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Induction of LTP in the human auditory cortex by sensory stimulation

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Abstract

High-frequency, repetitive, auditory stimulation was used to determine whether induction of a long-lasting increase of the human auditory evoked potential (AEP) was possible. Recording non-invasively with electroencephalogram scalp electrodes, stable increases in amplitude were observed in the N1 component of the AEP, which is thought to reflect activity within auditory cortex (N1). The increase was maintained over an hour and was shown to be independent of alterations in the state of arousal. This is the first demonstration of the induction of long-lasting plastic changes in AEPs, and suggest that this represents the first direct demonstration of long-term potentiation in the auditory cortex of normal, intact humans.

Introduction

The auditory system, like other sensory systems, is capable of long-term information storage of representations of past sensory events (Weinberger, 2004). In order to store information, the auditory system must have the ability to remain malleable in the face of changing environmental experience. Experience-dependent plasticity has been demonstrated within the human auditory system (Bakin & Weinberger, 1996; Morris *et al*., 1998; Thiel *et al*., 2002). A recent positron-emission tomography study found a modulation of tonotopic neural responses in a conditioning paradigm in which an aversive white noise burst was paired with one of two different frequency tones (Morris *et al*., 1998). As well as investigating short-term plastic changes (Pantev *et al*., 1998, 1999; Chowdhury & Suga, 2000; Jancke *et al*., 2001), recent research has also focused on long-term plastic changes within the auditory system (Weinberger *et al*., 1993; Jancke *et al*., 2001; Weinberger, 2004). Jancke *et al*. (2001), using functional magnetic resonance imaging, found that cortical representations change as one learns a skill. These researchers trained subjects to discriminate tones of very similar frequency, 950, 952, 954 and 958 Hz. The subjects who were able consistently to discriminate the tones after a week of training showed a difference in their blood oxygen-level-dependent response in comparison with before the training, thus indicating a plastic change had occurred. Long-term plastic changes in auditory cortex have been previously suggested to underlie modulations of the mismatch negativity (MMN) amplitude after the learning of tone sequence discrimination (Gottselig *et al*., 2004), non-speech sounds (Kujala *et al*., 2003) and in foreign language acquisition (Cheour *et al*., 2002). These results suggest that the human auditory system can remain plastic into adulthood.

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Further support of this notion comes from animal studies of auditory cortex, such as receptive field modifications (Bakin & Weinberger, 1990; Weinberger *et al*., 1993; Kisley & Gerstein, 2001), alterations of tonotopic maps (Recanzone *et al*., 1993) and associative learning (Edeline *et al*., 1993). Long-term potentiation (LTP) has been suggested as the underlying mechanism of these examples of synaptic plasticity (Kudoh & Shibuki, 1997), and has been readily shown in the auditory system of experimental animals (Gerren & Weinberger, 1983; Kudoh & Shibuki, 1994, 1996, 1997). LTP is an enduring increase in synaptic efficacy, and is the principal candidate mechanism underlying learning and memory (Bliss & Lomo, 1973; Martin *et al*., 2000; Malenka, 2003), and experience-dependent neuroplasticity in general. It has been studied extensively at the cellular level in laboratory animals (Malenka & Nicoll, 1999; Malenka, 2003) but has not been directly demonstrated in the intact human brain. It has, however, been documented in human tissue obtained from surgical patients (Chen *et al*., 1996; Beck *et al*., 2000) where it displays properties identical to those seen in non-human preparations.

In a previous study, we used rapidly presented checkerboards to induce a plastic change within the visual system that lasted over an hour (Teyler *et al*., 2005). In the current experiment we used the tetanic presentation of a tone pip to induce non-invasively a similar LTP-like change within the human auditory cortex.

Materials and methods

Subjects

Twenty-two male, right-handed students and staff at the University of Auckland participated in this experiment. Informed consent was obtained from each participant. All procedures were approved by the University of Auckland Human Subjects Ethics Committee.

The mean age of the subjects was 28.62 years (range 21–41 years). All subjects reported normal hearing and no history of psychiatric or neurological disease.

Stimuli and apparatus

Sinusoidal tones of 1000 Hz were generated using LabVIEW v6.0i (National Instruments). LabVIEW, and its associated National Instruments hardware, was housed in a Pentium III PC. Each sinusoid was constructed digitally using a sine wave function at 44 000 samples/s. The tone was 50 ms in duration, and therefore consisted of 2200 samples. The tone was subsequently passed through a Hanning (cos2) window, which imparted 0.005-s onset and offset ramps to the waveform. Subjects reported none of the audible clicks or thumps associated with rectangular windows, and scrutiny of the waveform's spectrum gave no evidence of unwanted transients or excessive side lobes. After waveforms were generated to the correct specifications, digital-to-analog conversion was performed using a National Instruments PCI-6052E card. The resulting analog waveform was then channeled to a National Instruments BNC-2090 shielded BNC adapter chassis mounted external to the PC. The waveform was then split and each division directed to a pair of Tucker-Davis Technologies (TDT) System 3 Programmable Attenuators (PA5). The PA5 was connected to the Pentium III PC through a USB port and communicated with LabVIEW using Active-X software driver components. The attenuators reduced the sinusoids to within the audible range, and once attenuated, a pair of 70-dB SPL sinusoids were routed through a headphone buffer (TDT HB7) on the way to the observer's ear inserts (ER2: Etymotic Research). Throughout the experiment the observers sat passively in a modular shielded enclosure (Belling-Lee L3000). Electroencephalogram (EEG) recordings were carried out in an electrically shielded room using Electrical Geodesics Inc. 128-channel Ag/AgCl electrode nets (Tucker, 1993). Signals were acquired and processed by Net Station (Version 2.0). EEG signal was recorded continuously (250 Hz sampling rate; 0.1–100 Hz analog bandpass) with Electrical Geodesics Inc. amplifiers (200-MΩ input impedance). Electrode impedances were kept below 40 kΩ, an acceptable level for this system (Ferree *et al*., 2001). A common vertex (C_z) reference was used in the EEG acquisition, and re-referenced offline to an average reference.

Experimental procedure

Experiment 1

Subjects were run in an AAB_xA design in which they received two baseline blocks (A), an experimental block (B_x either tetanic-stimulation or control) and then a final baseline block (A). Six subjects received the Tetanus, and six were in the Control condition. During all periods of auditory stimulation, subjects were asked to maintain fixation on a cross in the centre of a monitor.

Baseline condition (A). One hundred and twenty one bursts were played binaurally with a variable interstimulus interval (ISI). The ISI between any two presentations of the tone was determined randomly with the constraint that the value fell within the range 1800–2600 ms.

Tetanic-stimulation condition (BT). A train of 1000-Hz tones were presented at a rate of approximately 13 per second (50-ms tones punctuated by 25-ms gaps) for 2 min. Subjects were then asked to sit for 1 min in complete silence to allow any aural ringing to dissipate. After a minute of silence, the experimenter signalled the subject and the final baseline recording was started.

Control condition (BC). Subjects were required to participate in a 3-min oddball discrimination task in which they were presented with a block of the baseline stimuli (1-kHz tone pips at 0.4 Hz) and were asked to count the presence of infrequent target tones (990 Hz), which were presented on average 10% of the time.

Experiment 2

A group of ten naïve subjects were tested in an extended version of the tetanic-stimulation condition of Experiment 1. To summarize, two blocks of low frequency baseline stimulation were followed by the auditory tetanus. Subjects received an immediate post-tetanus block of baseline stimulation to determine that LTP was obtained. Thereafter, subjects received a block of the baseline stimulation every 15 min to track the potentiated response out to 1 h post-tetanus. Between these blocks subjects sat in silence (watching silent cartoons or reading).

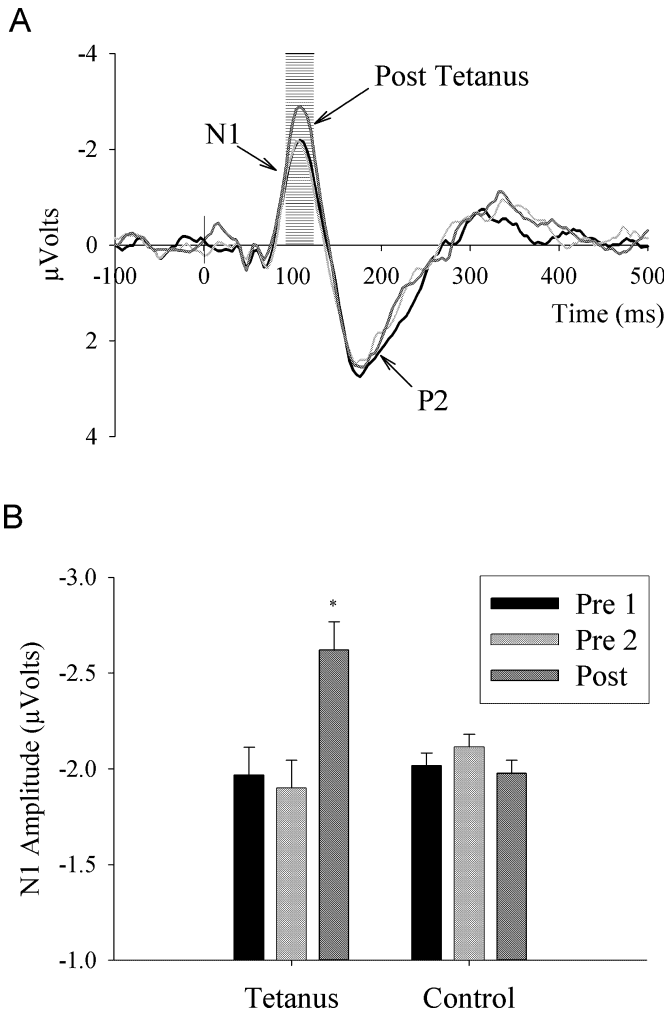

FIG. 1. Auditory tetanus induces LTP of the N1 component. (A) Group average auditory evoked potentials (AEP) to tone pip stimulation. The hatched section indicates the time window of interest. The light grey and black lines represent the two baseline blocks (pre-tetanus) and the dark grey line indicates the post-tetanus AEP. Note that the post-tetanus response is substantially larger than the two baseline blocks in our time window of interest (N1). (B) N1 amplitudes from Experiment 1. Group average N1 amplitudes are shown for the two pre-tetanus baseline periods, and the post-tetanus period. The data reveal that only the group of subjects who received an auditory tetanus had a significantly larger N1 amplitude. Error bars represent the standard error of the mean (SEM).

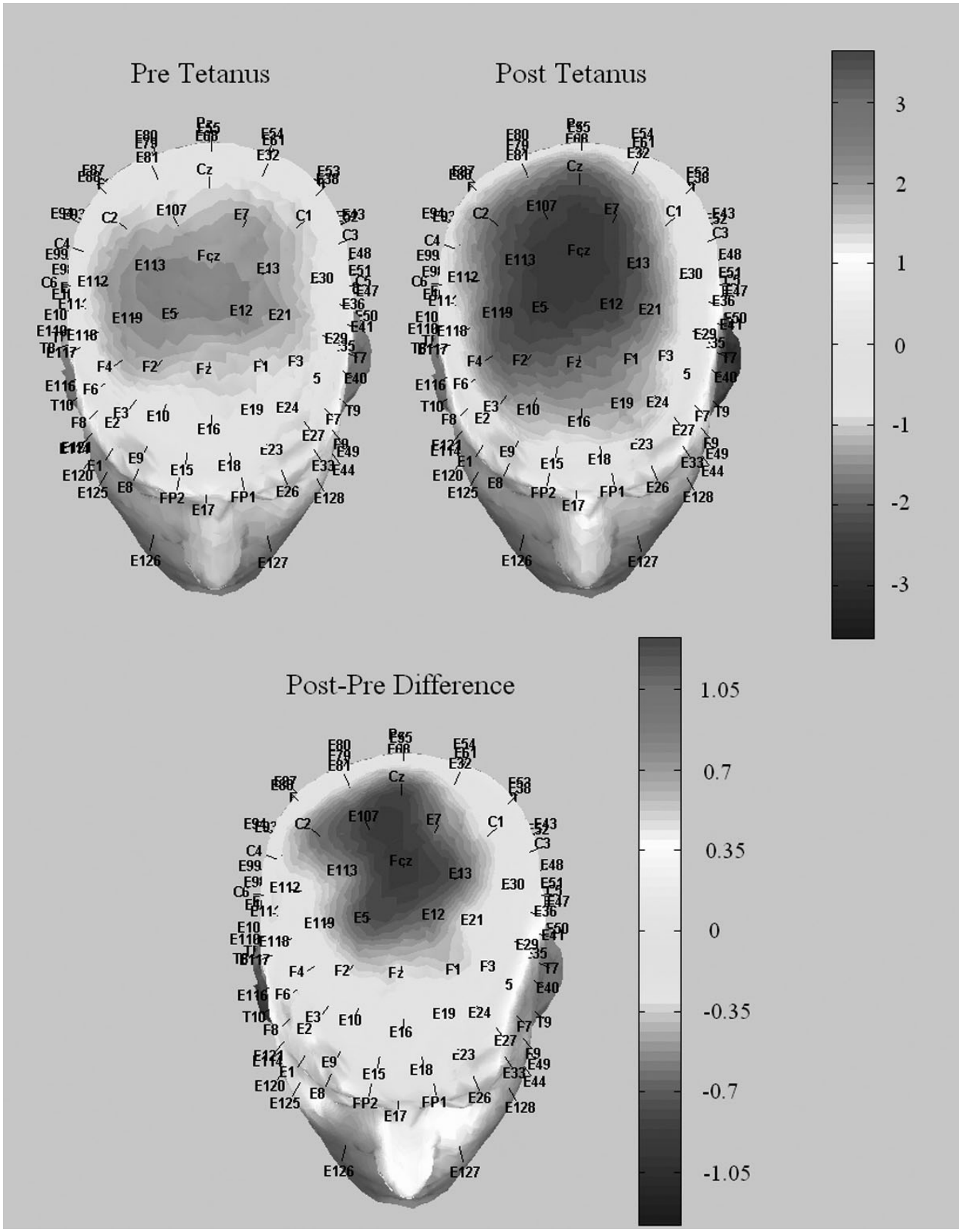

FIG. 2. Localization of potentiation. Grand averaged data showing the N1 (104–128 ms) distributions of pre- and post-tetanus conditions, as well as the difference between post- and pre-tetanus values.

Analysis

After completion of data collection, EEG files were segmented with respect to event markers into 600-ms epochs (including a 100-ms prestimulus baseline) during which ocular artefacts were removed from individual trial epochs (Jervis *et al.*, 1985). Event related potentials (ERPs) were subsequently re-referenced to the average reference. ERPs from individual subjects were combined to produce grand-averaged ERPs for each condition.

Using the grand-averaged data, the N1 peaked at 116 ms, and a time window was selected using 50% of this peak (104–128 ms). The eight electrodes at which the N1 amplitude was highest in the pre-tetanus condition were then averaged together over this time window (see Fig. 2). Using these parameters each individual's mean N1 voltage was calculated for each block for statistical analysis.

For Experiment 1 the mean voltage was then analysed in a two-way mixed-factor ANOVA with block and group as factors. Planned contrasts were used to analyse changes over block. Contrast 1 compared the two baseline blocks, whereas Contrast 2 compared the post-tetanus with the pre-tetanus blocks.

For Experiment 2 the mean voltage from the N1 time window was analysed in a one-way ANOVA. A planned contrast compared the first two blocks pre-tetanus with the post-tetanus blocks to test for the effect of the tetanus.

Results

Experiment 1: testing for LTP

In the control block, subjects' overall accuracy during the oddball task was 93.75% (7.5 out of 8).

The mean voltage was analysed in a two-way, mixed factor ANOVA, with block (three) as a within-subjects factor and group (control, tetanus) as a between-subjects factor. Planned contrasts were employed to examine the effect of block and its interaction with group. Contrast 1 compared blocks 1 and 2 (pre-tetanus), and Contrast 2 compared the pre-tetanus amplitude with block 3. Note, for the control group, the terms 'pre-' and 'post-' tetanus do not really apply as this group did not actually receive an auditory tetanus.

The main effect of block failed to reach significance ($F_{2,20} = 3.03$, $P = 0.07$) as did the main effect of group ($F_{1,10} < 1.0$). All main effects and interactions involving Contrast 1 failed to reach significance (all $F < 1.0$), but the planned Contrast 2 revealed that the amplitude in block 3 was significantly larger than during the two pre-conditions ($F_{1,20} = 6.06$, $P < 0.05$). There was a significant interaction between groups ($F_{2,20} = 5.21$, $P < 0.05$), and more importantly, this interaction was revealed in Contrast 2 ($F_{1,20} = 10.08$, $P < 0.01$), indicating the larger increase in the N1 amplitude from the pre-tetanus to the post-tetanus block was for the group which received the auditory tetanus (see Figs 1 and 2).

To explore this group interaction, both groups were analysed separately in a one-way ANOVA, using the same contrasts to explore the effect of block. For the control group, no effect of block was revealed ($F_{2,10} < 1.0$), nor did any of the contrasts reach significance ($F_{1,10} < 1.0$). However, analysis of the tetanus group demonstrated a main effect of block ($F_{2,10} = 6.41$, $P < 0.05$). Contrast 1 indicated no difference between the first two blocks ($F_{1,10} < 1.0$), whereas Contrast 2 indicated that the N1 amplitude was larger post-tetanus than pre-tetanus ($F_{1,10} = 12.72$, $P < 0.01$).

Both P50 and P200 were analysed similarly to the N1 and no significant differences were found.

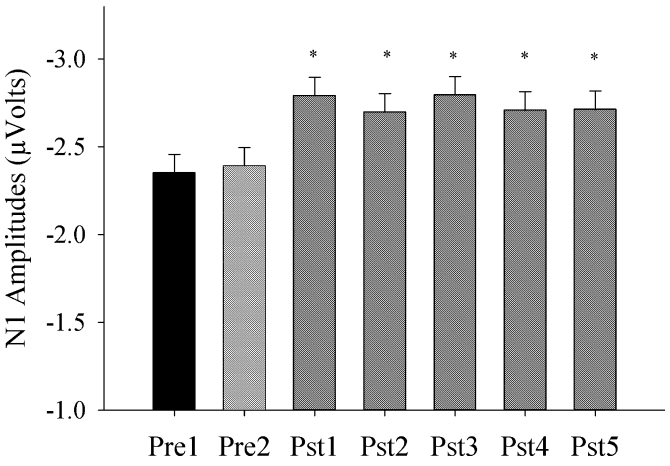

FIG. 3. N1 amplitudes over 1 h post-tetanus. Group average N1 amplitudes are plotted for the two pre-tetanus baseline periods, and the 1 h post-tetanus period. The potentiated response is maintained over the 1 h post-tetanus recording period. Error bars represent the SEM.

Experiment 2: the time course of LTP

In the second experiment, in which we tracked the time course of the potentiated auditory evoked potential (AEP), the results replicated Experiment 1 in that LTP was induced following the auditory tetanic-stimulation. The potentiated response was maintained for the 1-h post-tetanus period (see Fig. 3). A planned contrast comparing the baseline to the post-tetanus blocks (out to an hour) was significant (~120% of pre-tetanus levels, $F_{1,48} = 7.53$, $P < 0.01$) and accounted for 95.2% of the total variance. Examination of the residual variance after this contrast is accounted for indicates that no further comparisons can be supported (maximum $F_{1,48} = 0.38$, $P > 0.05$). These results reveal that over the hour post-tetanus there was no appreciable decrease in potentiation.

Discussion

Our results provide evidence that high-frequency, repetitive auditory stimulation can induce long-lasting plastic changes within the human auditory system. As we recorded non-invasively with scalp electrodes, any suggestions regarding the mechanism of these changes can only be speculative. It seems likely, however, that presenting tone pips at a rapid rate activates synapses within the auditory system in a manner similar to an electrical tetanic-stimulation, inducing changes within the auditory network akin to those seen in cellular studies of LTP. As the potentiation lasts for over 1 h, this further suggests that we have demonstrated LTP for the first time within intact human auditory cortex.

Previous animal studies have shown that stimulation at one set of synapses results in network changes further downstream. Heynen & Bear (2001) tetanized the lateral geniculate nucleus and recorded potentiation within the visual cortex. Using solely scalp recording electrodes, we are unable to specify the site where plastic changes are occurring within the auditory system, yet the potentiation of only the N1 component (see Fig. 2) suggests the primary and secondary auditory cortices are involved (Pantev *et al.*, 1995; Lutkenhoner & Steinstrater, 1998; Zouridakis *et al.*, 1998; Engelien *et al.*, 2000). Furthermore, the degree to which potentiation of the N1 is frequency specific cannot be determined from the present data. Past research has shown that the N1 and the MMN are tonotopically distributed (Yamamoto *et al.*, 1992; Tiitinen *et al.*, 1993; Woods *et al.*, 1993), and

thus it might be expected that potentiation would be limited to N1s evoked at, or near, the potentiated frequency. However, further experiments are required to determine if this is so.

It must be noted that past research has shown the N1 component can be modulated by attention (Woldorff & Hillyard, 1991). Thus, it is possible that our auditory tetanus may have enhanced the N1 amplitude through an increase in attention or arousal. However, the results from the demanding oddball discrimination task in our control condition (B_C) indicate that subjects were alert and attending to the tones (90% accuracy), and no change in the N1 amplitude resulted from performing this attention-demanding task. Furthermore, if different states of arousal accounted for the increase in N1 amplitude, we would expect variations or a decline during the 1-h post-tetanus period. However, we saw no discernible changes in the level of N1 potentiation in the five post-tetanus blocks in Experiment 2, again suggesting that the potentiation was independent of the state of arousal.

Our results demonstrate that sensory experience is sufficient to induce long-lasting changes in auditory cortex function. This has been supported by many studies which have shown the primary auditory system to be plastic, and to hold specific memory traces (Weinberger, 2004). In other sensory systems, repetitive sensory stimulation has been used to induce LTP. In a separate study, our group has shown that a block of quickly presented checkerboards can induce LTP within the visual cortex of humans, as recorded via EEG (Teyler *et al*., 2005). This potentiation has also been shown to last beyond an hour. Repetitive flashing has also been shown to induce LTP within retinotectal cells of tadpoles (Zhang *et al*., 2000). The present study indicates that the ability to induce LTP within human cortex using only the presentation of sensory stimuli can be shown in a different modality, namely the auditory system. Conceivably, such sensory-induced alterations in synaptic strength may underlie auditory cortex plasticity, including that involved in early language acquisition (Temple *et al*., 2003).

In summary, these results demonstrate that LTP, which is proposed as the cellular mechanism underlying long-term synaptic plasticity and memory, is a normal and readily induced synaptic modification in human sensory cortex and may underlie other examples of functional cortical plasticity. We also demonstrate that LTP induction can be studied non-invasively. This approach lends itself to the further study of the properties of LTP in humans and may have utility as a diagnostic and rehabilitation tool in neurodegenerative disorders.

Acknowledgements

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Abbreviations

AEP, auditory evoked potential; EEG, electroencephalogram; ISI, interstimulus interval; LTP, long-term potentiation; MMN, mismatch negativity.

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