MISMATCH RESPONSES TO SOUND DURATION CHANGES IN THE RAT AUDITORY CORTEX AND HIPPOCAMPUS

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ABSTRACT

Detection of changes in the auditory environment is important for survival. The mismatch negativity (MMN) of the event-related potentials (ERPs) reflects automatic change detection that occurs independently from attention. In experimental conditions, MMN can be elicited by rare 'deviant sounds', differing discernibly from the frequently occurring 'standard sounds' in respect of any stimulus feature (so-called oddball condition). The generation of MMN has generally been viewed as a cortical process. The hippocampus, then again, has been thought to contribute to the detection of more salient changes, to the switching of attention to these changes and to the generation of P3a of ERPs related to the attention shift. We measured auditory cortical and hippocampal local field potentials (LFPs) to sound duration changes in urethane-anesthetized rats in an oddball condition to study whether also the hippocampus plays a role in automatic change detection and generation of MMN. As the direction of the duration deviance has been suggested to have bearing on mismatch response, we applied two conditions with duration increments as deviant sounds in one condition and duration decrements as deviant sounds in the other condition. Moreover, two conditions with different inter-stimulus intervals (ISIs of 200 and 500 ms) were applied to study how the length of the intervals between the stimuli affects mismatch response. Mismatch responses were observed both in the auditory cortex and hippocampus at 25-149.5 ms after change onset. Duration increments elicited strong mismatch responses, but mismatch responses to duration decrements were almost completely absent. Stronger mismatch responses were also elicited when ISI was 500 ms than when it was 200 ms. These results indicate that hippocampus might play a role in automatic auditory change detection and in the generation of MMN. Moreover, the findings of the effect of duration deviation direction and ISI on mismatch response are consistent with the findings of human MMN. This lends further support for the use of rats when modeling central auditory processes related to both healthy and disrupted brain functions.

Key words: mismatch negativity, mismatch response, auditory change detection, auditory cortex, hippocampus, duration increment, duration decrement, inter-stimulus interval

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TIIVISTELMÄ

Ääniympäristön muutosten havaitseminen on tärkeää selviytymiselle. Aivojen herätevasteista niin sanotun poikkeavuusnegatiivisuusvasteen (mismatch negativity, MMN) on ajateltu heijastavan tällaisten muutosten tarkkaavuudesta riippumatonta havaitsemista. Tutkimustilanteissa poikkeavuusnegatiivisuusvaste voidaan synnyttää sirottelemalla toistuvien ’standardiäänten’ joukkoon joltakin ärsykeominaisuudeltaan havaittavissa määrin poikkeavia harvinaisia ’devianttiääniä’ (niin sanottu oddball-asetelma). Poikkeavuusnegatiivisuusvasteen tuottamista on yleisesti pidetty aivokuoren toimintona. Hippokampuksen sen sijaan on ajateltu vaikuttavan huomattavampien muutosten havaitsemiseen ja huomion kääntämiseen näihin muutoksiin sekä tähän liittyvään P3a-vasteen syntyyn. Me mittasimme kuuloaivokuoren ja hippokampuksen paikallisia kenttäpontetiaaleja (local field potentials, LFPs) äänen kestomuutoksiin uretaanilla nukutetuilla rotilla tutkiaksemme vaikuttaako myös hippokampus automaattiseen muutoksen havaitsemiseen ja poikkeavuusvasteen syntyyn. Tutkiaksemme muutoksen suunnan vaikutusta poikkeavuusvasteeseen käytimme kahta ärsyketilannetta, joista toisessa devianttiäänet olivat standardiääniä pidempiä ja toisessa lyhempiä. Lisäksi ärsykevälien pituuden vaikutusta poikkeavuusvasteeseen tutkittiin kahdella ärsyketilanteella, joista toisessa ärsykeväli oli 200 ja toisessa 500 millisekuntia. Poikkeavuusvasteita havaittiin sekä kuuloaivokuorella että hippokampusessa aikavälillä 25-149.5 millisekuntia muutoksen alusta. Kestopidennykset aiheuttivat voimakkaita poikkeavuusvasteita, mutta poikkeavuusvasteet puuttuivat lähes kokonaan kestolyhennyksiin. Poikkeavuusvasteet olivat voimakkaampia ärsykevälien ollessa 500 millisekuntia kuin niiden ollessa 200 millisekuntia. Nämä tulokset viittaavat siihen että hippokampus saattaa osallistua muutoksen havaitsemiseen ja poikkeavuusnegatiivisuusvasteen syntyyn. Lisäksi tulokset kestomuutoksen suunnan sekä ärsykevälin vaikutuksesta poikkeavuusvasteeseen ovat yhtenäisiä ihmisiltä mitattujen poikkeavuusnegatiivisuusvastetutkimusten tulosten kanssa. Tämä tukee rottien käyttöä mallinnettaessa sekä normaaleihin että häiriintyneisiin aivotoimintoihin liittyviä kuulotiedon käsittelyn prosesseja keskushermostossa.

Avainsanat: poikkeavuusnegatiivisuusvaste, poikkeavuusvaste, kuulonvarainen muutoksen havaitseminen, kuuloaivokuori, hippokampus, kestopidennys, kestolyhennys, ärsykeväli

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INTRODUCTION

Fast and automatic detection of changes in the auditory environment is crucial to survival, as a change may imply danger or an opportunity. In experimental conditions change detection can be studied in humans by observing the mismatch negativity (MMN), a component of the event-related potentials (ERPs) (Näätänen, Gaillard & Mäntysalo, 1978). MMN can be elicited by using oddball-paradigm, in which frequently occurring 'standard sounds' are interspersed with rare 'deviant sounds' that differ discernibly from the standard sounds in respect of duration (e.g. Jaramillo, Alku & Paavilainen, 1999; Jaramillo, Paavilainen & Näätänen, 2000), frequency (e.g. Näätänen et al., 1978), intensity (e.g. Näätänen et al., 1978) or some other stimulus feature. The term 'mismatch response' is used in the context of animal research as the response may also be of positive polarity.

The present study focuses on the automatic detection of sound duration changes in rats. In humans precise discrimination of sound durations is essential to speech perception, and difficulties in the detection of duration changes have been associated with dyslexia (Corbera, Escera & Artigas, 2006; for review, see Hämäläinen, Salminen & Leppänen, 2012). Furthermore, attenuation of MMN for sound duration changes is shown to characterize schizophrenia and this attenuation is thought to relate to the genetic aspects of the illness, instead of only reflecting its progress (for review, see Näätänen & Kähkönen, 2009).

Auditory change detection has usually been viewed as a cortical process and generators of MMN have been thought to reside in the auditory cortex and frontal lobes (Näätänen et al., 1978; Giard, Perrin, Pernier & Bouchet, 1990). Whereas MMN has been found to be elicited automatically even by changes so slight that they do not cause the involuntary switching of attention in the latency range of 150-250 milliseconds in humans (Näätänen, 1990), the hippocampus has been thought to contribute to the detection of more salient sound changes or novel stimuli and to the generation of the orienting response to these stimuli (Sokolov, 1975). For example, Knight (1996) found that bilateral hippocampal lesions resulted in reductions in P3a, a positive fronto-centrally distributed brain potential with a latency range of 220-280 milliseconds (Squires, Squires & Hillyard, 1975), which has been proposed to be a marker of the orienting response (Ritter, Herbert, Vaughan & Costa, 1968). Moreover, as MMN often precedes P3a it has been proposed that MMN might underlie the switching of attention and the emergence of P3a when the difference between the standard and the deviant stimuli is salient enough (Alho et al., 1998; Escera, Alho, Winkler & Näätänen, 1998; Näätänen, 1990; Schröger, 1996). However, electrophysiological responses of deep brain structures such as hippocampus are nearly impossible to measure by noninvasive

methods. Moreover, the few human studies conducted with intracranial electrodes on epileptic and obsessive-compulsive patients to study the bearing of hippocampus on auditory change detection have either found no differential responses to standard and deviant sounds (Kropotov et al., 1995), or have regarded the observed differential responses as P3a (Rosburg et al., 2007). These latter studies have further supported the role of hippocampus in the detection of salient changes and in the involuntary attention shift to these changes, but not in the automatic change detection occurring even in the absence of attention. However, as existence of mismatch response analogous to human MMN has been discovered in some animals such as rats (Ahmed et al., 2012; Astikainen et al., 2011; Jung et al., 2012; Nakamura et al., 2011) intracranial measurements in these animals are of utmost importance to discover whether hippocampus contributes to change detection. Differential responses to standard and deviant sounds have been observed also in the animal hippocampus (Ruusuvirta, Astikainen, Wikgren & Nokia, 2010 in rabbits; Ruusuvirta, Lipponen, Pellinen, Penttonen & Astikainen, 2013 in rats) in addition to auditory cortex and contrary to the findings in human subjects also these hippocampal responses have been interpreted to reflect genuine change detection (Ruusuvirta et al., 2010).

The present study also explored the effect of the duration deviance direction, which has been claimed to have some bearing on the amplitudes of MMN in humans and mismatch response in animals. The deviant sounds that are higher in frequency or longer in duration than standard sounds are called frequency/duration increments and MMN or mismatch response elicited by these 'increment MMN/mismatch response', whereas deviant sounds of lower frequency or shorter duration than standard sounds are referred to as frequency/duration decrements and MMN or mismatch response elicited by them as 'decrement MMN/mismatch response'. Whereas studies of frequency change detection have consistently implicated that mismatch response in animals (Nakamura et al., 2011; Astikainen et al., 2011 in rats) and MMN in humans (Karanasiou et al., 2011, Peter, McArthur and Thompson, 2010) is more sensitive to frequency increments than decrements, the studies conducted to explore the effect of duration deviance direction on MMN and mismatch response have yielded controversial results. While some studies have found larger MMNs and MMFs (mismatch field: equivalent of MMN in magnetoencefalography) to duration decrements (Colin et al., 2009; Inouchi, Kubota, Ferrari & Roberts, 2002; Inouchi, Kubota, Ferrari & Roberts, 2003) others have found that duration increments result in stronger MMNs in humans (Catts et al., 1995) and mismatch responses in animals (Nakamura et al., 2011 in rats) than decrements. Furthermore, in some studies no differences have been found in the MMN elicited by increments and decrements (Amenedo & Escera 2000; Jaramillo, Paavilainen, & Näätänen, 2000), and differences have also been found only in the latencies, but not in the magnitude of the responses

(Okazaki, Kanoh, Takaura, Tsukada & Oka, 2006; in quinea pigs). The inconsistency of the results can to a certain extent be explained by the methodological differences between the studies. The studies have differed for example in respect of the length and the sound type (sinusoidal, spectrally complex, vowel…) of the applied stimuli, both of which have been suggested to have impact on whether the sound duration increments or decrements result in stronger MMNs in humans. The studies of the effect of stimulus length on decrement and increment MMN have implied that the lengthening of the stimuli leads to diminution of increment MMN, whereas no effect has been found on decrement MMN (Colin et al., 2009; Takegata et al., 2008). Consistently with this, the studies that have found larger amplitudes of MMN or mismatch response to duration increments (Catts et al., 1995; Nakamura et al., 2012) have used relatively short stimuli compared to studies that have found greater responses to decrements (Inouchi et al., 2002 & 2003). On the other hand, even though some studies have indicated that the sound type has an influence on whether duration increments or decrements lead to larger MMN, the results have been contradicting (see Inouchi et al., 2008; Jaramillo et al., 1999; Takegata et al., 2008). Moreover, in addition to the traditional method of MMN calculation, in which the response to the standard sound is subtracted from the response to the deviant sound, other methods have also been employed in the calculation of MMN and mismatch negativity. This is noteworthy, as some studies in humans have indicated that the traditional method of MMN calculation might lead to underestimation of the decrement MMN (Jacobsen & Schröger, 2003; Peter, McArthur & Thompson, 2010).

The present study measured intracranial local field potentials (LFPs) to sound duration changes in the auditory cortex and CA1 of hippocampus of urethane-anesthetized rats in oddball condition. As previously mentioned, mismatch response studies in animals are necessary in clarifying which structures contribute to automatic change detection, since the electrophysiological responses of certain brain structures such as hippocampus cannot be studied reliably by non-invasive methods in human subjects. Moreover, studies of mismatch response in rats are important in gaining exact knowledge of the similarities and differences between human MMN and rodent mismatch response for the development of animal models of disorders such as schizophrenia in these animals (Bickel & Javitt, 2009). We expected to observe mismatch responses in the auditory cortex and hippocampus, as previous animal studies have indicated that also hippocampus, in addition to auditory cortex, plays a role in auditory change detection (Ruusuvirta et al., 2010; Ruusuvirta et al., 2013). To study the bearing of duration deviance direction on amplitudes of mismatch response, sinusoidal sounds of 25 and 75 ms in duration were used as standard and deviant sounds in two conditions, so that in the ‘decrement condition’ the standard sounds were 75 ms and deviant sounds 25 ms, and in the ‘increment condition’ the stimuli were reversed. Stronger increment than decrement mismatch

responses/MMNs have been observed in the auditory cortex of rats and humans in the previous studies that have applied stimuli relatively similar of their length and sound type to those used in the present study (Catts et al., 1995, sinusoidal tones of 50/100; Nakamura et al., 2011, sinusoidal tones of 50/150). Moreover, no decrement mismatch response was found in the auditory cortex or hippocampus of rats in the study by Ruusuvirta et al., (2013) which applied the exactly same stimuli as the present study in decrement condition, lending more support to the hypothesis of the superiority of duration increments in eliciting mismatch responses with these stimulus parameters. Therefore we hypothesized that stronger mismatch responses would be elicited by duration increments than by decrements both in the auditory cortex and CA1. Also, as the intervals between the stimuli have been proposed to have bearing on auditory change detection, we applied two conditions with different inter-stimulus intervals (ISIs of 200/500 ms) to study this effect. Some of the previous studies have implied that short intervals between the stimuli are related to strong mismatch responses in animals (Astikainen et al., 2011; Astikainen, Ruusuvirta & Korhonen, 2005) and MMNs in humans (Jääskeläinen, Hautamäki, Näätänen & Ilmoniemi, 1999; Mäntysalo & Näätänen, 1987). However, MMNs have been elicited both with very long and short ISIs (see Näätänen, 1992, for a review) and the effect of ISI on the amplitudes of MMN has been found to be surprisingly small in some studies (Böttcher-Gandor & Ullsperger, 1992; Sams, Hari, Rif & Knuutila, 1993). Moreover, it has been proposed that when ISI gets really short and the probability of the deviant sounds is kept the same (as in the present study), the shortening of the interval between the deviant sounds, the inter-deviant interval, results in the weakening of the MMN (Näätänen, 1992). Studies in both humans and animals have found evidence of the deteriorating effect of short inter-deviant intervals on MMN/mismatch response (Javitt, Grochowski, Shelley & Ritter, 1998; Sabri & Campbell, 2001 in humans; Pincze, Lakatos, Rajkai, Ulbert and Karmos, 2002 in cats). Therefore it was hypothesized that the ISI of 200 ms might be too short to be optimal for the elicitation of mismatch response and greater mismatch responses were expected to be elicited with the ISI of 500 ms.

METHODS

Animals and surgery

Two groups of rats were used in the experiment. Group 1 consisted of ten and group 2 of eleven Spraque Dawley rats (weight 305 – 375 g). The animals were housed as groups in cages with water

and feed ad libitum. The animals were anaesthetized with urethane (Sigma-Aldrich, St. Louis, MO, USA) i.p. (1.2 g/kg). The level of anesthesia was controlled by pedal withdrawal reflex, and if necessary, extra doses of urethane were given. The animal was positioned in a streotaxic instrument with blunt ear bars which afterwards were removed to allow auditory stimulation. Under lidocaine anesthesia (Lidocain 20%, Orion Pharma, Espoo, Finland) skin and muscle tissue were removed to expose unilaterally a 2 x 2 mm region over the left primary auditory cortex (from bregma anterior posterior (AP): -4.5 – (-6.5) mm, dorsoventral (DV) 3 – 5 mm lateral to the bone edge of the upper skull surface).

A tip of a Teflon-insulated stainless steel wire (diameter 200 µm, A-M Systems, Carlsberg, WA, USA) was positioned on the surface of the dura above the auditory cortex on the basis of on-line recorded potentials. In addition, intracranial electrodes were implanted (Formwar® insulated stainless steel wire, diameter 100 µm, California Fine Wire Company Co, Grover Beach, CA, USA). Two electrodes with 400-µm tip separation were lowered to the ventral subiculum to coordinates AP: -6.5 mm, ML: 5.5 mm and DV 6.6. Three intermediate (caudal) hippocampal electrodes with 0.6 mm spacing between electrodes were lowered to coordinates AP: 6.0 mm, ML: 4.8, 5.4 and 6.0 mm, and DV: 4.6 mm. Based on histology, electrodes located in the area of interest were selected for further analysis. For the reference electrode, a hole was drilled in the scull over the right side of the cerebellum and a small insulin needle (BD Lo-Dose syringe, USA) was inserted in the cerebellum (AP -10 mm, ML: 2-3 mm and DV: 2 mm) and the animal was grounded by inserting a needle (18G, Terumo, Somerset, NJ, USA) subcutaneously into the neck.

Auditory stimulus paradigms

Sinusoidal tones of 25/75 ms in duration, including 5-ms rise and fall times, were used as stimuli. For the rats in group 1, tones of 75 ms were used as standard sounds and the tones of 25 ms as deviant sounds (decrement condition), for group 2 the stimuli were reversed (increment condition). The probability of the deviant sound was 0.1, and there were always at least two standard sounds between deviant sounds. There were two stimulus conditions with different inter-stimulus intervals for both of the groups, ISI being 200 ms in the first condition and 500 ms in the second. For the group 1 there were also other stimulus conditions but they are reported elsewhere (Ruusuvirta et al., 2013). The tones were created using the Adobe Audition software (Adobe Systems Incorporated, CA, USA), and played from a PC via an active loudspeaker system (Studiopro 3, M-audio, Irwindale, CA, USA). The stimulation was presented with the passive part of the loudspeaker system directed towards the right ear of the animal at a distance of 20 cm. In all conditions, the

sound pressure level for each tone was 70 dB, as measured with a sound level meter (type 2235, Bruel & Kjaer, Nærum Denmark) with C-weighting (optimized for 40-100 dB measurement) in the location where the animal's right pinna was during the recording.

Electrocortical and hippocampal recordings

After surgery, the right ear bar was removed and recording started. Continuous electrocorticogram and hippocampal EEG were first 10-fold amplified using the MPA8I preamplifier (Multichannelsystems, Reutlingen, Germany), high-pass filtered at 0.1 Hz, 50-fold amplified, and low-pass filtered at 5000 Hz using an FA32I filter amplifier (Multichannelsystems), low-pass filtered at 400 Hz using a CyberAmp 380 filter amplifier (Molecular Devices Corporation), and finally sampled with 16-bit precision at 2 kHz (DigiData 1320A, Molecular Devices Corporation). The data were stored on a computer hard disk using Axoscope 9.0 data acquisition software (Molecular Devices Corporation).

Data analysis

The data analyses were performed offline using a Vision Analyzer (Brain Products, Gilching, Germany), Matlab 7.5 (MathWorks Inc., Natick, MA, USA). Electrodes successfully implanted in the targeted areas in hippocampus were applied in the analysis. However, from group 2 two animals were left out of the analysis in CA1 and one animal in the auditory cortex to match sample sizes to those of group 1 (8 animals for both groups in CA1 and 10 for both groups in the auditory cortex). Even though there were electrodes implanted in other parts of hippocampus, only results relating to CA1 are reported here in addition to results from the auditory cortex.

First, artifacts were removed from the data. Electrocorticogram epochs containing voltage steps larger than 300 µV/ms were deleted for 200 ms before and after the artifact. Visual inspection of the data revealed that no other types of artifacts were present in the data.

The data were then offline-filtered (0.1–20 Hz, 24 dB/octave, Butterworth Zero Phase filters), segmented (for each deviant sound and standard sound immediately preceding it), and baseline corrected against the mean activity in the ±25 ms from tone onset and, hence in the 50-ms time window prior to duration deviance.

Finally, the artifact-free segments were averaged for each animal separately for deviant stimuli and immediately preceding standard stimuli for each condition. Not less than 67 out of 100 sweeps

in group 1 and 97 out of 100 sweeps in group 2 were included in calculating the average values per stimulus type and ISI condition both in the auditory cortex and CA1. The average number of sweeps was between 96.1 and 97.6 sweeps for both stimulus types, ISI types and brain areas in group 1 and between 99.7 and 99.9 in group 2.

The statistical analyses were performed with SPSS for Windows (SPSS Inc., Chicago, IL, USA). On the basis of visual inspection the range of 25-149.5 ms after change onset was taken into analysis and divided into five analysis windows (25-49.5, 50-74.5, 75-99.5, 100-124.5, and 125-149.5 ms after change onset) to study whether the responses emerge at the same latency range in the auditory cortex and CA1. ANOVA for repeated measures with stimulus (standard, deviant) and ISI (200, 500) as within subject factors and deviant type (increment, decrement) as between subject factor was applied separately for different analysis windows. Degrees of freedom were Greenhouse-Geisser corrected whenever the sphericity assumption was violated, and corrected P values were reported. Pairwise deviant-standard comparison was made using the paired t test (two-tailed). An alpha level of 0.05 was used in analyses, but t-tests were conducted also to ANOVA effects that were nearly significant (<0.06).

Histology

After recording, the tips of the intracranial electrodes were marked in the tissue by anodal 30-µA 5-s current. The animal was sacrificed by cervical dislocation and the brain was removed from the skull and left for immersion post-fixation for 4 h in 4 % paraformaldehyde (PFA) solution and after that in 30 % sucrose solution for two days. The brains were stored in -20 °C until slicing. Coronal sections (thickness 35 µm) were cut with a freezing slide microtome. The electrode locations were verified from the sections by cresyl violet staining and the exact locations of the electrode tips were confirmed by microscope observation.

RESULTS

Auditory cortex

As shown in figure 1, both standard and deviant sounds evoked a positive deflection that peaked at about 40 ms from the stimulus onset (i.e. not from change onset) in all conditions. On the basis of visual inspection it seemed that LFPs elicited by standard and deviant sounds differed from each

other, but only in the increment condition. The difference seemed to be larger when ISI was 500 ms than when it was 200 ms.

An interaction between stimulus type, deviant type and ISI type was found in the fourth and fifth analysis window (100 – 149.5 ms from change onset), F (1, 18) = 5.308 – 6.339, p = 0.033 – 0.021, and a nearly significant trend towards this effect was found in the third analysis window (75-99.5 ms from change onset), F (1, 18) = 4.278, p = 0.053. t-tests revealed a significant difference between the response elicited by the standard and deviant sounds in the increment condition in all three analysis windows, the significance of the difference, however, being greater when ISI was 500 ms, t (9) = 4.311 – 4.828, p = 0.002 – 0.001 than when it was 200 ms, t (9) = 2.362 – 3.687, p = 0.042 – 0.005.

Interaction between deviant type and stimulus type was found in all five analysis windows (25 – 149.5 ms from change onset), F (1, 18) = 6.061 – 22.140, p = 0.024 – < 0.001, alongside with an interaction between ISI type and stimulus type in the fourth analysis window (100 – 124.5 ms from change onset), F (1, 18) = 5.569, p = 0.030. As no three-way interactions were found in the first two analysis windows (25 – 74.5 ms from change), the values for the two ISI conditions were averaged for the different deviant types and t-tests were conducted to these. Deviant sounds were found to elicit significantly larger LFPs than standard sounds in the increment condition t (9) = 2.737 - (-3.633), p = 0.023 – 0.005, whereas no significant difference was found between standard sounds and deviant sounds in the decrement condition.

A main effect of stimulus type was found in all analysis windows except for the very first (i.e. 50 – 149.5 ms after change onset), F (1, 18) = 6.061 – 13.029, p = 0.024 – 0.002. Main effect of deviant type was found in the third, fourth and fifth analysis windows (75 - 149.5 ms from change) F (1, 18) = 5.201 – 7.071, p = 0.035 – 0.016. No main effect of ISI was found.

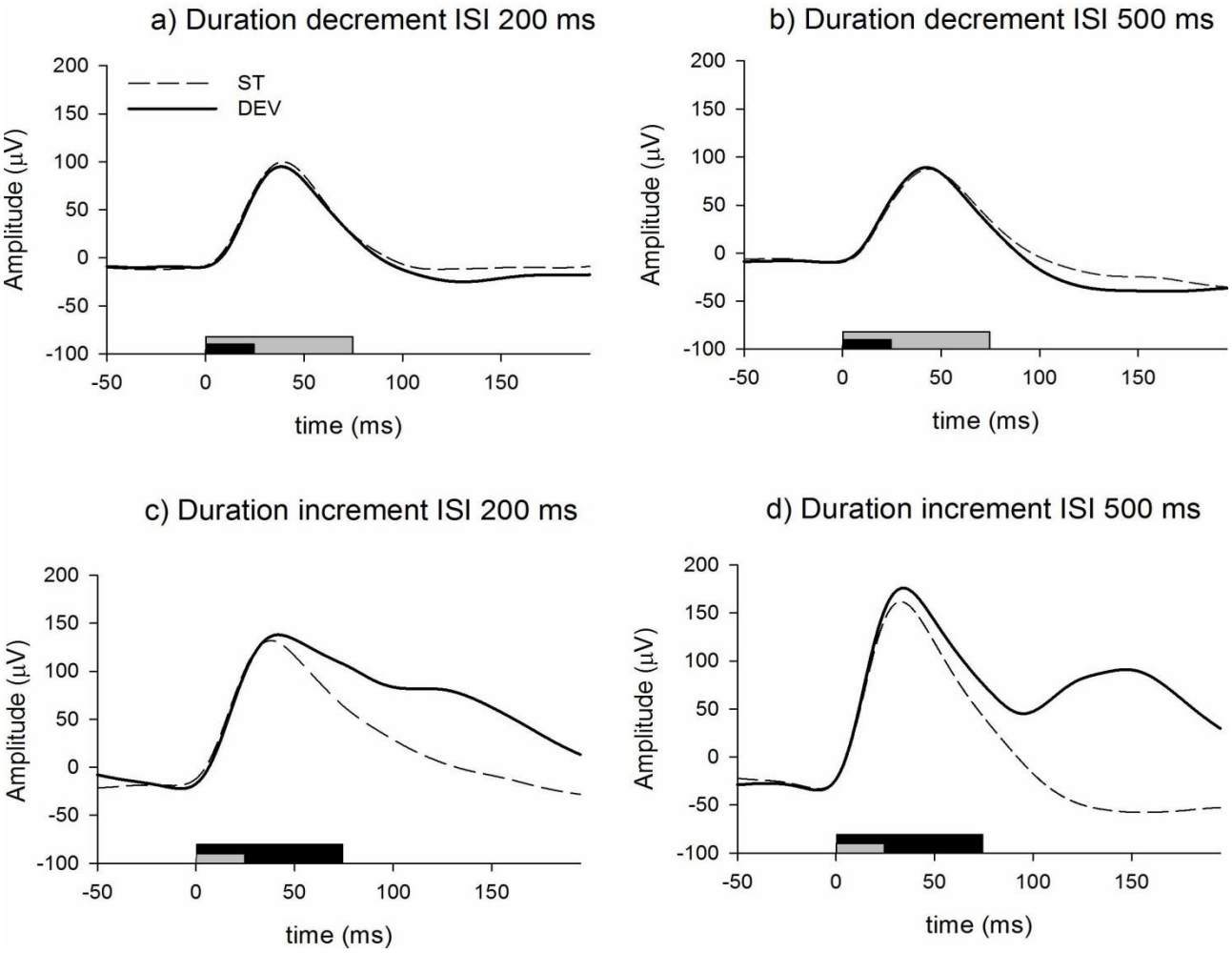

FIGURE 1.Grand-averaged local field potentials (LFPs) to standard and deviant sounds in different stimulus conditions in the auditory cortex. The change onset occurs at 25 ms after stimulus onset in all stimulus conditions. LFPs elicited by deviant sounds are depicted by solid lines and LFPs elicited by standard sounds by dashed lines. The black bar represents the deviant sound and the grey bar the standard sound. In the decrement condition (a & b) deviant sounds were 25 ms and standard sounds 75 ms in duration, and in the increment condition (c & d) deviant sounds were 75 ms and standard sounds 25 ms in duration. Two blocks of stimuli with different inter-stimulus intervals, ISI of 200 ms (a & c) and ISI of 500 ms (b & d), were applied for both increment and decrement condition.

TABLE 1. P-values from ANOVA and post hoc tests. Effects of stimulus type, inter-stimulus interval and deviant type on response amplitudes measured from the auditory cortex were tested in ANOVA for repeated measures, separately for five analysis windows (ms after change onset). P-values of main effects and interactions tested in ANOVA are expressed in black text. Standard and

deviant response amplitudes were compared in post hoc paired t- tests (p-values in grey text) for those ANOVA effects that reached significance (alpha level .05) or were nearly significant (<0.06).

	25-49.5	50-74.5	75-99.5	100-124.5	125-149.5
Stimulus type	.067	.024*	.002**	.002*	.004*
ISI	.812	.126	.071	.176	.290
Deviant type	.053	.082	.035*	.016*	.018*
Stimulus type* ISI	.791	.523	.165	.030*	.054
Stimulus type* Deviant type	.024*	.004**	<.001**	<.001**	.001**
Short deviant	.673	.523			
Long deviant	.023*	.005**			
ISI*Deviant type	.397	.065	.191	.824	.586
Stimulus type* ISI*Deviant type	.940	.938	.053	.021*	.033*
Short deviant ISI 200			.416	.306	.563
Short deviant ISI 500			.248	.164	.228
Long deviant ISI 200			.005**	.016*	.042*
Long deviant ISI 500			.001**	.001**	.002**

*P<0.05, ** P<0.01.

CA1 of the hippocampus

As shown in figure 2, in CA1 a negative deflection peaked at about 40 ms after stimulus onset (i.e. not from change onset) for both standard and deviant sounds. The responses elicited by deviant sounds seemed to be more negative than those elicited by standard sounds in the increment condition.

A nearly significant interaction between stimulus type and ISI type was found in the first analysis window (25-49.5 ms from change onset), F (1, 14) = 4.275, p = 0.058, and in the second window (50-74.5 ms from change onset) this interaction reached significance, F (1, 14) = 4.891, p = 0.044. Values of the deviant types were averaged for both ISI types, and t-tests were conducted to these. The difference between LFPs elicited by standard and deviant sounds was found to be significant only when ISI was 500 ms, t (7) = -2.602 – (-3.043), p = 0.035 - 0.019.

Interaction between deviant type and stimulus type was found in all but the first analysis window (i.e. 50-149.5 ms from change onset), F (1, 14) = 4.631 – 22.680, p = 0.049 - < 0.001. When values of ISI types were averaged for both deviant types t-tests revealed that responses to duration increments differed significantly from responses to standard sounds, t (7) = -2.806 – (-5.241), p =

0.026 – 0.001, whereas no significant difference was observed between the responses to duration decrements and standard sounds. No main effects were found.

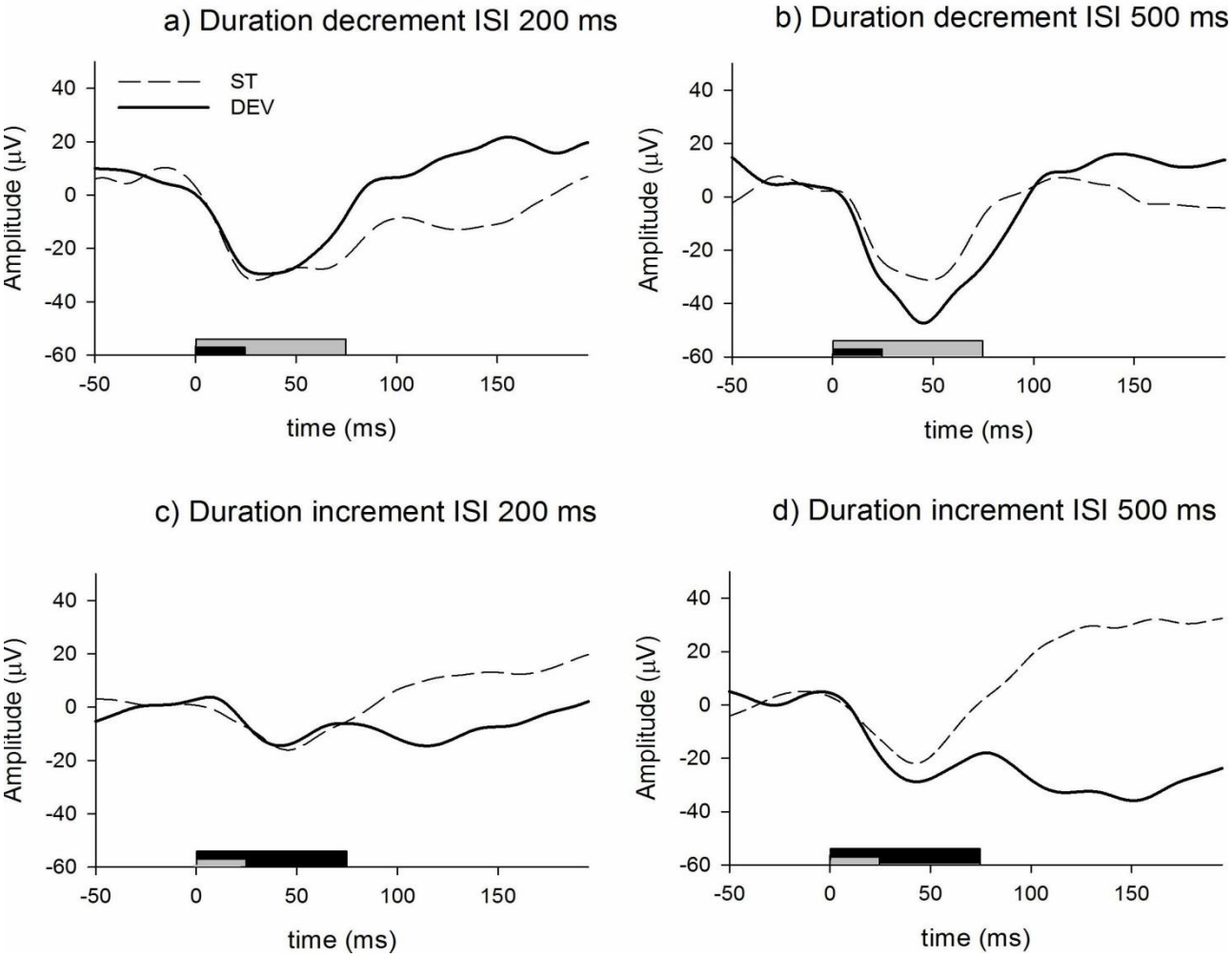

FIGURE 2. Grand-averaged local field potentials (LFPs) to standard and deviant sounds in different stimulus conditions in CA1 of hippocampus. The change onset occurs at 25 ms after stimulus onset in all stimulus conditions. LFPs elicited by deviant sounds are depicted by solid lines and LFPs elicited by standard sounds by dashed lines. The black bar represents the deviant sound and the grey bar the standard sound. In the decrement condition (a & b) deviant sounds were 25 ms and standard sounds 75 ms in duration, and in the increment condition (c & d) deviant sounds were 75 ms and standard sounds 25 ms in duration. Two blocks of stimuli with different inter-stimulus intervals, ISI of 200 ms (a & c) and ISI of 500 ms (b & d), were applied for both increment and decrement condition.

TABLE 2. P-values from ANOVA and post hoc tests. Effects of stimulus type, inter-stimulus interval and deviant type on response amplitudes measured from CA1 were tested in ANOVA for repeated measures, separately for five analysis windows (ms after change onset). P-values of main

effects and interactions tested in ANOVA are expressed in black text. Standard and deviant response amplitudes were compared in post hoc paired t- tests (P-values in grey text) for those ANOVA effects that reached significance (alpha level 0.05) or were nearly significant (<0.06).

	25-49.5	**50-74.5**	**75-99.5**	**100-124.5**	**125-149.5**
Stimulus type	.315	.131	.070	.145	.139
ISI	.412	.874	.697	.852	.747
Deviant type	.152	.920	.462	.508	.624
Stimulus type*	.058	.044*	.086	.064	.128
ISI					
ISI 200	.452	.561			
ISI 500	.035*	.019*			
Stimulus type*	.714	.049*	.003**	.001**	< .001**
Deviant type					
Short deviant		.724	.238	.095	.085
Long deviant		.026*	.011*	.003**	.001**
ISI*Deviant type	.951	.906	.562	.489	.128
Stimulus type*	.750	.791	.588	.450	.327
ISI*Deviant type					

*P<0.05, ** P<0.01.

DISCUSSION

We studied whether duration deviant sounds elicit mismatch responses in the auditory cortex and CA1 of hippocampus in urethane-anesthetized rats in oddball condition, and whether the duration deviance direction has a bearing on mismatch response. Furthermore, the effect of inter-stimulus interval on change detection was investigated. Differential LFPs to standard and deviant sounds were observed both in the auditory cortex and in the CA1 at a latency range of 25 – 149.5 milliseconds after change onset. The duration deviance direction and ISI were found to have bearing on the elicitation of mismatch response both in the auditory cortex and hippocampus, although these effects appeared at a different time range in these two areas. In the auditory cortex, only duration increments were found to elicit mismatch responses, and in the time range of 75 - 149.5 ms after change onset these responses were found to be larger when ISI was 500 ms than when it was 200 ms. In CA1 no effect of deviance direction was found in the time range of 25 - 49.5ms after change onset, but between 50 - 149.5 ms after change onset only duration increments

were found to elicit mismatch responses. The effect of ISI was found only in the time range of 25 - 74.5 ms after change onset, and in this time range differential responses to standard and deviant sounds were elicited only when ISI was 500 ms.

Mismatch responses in the auditory cortex and CA1

Contrary to the few studies conducted with intracranial electrodes in human subjects (Kropotov et al., 1995; Rosburg et al., 2007), previous studies in animals have lent support for the role of hippocampus also in automatic, pre-attentive change detection (Ruusuvirta et al., 2010; Ruusuvirta et al., 2013), in addition to its contribution to the generation of the orienting response (Sokolov, 1975). The latency range (25 – 149.5 milliseconds after change onset) of the responses observed in the present study is similar to mismatch responses observed in the auditory cortex of rats in the previous studies (Ahmed et al., 2011; Roger et al., 2009; Ruusuvirta, Penttonen & Korhonen, 1998), whereas P3a (reflecting the involuntary shifting of attention) has been found to appear considerably later in awake rats, at about 240 ms after change (Yamaguchi, Globus & Knight, 1993). Also, the positive polarity of auditory cortical responses corresponds to mismatch responses elicited in the previous studies in urethane-anesthetized rats (e.g. Ahmed et al., 2011; Astikainen et al., 2011; Ruusuvirta et al., 2013). The simultaneous occurrence of responses in the auditory cortex and CA1 of hippocampus suggests that both structures contribute to auditory duration change detection and to the generation of mismatch response. However, the possibility that the emergence of response in hippocampus is due to transmission of the electric current from auditory cortex to hippocampus cannot be discounted.

The effect of duration deviance direction

Increments in sound duration were found to lead to strong mismatch responses. Mismatch responses to sound decrements, however, were totally absent in the auditory cortex and found only in one of the applied analysis windows in the hippocampus. These results are consistent with the studies by Catts et al. (1995) in humans and Nakamura et al. (2012) in rats, in which short duration sinusoidal sounds were applied as stimuli similarly to the present study. In the former study decrement MMN was found to be considerably weaker than increment MMN, and in the latter study no decrement mismatch response was observed. However, whereas the aforementioned studies have investigated the effect of duration deviance direction only in the auditory cortex, the present study expanded the findings to hippocampus. At least two explanations could be given to explain the differential

mismatch responses to sound duration increments and decrements. Firstly, stronger responses to duration increments could reflect greater biological significance of discriminating duration increments than decrements, as has been proposed to be the case with frequencies (Astikainen et al., 2011). Secondly, the physical differences between the sounds themselves could cause the difference, by affecting other components of the event-related potentials than mismatch response. For example sound offset responses and sustained potentials that last as long as the sounds eliciting them occur at a different time range for sounds of different durations (see Näätänen, 1992, p. 133 for a review). Studies in humans have implied that the different timing of these responses might lead to underestimation of the decrement MMN because of two reasons when MMN is calculated by using the traditional method, that is, when the response to the standard sound is subtracted from the response to the deviant sound. The longer standard sound might elicit a response occurring at the same time and with the same polarity (negative) as MMN to the short deviant sound, and thus the difference between the responses elicited by standard and deviant sounds would diminish (Jacobsen & Schröger, 2003). Moreover, the early offset of the short deviant sound could lead to early offset response that is of an opposite polarity (positive) compared to MMN and this could thus diminish the response elicited by the deviant sound (Peter, MacArthur & Thompson, 2010). These explanations are supported by the studies that have found that the duration decrement MMN that is absent when the traditional method of MMN calculation is used, emerges when MMN is calculated by comparing response to the deviant sound to response to the same stimulus presented as a standard sound in other stimulus block ('the reverse-standard-deviant method') (Jacobsen & Schröger, 2003; Peter et al., 2010). However**,** in the study by Nakamura et al. (2012), in which mismatch responses were found to duration increments but not to decrements in rats, the reverse-standard-deviant method was used. Therefore these findings cannot be explained by differences between the standard and deviant sounds themselves.

However, the studies that have found greater increment than decrement mismatch responses and MMNs have used short duration sounds as stimuli. In human studies the use of long duration stimuli has been found to lead to weaker increment MMN or to its total disappearance, regardless of the calculation method of MMN, whereas no similar effect has been found on decrement MMN (Colin et al., 2009; Takegata et al., 2008). In these studies the weakening of the increment MMN when the stimuli are lengthened has been proposed to result from the widening temporal gap between the moment of change detection and the moment when information about the magnitude of the change is present, as the magnitude of the change is known to affect the amplitudes of MMN. On the other hand, when duration decrements are used this information is observable at the moment

of the change regardless of the length of the sounds, and therefore their length does not affect decrement MMN.

The effect of inter-stimulus interval

The ISI of 500 ms was found to be more optimal for the elicitation of mismatch response than ISI of 200 ms. In general, the lengthening of the ISI is thought to result in poorer formation of memory trace of the standard sound and/or in more deteriorated memory trace of the standard sound when it is compared with the deviant sound and therefore it is expected to lead to weaker MMN (Jääskeläinen et al., 1999). However, the previous studies researching the effect of ISI on mismatch response and MMN have applied considerably longer ISIs than those used in the present study (Astikainen et al., 2005: Astikainen et al., 2011; Jääskeläinen et al., 1999; Mäntysalo & Näätänen, 1987). The ISI of 200 ms used in the present study might have been too short to be optimal due to the shortening of the inter-deviant interval as the memory trace of the previous deviant sound might have still existed while the next deviant sound was delivered (see Näätänen, 1992, p. 153). This is consistent with the studies by Javitt et al., (1998) in humans and Pincze et al., (2002) in cats, in which short ISIs (< 500 ms) were used and the shortening of the inter-deviant interval was associated with deterioration of MMN/mismatch response. However, as the inter-deviant interval is determined on the basis of both the length of ISI and the probability of the deviant sounds, both of these factors must be taken into account when trying to avoid the diminution of mismatch response due to the shortening of the inter-deviant interval.

Limitations of the present study

There are a few limitations in the present study. Firstly, as there is evidence that the processing of duration is carried out by duration-specific neurons that respond most strongly to sounds of certain durations (Aubie, Sayegh & Faure, 2012; Brand, Urban & Grothe, 2000; Casseday, Ehrlich & Covey, 1994: He, Hashikawa, Ojima & Kinouchi, 1997) a control paradigm would have been needed to control the so called refractoriness effects. It is thought, that as a consequence of repetitive presentation of the standard sound, the neural population processing it becomes more refractory than that processing the rarely presented deviant sound, and therefore the response elicited by the deviant sound is stronger than the attenuated response by the standard sound (May & Tiitinen, 2010). The human MMN is found to be generated by a memory-based comparison process

between the standard and the deviant sound and the detection of the deviant sound as a change in the standard sound, that is, it is not only a result of differential refractoriness of neural populations processing the standard and deviant sounds (Näätänen, Jacobsen & Winkler, 2005). Previous studies using frequency deviant sounds have indicated that auditory cortical mismatch responses in both awake and urethane-anesthetized rats and mismatch responses in the rabbit hippocampus reflect such change-specific processes in similar manner as in humans (Astikainen et al., 2011; Nakamura et al., 2012 in rats; Ruusuvirta et al., 2010 in rabbits). However, further studies applying control procedures such as equal probability condition should be conducted to verify that mismatch response to duration deviant sounds in rats is also analogous to duration MMN in humans. Secondly, two groups of rats were used to study the effect of duration deviance direction on mismatch response. One could argue that the almost total absence of mismatch response to duration decrements results from poorer physical state of the rats in this group or from some defect in the measurements conducted to this group. However, as mismatch responses were found also with this group of rats for another stimulus condition (reported in Ruusuvirta et al., 2013 study), it seems that the results reflect genuinely differential responses to duration increments and decrements, and are not only a consequence of the use of different groups of rats. Thirdly, the sample size was smaller in CA1 than in the auditory cortex and accordingly the degrees of freedom were different in the statistical analyses conducted to study responses in these two brain areas.

Future directions

The results of the present study entail several implications for future research. First, the results indicated that hippocampus might be involved in change detection and generation of mismatch response. These results should be taken into account both in theory construction and in practice, for example when conducting source location studies of human scalp-recorded EEG. Second, the mismatch response of a rat was found to be sensitive to the shortening of ISI from 500 ms to 200 ms and consecutive shortening of inter-deviant interval. Similar deterioration of MMN due to shortening of the inter-deviant interval has been found in humans (Javitt et al., 1998; Sabri & Campbell, 2001), and this similarity lends further support for the feasibility of using rats when studying both the normal generation of MMN and when developing animal models for disorders that are characterized by disrupted generation of MMN, like schizophrenia. Thirdly, consistently with previous animal and human studies the duration deviance direction was found to have bearing on the elicitation of mismatch response, although the reasons for this are unknown. Moreover, even though the present study did not address the issue, it seems that also the length of the stimuli,

calculation method of mismatch response and possibly also the sound type (sinusoidal, spectrally complex, vowel..) of the stimuli should be planned cautiously in conjunction with duration deviance direction in order to avoid erroneous negative results arising from careless research design. Further studies that systematically employ varying sound durations, sound types and the calculation methods of mismatch response together with duration increments and decrements are needed to clarify how changes in these factors affect decrement and increment mismatch responses and what are the mechanisms explaining these effects. These studies should also be conducted in both humans and animals, to examine whether these effects and mechanisms operate similarly across species.

Conclusion

We observed mismatch responses to sound duration changes in the hippocampus and auditory cortex of urethane-anesthetized rats. These results indicate that also hippocampus has a role in auditory change detection that occurs regardless of the direction of attention and might thus contribute to the generation of human MMN. Moreover, the duration deviance direction and inter-stimulus interval were found to affect mismatch response. These results should be taken into account when conducting future studies, but as the results are consistent with the studies of human MMN (Catts et al., 1995; Javitt et al., 1998; Sabri & Campbell, 2001), they also encourage to the use of rats when modeling healthy and abnormal brain functions related to auditory change detection and generation of MMN.

CONTRIBUTIONS

Piia Astikainen: experimental design, writing of the "methods" section
Timo Ruusuvirta: experimental design
Petri Kinnunen: stimulus materials
Arto Lipponen: data recording, histology, writing of the "methods" section
Mustak Ahmed: assisting in data recording
Eeva Pellinen: writing of the thesis

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