Research reports

Auditory evoked potentials to changes in sound duration in urethane anesthetized mice

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Abstract

Spectrotemporally complex sounds carry important information for acoustic communication. Among the important features of these sounds is the temporal duration. An event-related potential called mismatch negativity indexes auditory change detection in humans. An analogous response (mismatch response) has been found to duration changes in speech sounds in rats but not yet in mice. We addressed whether mice show this response, and, if elicited, whether this response is functionally analogous to mismatch negativity or whether adaptation-based models suffice to explain them. Auditory evoked potentials were epidurally recorded above the mice auditory cortex. The differential response to the changes in a repeated human speech sound /a/ was elicited 53–259 ms post-change (oddball condition). The differential response was observable to the largest duration change (from 200 ms to 110 ms). Any smaller (from 200 ms to 120-180 ms at 10 ms steps) duration changes did elicit an observable response. The response to the largest duration change did not robustly differ in amplitude from the response to the change-inducing sound presented without its repetitive background (equiprobable condition). The findings suggest that adaptation may suffice to explain responses to duration changes in spectrotemporally complex sounds in anesthetized mice. The results pave way for development of a variety of murine models of acoustic communication.

Introduction

Change detection in sounds is a fundamentally important ability of the brain that supports adaptive behavior. Automatic auditory change detection can be investigated via an electrophysiological response called mismatch negativity (MMN) (Näätänen *et al.*, 1978, for a review see Näätänen, 2010). In humans, MMN has been observed in scalp-recorded event-

related potentials to rare 'deviant' stimulus, which occasionally replaces the frequently presented 'standard' stimulus at 100–250 ms after the change in stimulus occurs (Näätänen *et al.*, 1978). Importantly, MMN is elicited only when deviant sound input violates regularity formed by repetitive standard stimuli and not, for instance, by the first stimulus in a sound series. (Näätänen *et al.*, 2005).

Mismatch response (MMR) analogous to the MMN has been found in several animal species, including cats (Csépe *et al.*, 1987), monkeys (Javitt *et al.*, 1992), guinea pigs (Kraus *et al.*, 1994) and mice (Umbricht *et al.*, 2005). Most of the animal studies have been conducted in rats (e.g. Ruusuvirta *et al.*, 1998; Eriksson & Villa, 2005; von der Behrens *et al.*, 2009; Tikhonravov *et al.*, 2010; Astikainen *et al.*, 2006, 2011; Nakamura *et al.*, 2011; Klein *et al.*, 2014, for a review see Harms *et al.*, 2016). In common with the findings of research on MMN in humans (Näätänen et al,. 2005) most studies on rats support the view that the MMR in rats reflects the detection of violations of regular (standard) sounds (e.g. Ahmed *et al.*, 2011; Astikainen *et al.*, 2011; Nakamura *et al.*, 2011; Jung *et al.*, 2013; Shiramatsu *et al.*, 2013; Parras *et al.*, 2017). According to this view, the MMR disappears under stimulus conditions where regular (standard) sounds are replaced by a set of constantly varying sounds. This condition is termed the equiprobable condition, also known as the many standards condition (Schröger & Wolff, 1996; Jacobsen & Schröger, 2001). Some studies have suggested that neural adaptation, which is stronger for the responses to repetitive standard sounds than rare deviants, is sufficient to explain MMR-like responses to deviant sounds (Lazar & Metherate, 2003; Eriksson & Villa, 2005). There are only few MMR studies conducted in mice where the equiprobable control condition has been applied (Kurkela *et al.*, 2018; Parras *et al.*, 2017). These have demonstrated a MMR to sinusoidal sounds that differ from standard sounds in frequency.

MMR has been recorded in anesthetized guinea pigs and rats to changes in repetitive vowels (Kurkela et al., 2016), syllables (Kraus *et al.*, 1994; McGee *et al.*, 2001; Ahmed *et al.*, 2011) and syllable patterns (Astikainen *et al.*, 2014). However, it has not been investigated whether the MMR is elicited to spectrotemporally complex sounds in mice. A mice model for MMR to such sounds would be particularly applicable for instance to determine the effect of language-related Foxp2 gene in change detection (Enard *et al.*, 2009). Here we investigated detection of changes in vowel duration in anaesthetized mice. Epidural recordings of auditory evoked potentials were obtained in anesthetized mice exposed to changes in the duration of a sound (110 ms, 120 ms, 130 ms, 140 ms, 150 ms, 160 ms, 170 ms or 180 ms vs. 200 ms standard sound). Only decrements in sound durations were applied because increments in the sound durations would have elicited larger responses due to the higher stimulus energy delivered by deviants than standards. In addition to the oddball condition, we used an equiprobable control condition (Schröger & Wolff, 1996) to probe whether the MMR, if observed, reflected the detection of violations of standard sound durations (Näätänen *et al.*, 2005) or the actual stimulus rate (May & Tiitinen, 2010).

Materials and methods

Animals

The experiments were approved by the Finnish National Animal Experiment Board (ESAVI/10646/04.10.07/2014), and they were carried out in accordance with the European Communities Council Directive (86/609/EEC) on the care and use of animals in experimental procedures. Eight male (n = 8) C57Bl/6J (RRID: MGI:5811150) mice from the Animal Center of UEF, Kuopio, Finland were used in the experiment (weight: 24.8 ± 2.0 g; age: 12.1 ± 1.4 weeks; mean ± SEM). The animals were housed in groups, with access to water and food ad libitum in a controlled environment (constant temperature of 22 ± 1°C, humidity of

50–60%, lights on from 07.00 to 19.00 h). At the end of the experiment, the anesthetized animals were sacrificed via cervical dislocation.

Epidural Recordings of Auditory Evoked Potentials

For the recordings of auditory evoked potentials, the animals were first anaesthetized with isoflurane (an initial dose of 5% in 1 l/min of pressure air, followed by a maintenance dose of 1–2 % in 1 l/min of pressure air). The animal's head was fixed to a stereotactic device (Kopf, CA, USA) equipped with an external supporting arm that allowed the removal of an ear bar. Immediately, a single dose of urethane (Sigma-Aldrich, MO, USA) (7.5 g/100 ml solution) was administered intraperitoneally (1.2 g/kg), and the administration of isoflurane was gradually reduced over a 5-min period (Barth & Mody, 2011). The level of anesthesia was controlled by regular testing of the pedal withdrawal reflex. If required, extra doses (0.1–0.2 ml) of urethane were administered.

Under full anaesthesia, the skin and muscle tissue over the skull were removed. For the reference electrode, a hole was drilled in the skull over the right side of the cerebellum, and a small insulin needle (BD Lo-Dose syringe; USA) was inserted in the cerebellum as the reference electrode (AP: -5.8 mm, ML: 2–3 mm and DV: 2 mm). A similar needle electrode inserted subcutaneously into the neck served as the ground electrode. Next, the upper half of the squamosal skull bone was removed to reveal the left primary auditory cortex. The dura was left intact (Stiebler *et al.*, 1997).

The tip of a Teflon-insulated silver wire (A-M Systems, WA, USA) with a diameter of 200 μm was placed on the surface of the dura above the auditory cortex (2.2–3.2 mm posterior and 4–4.5 mm ventral to bregma). Although the locations of the electrodes in the craniotomy were intended to capture primary auditory cortex activity, some activity from higher sensory areas may also have been captured. The latter is due to differences between animals in the organization of the primary auditory cortex and the relatively large size of the tip of the electrode allowing signals to be conducted from adjacent areas. To reduce the variability of the electrode location, the location of the electrode was guided by on-line recorded auditory evoked potentials in response to a stimulus of 200 ms, which was presented as the standard tone in the actual experiment.

A continuous electrocorticogram was first 10-fold amplified using a low-noise MPA8I pre-amplifier (MultiChannel Systems MCS GmbH, Germany). The signal was further fed to a filter amplifier (FA64I, filter: 1–5000 Hz, MultiChannel Systems MCS GmbH, Germany). All the signals were digitized (USBME-64 System, MultiChannel Systems MCS GmbH, Germany) and recorded using McRack software (MultiChannel Systems MCS GmbH, Germany) at a 2000-Hz sampling rate. Finally, all the signals were digitally band-pass filtered between 1 and 500 Hz (high-pass: low-pass: fourth-order Bessel).

Stimuli

The speech sound /a/ was used in the experiment. The speech sound was originally recorded at a sampling rate of 44.1 kHz using a female native Finnish speaker. The sound was then digitally edited using SoundForge software (SoundForge 10, Sony Corporation, Japan) to ensure it had a constant duration of 200 ms. The 200-ms speech sound was digitally

shortened in 10-ms steps, and a 5-ms fade-out was added in each sound in Soundforge Pro 10.0 (MAGIX Software GmbH, Germany). This resulted in 10 speech sounds (200, 190, 180, 170, 160, 150, 140, 130, 120 and 110 ms in duration), which were used in the experiment (Fig. 1).

The sounds were presented via an active loudspeaker system (Studiopro 3; N-audio, CA, USA), and the presentation of each stimulus was controlled by E-prime 2.0 software (Psychology Software Tools, PA, USA). The stimuli were presented using the passive part of the loudspeaker system directed towards the right ear of the animal at a distance of 20 cm, with a sound pressure level of 70 dB, as measured using a C-weighted sound level meter (Sound level meter Type 2240; Brüel & Kjær Sound & Vibration, Denmark).

Two different types of stimulus conditions were presented to each animal: an equiprobable condition and an oddball condition (Fig. 2). In one stimulus block, the equiprobable condition was applied. Under this condition, all 10 speech sounds were presented with the same probability ($p = 0.10$) in random order at an inter-stimulus interval of 400 ms. In the oddball condition, nine stimulus blocks were applied. Under this condition, the durations of the deviant sounds were 110, 120, 130, 140, 150, 160, 170, 180 and 190 ms. Due to a technical failure, the oddball stimulus block with the 190-ms deviant tone is not reported. In each oddball condition, the 200-ms speech sound served as the repeatedly presented standard sound ($p = 0.90$), and one of the nine shorter sounds served as the deviant sound ($p = 0.10$). When delivering the sounds, the deviant sounds were interspersed with the standard sounds in a random order, but there were always at least two standard sounds between two deviant sounds. There were 1,000 stimuli in each stimulus block, and these were presented in a counterbalanced order between the subjects.

Data analysis

The data analyses were performed offline using Brain Vision Analyzer (Brain Products, Gilching, Germany), GraphPad Prism 5.03 (GraphPad Software), Excel 2016 (Microsoft Office), Rstudio v. 1.1.456 and Matlab R2017b.

The data were segmented (from -50 to 400 ms from stimulus onset) separately for the responses to the deviant and standard sounds immediately preceding the deviant sound in the oddball condition and for the responses to each tone in the equiprobable condition. The data segments were baseline corrected against the mean of the signal during a 50-ms time window prior to sound onset. The data segments were averaged for each animal separately for the different deviant and standard tones preceding the deviant tones and for each tone presented in the equiprobable condition.

Statistical analysis

Paired timepoint-by-timepoint *t*-tests were applied to compare the averaged response amplitudes. The averaged response amplitudes of the responses to the standard and deviant sounds for each oddball condition were first compared. If the timepoint-by-timepoint comparison values reached statistical significance ($p < .05$) for at least 20 consecutive sample points (i.e. over a 10-ms time span), differential responses to the oddball deviant sounds were considered to exist and not to be accounted for by random signal fluctuations (Guthrie & Buchwald, 1991). See below for data-driven confirmation of this. Next, if a significant difference was observed between the standard and deviant responses in the oddball condition, the oddball deviant response and control-deviant response (i.e. response to the same sound presented in the equiprobable condition) were compared. Due to technical problems, the

recording of the equiprobable control condition in one animal could not be recorded. Therefore, the comparisons of the responses in the oddball and control conditions were based on those of seven animals. Two-tailed *t*-tests were used to compare the standard and deviant responses in the oddball condition because we were not able to predict the direction of the potential differential response. The latter was not possible because the location of the reference electrode and anaesthesia in experimental animal models can affect the polarity of the differential response (Harms *et al.*, 2016). The t-tests comparing deviant and control-deviant responses were one-tailed because we specifically tested, whether the responses were larger for the deviant than for the control-deviant sounds. Cohen's *d* is reported for the effect size.

In addition, to provide data driven estimate of the probability of finding a random consecutive sequence of p-values below 0.05 of the same length as that found in the present data, randomization procedure was applied. First, the labels of the standard and deviant conditions were assigned randomly for each animal and a timepoint-by-timepoint two-tailed t-test was calculated. This was carried out 56 times (the maximum number of permutations for 8 animals). Second, the maximum number of consecutive time points with $p < 0.05$ was extracted for each permutation. Third, these values were sorted into ascending order and the original number of time points was compared against this vector providing an estimate of the probability for randomly finding equally long significant time window.

To investigate whether the differential response was significant in individual animals, we performed paired timepoint-by-timepoint *t*-tests for single-trial data. For each animal, the amplitude values for the standard and deviant responses in each trial were compared. Similarly, the responses of each animal to the deviant sounds and control sounds were compared whenever difference was found between deviant and standard responses. Again, at

least 20 consecutive sample points we expected to significant for a robust effect. Similarly, to the group-level analysis, two tailed tests were applied for the standard vs. deviant response comparisons and one-tailed tests for deviant vs. control-deviant response comparisons. Individual-level of analysis was conducted for those deviant sound durations that showed a significant differential response in oddball condition at the group-level analyses.

Results

Overall, the sounds evoked a prominent response, with positive polarity peaking approximately 35 ms after the stimulus onset (Fig. 3). A visual inspection revealed a larger response of positive polarity to the deviant sound in comparison to the standard sound (200 ms) in the oddball condition, especially to the shortest (110 ms) deviant sound (Fig. 3).

At group-level, the timepoint-by-timepoint t-tests revealed a statistically significant difference in the amplitude values in response to the standard and 110-ms deviant sounds 53–259 ms post-change (all tests, $p < 0.05$). The effect size was largest 117 ms post-change (Cohen's $d = 1.56$). The randomization procedure used to validate this finding showed that the probability of finding 206 ms long time window by chance is below 0.017.

Deviant sounds of longer durations than 110 ms, and therefore higher similarity to standard sounds, did not elicit responses different in amplitude from those to standard sounds as analysed with the timepoint-by-timepoint t-tests (Fig. 3).

Next, the responses to the 110-ms deviant sound in the oddball condition were compared in amplitude to those to the corresponding control-deviant sound in the equiprobable condition. There was no difference in the response amplitudes elicited by the deviant and control-deviant sound. The effect size was largest 227 ms post-change (p = 0.06, Cohen's d = 0.8). Figure 3 shows the p-values for the whole response time.

Single trial analysis showed that responses to the 110-ms deviant sound and those to 200-ms standard sound in the oddball condition differed in five of eight animals. The same analysis revealed that responses to the 110-ms deviant sound and 110-ms control-deviant sound differed only in one of seven animals (Table 1 and Fig. 4).

Discussion

In this study, we investigated whether the MMR analogous to MMN in humans, is elicited in anaesthetized mice in response to changes in the durations of spectrotemporally complex sounds (a human speech sound /a/). We studied not only whether such changes elicited differential responses to rare sounds in comparison to frequently presented sounds but also whether these differential responses reflected the detection of sound duration changes rather than the lower presentation rate of the deviant sound relative to that of the standard sound (May & Tiitinen, 2010). To shed light on the aforementioned issue, we used an equiprobable condition (Harms *et al.*, 2016) as a control condition for the oddball condition.

In the oddball condition, we found a differential response only to the shortest (110-ms) deviant sound interspersed with the 200-ms standard sound (45% duration decrease). As shown by the analysis of the individual-level data, five of eight animals showed a significant

differential response to the 110-ms deviant sound. Consistently, freely-moving mice have been found to generate a differential response to a 50% reduction (from 100 ms to 50 ms) in the duration of a repeated sinusoidal sound (Umbricht et al., 2005). In another study (Roger et al., 2009), freely-moving rats showed a differential response to a 33% (100-ms deviant vs. 150-ms standard) but not a 16% change in the duration of a sinusoidal sound. In contrast, robust MMN has been detected in humans, even to 10% change in sound duration (100 ms vs. 110 ms, Jaramillo et al., 2000). Thus, the neurophysiological detection of sound duration changes in rodents seems not to be as advanced as it is in humans.

The current experiments were conducted in anesthetized animals, and it is not known how anesthesia affects representation of sound duration in spectrotemporarily complex sounds. However, previous studies applied in urethane-anesthetized rodents have shown that MMR is elicited to changes in vowels (Kurkela et al., 2016), syllables (Ahmed et al., 2011) and syllable patterns (Astikainen et al., 2014). Future studies should investigate MMR to complex sounds in awake and anaesthetized animals to reveal possible effect of anesthesia on neural change detection.

We also investigated whether the differential response reflected the detection of regularity violations (i.e. a true MMR) or merely the different presentation rate of the stimuli. At the group-level analysis, we found no difference between the responses to the deviant and control sound (110 ms sounds). When single trial analysis was conducted for each animal separately, we detected a significant difference in the responses to the 110-ms deviant and corresponding control sound in only one of the seven animals. This pattern of results suggests that the differential response in the oddball condition could be explained by the different presentation rates of the standard and deviant stimuli (May & Tiitinen, 2010). This finding is in contrast

with results in humans showing larger responses to deviant than control sounds (Jabobsen & Schröger, 2003). While the human data suggest that duration changes are detected as violation in regularity (Jabobsen & Schröger, 2003), our data suggest that in mice the detection of duration deviations could be processed as physical feature encoding.

Differential responses to deviants were reasonably long in duration considering that no comparison mechanism could be postulated to precede these responses. However, at the auditory cortical level, such slow responses are expected. Rodent auditory pathway has been under extensive studies related to spectrotemporally complex sounds. By applying dynamically changing stimuli in which temporal modulations were defined by the speed and direction of the amplitude peaks' change, it has been found that temporal response has been faster in thalamic than cortical cells. Namely, the thalamic and cortical neural populations seem to be simultaneously active for most of their response durations, but cortical neurons seem to have longer response latencies than the thalamic neurons (Miller *et al.*, 2002).

In summary, the results show that mice can detect changes in the durations of spectrotemporally complex sounds if the difference in the durations of these sounds is large (at least 45%). The neural detection of rare sounds can be based on different presentation rates of rare and frequent sounds, leading to different levels of neural refractoriness or adaptation in the neural populations responding to these sounds.

Statement of conflicts of interest

None declared.

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Author Contributions

Conception or design of the work (AL, PA)

Data collection (AL)

Data analysis and interpretation (AL, JLOK, IK, SH, TR, JAH, PA)

Drafting the article (AL, JLOK, TR, PA)

Critical revision of the article (AL, JLOK, TR, JAH, PA)

Final approval of the version to be published (AL, JLOK, IK, SH, TR, JAH, PA)

Data accessibility

All data is available by request (Arto.Lipponen@jyu.fi).

References

Ahmed, M., Mällo, T., Leppänen, P.H.T., Hämäläinen, J., Ayräväinen, L., Ruusuvirta, T., & Astikainen, P. (2011) Mismatch brain response to speech sound changes in rats. *Front. Psychol.*, **2**, 283.

Astikainen, P., Mällo, T., Ruusuvirta, T., & Näätänen, R. (2014) Electrophysiological evidence for change detection in speech sound patterns by anesthetized rats. *Front. Neurosci.*, **8**, 374.

Astikainen, P., Stefanics, G., Nokia, M., Lipponen, A., Cong, F., Penttonen, M., & Ruusuvirta, T. (2011) Memory-based mismatch response to frequency changes in rats. *PloS One*, **6**, e24208.

Barth, A.M.I. & Mody, I. (2011) Changes in hippocampal neuronal activity during and after unilateral selective hippocampal ischemia in vivo. *J. Neurosci. Off. J. Soc. Neurosci.*, **31**, 851–860.

Csépe, V., Karmos, G., & Molnár, M. (1987) Evoked potential correlates of stimulus deviance during wakefulness and sleep in cat--animal model of mismatch negativity. *Electroencephalogr. Clin. Neurophysiol.*, **66**, 571–578.

Enard, W., Gehre, S., Hammerschmidt, K., Hölter, S.M., Blass, T., Somel, M., Brückner, M.K., Schreiweis, C., Winter, C., Sohr, R., Becker, L., Wiebe, V., Nickel, B., Giger, T., Müller, U., Groszer, M., Adler, T., Aguilar, A., Bolle, I., Calzada-Wack, J., Dalke, C., Ehrhardt, N., Favor, J., Fuchs, H., Gailus-Durner, V., Hans, W., Hölzlwimmer, G., Javaheri, A., Kalaydjiev, S., Kallnik, M., Kling, E., Kunder, S., Mossbrugger, I., Naton, B., Racz, I., Rathkolb, B., Rozman, J., Schrewe, A., Busch, D.H., Graw, J., Ivandic, B., Klingenspor, M., Klopstock, T., Ollert, M., Quintanilla-Martinez, L., Schulz, H., Wolf, E., Wurst, W., Zimmer, A., Fisher, S.E., Morgenstern, R., Arendt,

T., de Angelis, M.H., Fischer, J., Schwarz, J., & Pääbo, S. (2009) A humanized version of Foxp2 affects cortico-basal ganglia circuits in mice. *Cell*, **137**, 961–971.

Eriksson, J. & Villa, A.E.P. (2005) Event-related potentials in an auditory oddball situation in the rat. *Biosystems*, **79**, 207–212.

Grimm, S., Escera, C., & Nelken, I. (2016) Early indices of deviance detection in humans and animal models. *Biol. Psychol.*, **116**, 23–27.

Guthrie, D. & Buchwald, J.S. (1991) Significance testing of difference potentials. *Psychophysiology*, **28**, 240–244.

Harms, L., Michie, P.T., & Näätänen, R. (2016) Criteria for determining whether mismatch responses exist in animal models: Focus on rodents. *Biol. Psychol.*, **116**, 28–35.

Jacobsen, T. & Schröger, E. (2003) Measuring duration mismatch negativity. *Clin. Neurophysiol. Off. J. Int. Fed. Clin. Neurophysiol.*, **114**, 1133–1143.

Jaramillo, M., Paavilainen, P., & Näätänen, R. (2000) Mismatch negativity and behavioural discrimination in humans as a function of the magnitude of change in sound duration. *Neurosci. Lett.*, **290**, 101–104.

Javitt, D.C., Schroeder, C.E., Steinschneider, M., Arezzo, J.C., & Vaughan, H.G. (1992) Demonstration of mismatch negativity in the monkey. *Electroencephalogr. Clin. Neurophysiol.*, **83**, 87–90.

Jung, F., Stephan, K.E., Backes, H., Moran, R., Gramer, M., Kumagai, T., Graf, R., Endepols, H., & Tittgemeyer, M. (2013) Mismatch responses in the awake rat: evidence from epidural recordings of auditory cortical fields. *PloS One*, **8**, e63203.

Klein, C., von der Behrens, W., & Gaese, B.H. (2014) Stimulus-specific adaptation in field potentials and neuronal responses to frequency-modulated tones in the primary auditory cortex. *Brain Topogr.*, **27**, 599–610.

Kraus, N., McGee, T., Carrell, T., King, C., Littman, T., & Nicol, T. (1994) Discrimination of speech-like contrasts in the auditory thalamus and cortex. *J. Acoust. Soc. Am.*, **96**, 2758–2768.

Kurkela, J.L.O., Lipponen, A., Kyläheiko, I., & Astikainen, P. (2018) Electrophysiological evidence of memory-based detection of auditory regularity violations in anesthetized mice. *Sci. Rep.*, **8**, 3027.

Lazar, R. & Metherate, R. (2003) Spectral interactions, but no mismatch negativity, in auditory cortex of anesthetized rat. *Hear. Res.*, **181**, 51–56.

May, P.J.C. & Tiitinen, H. (2010) Mismatch negativity (MMN), the deviance-elicited auditory deflection, explained. *Psychophysiology*, **47**, 66–122.

McGee, T.J., King, C., Tremblay, K., Nicol, T.G., Cunningham, J., & Kraus, N. (2001) Long-term habituation of the speech-elicited mismatch negativity. *Psychophysiology*, **38**, 653–658.

Miller, L.M., Escabí, M.A., Read, H.L., & Schreiner, C.E. (2002) Spectrotemporal receptive fields in the lemniscal auditory thalamus and cortex. *J. Neurophysiol.*, **87**, 516–527.

Näätänen, R., Astikainen, P., Ruusuvirta, T., & Huotilainen, M. (2010) Automatic auditory intelligence: an expression of the sensory-cognitive core of cognitive processes. *Brain Res. Rev.*, **64**, 123–136.

Näätänen, R., Gaillard, A.W., & Mäntysalo, S. (1978) Early selective-attention effect on evoked potential reinterpreted. *Acta Psychol. (Amst.)*, **42**, 313–329.

Näätänen, R., Jacobsen, T., & Winkler, I. (2005) Memory-based or afferent processes in mismatch negativity (MMN): a review of the evidence. *Psychophysiology*, **42**, 25–32.

Parras, G.G., Nieto-Diego, J., Carbajal, G.V., Valdés-Baizabal, C., Escera, C., & Malmierca, M.S. (2017) Neurons along the auditory pathway exhibit a hierarchical organization of prediction error. *Nat. Commun.*, **8**, 2148.

Roger, C., Hasbroucq, T., Rabat, A., Vidal, F., & Burle, B. (2009) Neurophysics of temporal discrimination in the rat: a mismatch negativity study. *Psychophysiology*, **46**, 1028–1032.

Ruusuvirta, T., Penttonen, M., & Korhonen, T. (1998) Auditory cortical event-related potentials to pitch deviances in rats. *Neurosci. Lett.*, **248**, 45–48.

Shiramatsu, T.I., Kanzaki, R., & Takahashi, H. (2013) Cortical mapping of mismatch negativity with deviance detection property in rat. *PloS One*, **8**, e82663.

Stiebler, I., Neulist, R., Fichtel, I., & Ehret, G. (1997) The auditory cortex of the house mouse: left-right differences, tonotopic organization and quantitative analysis of frequency representation. *J. Comp. Physiol. [A]*, **181**, 559–571.

Tikhonravov, D., Neuvonen, T., Pertovaara, A., Savioja, K., Ruusuvirta, T., Näätänen, R., & Carlson, S. (2010) Dose-related effects of memantine on a mismatch negativity-like response in anesthetized rats. *Neuroscience*, **167**, 1175–1182.

Umbricht, D., Vyssotki, D., Latanov, A., Nitsch, R., & Lipp, H.-P. (2005) Deviance-related electrophysiological activity in mice: is there mismatch negativity in mice? *Clin. Neurophysiol. Off. J. Int. Fed. Clin. Neurophysiol.*, **116**, 353–363.

Animal id	deviant vs. standard	deviant vs. control-deviant
1	66-147	NA
2	42-217	42-211
3	36-271	NS
4	1-167	NS
5	NS	NS
6	NS	NS
7	NS	NS
8	39-194	NS

Table 1. ***Results of the analyses at single trial level conducted for each animal separately.*** *Table shows the latency for significant (P < 0.05) differential response in each animal for deviant vs. standard and for deviant vs. control-deviant comparison. Analyses were conducted for the 110-ms deviant condition, since there was no differential response (deviant vs. standard) in the group-level analysis for the other deviant durations. For the details, please see Methods. Latency range is presented in milliseconds after the change occurred in the deviant response. NS = non-significant, NA = non-applicable (no data available).*

Figure captions

Figure 1. Human speech sounds used in the experiment. (A) The spectrogram and F0, F1, F2, F3 and F4 formants of the standard speech sound /a/. (B) The time-amplitude patterns of the sounds (110, 120, 130, 140, 150, 160, 170, 180 and 200 ms), and (C) the intensity of the same sounds. The intensity of all the sounds is the same till the last 5-ms fade-out in each sound.

Figure 2. Stimulus series used in the experiment. The tones were presented in the oddball condition (A) and in the equiprobable condition (B). In the oddball condition, a deviant sound (P= 0.1) was interspersed with a repetitive standard sound (P = 0.9). In the equiprobable condition, control stimuli of 10 different frequencies were presented with the same probability (p = 0.1).

Figure 3. Grand-averaged responses recorded from the dura above the auditory cortex. A) Evoked potentials for the deviant (110, 120, 130, 140,150,160, 170 and 180 ms) and to the 200-ms standard sound (n = 8). The sounds were presented in the oddball condition. B) Evoked potentials to the 110-ms deviant and 200-ms standard stimulus in the oddball condition (n = 8). This was the only deviant-condition where responses between the standard and deviant sounds were significantly different in amplitude. The point-by-point t-tests to response amplitudes showed that these responses differed (p < .05) at latency of 163-369 ms (corresponding to 53-259 ms after the change onset). The grey bar refers to 95 % confidence interval (CI) for the deviant-standard difference from the t-test without zero. C) Evoked potentials to the 110-ms deviant sound (oddball condition, n = 8) and corresponding control

sound (equiprobable condition, n = 7). Stimulus onset at 0 ms. The waveforms are presented as mean (A) and mean ± SEM (B and C).

Figure 4. Difference waves for the oddball (A, deviant minus standard) and control (B, oddball-deviant minus control-deviant) responses in individual animals and group mean (mean) for the 110-ms deviant condition. Statistical analysis revealed that five (out of eight) animals showed significant difference in the oddball condition between the standard and deviant responses, and that only one (out of seven) animals showed significant difference between the deviant and control-deviant responses. Stimulus onset at time 0 ms, and change onset at 110 ms (dotted line) (C).