or anatomical properties of cells in the central nervous system. Synaptic function, synchronization in neuronal networks, and/or new connection patterns within neuronal networks can alter and may be different depending on the age when neuroplastic changes occur. Auditory neuroplasticity refers to modifications occurring within the auditory system specifically (Ponton et al., 2001; Tremblay, 2003; Tremblay & Kraus, 2002).

1.1 Introduction to Neuroplasticity

There are many intrinsic and extrinsic factors that play a role in auditory neuroplasticity. Throughout the lifespan, external and intrinsic factors work together and can lead to changes at the molecular level (e.g. molecules that can change the expression of genes), and cellular level (e.g. structure and function of synapses) which in turn can induce changes at the neural network level (strength of connections, maps of sound stimulus characteristics) (see Figure 1). These levels interact with each other to allow for different forms of plastic change. In the auditory system, extrinsic factors such as the amount and pattern of activity in input pathways contribute to the development and maintenance of the central auditory system structure and function. These factors may be passive or combined with other extrinsic factors such as learning. During the earliest periods of development, intrinsic electrical activity, even before sound can activate the

ear and central auditory neurons, is generated within the developing brain and contributes to the initial establishment of central auditory neurons and their network connections. As an animal matures, both intrinsic neural activity, and modifications caused by various extrinsic factors, both contribute to neuroplastic changes.

Long-term potentiation (LTP) is a type of synaptic plasticity which results in a long-lasting increase in synaptic efficacy. LTP was discovered in hippocampus of the rabbit by Terje Lomo in 1966, in Norway, at the laboratory of Per Andersen. Lomo first observed LTP while conducting a series of neurophysiological experiments to explore the role of the hippocampus in short-term memory on anesthetized rabbits. Since then LTP has remained a focus of neuroscientific research in the area of plasticity and learning. LTP has been observed both in experimental preparations (*in vitro*) and in living animals (*in vivo*) (Eckert & Abraham, 2010). Ground-breaking results from animal models and human studies have shown that LTP is involved in information storage in the brain due to an increase in strength of chemical synapses between neurons. This form of synaptic plasticity lasts from minutes to several days, and is elicited in the brain by the patterned electrical stimulation of an afferent pathway (Blisss & Lomo, 1973). LTP is considered to be one of the major cellular mechanisms for learning, memory, and passive experience-dependent plasticity in the nervous system. LTP has been studied largely in laboratory animals at the cellular level, and in human tissue collected during surgery (Teyler et al., 2005).

There are several properties of LTP that make it a suitable model for activity-dependent plasticity in the nervous system, one of which is the associative nature of LTP. LTP induction requires simultaneous activation of the presynaptic neuron and depolarization of the postsynaptic neuron. Presynaptic neurons, when activated, release glutamate that binds to either alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) or N-methyl-D-aspartate (NMDA) receptor subunits (Collingridge & Bliss, 1987). NMDA is the one that is important for LTP induction (Malenka & Bear, 2004). Only when the postsynaptic neuron is depolarized, NMDA receptor (NMDAR) channels permit current flow (Mayer, Westbrook & Guthrie, 1984; Mayer & Westbrook, 1987). There are different phases of LTP on the basis of LTP persistence over the course of

time; short-term (STP, recently LTP1), early (E-LTP, LTP2) and late (L-LTP, LTP3). LTP1 lasts between 1 and 2 hours which decays (Córdoba-Montoya, Albert, & López-Martín 2010).
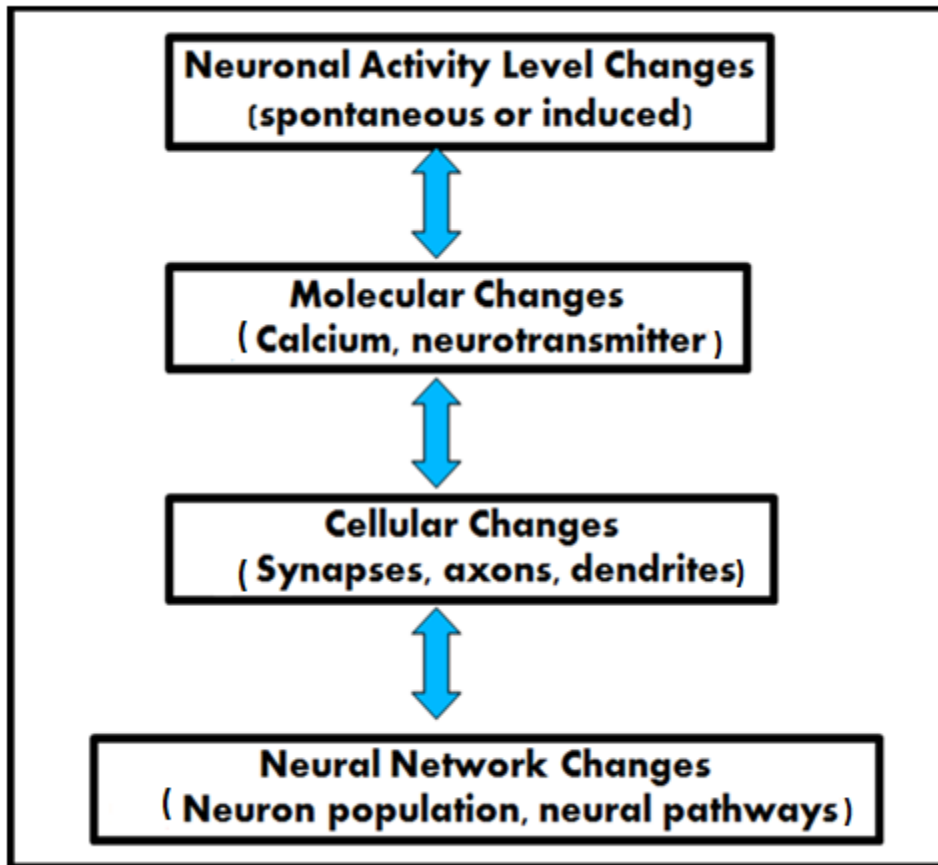
Figure 1: Mechanism of plasticity in the central nervous system (as reviewed by Syka and Merzenich, 2005)

1.2 Auditory Neuroplasticity

Auditory neuroplasticity refers to the changes in the biochemistry, physiology or anatomy of auditory structures following a change in spontaneous activity or stimulation patterns that alter activity within the auditory system neurons. Changes in the acoustic environment alter auditory input and can also induce neuroplastic changes in animals with a normal auditory system and in those with sensory or neural damage. Electrical

3

stimulation of the cochlea or the brain can also modify the central auditory system in animal models (Kral, Hartmann, Tillein, Heid & Klinke, 2002). Clapp, Wesley, Hamm, Krik and Teyler (2005) directly demonstrated plasticity in the auditory cortex of an intact human brain using high rate acoustic rather than electrical stimulation.
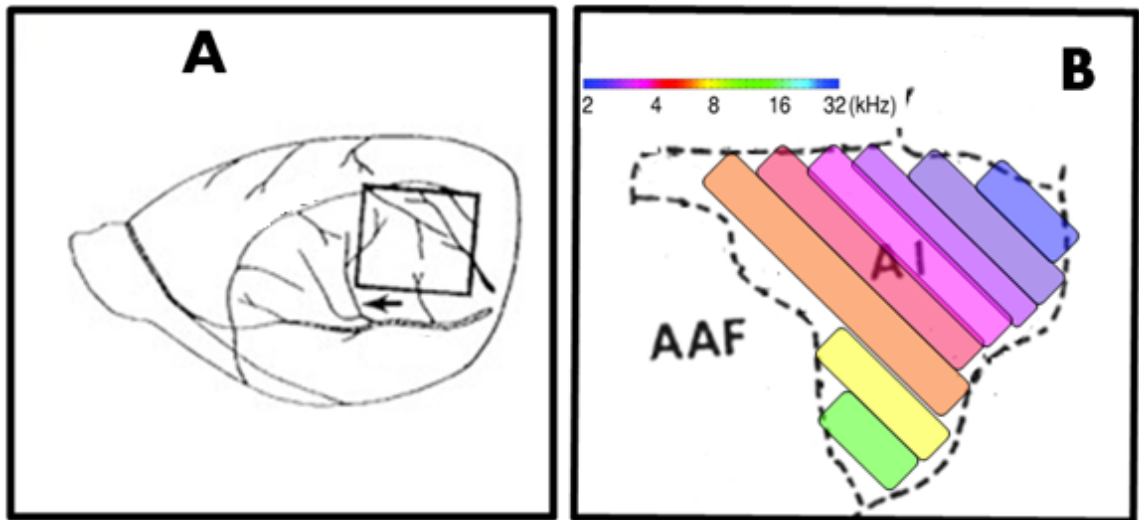
Figure 2: A and B represent the auditory cortex in the rat. B shows a representation of the tonotopicorganization in the primary auditory cortex AI (modified from data in Kalatsky et al., 2005). AAF—Anterior Auditory Field; AI-Primary auditory cortex.

The type of neuroplasticity associated with a decrease or removal of stimulation has been investigated following cochlear hearing loss or nerve injury. Deprivation-induced plasticity and its effects on how neurons process sound frequency have been studied extensively in animal models and also in humans. Peripheral hearing loss is capable of inducing changes in the number and properties of central auditory system neurons, and in neuronal network organization, including brain maps of sound frequency in humans and animal models. Areas of the central auditory system are organized based on the best frequency coding within a group of neurons into spatial maps, known as tonotopic maps (Langers & Dijk, 2011). Tonotopic maps in the auditory cortex have been identified in animal models and also in humans. In humans, fMRI studies have shown a fine scale tonotopic organization in the auditory cortex (Talavage, Ledden, Sereno, Rosen

4

& Dale, 1996; Kalatsky, Poley, Merzenich, Schreiner & Stryker, 2005) (see Figures 2 and 3).

The expression of auditory plasticity increases along the auditory pathways, between the cochlea and the cortex (Kamke, Brown & Irvine, 2003). Thus, the auditory cortex and the thalamus have a higher plasticity than the brainstem structures such as the inferior colliculus or cochlear nucleus. Furthermore, the higher-order auditory cortices have a higher capacity for plastic reorganisation than the primary auditory areas. However, recently, long-term plasticity has been shown to occur in the auditory brainstem (Tzounopoulos and Kraus, 2009).
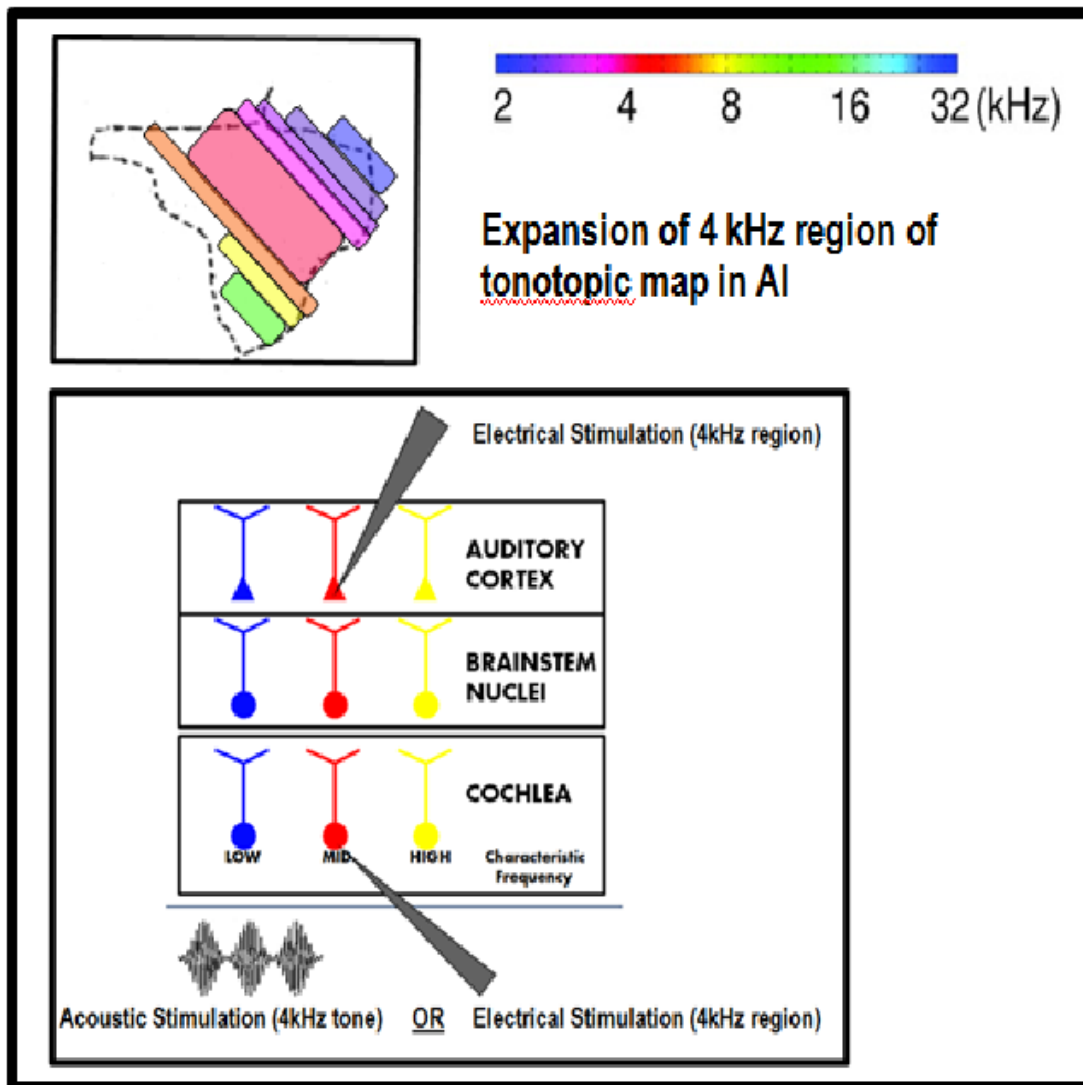
Figure 3: Altered patterns of stimulation can alter the tonotopic map in the auditory cortex. Stimulation of the cortex or the cochlea electrically as well as acoustic stimulation can change the tonotopic map, as shown for different animal models (Stanton and Harrison, 1996).

1.3   Human Auditory Neuroplasticity

In humans, auditory neuroplasticity has also been studied using auditory evoked potentials (AEPs) and other neuroimaging techniques such as fMRI. Secondary plasticity is induced when stimulation is reintroduced to the auditory system after damage, for example when sound or electrical stimuli are introduced in a hearing impaired individual using amplification devices or cochlear implants (Tremblay, 2003). Exposure to altered acoustic or electrical stimuli can induce physiological changes in adults, but the effects are usually greater during auditory development. This type of plasticity is often referred to as developmental plasticity and seen in children with early onset hearing loss. Although much less extensive, neuroplastic changes can also occur across the lifespan, following this early period of development.

Studies related to long-term plasticity and learning-related phenomena have focused on higher processing stages of the auditory system, such as the auditory cortex. Mechanisms of plasticity have traditionally been ascribed to higher-order sensory processing areas such as the cortex (Schreiner & Winer, 2007; Fritz, Elhitali, David & Shamma 2007; Weinberger 2007; Atiani, Elhilali,David, Fritz, & Shamma, 2009). Knowing that neurons in the auditory brainstem are specialized for generating fast, reliable and consistent electrical signals, it has been assumed that the synaptic relays of auditory brainstem nuclei are ill-suited to plasticity. Electrophysiological studies in humans have uncovered new forms of learning and behavior that are mediated by auditory brainstem structures. Using the complex auditory brainstem response, Skoe, Kraus and Ashley (2009) showed enhanced processing of the fundamental frequency of vocal emotions in musicians which suggests that auditory plasticity occurs following musical training.

6

1.4 Learning-Induced Auditory Neuroplasticity

In the above sections, the effects of environmental deprivation and altered stimulation on auditory neuroplasticity are described and also the role that plasticity plays in the restoration of central nervous system activity after neural injury or sensory cell damage. However, the plastic property of neurons plays an important role in memory and learning. Like other sensory systems, the auditory system is capable of long-term storage of information that represents past sensory events (Weinberger, 2004). To store information of past sensory events, the auditory system remains flexible to change in the acoustic environment through the lifespan.

In lab experiments, neuroplasticity can be induced by passive exposure to a change in the acoustic environment, or tied to different types of passive and active learning tasks. Changes in the acoustic environment will modify sensory experience and can result in learning-induced reorganisation within the central auditory nervous system when an actively learned a task that relates to this environmental change is also required. Passive conditioning, which is the neuroplasticity that occurs after an association between a sound stimulus and a positive outcome (e.g. food reward) or penalty (e.g. electric shock), is induced by a period of paired exposure, and leads to a passive form of learning in a conditioned subject. These neuroplasticity-inducing environmental triggers can be either a change in the stimulus level or a change in the stimulus pattern. The task requirements (passive exposure, or learning), type of the environmental trigger, duration of the exposure and age of the individual are some of the factors that can influence neuroplasticity. Evidence from the literature reports experience-dependent plasticity (Thiel, Friston, & Dolan, 2002), long-term plastic changes (Weinberger, Javid, & Lepan 1993; Weinberger, 2004), and short-term plastic changes (Pantev et al., 1998: Chowdhury & Suga, 2000) in brain frequency maps in animal models and within the human auditory system. In animals, neurophysiological recordings show that the physiological representation of sound alters with training exercises (Kraus & Disterhoft, 1982: Weinberger, Hopkins & Diamond, 1984).

1.5 Passive Exposure to Altered Patterns of Stimulation

Acoustic or electrical stimulation of the brain or auditory periphery can also induce this type of neuroplasticity. Plasticity which results in cortical reorganization has been found to be dependent on sensory input. Cortical receptive fields can be broadened or narrowed and response latency can increase or decrease based on the spatial and temporal pattern of sensory input (Moucha & Kilgard, 2006).

Training that engages a smaller area of the sensory epithelium results in enlarged input-specific cortical maps. Recanzone, Schreiner & Merzenich. (1993) found those owl monkeys who were trained for tone frequency discrimination had A1 neurons with smaller RFs and longer latency than untrained owl monkeys. On the contrary larger receptive fields (RF) and decreased response latencies were observed in monkeys who were trained to detect changes in the rate of tactile vibration compared to their control counterparts.

Sensory inputs that are correlated in time are expected to change cortical maps more than uncorrelated inputs. Chang and Merzenich (2003) showed that simultaneous stimulation of the auditory system with broadband noise resulted in increased cortical RF and degraded tonotopic maps. Sensory inputs correlated in time were also found to induce rapid plasticity (10s of milliseconds) in vivo and in vitro experiments (Tsodyks, 2002; Dan & Poo, 2004).

It is also established that distinct forms of plasticity are generated when nucleus basalis (NB) stimulation is paired with different sensory auditory input. NB stimulation combined with single frequency tone resulted in an expanded response map, decreased latency and modest RF broadening while NB stimulation with seven frequency tones caused RF narrowing, increased latency and prevented map reorganization (Kilgard&Merzenich, 1998). Kilgard and Merzenich (2002) demonstrated that: 1) expansion of the map is only possible when the sensory activation is focal, 2) RF size reduces then different frequency sensory input stimulates cochlea, 3) modulated stimuli increase while unmodulated stimuli decrease RF size.

Increased and decreased frequency correlation of the auditory sensory stimuli also leads to different types of plasticity (Pandya et al., 2005). When the auditory neurons are stimulated with non-overlapping tones (2 and 14 kHz) then it results in map segregation, decreased excitability and longer latencies of the activated neurons. These changes were not observed when NB stimulation and noise burst stimulate a large group of neurons.

1.6 Neuroplasticity Induced by Tetanic Stimulation

Tetanic stimulation (TS) is a high rate sequence of individual stimulation of a neuron or group of neurons. Depending on the nervous system under investigation, TS can be sensory, electrical, and magnetic. In humans, TS can induce changes in the auditory (Clapp et al., 2005; Mears & Spencer, 2012), visual (Tyler et al., 2005; Clapp et al., 2005; Clapp, Muthukumaraswamy, Hamm, Teyler & Kirk, 2006; Clapp, Hamm, Kirk & Teyler, 2012) and somato-sensory and motor systems (Ragert et al., 2003; Katyama & Rothwell, 2007; Esser et al., 2006; Huang, Chen, Rothwell & Wen., 2007). Table 1 summarizes the studies done to show the effect of TS on human visual cortex. Table 2 summarizes the studies done to show the effect of TS on human somato-sensory and motor cortices.

Teyler et al. (2005) were the first to report changes in human visual cortex using photic tetanus stimulus of 9 Hz. Visual evoked potentials (VEP) were measured in six adult males, pre and post visual stimuli of checkerboards as tetanic stimulation which were presented at equal times to the right and left visual field. After tetanic stimulation, VEPs were recorded at 15 minute intervals. Results showed that the amplitude of the VEP component (N1b) was significantly increased and lasted over one hour. They concluded non-invasive photic tetanic stimulation could induce plasticity or LTP-like changes in the human occipital cortex. Clapp et al. (2005) demonstrated reorganizational changes using functional magnetic resonance imaging techniques (fMRI). Blood oxygenation levels-dependent activation increased after photic tetanic stimulation (9 Hz) of checkerboard stimuli. Clapp et al. (2006) demonstrated the effect of photic tetanic stimulation on event-related desynchronization (ERD) of alpha rhythm. EEGs were measured in pre and post tetanic stimulation (9 Hz of checkerboard). ERD of alpha

9

rhythm was enhanced significantly after tetanic stimulation and lasted for an hour. Although this study was conducted with few participants, they provide a strong demonstration of the usefulness of tetanic stimulation to induce plasticity or LTP-like changes in the visual cortex of an intact human brain.

Table 1: Summary of different studies where human visual cortex was stimulated non-invasively by photic tetanic stimulation. NA: not applicable.

Technique	Stimulus	Tetanic Stimulation	ERP component tested	Main Results
VEP (Teyler et al., 2005)	Checkerboard to the left or right hemisphere	Photic tetanus, 9 Hz	N1b, P100, N1a, P2 &P3	Increased amplitude of N1b
fMRI (Clapp et al., 2005)	Checkerboard to the left or right hemisphere	Photic tetanus, 9 Hz	NA	Increased area of MRI activity
EEG (Clapp et al., 2006)	Checkerboard with target fixation centered on-screen	Photic tetanus, 9 Hz	NA	Increased desynchronizati-on alpha rhythm

Ragert et al. (2005) measured tactile discrimination thresholds in 12 right-handed healthy adults for pre and post-repetitive transcranial magnetic stimulation (rTMS) and coactivation condition. A combination of co-activation protocol (Godde, Stauffenberg, Spengler & Dinse, 2000) to the right index finger and rTMS (5 Hz) over left primary somatosensory cortex were applied as tetanic stimulation. Tactile discrimination

thresholds were improved after three hours of coactivation. The results of this study showed improvement of discrimination thresholds by 0.25mm when coactivation was applied alone, and with rTMS the discrimination thresholds were significantly improved. The authors suggested that the improvement in discrimination thresholds by tetanic stimulation was because of sufficient polarization to induce cortical changes.

Katayama et al. (2007) measured somatosensory evoked potentials (SEP) elicited by transcranial magnetic intermittent theta burst stimulation (iTBS) in the human primary sensory (S1) and motor (M1) cortices. SEPs were recorded pre and post 600-pulse, iTBS at an intensity of 80% motor threshold over S1 and M1 of the left hemisphere in eleven healthy individuals. After15 minutes of iTBS stimulation, amplitude of several components of SEP such as N20o-N20p, N20p-P25 and P25-N33 were enhanced area S1. No changes were reported in area M1 after iTBS tetanic stimulation. The findings of this study suggest that iTBS can induce changes in the primary sensory cortex resulting in the enhancement of synaptic response.

Cortical synaptic changes in the human somatosensory system were directly demonstrated by Esser et al. (2006) using a combination of rTMS and electroencephalogram (EEG). Cortical responses in left motor cortex were measured with a high density EEG (60channels) to a single pulse TMS before and after rTMS tetanic stimulation (5Hz, 1500pulses). After rTMS stimulation, EEG responses were significantly potentiated at latencies of 15-55 msec and potentiation was highest at the electrode site of bilateral premotor cortex.

Huang, Chen, Rothwell and Wen (2007) measured motor threshold in rest (RMT) and active (AMT) conditions in six healthy individuals. The amplitude of MEP was measured before and after intermittent and continuous TBS (iTBS/cTBS, 3pulses at 50Hz). The administration of N-methyl-D-aspartate (NMDA) antagonist (memantine) showed no effect on resting or active motor threshold, but it blocked the facilitatory effect of iTBS and the suppressive the effect of cTBS. They suggest that effects of TBS depend upon NMDA, which is a molecular unit controlling synaptic plasticity.

11

Table 2: Summary of different studies where human somato-sensory and motor cortices were stimulated by tetanic stimulation

Technique	Stimulus	Tetanic Stimulation	ERP Component tested	Main Results
TMS, tactile Co-activation (Ragert et al.	EMTr	50 TMS pulses (50 Hz)	NA	Improvement of discriminatio
TMS, EEG (Katyama et al., 2007)	EMTr	1500 TMS pulses (5 Hz)	Amplitude MEP	Increased EEG
TMS, MEP (Esser et al., 2006)	cTBS, rTBS	3 TMS pulses (50 Hz)	Amplitude MEP	Increased MEP
TMS, MEP (Huang et al., 2007)	cTBS, rTBS	3 TMS pulses (50 Hz)	Amplitude MEP	Changes in MEP effect

The motivation for this thesis was a study by Clapp et al. (2005) showing that tetanic stimulation can induce changes within the human auditory system as measured by auditory long latency responses. Auditory evoked potentials were recorded at 70 dB SPL in the baseline condition, tetanic stimulation condition and control condition from twenty two normal hearing young adults. During tetanic stimulation, 1 kHz tone pips (50 msec

12

duration) were presented binaurally with a rate of 13/sec for two minutes. This study revealed an increase in the N1 component of the long latency response after tetanic stimulation in the experimental group which lasted for an hour. They concluded that like electrical tetanic stimulation, presenting auditory tone pips at a rapid rate activates synapses in auditory cortex and induces synaptic plasticity like Long-term potentiation (LTP) in auditory system.

Mears and Spencer (2012) studied the effect of tetanic stimulation in individuals with schizophrenia. They used the same paradigm as Clapp et al. (2005). Experimental groups consisted of 17 individuals with schizophrenia (SZ) ranging in age from 21 to 54 years. The control group was age matched with 15 healthy adults (HC). They recorded event related potentials (ERPs) at 64 standard scalp sites and measured P50, N100 and P200 components. ERPs were elicited by three different tones; standard TS+ (1000, 45%), standard TS- (1500, 45%) and rare (400 Hz, 10%) tone bursts. Tetanic stimulation was the presentation of 1 kHz tone pips binaurally for 2 minutes at 70 dB SPL. After tetanic stimulation in both the groups, ERPs were recorded twice with a gap of twenty minutes. ERPs were different in schizophrenic patients and healthy adults in terms of latency and polarity. Also in both the groups, amplitude of ERP changed when elicited only by TS+ after tetanic stimulation. They concluded that these changes in ERPs show induction of plasticity and the input-specific characteristic of tetanic stimulation and were believed to be stimulus specific plasticity (SSP) induced by tetanic stimulation.

1.7 Auditory Long Latency Response (ALLR)

ALLR are event-related potentials occurring 50 to 300 msec following stimulus onset (McPherson and Starr, 1993). These auditory evoked potentials are evoked by the presentation of auditory stimuli and processed in or near the auditory cortex, and are referred to as cortical. This ALLR response is traditionally considered to be comprised of slow components (50-300 msec) and obligatory, exogenous potentials; meaning their latencies and amplitudes are primarily determined by temporal and physical characteristics of the stimulus, such as frequency or intensity.

The components of ALLR are labelled according to their latency and polarity at the vertex (Picton, Woods, Stuss, & Compbell, 1978). The first component in ALLR is characterized by an initial positive peak which is labelled as P1. The second is a negative peak and labelled as N1. The third peak is a positive peak which is labelled as P2. The fourth peak is a negative peak and labelled as N2. N2 might or might not be present even in normal hearing adults, so not much importance is given to N2.   The P1, N1 and P2 are predominantly exogenous potentials. N2 is not truly exogenous; it is affected by intrinsic factors of the subject such as attention and sleep (Ritter, Simmon & Vaughan, 1983). P1. N1 and P2 are typically recorded together in normal hearing individuals. When elicited together, the response is referred to as the P1-N1-P2 complex.

P1 is a vertex-positive voltage deflection that often occurs between 55 to 80 msec after sound onset. P1 usually has a small amplitude in adults (typically <2 µv), but the amplitude is large in young children. Neurons in the primary auditory cortex have been traditionally identified as generators of P1 peak (Simson, Vaughan & Ritter, 1977).

N1 appears as a negative peak that often occurs between 90 to 110 msec after sound onset. N1 latency can be longer in some cases depending on the complexity and duration of the stimuli used to elicit the response. Compared to P1, N1 has larger amplitude in adults (typically 2-5 µv, depending on stimulus parameters). N1 is known to have multiple generators in the primary and secondary auditory cortex (Makela & Hari, 1990). It is thought that this component reflects attention to sound arrival in the auditory cortex, the formation of a sensory memory of the sound stimulus in the auditory cortex and/or reading out of sensory information from the auditory cortex.

P2 is a positive peak that occurs approximately 180 msec after sound onset. It is relatively large in amplitude in adults (approx. 2-5 µv or more), but may be absent in young children. P2 is not as well understood as the P1 and N1 components, but it appears to have multiple generators in the primary auditory cortex, the secondary cortex and the mescencephalic reticular activating system (Naatanen & Picton, 1987).
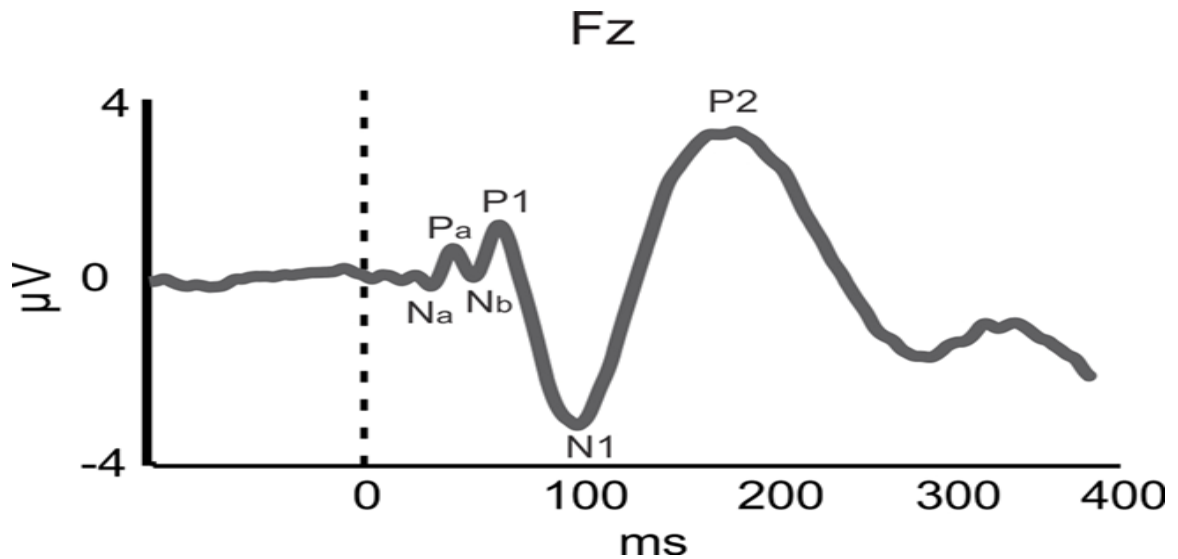
Figure 4: Sample ALLR waveform (adapted from information presented by Shahin, 2011)

1.8 Auditory Steady State Potential (ASSR)

ASSR is recorded from the human scalp in response to auditory stimuli presented at modulation rates between 1 and 200 Hz, or by periodic modulations of the amplitude and/or frequency of a continuous tone. ASSR is proved to be a reliable measure of frequency specific threshold estimation and assessing supra-threshold hearing (Picton, John, Dimitrijevic & Purcell, 2003). As a supra-threshold measure, ASSR has promise to measure auditory processing of a sound signal by systematically varying rates of amplitude and frequency modulation. Currently there is no literature investigating the effect of TS on the human auditory brainstem (Tzounopoulos & Kraus, 2009).

1.9 Rationale for the Thesis

It is well documented that tetanic stimulation can induce changes in human visual, somato-sensory and motor cortices. Changes that occur in these cortices are defined as a type of short-term synaptic plasticity which lasts for a time period ranging from seconds to hours (Tyler et al., 2005; Clapp et al., 2005; Clapp et al., 2006; Clapp, Hamm, Kirk & Teyler, 2012; Ragert et al., 2003; Katyama et al., 2007; Esser et. al., 2006; Huang, Chen,

Rothwell & Wen, 2007). This thesis was motivated by work by Clapp et al. (2005) who showed that TS stimulation, as in other sensory and motor modalities, can bring about short-term changes in the ALLR that represent a form of auditory cortical plasticity in humans (Clapp et al., 2006; Mears & Spencer, 2012). Currently, there are no reports that have estimated the effect of TS on the auditory brainstem. ASSR is a reliable tool to estimate the processing of amplitude modulated pure tone stimuli at the level of the brainstem. The following is a brief description of the AEPs that were used to study neuroplasticity in this thesis.

Research Questions and Specific Aims

The objective of this thesis is to replicate and extend current knowledge regarding tetanic acoustic stimulation and its effects on the human auditory system. The specific aims and research questions of this thesis were:

Research Question 1:

Hypothesis 1: The ALLR is changed by stimulus frequency specific tetanic stimulation

Specific Aim 1: To obtain 1 and 4 kHz ALLR before and after the presentation of TS to investigate the effect of a 1 kHz TS on the auditory cortex.

Specific Aim 2: To examine the stimulus specific characteristic of TS by comparing the ALLR obtained for 1 and 4 kHz.

Research Question 2:

Hypothesis 1: The ASSR is changed by stimulus frequency specific tetanic stimulation

Specific Aim 1: To obtain 1 and 4 kHz ASSR before and after the presentation of TS to investigate the effect of a 1 kHz TS on the auditory brainstem.

Specific Aim 2: To examine the stimulus specific characteristic of TS by comparing the ASSR obtained for 1 and 4 kHz.

Chapter 2

2   Methods

The basic procedure involved recording Auditory Evoked Potentials (AEPs) before and after tetanic acoustic stimulation: The AEPs measured were the Auditory Long Latency Response (ALLR) and the Auditory Steady State Response (ASSR) over one or two recording sessions. At the beginning of the first AEP recording session, following the completion of the consent form, the participants were asked to fill out a confidential questionnaire. Data was collected regarding age, gender, health information including current medications and history of hearing, neurologic and psychiatric disorders. A basic hearing assessment was then completed and included: (1) an inspection of the ear canal and ear drum of each ear using an otoscope, (2) a pure-tone audiogram for each ear using air conduction stimuli and (3) transient otoacoustic emissions (TEOAEs) for each ear.

The AEP data were acquired using Intelligent Hearing System Smart EP hardware and software to deliver sound stimuli and record and analyze EEG activity. The subjects were seated in a comfortable posture in a reclining chair, with the head fully supported to minimize noise during the recording session. The subjects were instructed to be alert but relaxed throughout the recording and to relax neck and jaw muscles. All recordings were performed in a double walled sound attenuating chamber. Subjects were allowed to read or watch a silent video. AEPS recorded were the ALLR and the ASSR, and these responses were recorded over 2 sessions when possible. An overview of recording procedures is shown in Figure 4.The TS was a 1 kHz tone burst delivered at 60 dB SL at a rate of 13/sec for a duration of 2 minutes.
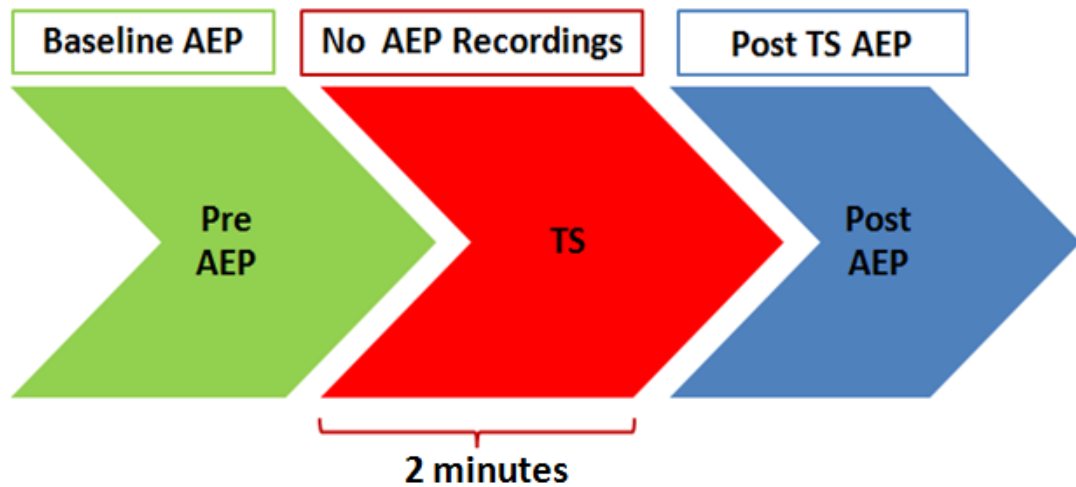
17

Figure 5: Overview of the auditory evoked potential (AEP) recording and TS Protocol. This protocol was repeated, once for the ALLR and for the ASSR.

2.1 Participants

Twelve subjects (23-57 years, 8 male and 4 female) with a mean age 31 years participated in this study. All the participants had normal hearing sensitivity (< 20 dB HL), normal middle ear functioning bilaterally and no participants reported a history of otologic, psychiatric or neurological disorder.

2.2 ALLR Stimuli and Recording Parameters

ALLRs were elicited with 1 kHz and 4 kHz binaural tone bursts of 50 msec duration (Blackman window) presented at a rate of 1.1/sec. ER-3A insert phones were used for presenting the stimulus. Tone burst were presented simultaneously at 60 dB SL at a probability ratio of 1:1 for 1 kHz and 4 kHz tone bursts of alternating polarity (P300 protocol of Intelligent Hearing System software. ALLRs were recorded by placing gold cup electrodes on the right ear mastoid (inverting electrode), Cz (vertex non-inverting electrode) and left ear mastoid (ground electrode). Inter-electrode impedances were less than 5 kΩ. Each ALLR recording consisted of 300 sweeps repeated up to 4 times. A gain

of 100,000 with a filter setting of 1–30 Hz and a 500 msec analysis window were used during recording and analysis.

2.3 ASSR Stimuli and Recording Parameters

In this thesis, ASSR was used to estimate auditory activity at the level of the brainstem, therefore a modulation rate of about 80 Hz was used for both the carrier frequencies as it is established that ASSR responses for modulation rates of >60 Hz are generated from auditory brainstem (Picton et al., 2003).

Surface electrodes record electrical activity from the right ear mastoid (inverting electrode), forehead (non-inverting electrode) and left ear mastoid (ground electrode) using gold cup electrodes. Inter-electrode impedance was less than 5 kΩ. The ASSR responses were amplified (100k) and filtered (30 – 300 Hz).

Mixed modulated stimuli were used with a depth of amplitude modulation and frequency modulation depth of 100% and 15%, respectively. ASSR was recorded for carrier frequencies of 1 kHz and 4 kHz (modulation frequency (fm) = 83Hz for 1000Hz, 93Hz for4 kHz). All ASSR measurements were carried out binaurally using ER-3 insert earphones, at an intensity of 70 dB SPL for all the participants.

Recording and detection of the ASSR was automated using the IHS proprietary software algorithm. The IHS method for ASSR identification uses the following criteria to identify the presence of a response: 1) signal to noise ratio of 6.13 dB at the modulation frequency (fm) compared to the 5 frequency bins on either side of fm, 2) Absolute amplitude of the response at the fm of at least 12.5nV.

2.4 Data Analyses

ALLR peaks were identified as present and the peaks were marked using the criteria used by Thornton (1975). According to this criteria each ALLR complex must contain three peaks beginning with a positive peak (P1, latency between 50 -80 msec), followed by a negative peak (N1, latency between 80-140 msec) and ending with a

positive peak (P2, latency between 140-250 msec). Peaks P1, N1 and P2 were identified and the latencies for each were measured. The N1-P2 amplitude was also recorded. Of the 12 subjects, 9 had ALLR responses present for all conditions and test frequencies.

The ASSR amplitudes were generated by the IHS software, and were also evaluated for the pre-TS and post-TS conditions for each carrier stimulus. Of the 12 subjects, nine had ASSR responses present for both the 1 kHz and 4 kHz carrier tones in both the pre-TS and post-TS conditions, in at least one ear (6 in one ear only; 3 in both ears). Data was analyzed for one ear of each subject (ear was randomly chosen for those with ASSRs present bilaterally).

As noted above, 9 of the 12 subjects had ALLR and ASSR responses present for all conditions and test frequencies; replicable responses could not be recorded for 3 subjects and their data was excluded from analyses. Separate repeated measures analyses of variance (ANOVA) were performed for the P1, N1, and P2 latency and for the N1-P2 amplitude of the ALLR. The repeated measures ANOVAs were performed to study the effects of TS on the ALLR and also the effects of the tone frequency (1 kHz or 4 kHz tone burst) used to evoke the ALLR. For each ALLR latency and amplitude component, a repeated measures ANOVA was performed to examine the effects of TS (TS factor: 2 levels, pre-TS and post-TS) stimulation and stimulus frequency (Frequency factor: 2 levels, 1 kHz and 4 kHz). A repeated measures ANOVA was performed to examine the effects of TS (TS factor: 2 levels, pre-TS and post-TS) stimulation and carrier frequency (Frequency factor: 2 levels, 1 kHz and 4 kHz).

The data collection for this thesis was done under the REB #18646E which was approved by the Research Ethics Board of Health Sciences, Western University.

Chapter 3

3   Results

The results of TS stimulation were examined for human AEPs to evaluate whether this TS can induce a rapid-onset neuroplasticity.   The effects on the ALLR were used to study whether neuroplastic changes occur in the auditory cortex while the 80 Hz ASSR was studied to determine if changes would occur in the auditory brainstem.

3.1   Effects of 1 kHz TS on the ALLR

3.1.1 Grand Average ALLR

Individual waveforms were averaged across all subjects for the pre-TS and post-TS conditions and separately for the1 kHz ALLR and the 4 kHz ALLR. Figure 5 shows the ALLR waveforms for the pre and post-TS conditions; result for the ALLR evoked by a 1 kHz tone burst are shown above, and for 4 kHz evoked ALLR, the results are shown below. The ALLR components, P1, N1 and P2 are readily apparent for all conditions.
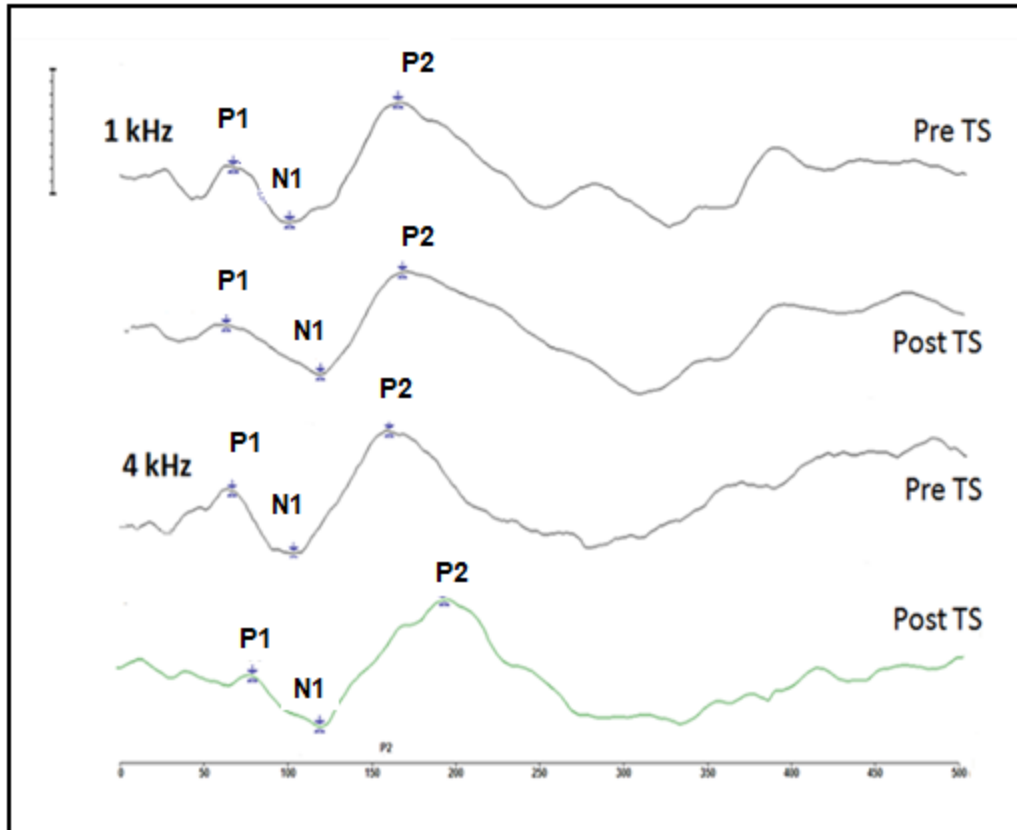
Figure 6: The grand average ALLR for 9 study subjects. Components of the ALLR are marked. ALLR waveforms are shown for both TS conditions (Pre and Post TS) and for the 1 kHz and 4 kHz tone burst stimuli used to evoke this AEP.

3.1.2 ALLR Component Analyses

3.1.2.1   P1 Latency

A Repeated Measures Analysis of Variance (RM ANOVA) was performed to determine the effect of tone and the effects of the high rate 1 kHz tetanic Stimulation (TS) on the pre-TS versus post-TS P1 latency.   The main effect of frequency [$F_{(1,8)}=10.78$, p=0.011]   and the main effect of high rate 1 kHz TS [$F_{(1,8)}=9.55$, p=0.015] on the P1 latency were significant. However, the interaction of frequency with TS [$F_{(1,8)}=0.21$, p=0.656] was not significant.   Figure 6 shows that the 1 kHz P1 latency was lower compared to the 4 kHz evoked P1 latency. The effect of TS resulted in a decrease in the P1 latency, and this occurred for both of the stimulating sound

frequencies. However, the 1 kHz TS effect was not frequency-specific - in other words there was no significant interaction and the reduction in P1 latency occurred for both the 1 kHz ALLR and the 4 kHz ALLR.
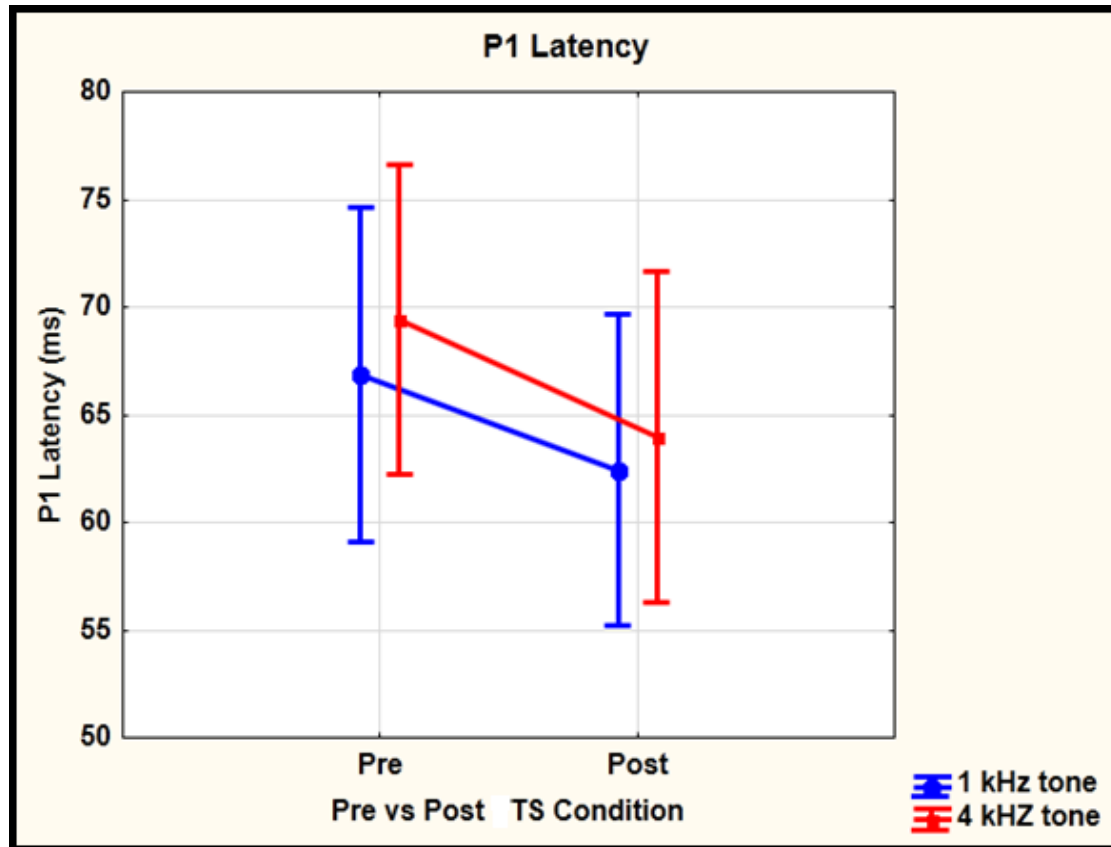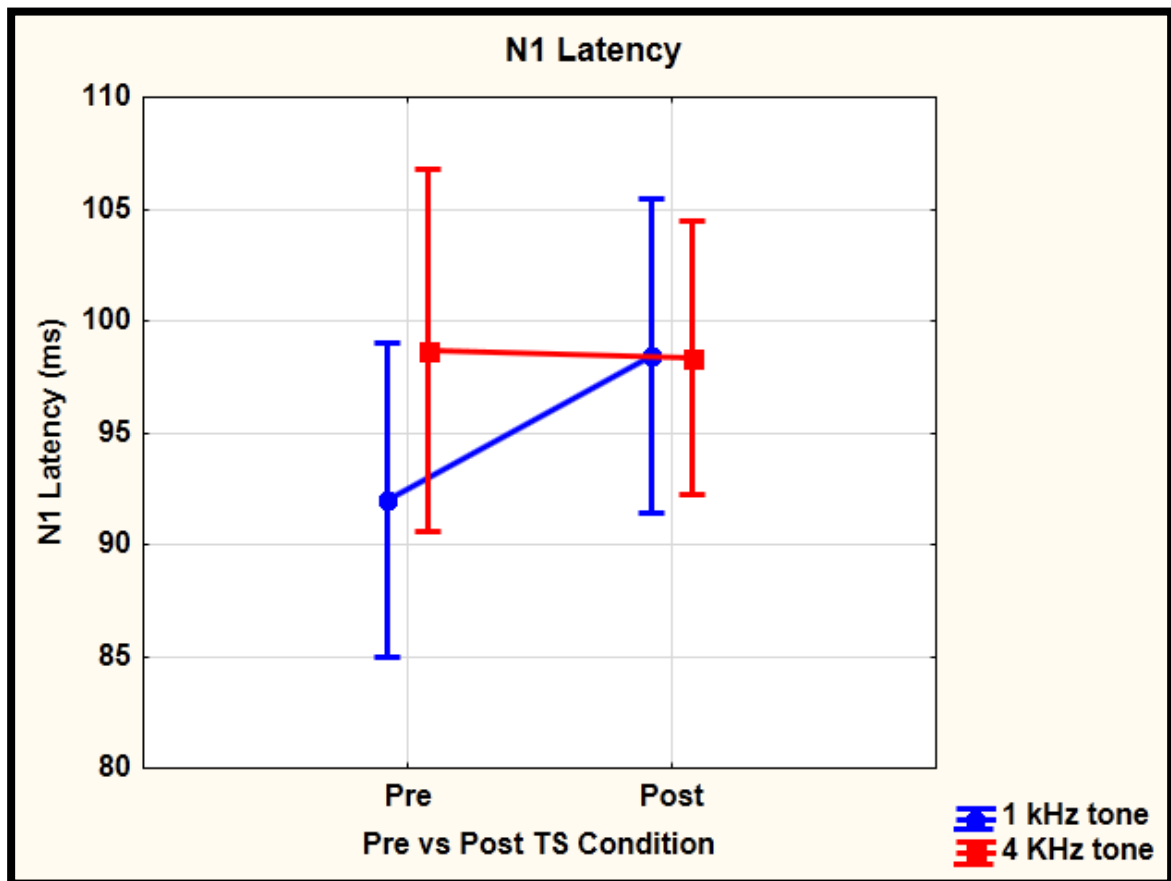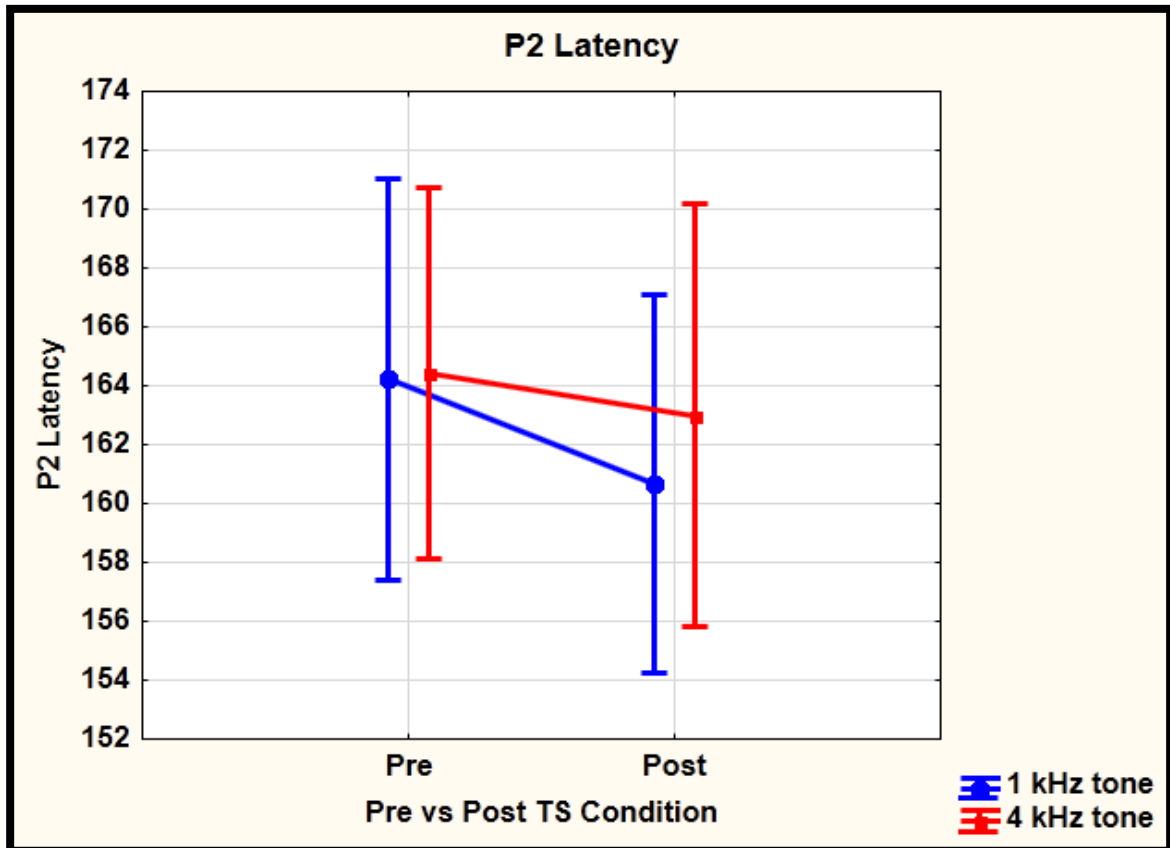

Figure 7: Mean P1 latency results for both TS conditions and for the 1 kHz and 4 kHz tone burst stimuli used to evoke the ALLR. The main effect of frequency [F(1,8)=10.78 , p=0.011] and the main effect of TS [F(1,8)=9.55 , p=0.015] on the P1 latency were significant.

3.1.2.2 N1 Latency

A Repeated Measures Analysis of Variance (RM ANOVA) was performed to determine the effect of tone and the effects of the high rate, 1 kHz Tetanic Stimulation (TS) on the pre-TS versus post-TS N1 latency. The main effect of frequency [F(1,8)=5.836 , p =0.042] was significant, and also the interaction of frequency with TS [F(1,8)=5.339, p=0.050] was significant. The main effect of high rate 1 kHz TS

[F(1,8)=1.480 , p=0.258] was not significant. These results and Figure7 shows that there was an interaction between the TTS condition and stimulus frequency used to evoke the ALLR. Figure X shows that the change in N1 latency occurred for the 1 kHz tone burst evoked ALLR only, and was not apparent for the 4 kHz evoked N1 latency component of the ALLR. The N1 latency evoked by the 1 kHz tone burst was prolonged, while no change was apparent for the 4 kHz evoked ALLR N1 latency.
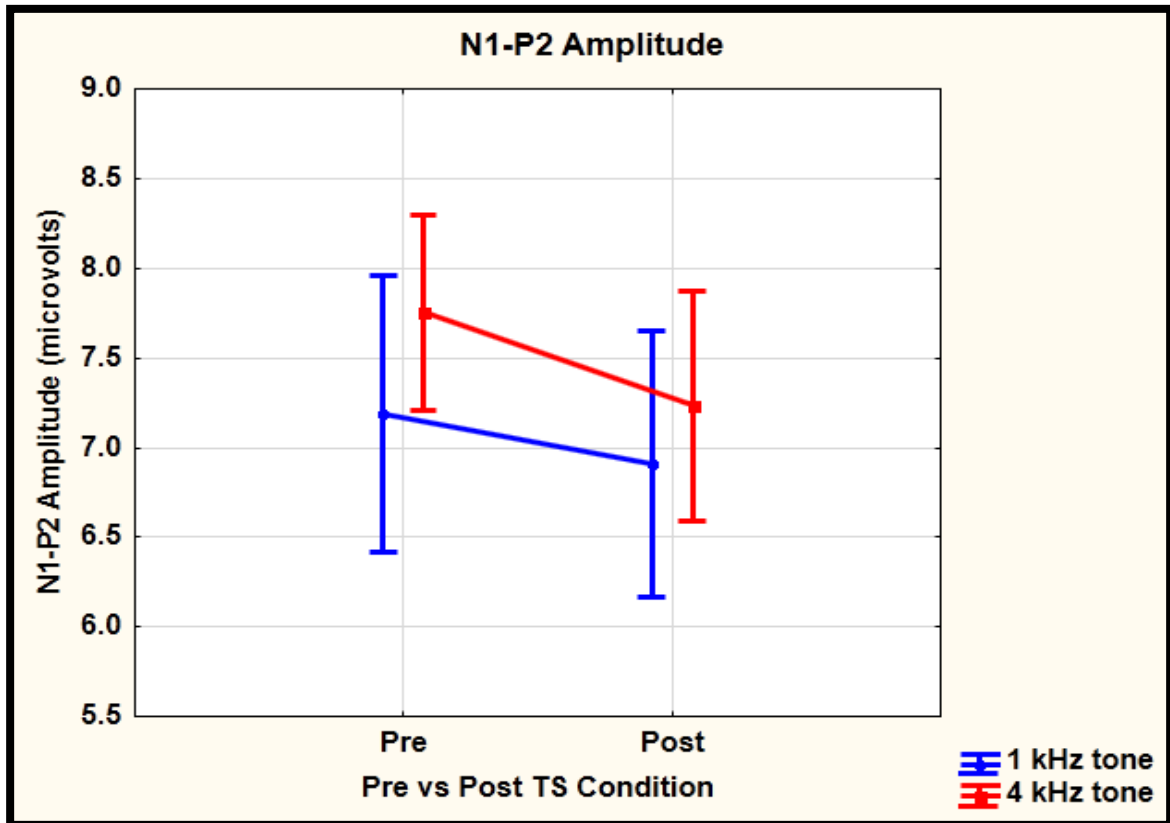

Figure 8: Mean N1 latency results for both TS conditions and for the 1 kHz and 4 kHz tone burst stimuli used to evoke the ALLR. The main effect of Frequency [F(1,8)=5.836 , p =0.042] was significant. The interaction of Frequency with TS [F(1,8)=5.339, p=0.050] was significant.

3.1.2.3 P2 Latency

A Repeated Measures Analysis of Variance (RM ANOVA) was performed to determine the effect of tone and the effects of the high rate, 1 kHz Tetanic Stimulation (TS) on the pre-TS versus post-TS P2 latency. The main effect of high rate TS $[F(1,8)=5.696$, p $=0.044]$ was significant. However, the main effect of tone $[F(1,8)=1.620$, p$=0.239]$ was not significant, and the interaction of frequency with TS $[F(1,8)=10.03$, p $=0.477]$ was not significant. These results and Figure 8 show that the change in the P2 latency was significant but similar and induced a slight reduction in the P2 latency, which occurred for both of the stimuli, 1 kHz and 4 kHz, used to evoked the ALLR.
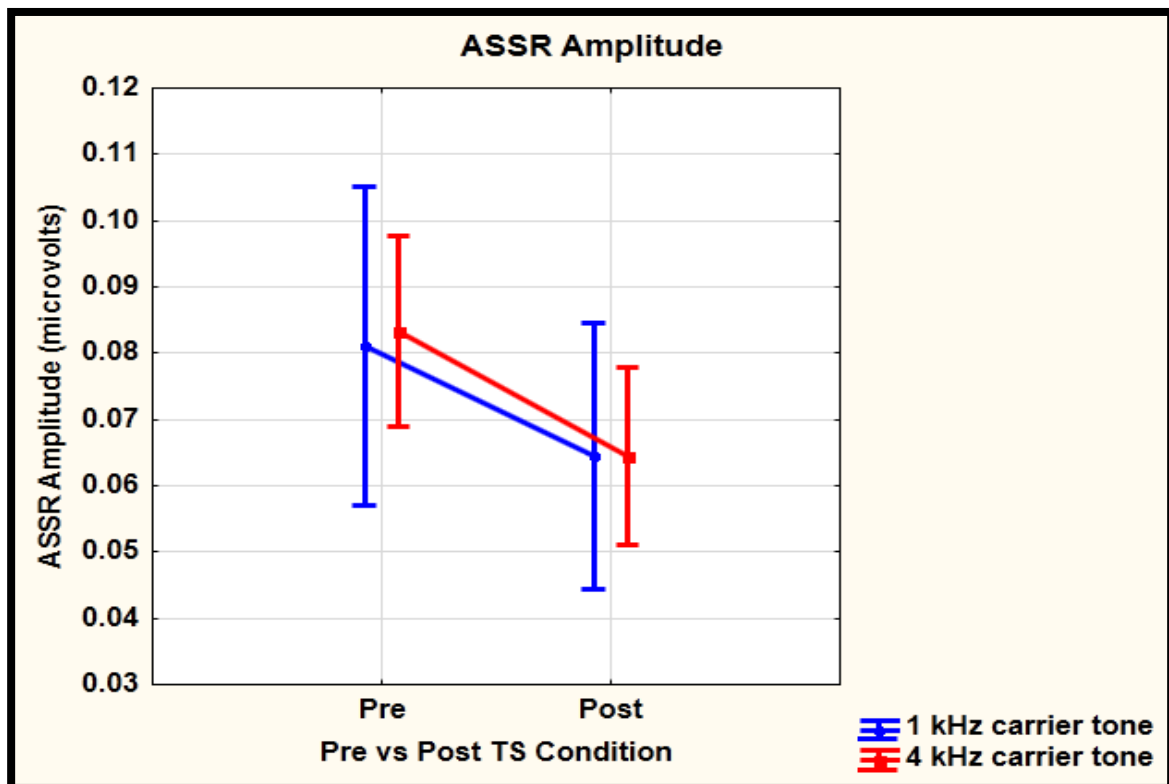

Figure 9: Mean P2 latency results for both TS conditions and for the 1 kHz and 4 kHz tone burst stimuli used to evoke the ALLR. The main effect of TS [F(1,8)=5.696 , p =0.044] was significant.

25

3.1.2.4   N1-P2 Amplitude

A Repeated Measures Analysis of Variance (RM ANOVA) was performed to determine the effect of tone and the effects of the high rate 1 kHz Tetanic Stimulation (TS) on the pre-TS versus post-TS N1-P2 amplitude. The main effect of tone frequency [$F(1,8)=10.40$, $p=0.012$] on the N1-P2 amplitude was significant. These results and Figure 9 show that the N1-P2 amplitude was greater when the ALLR was evoked by a 4 kHz tone compared to a 1 kHz tone. However, the main effect of high rate TS [$F(1,8)=3.99$, $p =0.81$]   was not significant and the interaction of frequency with TS [$F(1,8)=2.69$, $p =0.140$] was also not significant. These results indicate that TS had no significant effect on the N1-P2 amplitude.

Figure 10: Mean N1-P2 amplitude results for both TS conditions and for the 1 kHz and 4 kHz tone burst stimuli used to evoke the ALLR. The main effect of Frequency [$F(1,8)=10.40$, $p=0.012$] on the N1-P2 amplitude was significant

3.2 Effects of 1 kHz TS on the ASSR Amplitude

A Repeated Measures Analysis of Variance (RM ANOVA) was performed to determine the effect of ASSR carrier frequency and the effects of the high rate, 1 kHz Tetanic Stimulation (TS) on the pre-TS versus post-TS ASSR amplitude. The main effect of high rate 1 kHz TS [$F(1,8)=10.81$, $p=0.011$] was significant and Figure 10 shows that the ASSR amplitude was reduced in the post-TS condition compared to the baseline pre-TS condition. However, the main effect of carrier frequency [$F(1,8)=0.06$, $p=0.816$] was not significant and there was no significant interaction effect of frequency with TS [$F(1,8)=0.12$, $p=0.738$] . These results suggest that TS did induce a reduction in the ASSR amplitude, but there was no frequency specific effect of the 1 kHz TS stimulation on the ASSR response amplitude associated with the different carrier tone stimuli (1 kHz and 4 kHz) used to generate the ASSR.

Figure 11: Mean ASSR amplitude results for both TS conditions and for the 1 kHz and 4 kHz carrier tone stimuli used to evoke the ALLR. The main effect of TS [$F(1,8)=10.81$, $p=0.011$] was significant.

Chapter 4

4   Discussion

This thesis consisted of two separate experiments in which the effect of TS on the auditory brainstem and auditory cortex were observed. For the ALLR experiment, results were obtained for 9 of the 12 subjects, and the effect of TS was studied for the following components; latency of P1, N1 and P2, and the N1-P2 amplitude.   ALLR was recorded for 1000 and 4 kHz carrier tones both before and after TS.   TS did induce a change for some ALLR components but was not frequency-specific.   Also, the effects of TS occurred for the ALLR latency rather than the amplitude features of this AEP.

Of the 12 subjects who participated in the study, 80 Hz ASSR data was obtained for 9 subjects, providing information about the effects of TS on the auditory brainstem. In this experiment, the 80 Hz ASSR was completed at carrier frequencies of 1000 and 4 kHz in all the participants before and after high rate 1 kHz TS. The ASSR amplitude at both 1 kHz and 4 kHz carrier tones was reduced following the short period of TTS. The results of this experiment suggest that TS can induce changes in the human AEPs.   However, in general, the effects of TS on the ALLR components and on the ASSR amplitude were not specific to the 1 kHz frequency of high rate tetanic stimulation, and did not induce an enhancement as expected.

4.1   Tetanic Stimulation and ALLR

The neural generators of ALLR components are located within the auditory cortex (Martin, Tremblay & Stapells, 2007). The hippocampus, planum temporal and lateral temporal cortex are recognized as possible sites that contribute to the ALLR peak P1 generation. The N1 component of the ALLR also has multiple generators, located in the primary and secondary auditory cortex which include the superior portion of the temporal lobe and superior temporal gyrus. Generators of the P2 component of ALLR are less clear. Heschl's gyrus is supposed to be mainly responsible for generating P2 component.

Tonotopic maps of auditory frequency occur throughout the central auditory system, including in the auditory cortex (Morrel, Garraghty & Kaas, 1993; Talavage, Ledden, Sereno, Rosen & Dale, 1996), and therefore stimuli of different frequency stimulate separate neurons within these central auditory nuclei and in primary auditory cortex. It is well known that plastic changes occur in the auditory cortex following a period of deprivation and/or altered stimulation. These changes can involve alternations in tonotopic cortical map reorganization, receptive field size, neuronal firing rate and temporal precision (Moucha and Kilgard, 2006). The results of Clapp et al. (2005, 2006) supported the work in animal models, and suggested that a short duration, high rate TS can cause a rapid form of neuroplasticity in human auditory cortex when evoked by a 1 kHz tone burst. Although this neuroplastic change was observed for the 1 kHz tone-evoked ALLR and therefore matched the frequency of the TS, in these experiments by Clapp et al. (2005), no other sound frequencies of stimulation were tested.

In this thesis, the frequency specific effects of the 1 kHz TS were studied and indicate that this stimulation affects ALLR component latencies, but not the N1-P2 amplitude. These TS effects were not frequency-specific in the cortex, and may suggest a broad effect within the auditory cortex that was not limited to the TS frequency. For the P1 and P2 ALLR components, this 1 kHz TS stimulation affected both the 1 kHz and the 4 kHz tone evoked ALLR latencies. For the N1 latency the effect was opposite, causing a prolonged latency, and for this component only, the effect was specific to 1 kHz. These results suggest that the effects of TS may be different for different neural generators in the auditory cortex.

For the N1-P2 amplitude, no significant change was found as a result of the TS stimulation used in this study. The results of Clapp et al. (2005, 2006) suggest an enhancement of activity in the auditory cortex of humans following a 1 kHz TS, as shown by measurement of the ALLR and fMRI. Clapp et al. (2005) found an increase in the N1 amplitude elicited by a 1 kHz tone after high rate 1 kHz TS, a stimulation method similar to the one used in this study. From these neuroimaging studies, Clapp and colleagues suggest that LTP mechanisms occur at the synapses of neurons within the auditory cortex of humans and are responsible for neuroplastic changes. These author report no changes

in the latency of the N1 or other ALLR components, in contrast to the results of this thesis.

4.2 Tetanic Stimulation and the ASSR

The 80 Hz ASSR is generated primarily by the activity of the nuclei in the auditory brainstem; the superior olivary complex, inferior colliculus, and cochlear nucleus (Cone-Wesson, Dowell, Tomolin, Rance & Ming, 2002; Herdman et al., 2002; Picton, Jojn, Dimitrijevic & Purcell, 2003). We recorded the 80 Hz ASSR before and after TS to investigate the effect of TS on the auditory brainstem. TS is thought to induce LTP in neural synapses in humans (Clapp et al., 2005; 2006; Mears and Spencer, 2012). However, these studies have reported the effects of TS only at the level of cortical neurons. There are no reports of neuroplasticity at the auditory brainstem level following TS in humans. The results of this thesis suggest that a 1 kHz TS does induce a reduction in ASSR amplitude for both the 1 and 4 kHz carrier frequencies. This indicates that TS is able to induce a change at the level of the auditory brainstem. However, reduced amplitude may reflect a temporary change and be associated with a variety of possible mechanisms such as temporary neural fatigue, neurotransmitter depletion or altered patterns of inhibition.

Experiments done to investigate auditory plasticity have mainly focused on the auditory cortex (Clapp et al., 2005; 2006; Mears and Spencer, 2012; Schreiner and Winer, Weinberger, 2007). This is because it was believed that neural synapses of the auditory brainstem are not appropriate for plastic changes, as these nuclei are specialized for generating fast, reliable, and consistent electrical signals (Tzounopoulos and Kraus, 2009). However, there are studies that now support the possibility of plastic changes at the auditory brainstem level. In one of the first experiments to investigate plasticity at the level of auditory brainstem, Krishan, Xu, Gandour and Cariani (2005), found increased representation of pitch in the auditory brainstem of tonal speaking individuals which indicate that language experience affects the auditory brainstem processing. Alteration in the activity of the auditory brainstem has also been seen following music experience.

Strait, Skoe, Kraus and Ashley (2009) showed enhanced processing of the fundamental frequency in vocal musicians.

4.3 Conclusions

The experiments in this thesis show that TS does induce changes at the level of auditory cortex and brainstem. In human adults the effects of TS on the brain can be recorded noninvasively and show a reduced response amplitude, regardless of the carrier tone stimulation frequency, for the brainstem ASSR and also for TS-induced cortical changes using the ALLR. The effects are, however, different from those reported by Clapp et al. (2005; 2006), with changes in latency rather than amplitude of the ALLR. A common interpretation of these findings is that tetanic stimulation-related changes in the ALLR represent LTP with improved representation of the TS stimulus frequency, which may contribute to improved auditory processing and possibly perception. Other studies of TS that use different measures of auditory function at the level of auditory cortex and brainstem should be used to further investigate the short-term auditory neuroplasticity and perceptual changes.

The experiments in the thesis have several differences and limitations that may explain the contrast in results between those reported here and those of Clapp et al. (2005; 2006). Clapp and colleagues used a different recording technique with high impedance electrodes and multiple electrode recording sites. The experiments in this thesis did not include a non-TS control condition. Clapp et al. (2005) also included a control group who did not receive the TS. In this thesis, a silent control condition in a control group was replaced by a design in which the frequency-specific feature of the TS effect was studied. The persistence of the TS effect on human AEPSs was also not studied in this thesis, although Clapp et al. (2005) report enhanced N1 amplitude for at least one hour post-TS. Clapp et al. (2005; 2006) interpret their results to mean that the 1 kHz TS has an LTP-like induction effect, which should be specific to the region of cortex stimulated by the 1 kHz TS tone. However, this was not tested by Clapp et al (2005; 2006); the results of the experiments reported in this thesis suggest that the changes induced by TS are not limited to specific frequency regions of the auditory brainstem or

cortex that should be affected by the 1 kHz TS. Future experiments are needed to further explore this possibility.

This thesis is among one of very few investigations studying the effects of TS in normal hearing individuals. Through this study we wanted to measure short-term induced plasticity in the primary auditory cortex of normal hearing individuals as it is may be related to human auditory learning and memory abilities. This TS method may be a useful objective method to assess the extent to which humans learn and remember new acoustic stimuli. For this reason, the TS method could be useful for clinical assessment if TS exposure reflects the presence of auditory and learning problems in a clinical population, or for rehabilitation is TS facilitates auditory communication abilities. Plasticity of the auditory cortex in individuals with neurological disorders (e.g., schizophrenia, Alzheimer's disease) could also be measured using this AEP approach combined with TS. This type of non-invasive method of cortical plasticity measurement would provide a new and clinical feasible direction towards the diagnosis of auditory learning and memory deficits in patients with psychiatric or learning related disorders.

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Appendix: ALLR and ASSR data for each subject

Subject: 20127B02

42

20127B02
N1-P2 Amplitude

20127B02
ASSR Amplitude

Subject: 20126G01

45

20126G01
ASSR Amplitude

Subject: 20128C01

20128C01
P2 Latency

20128C01
N1-P2 Amplitude

20128C01
ASSR Amplitude

Subject: 20127L01

20127L01
P1 Latency

50

Subject: 20127E02

**20127E02
P2 Latency**

**20127E02
N1-P2 Amplitude**

**20127E02
ASSR Amplitude**

Subject: 20126X01

**20126X01
P1 Latency**

20126X01
N1 Latency

20126X01
P2 Latency

20126X01
N1-P2 Amplitude

20126X01
ASSR Amplitude

Subject: 20127M02

20127M02
P2 Latency

20127M02
N1-P2 Amplitude

20127M02
ASSR Amplitude

Subject: 20128L01

20128L01
P1 Latency

20128L01
N1 Latency

20128L01
P2 Latency

20128L01
N1-P2 Amplitude

20128L01
ASSR Amplitude

Subject: 20128K01

20128K01
ASSR Amplitude

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