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Research article

# Increased MMN amplitude following passive perceptual learning with LTP-like rapid stimulation

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ABSTRACT

An important feature of perception is plasticity, enabling the acquisition of new perceptual representations to facilitate responding to regular stimuli in the environment. The auditory system has shown capacity for plasticity into adulthood, allowing the perceptual discrimination abilities to be improved by training. It has been suggested that a certain form of passive learning using rapid sensory stimulation can lead to plasticity in the sensory cortex through mechanisms similar to long-term potentiation. Here we demonstrate using electroencephalography that brief rapid auditory stimulation (2 min, 13 Hz) with a sinusoidal tone (1025 Hz) led to increased discriminability of the stimulated tone from a standard tone (1000 Hz) as indexed by mismatch negativity event-related potential. This shows that perceptual learning with brief exposure can cause plastic changes similar to long-term training.

## 1. Introduction

Auditory system demonstrates extensive capacity for plastic changes, which supports its ability to acquire new distinctions between environmental sounds. Discrimination training leads to improvement in distinguishing sounds which previously were not perceived as distinct [1], indicating that learning leads to development of new auditory categories. This is also accompanied by neural changes, with reorganization of the cortical areas which are responsive to the auditory stimuli [2]. Such experience-dependent plasticity is a crucial part of adaptive behavior and underlies successful coping with novel environmental circumstances.

The neural changes to novel stimuli can be indexed by electrophysiological brain responses which are independent of attentional processing, such as mismatch negativity (MMN), a scalp-measured event-related potential difference wave [3]. MMN is a difference wave elicited by an unpredicted auditory stimulus relative to a predicted stimulus, expressed as a negative-going wave peaking 150–250 ms after the onset of the deviance. MMN can be used to explore the difference in the central sound representations of different stimuli, as its amplitude increases with increased distance between the perceptual sound representations [4]. The MMN elicitation depends on long-term memory traces guiding the perceptual decision-making, as demonstrated by experiments with native and non-native phonemes [5,6]. MMN is affected by discrimination training, as demonstrated by several studies. For example, it has been shown that training leads to increased MMN amplitude and corresponding change in behavioral accuracy in response to deviations in speech sounds or complex auditory patterns in healthy adults, but also in children with dyslexia [7–9], highlighting the applied relevance of using MMN to study training-related changes in auditory cortex. However, the training required to lead to measurable plasticity tends to need attentive and long-term training. Passive exposure to stimuli does not appear to cause the learning effect leading to improved perceptual discrimination as indexed by the MMN [8].

Recently, the phenomenon of unsupervised perceptual learning using passive stimulation has come under scrutiny. One particular type of perceptual learning protocol consists of exposing the subject passively to rapidly presented stimulation (frequency 10–20 Hz), aiming to mimic the long-term potentiation (LTP) effects seen *in vitro* [10]. Such LTP-like stimulation has been shown to alter visual discrimination performance [11,12], and have an effect on event-related potentials as well as fMRI measures of auditory [13,14] and visual processing [12,15,16].

The mechanisms of cortical plasticity following training are an important avenue of study due to their importance for learning and memory, as well as possibilities for intervention in individuals with disturbances to sensory processing. In this experiment, we examined whether the auditory discrimination as reflected by MMN can be

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augmented using rapid, short-term auditory training. The short-term auditory training was conducted using a LTP-like stimulation protocol, which has been shown in preliminary reports to affect electrophysiological responses to the processing of visual and auditory stimuli [13,15,17]. The LTP-like stimulation refers to rapid repetitive stimulation in the frequency range which elicits long-term potentiation in neuronal circuits [13]. The effect of this on processes relevant for the mismatch negativity generation has not yet been studied. We hypothesized that LTP-like auditory stimulation will lead to improvement of auditory discrimination as indexed by increased amplitude and/or shortened peak latency of the auditory MMN wave.

## 2. Material and methods

### 2.1. Participants

The participants were 21 healthy young adults (12 female) recruited among the community of University of Bergen. The mean age of the subjects was 23.5 years (range 19–35 yrs, SD 2.9). The subjects with a history of psychiatric or neurological disease (assessed by self-report) were excluded. The hearing threshold of all participants for frequencies 250, 500, 1000, 2000 and 3000 Hz was tested using the Hughson-Westlake audiometric test (Oscilla USB-300, Inmedico, Lystrup, Denmark). All participants had auditory thresholds $< 25$ dB in both ears and for all tested frequencies. The caffeine and nicotine consumption on the day of the recording was recorded and treated as binary variables (no consumption/consumption). The caffeine and nicotine consumption on the day was shown to be significantly related ($\chi^2 = 4.677$; $p = .03$); to avoid correlated predictors and due to well-established neurophysiological effect of nicotine on MMN [18] only nicotine was considered in the subsequent analyses. The participants were informed of the study procedures and signed an informed consent form. The study was approved by the regional ethical committee (REK-NORD).

### 2.2. MMN paradigm

The MMN paradigm consisted of a standard sinusoidal tone (1000 Hz) with 50 ms duration alternating with two sinusoidal tones: frequency-deviant 1 (Dev1, 1025 Hz, probability 5%) and frequency-deviant 2 (Dev2, 975 Hz, probability 5%). The interstimulus interval was 400 ms. The deviance magnitude of 2.5% is in the lower range of frequency deviance to elicit a measurable MMN, with a small amplitude [19]. Deviants with magnitude 1% to 5% have been found to show change in MMN amplitude after auditory discrimination training [20]. The deviance magnitude of 2.5% was chosen for the present study to ensure that the effect of LTP-like stimulation on the MMN would not be overshadowed by ceiling effects in the auditory discrimination of healthy adult subjects. Following a baseline measurement of MMN to both deviant types, the subjects were exposed to 2 min of frequency-modulated stimulation with 1025 Hz-tone (corresponding to Dev1), presented continuously at 13 Hz frequency. The stimulation parameters were chosen based on previous studies demonstrating the modulation of earlier, perceptual ERPs and fMRI response in the primary auditory cortex [14,21].

Subsequently, the MMN to both deviant types was measured again, yielding in total four distinct stimulus categories (Dev1 and Dev2 before and after the LTP-like stimulation). There were 150 deviant events in each of the four categories. The tones were presented at a constant intensity of 60 dB for all subjects via headphones.

### 2.3. EEG recording

The data were recorded in a silent, electromagnetically shielded EEG recording chamber. EEG data was acquired from 12 Ag/AgCl electrodes (F3, Fz, F4, FCz, C3, Cz, C4, TP9, TP10, P3, Pz, P4), placed according to the International 10–20 system, using the EasyCap electrode caps (Falk Minow Services, Breitenbrunn, Germany) and Abralyt 2000 electrode gel. Interelectrode impedance was kept under 10 kΩ. The reference electrode was placed at nosetip, the ground at FT10. Two electrodes were used for monitoring eye movements, placed under the right eye and at the outer canthus of right eye. The subjects were instructed to relax, not attend the auditory stimuli and watch a silent subtitled nature documentary throughout the EEG session. Data were recorded with BrainVision Recorder 1.0 (Brain Products, Munich, Germany), sampled at 500 Hz, filter band 0–100.

### 2.4. EEG analysis

EEG data analysis was performed using BrainVision Analyzer 2.0 (Brain Products). The EEG data were filtered using a zero-phase Butterworth IIR filter with high-pass threshold 0.01 Hz (slope 12 dB/oct) and low-pass threshold 30 Hz (slope 12 dB/oct). The data were down-sampled to 250 Hz. Eye movements were removed using Gratton-Coles algorithm implemented in the BrainVision Analyzer. Subsequently, the data was epoched into segments spanning −50–300 ms relative to the onset of the auditory stimuli. Epochs with values exceeding +–100 μV were rejected, and the epochs were baseline corrected relative to the pre-stimulus period. The MMN for each of the four deviant types was identified by averaging the epochs corresponding to the deviant, and subtracting from them the average of standard stimuli immediately preceding the deviant. The MMN amplitude was quantified as the mean value in the time window 150–250 ms after stimulus onset in the electrode FCz.

### 2.5. Statistical analysis

Statistical analysis was performed using SPSS 23 (IBM). The presence of MMN on the group level was examined using a *t*-test against zero within each condition (one-sided significance level $\alpha = .05$). The hypothesis of the effect of LTP-like stimulation on the MMN was tested with a mixed general linear model with within-subject factors Timepoint (pre/post) and Deviant type (Dev1/Dev2). Nicotine was entered as between-subjects factor. The significance level was set at $p < .05$.

## 3. Results

First, we examined whether a significant MMN was elicited during the conditions by comparing the MMN amplitudes against zero for each of the four conditions (one-sided significance level $\alpha = .05$). At the baseline measurement, both Dev1 (frequency +2.5%) as well as Dev2 (frequency −2.5%) elicited significant negativity (Dev1: $t(20) = -1.8$, $p = .04$; Dev2: $t(20) = -5.8$, $p < .001$). This shows that the expected MMN was present for both deviant types at the baseline measurement. Also, at the post-stimulation measurement both deviant types elicited significant negativity (Dev1: $t(20) = -3.053$, $p = .003$; Dev2: $t(20) = -3.162$, $p = .003$).

Testing the hypothesis of the effect of the LTP-like stimulation on the MMN amplitude showed a significant interaction of Timepoint*Deviant type ($F(1,19) = 4.962$; $p = .038$, $\eta^2 = .09$). No other effects were significant. Follow-up GLMs testing for Timepoint effect separately within each deviant type indicated that there was a significant main effect of Timepoint within the stimulated Dev1 ($F(1,19) = 8.559$; $p = .009$; $\eta^2 = .10$), with MMN amplitude showing larger negativity in the post-stimulation phase ($M = -1.66$ μV, $SD = 2.5$) compared to the pre-stimulation phase ($M = -0.62$ μV, $SD = 1.57$). By contrast, no significant Timepoint effect was found for the non-stimulated Dev2 ($F(1,19) = 1.41$; $p = .249$; $\eta^2 = .03$), indicating that the MMN for the non-stimulated stimulus did not change significantly from pre-stimulation ($M = -1.88$ μV, $SD = 1.5$) to post-stimulation phase ($M = -1.5$ μV, $SD = 2.17$). The MMN time-course

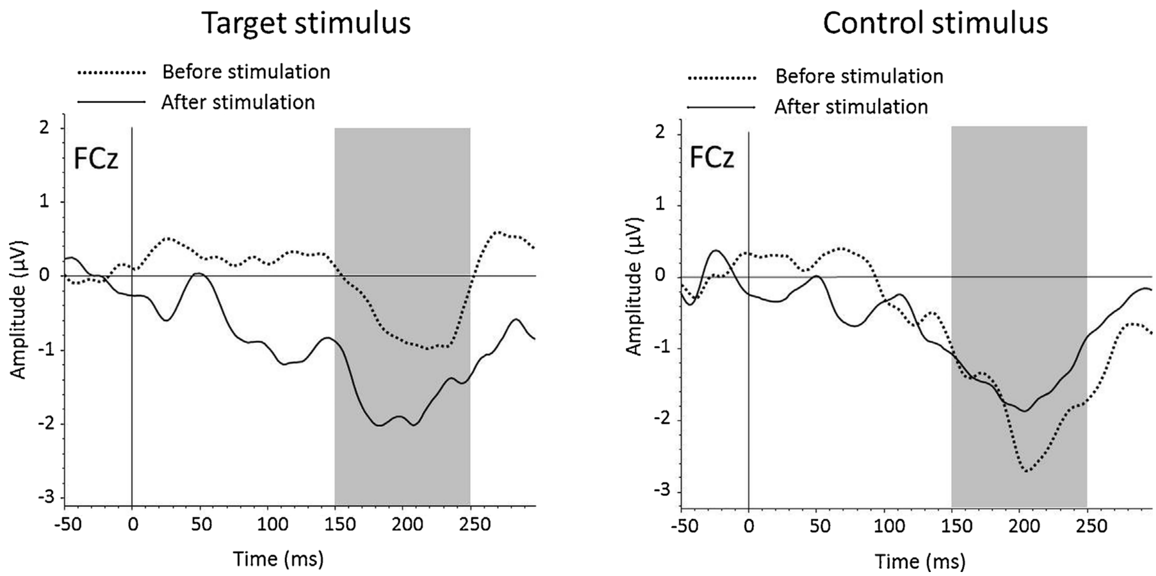


**Fig. 1.** The MMN depicted as a difference wave (deviant *vs* standard) for the four stimulus conditions at the electrode FCz. LEFT: Target stimulus Dev1 before (dashed line) and after (solid line) LTP-like stimulation, showing significantly increased negativity after stimulation in the time period 150–250 ms (shaded area). RIGHT: Control stimulus Dev2 before (dashed line) and after (solid line) LTP-like stimulation, with no significant difference in the time period 150–250 ms (shaded area).

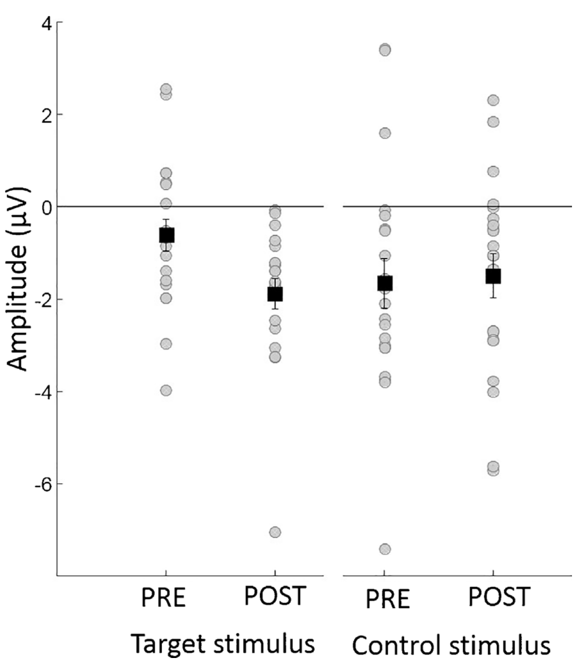


**Fig. 2.** Scatter plot depicting the subject means (grey circles) and sample mean (black square) with error bars representing one standard error, averaged over the time window 150–250 ms at the electrode FCz, for the four conditions: target stimulus Dev 1 before (pre) and after (post) LTP-like stimulation; control stimulus Dev2 before (pre) and after (post) LTP-like stimulation.

per condition can be seen in Fig. 1, and the scatter plot representing the individual and sample mean values averaged over the time window is depicted on Fig. 2.

## 4. Discussion

In this experiment we tested the hypothesis that LTP-like stimulation leads to altered perceptual representation of auditory stimuli as indexed by MMN. The hypothesis was confirmed, as the LTP-like stimulation led to increased amplitude of the negative-going MMN wave. Importantly, this change was selective to the stimulated auditory stimulus (deviant with frequency 1025 Hz), whereas the MMN to the non-stimulated stimulus (deviant with frequency 975 Hz) was not altered after the manipulation with high-frequency auditory stimulation. The changes presumably represent a short-term plasticity mechanism altering the perceptual representation of the stimulated sound.

The MMN elicitation has been conceptualized as a signal of prediction error in the hierarchical perceptual system which is generated when the bottom-up sensory information does not match the top-down predictions [22]. On neurophysiological level, it has been proposed that the top-down predictions are implemented as inhibitory signaling concerned with "explaining away" the information arriving from lower levels in the hierarchy, whereas the prediction errors are excitatory signals conveyed to hierarchically higher levels in order to update the model which proved erroneous [23]. A central factor in determining the generation of the prediction error is precision of the estimate, or the confidence in the prediction error resulting from the interaction of the bottom-up and the top-down information [22–24]. Learning leads to a stimulus processing being supported by a stronger prior probability [25] which increases the confidence in the bottom-up information and, consequently, a stronger error signal relative to an unlearned stimulus. We propose that in this experiment, the high-frequency stimulation caused increased precision of the error signal resulting from the bottom-up representation of the targeted stimulus in interaction with the prediction. Familiar stimuli, for which there exist corresponding long-term memory traces, have been shown to elicit stronger MMN, as strikingly demonstrated by studies with native and non-native speech sounds [[25],6,26,27]. The present results highlight the potential of perceptual learning to bias perception in similar ways as memory traces acquired via long-term, intentional learning.

It has previously been demonstrated that the primary auditory cortex response to the auditory stimuli as indexed by N1 event-related potential can be potentiated using short-term, rapid stimulation [21]. However, this is the first study to demonstrate that such changes also bias the further perceptual processing in the perceptual hierarchy, in stages which have been shown to be separate from the initial response to the auditory stimulus.

A limitation of the present study is that there is no estimate for whether the change in the MMN amplitude was matched by a change in the behavioral discrimination acuity for the stimulated sound. MMN paradigm indexes unattended, automatic discrimination process and the paradigms eliciting MMN therefore do not provide a direct behavioral measure of discrimination. However, it has been demonstrated that MMN parameters are related to behavioral discrimination of speech sounds, with increased MMN amplitude following a discrimination training [9,19]. Thus the present study, by demonstrating a change in MMN following a brief passive intervention offers a potential novel approach for improving discrimination performance, but this will need to be examined in future studies.

Finally, the current experiment also provides information about the temporal persistence of the observed MMN amplitude modulation. The previous reports of the LTP-like plasticity with perceptual stimulation have shown that using the same stimulation parameters (2 min at 13 Hz), an enhancement maintained over 1 h post-stimulation was found [21]. In the present study, the post-stimulation recording time over which the MMN was measured lasted approximately 20 min, representing a plausible minimum estimate for the time interval over which the effect persists. Whether the effect on MMN amplitude will persist for longer time will need to be examined in further studies; however, due to the increased length of an MMN paradigm compared to a N1-eliciting stimulation the possible confounding effect of fatigue will need to be carefully controlled for.

## 5. Conclusions

The auditory system shows considerable plasticity into adulthood, allowing the brain to acquire new relevant stimulus categories to facilitate the processing of auditory scene. As shown by the present results, plastic changes can be caused by brief passive perceptual learning protocol which has been suggested to cause LTP-like plasticity in the auditory cortex.

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