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Early change detection in humans as revealed by auditory brainstem and middle-latency evoked potentials

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Keywords: ABR, change detection, mismatch negativity (MMN), MLR, sensory memory

Abstract

The ability to detect unexpected novel stimuli is crucial for survival, as it might urge a prompt adaptive response. Human auditory novelty detection has been associated to the mismatch negativity long-latency auditory-evoked potential, peaking at 100–200 ms. Yet, recent animal studies showing novelty responses at a very short latency (about 20–30 ms) in individual neurons already at the level of the midbrain and thalamus suggest that novelty detection might be a basic principle of the functional organization of the auditory system, expanding from lower levels in the brainstem along the auditory pathway up to higher-order areas of the cerebral cortex. To test this suggestion, we here measured auditory brainstem and middle latency response (MLR) to frequency novel stimuli embedded in an oddball sequence. To oversee refractoriness confounds a ‘control block’ was used. The results showed that occasional changes in auditory frequency information were detected as early as 30 ms (Pa waveform of the MLR) after stimulus onset. The control block precluded these effects as resulting merely from refractoriness, altogether supporting the notion of ‘true’ early auditory change detection in humans, matching the latency range of auditory novelty responses described in individual neurons of subhuman species. Our results suggest that auditory change detection of frequency information is a multistage process that occurs at the primary auditory cortex and is transmitted to the higher levels of the auditory pathway.

Introduction

The detection of unexpected events in the acoustic environment is crucial for survival, as preparing the organism for rapidly changing surrounding conditions. Change detection has been associated to a particular brain response, the mismatch negativity (MMN; Naatanen et al., 1978), derived from the auditory-evoked potential (AEP) as recorded with the oddball paradigm. In this paradigm, rare novel (deviant) stimuli are embedded within a sequence of repeating homogenous (standard) stimuli. Subtracting the AEP elicited to the standard stimuli from that to the deviant stimuli, a negative deflection, the MMN, is obtained at approximately 100–200 ms after the stimulus onset. According to the accepted account, the MMN is thought to reflect that the acoustic regularity embedded in the standard stimulus repetition has been extracted and encoded into a memory trace (Winkler, 2007).

Recent results from single-unit recordings in animals using an oddball paradigm establish the premises for new questions in humans. Indeed, Ulanovsky et al. (2003) described the existence of neurons in the primary auditory cortex of the cat that show strong stimulus-specific adaptation (SSA) to a repeating stimulus, but restore their firing rates at the occurrence of any change in the stimulus features. Additional primary cortical contribution has been reported by von der

Behrens et al. (2009). Further data have shown the existence of SSA along the subcortical auditory pathway, including the thalamus (Anderson et al., 2009; Antunes et al., 2010) and the inferior colliculi (Perez-Gonzalez et al., 2005; Reches & Gutfreund, 2008; Malmierca et al., 2009). Taken together, these results suggest that the MMN recorded from the human scalp might be preceded by earlier novelty-related activity, and that the detection of novel sounds in humans might involve different levels of the auditory system. Consequently, the detection of rare deviant stimuli can be considered as a multi-stage process, implemented in the auditory pathway from the brainstem up to higher-order areas of the cortex.

In contrast to the large amount of research in humans dealing with this neurophysiological phenomenon, limited data exist on early processing stages involved in the detection of novel sounds. One study in humans obtained deviance-related responses as early as 25 ms from stimulus onset using an oddball paradigm (Sonnadara et al., 2006). The lack of a proper control condition in this study, however, does not allow relating this neural response to ‘true’ novelty detection. One way to overcome this limitation is to implement a ‘control condition’ to rule out the refractoriness effects by presenting the same physical stimulus used as deviant in the oddball block with the same probability, but embedded in a context of other rare stimuli (Schroger Wolff, 1996).

The present study aimed at testing whether the detection of frequency changes was already reflected in early stages of human auditory processing. For that purpose, a typical frequency oddball

paradigm and the corresponding control conditions were used, while the parameters of electroencephalogram (EEG) acquisition were adjusted to record simultaneously the auditory brainstem (ABRs) and the middle latency responses (MLRs) in a sample of healthy human subjects.

Materials and methods

Eighteen volunteers (aged 18–29 years, 11 females, three left-handed) with audiometric thresholds below 25 dB SPL for the five different frequency bands used in the experiment were included in the study. Threshold values were obtained for each experimental auditory stimulus from 0 to 60 dB SPL in 5-dB increments, for each ear. All values were measured three times and the threshold was determined as the average of the three measurements. The experimental protocol was approved by the Ethical Committee of University of Barcelona, and was in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki). Subjects were paid for their participation and written informed consent was obtained from each participant prior to the experiment.

Stimuli and procedure

The auditory stimuli consisted of short bursts of band-pass-filtered broadband noises in the range 500–3000 Hz in steps of 500 Hz, generated with the Neurosoft (El Paso, TX, USA). They had a duration of 40 ms and were delivered monaurally via Beyerdynamic DT 48 A headphone (Heilbronn, Germany) to the right ear at an intensity of 80 dB SPL with a stimulus-onset asynchrony of 96 ms. The left ear was masked with white noise at an intensity of 60 dB SPL to prevent the early brain responses to be contaminated by a cross-heard response from the opposite cochlea (Gorga & Thornton, 1989). Three different conditions were used. First, an oddball condition was presented with a deviant probability of $P = 0.2$, in which the standard stimulus was a broadband noise band-pass-filtered from 500 to 1000 Hz (termed S1), and the deviant frequency was a broadband noise filtered from 1000 to 1500 Hz (termed S2); the stimulus sequence in this condition was constrained in a way that at least two standard stimuli followed each deviant stimulus. Second, a reverse oddball condition was applied, in which the deviant and standard stimuli used in the oddball condition switched their roles. Finally, a control condition was presented in which stimuli of five different band-pass-filtered broadband noises, 500–1000 Hz (S1), 1000–1500 Hz (S2), 1500–2000 Hz (S3), 2000–2500 Hz (S4) and 2500–3000 Hz (S5), were presented randomly, each with a probability of $P = 0.2$, as introduced by Schroger & Wolff (1996). A total of 60 000 stimuli were delivered in the three conditions, including 4000 deviants per oddball condition and corresponding relevant stimuli in the control one. Conditions were split into a total number of six blocks of 10 000 stimuli, each lasting approximately 16 min, which were arranged in a randomized order. During the experiment, subjects sat comfortably in a recliner chair in an acoustically and electrically shielded cabin. They were instructed to relax and to watch a silent movie with subtitles, while ignoring the auditory stimulation. After each run, subjects had a short break allowing for movements.

Data acquisition

ABRs and MLRs were both extracted from the same continuous EEG recording, which was acquired with a Neuroscan SynAmps amplifier and Scan software (NeuroScan, Herndon, VA, USA) from the Cz

electrode. Electrodes placed at the left ear lobe and forehead served as reference and ground, respectively. All electrode impedances were maintained below 5 k Ω . The continuous EEG was online band-pass-filtered from 0.05 to 1500 Hz. The data were collected at a sampling rate of 20 000 Hz and a gain of 5000.

Statistical analysis

Epochs for deviant, standard and the control stimuli were averaged separately. In order to obtain a similar number of trials for each type of stimuli, the average for standard stimuli only included those standard stimuli that strictly preceded the deviant stimuli.

Epochs for deviant stimuli, standard stimuli preceding immediately the deviant ones, and the control stimuli were averaged separately. To better isolate the different frequency characteristics of the corresponding brain responses in the two latency ranges of interest (ABR and MLR), different epoch duration, filtering and rejection criteria were used and therefore distinct averages were extracted from the raw EEG, one optimized to identify the ABR and one to determine the MLR. For the analysis of the ABR, data were filtered off-line with a band-pass filter from 100 to 1500 Hz. Averaged evoked potentials were baseline-corrected for a 30-ms interval before sound onset for the deviant, standard preceding the deviant and control stimuli. Trials with artefacts exceeding 35 μ V were rejected off-line (Russo et al., 2008). For MLR analysis, data were filtered off-line with a band-pass filter from 15 to 250 Hz (Baess et al., 2009). Averages were baseline-corrected for 50 ms before sound onset for the deviant, standard preceding the deviant and control stimuli. Trials with artefacts exceeding 80 μ V were rejected from further analysis. The waveforms V of the ABR and Na, Pa, and Nb of the MLR were identified for the three stimulus types and the two frequency ranges.

Individual peak latencies were measured as the maximum peak in the time windows 7–9 ms for waveform V of ABR, and 28–32 ms for waveform Pa of MLR, and as the minimum peak in the time windows 18–22 ms for the Na, and 41–43 ms for the Nb of the MLR. Mean amplitude instead of peak amplitude measurements were chosen in the present study to allow for a better signal-to-noise ratio while determining these minuscule neuroelectric responses (Picton et al., 2000). Thus, the mean amplitude of the wave V of the ABR was calculated in a 2-ms time window, and that of the Na, Pa and Nb waves of the MLR in a 4-ms time window, centred in both cases around the peak latency identified in the respective grand-averages.

The data were analysed by means of repeated-measures analyses of variance (ANOVA) on the mean amplitudes of the V and Na, Pa, Nb waveforms separately, including the factors Frequency (S1, S2) and Stimulus Type (deviant, standard, control). Bonferroni correction was applied to adjust for multiple testing, with the statistical significance being defined for values of $P < 0.016$. Post hoc pairwise differences between single levels of Stimulus Type were tested applying repeated measures contrasts. All significant effects for the post hoc evaluations were for values of $P < 0.05$. In addition, similar analyses were performed for the peak latencies of the V, Na, Pa and Nb waveforms elicited by deviant, standard and control stimuli.

Results

The control stimuli elicited robust ABR and MLR responses for the five different band-pass-filtered broadband noises used in the experiment (Fig. 1), with similar waveforms obtained for the control stimuli of interest, S1 and S2. Grand-average ABRs and MLRs to deviant, standard and control stimuli are shown in Fig. 2. In the grand-average

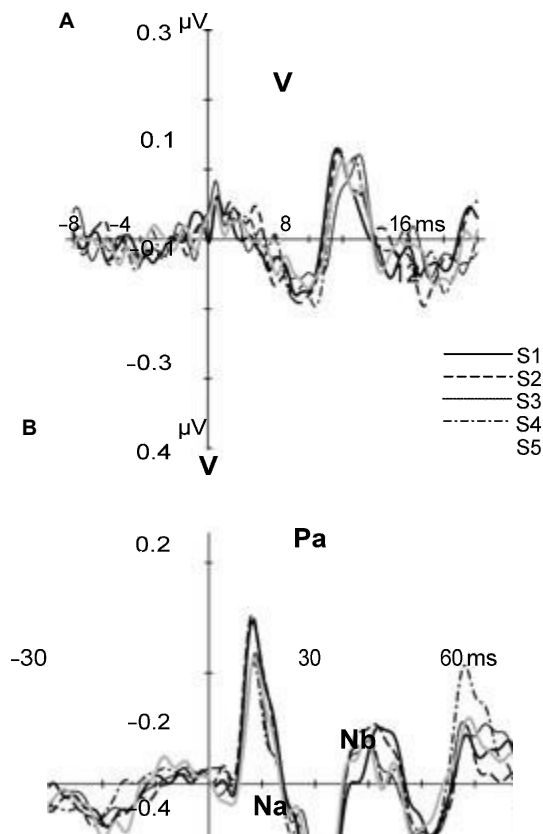


Fig. 1. Grand-average ABR (A) and MLR (B) of $N = 18$ subjects for the control stimuli: S1 (500–1000 Hz), S2 (1000–1500 Hz), S3 (1500–2000 Hz), S4 (2000–2500 Hz) and S5 (2500–3000 Hz) broadband filtered noises.

AEPs for all conditions we could clearly identify the waveforms V in the ABR, and Na, Pa and Nb in the MLR, with the corresponding mean amplitudes and mean peak latencies presented in Tables 1 and 2, respectively.

For the V component of the ABR, the repeated-measures anova revealed no significant effects of Frequency ($F_{1,17} = 0.794$, n.s.) or Stimulus Type effect ($F_{2,34} = 0.071$, n.s.) on its mean amplitudes. No significant difference in peak latency was observed either ($F_{1,17} = 0.486$, n.s.; $F_{2,34} = 0.337$, n.s.).

As for the MLR components, the repeated-measures anova showed that there were no significant effects of Frequency for the time windows of Na ($F_{1,17} = 0.237$, n.s.), Pa ($F_{1,17} = 0.726$, n.s.) and Nb ($F_{1,17} = 0.013$, n.s.). Remarkably, however, a Stimulus Type effect was observed for the time window of the Pa component ($F_{2,34} = 4.792$, $P = 0.015$), which did not become evident for any of the other components Na ($F_{2,34} = 0.920$, n.s.) and Nb ($F_{2,34} = 0.649$, n.s.). Similar analysis of the peak latency showed that there were no significant effects of Frequency (Na: $F_{1,17} = 0.177$, n.s.; Pa: $F_{1,17} = 1.510$, n.s.; and Nb: $F_{1,17} = 0.270$, n.s.) or of the Stimulus Type (Na: $F_{2,34} = 2.572$, n.s.; Pa: $F_{2,34} = 0.312$, n.s.; and Nb: $F_{2,34} = 0.355$, n.s.). Post hoc repeated-measures contrasts confirmed statistical significant differences on the mean amplitude between deviant and standard AEPs ($F_{1,17} = 5.313$, $P = 0.034$), and between deviant and control AEPs ($F_{1,17} = 7.297$, $P = 0.015$) in the Pa latency window. These effects resulted from the deviant stimuli eliciting larger amplitudes compared with the standard and the control stimuli for the Pa component of the MLR (Fig. 2). For an easier visualization of the effect, Fig. 3 shows the bar-graph of the grand-average mean amplitudes, including the standard errors of the

V, Na, Pa and Nb components, elicited by the deviant, control and standard stimuli.

Discussion

The results of the present study have revealed that auditory novelty (deviance) detection can take place in humans as early as 30 ms from the onset of the stimulus feature that is novel compared with a repetitive background (i.e. the standard stimuli). This was supported by the fact that the Pa component of the MLR, peaking at 30 ms from change onset, was larger for the deviant stimulus than for the responses elicited both to the standard and the control stimuli. It is worth noting that all three responses used for comparison (to deviant, to standard, and to control stimuli) were elicited by the same physical stimulus occurring, in the three different experimental conditions, with a different probability and different regularity role.

Auditory novelty detection has been studied so far mainly in humans by means of the MMN, which has been obtained to simple features changes in frequency (Sams et al., 1985; Müller et al., 2002), intensity (Naatanen et al., 1987), duration (Naatanen et al., 1989) and spatial location (Paavilainen et al., 1989). Also, MMN has been elicited by changes in more complex levels of regularity, such as the frequency relationship of two tones within a pair (Saarinen et al., 1992; Carral et al., 2005). The nature of the MMN as a ‘genuine’ novelty detector was not, however, supported until the use of the control block introduced by Schroger & Wolff (1996). With the use of this block, the responses to the deviant stimuli are compared with the responses to the very same stimuli occurring in a context of other different stimuli of the same low probability to oversee for refractoriness. Using this type of control condition, ‘true’ novelty detection in humans reflecting regularity extraction and encoding (Winkler, 2007) has been shown for location (Schroger & Wolff, 1996), pitch (Jacobsen & Schroger, 2001), intensity (Jacobsen et al., 2003a) and duration (Jacobsen & Schroger, 2003b) deviant stimuli. Although previous studies on humans have shown frequency novelty detection in the long latency range, no work has focused on the early latency range so far.

Müller et al. (2001) provided empirical evidence that the earlier components of MLR (Na, Pa, Nb with a window for MLR mean amplitude between 15 and 23 ms, 25 and 30 ms, and 35 and 41 ms, respectively) exhibit amplitude suppression to a repeated sound in a paired-click paradigm, reflecting the primary cortical ability to distinguish repetitive stimuli. This phenomenon was proposed to reflect the existence of a neural inhibition that contributes to the suppression of the response for the second identical stimulus or by an increased refractoriness and/or habituation of the specific neurons (Müller et al., 2001). Although showing the sensitivity of the MLR to stimulus repetition, this study did not address whether the MLR could exhibit novelty responses when a stimulus parameter is changed. On the other hand, Sonnadara et al. (2006) observed an enhancement of the Na component (25 ms) elicited by location deviant stimuli compared with standard stimuli in an oddball paradigm with stimuli consisting of brief noise bursts. In lack of a proper control, however, the increase in amplitude between deviant and standard stimuli in this study could have resulted from a different state of refractoriness of location-specific neurons (Schroger & Wolff, 1996) responding to the two types of sounds presented within the oddball sequence.

A step forward in understanding the neural mechanisms of novelty detection in the auditory system has been recently provided by studies of single-unit recordings in anaesthetized animals. For instance, in the primary auditory cortex of the cat, Ulanovsky et al. (2003) have

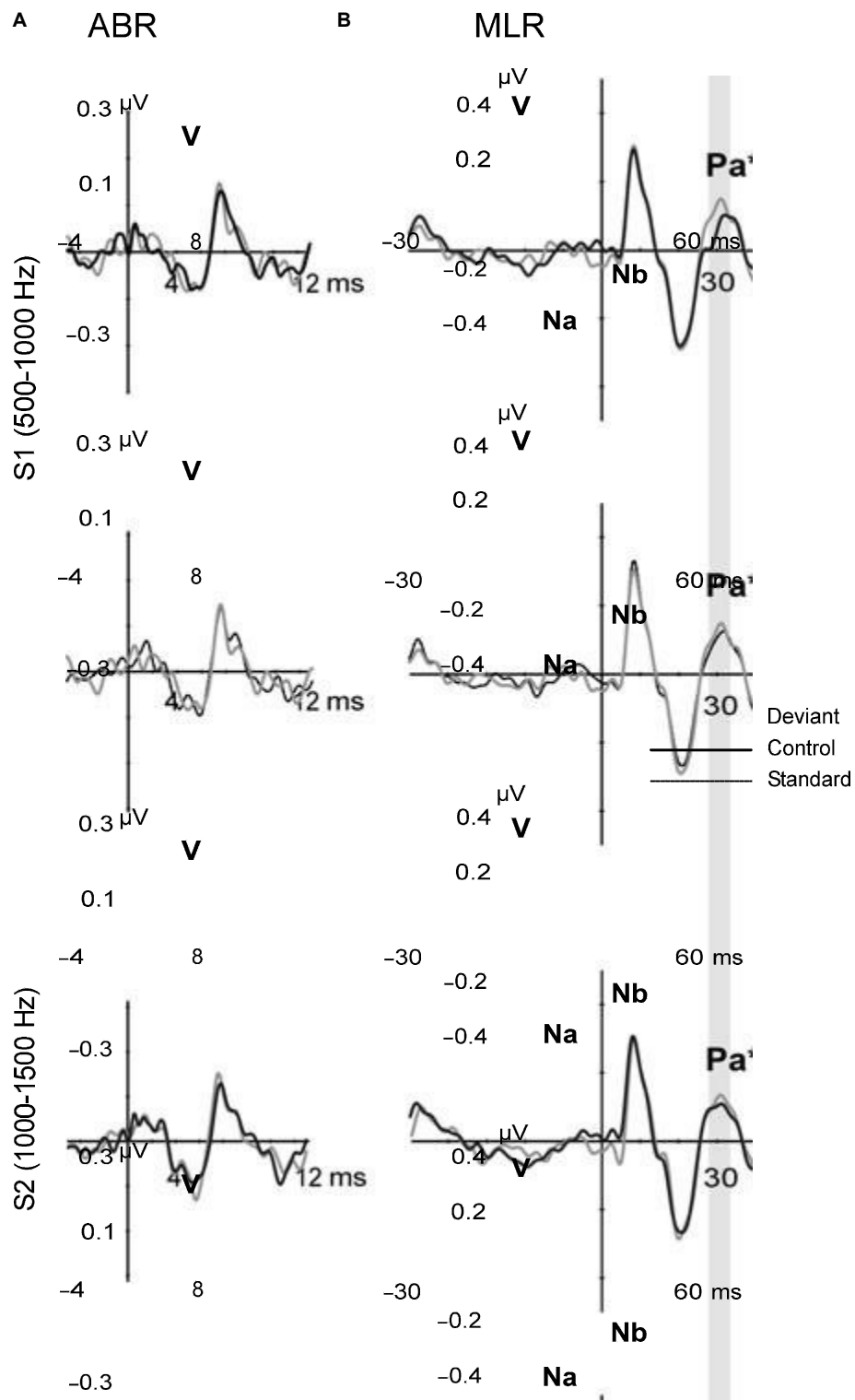


Fig. 2. Grand-average AEPs of $N = 18$ subjects for the frequencies S1 and S2. (A) The auditory brainstem (ABR) for the standard stimuli that preceded the deviant stimuli (solid grey line) and the control stimuli (solid black line) compared with the deviant stimuli (dashed black line). (B) The middle latency responses (MLR) for the same stimulus type as specified in (A). The grey bar denotes the latency window for Pa waveform measurement, for which a significant deviant enhancement was observed compared with both standard and control stimuli ($*P < 0.05$, Bonferroni corrected). Notice that the responses corresponding to the three types of stimuli are in fact elicited to the same physical stimulus (either S1 or S2) that had different contextual roles in the three different experimental conditions.

described the existence of the neurons that show strong SSA to repeating stimuli, but restore their firing rates when a stimulus parameter is changed. Therefore these neurons were proposed as the

neural correlate of MMN. To a greater extent, however, Antunes et al. (2010) could identify novelty neurons in the thalamus of rat, supporting the seminal observations by Kraus et al. (1994) who,

Table 1. Mean amplitude (in μV) of the V, Na, Pa and Nb waveforms of the AEPs elicited by the control, deviant and standard stimuli

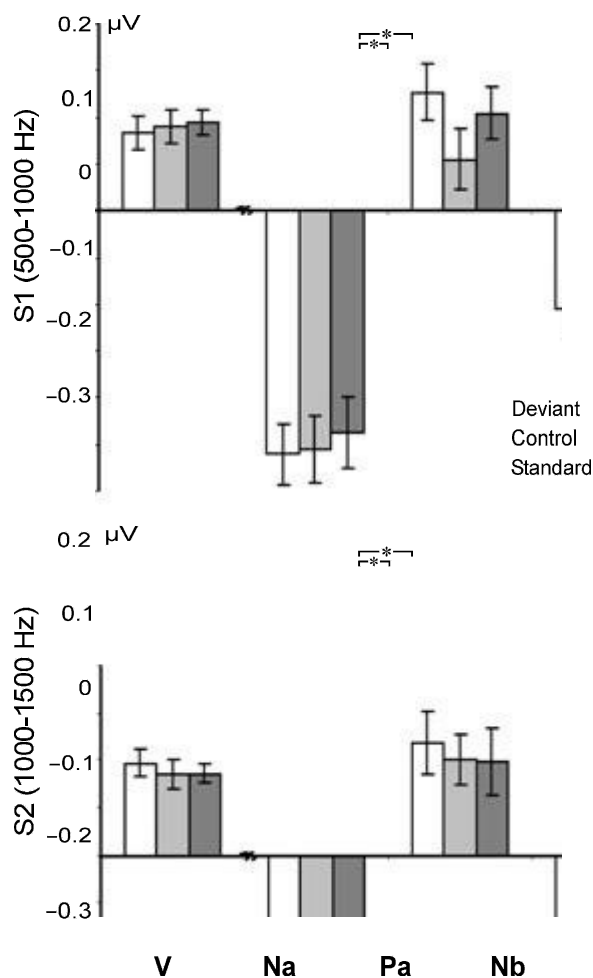
Wave forms	Mean amplitude (Standard error)					
	S1 (500–1000 Hz)			S2 (1000–1500 Hz)		
	Control	Deviant	Standard	Control	Deviant	Standard
V	0.091(0.018)	0.083 (0.018)	0.095 (0.013)	0.085 (0.014)	0.097 (0.013)	0.086(0.009)
Na	0.255 (0.035)	0.260 (0.031)	0.238 (0.038)	0.250 (0.041)	0.251 (0.036)	0.228(0.039)
Pa	0.055(0.032)	0.127 (0.031)	0.105 (0.027)	0.100 (0.026)	0.118 (0.034)	0.09 (0.035)
Nb	0.081(0.040)	0.104 (0.039)	0.109 (0.032)	0.088 (0.036)	0.109 (0.028)	0.103 (0.031)

Standard errors of mean are given in parentheses.

Table 2. Mean values (in ms) of the peak latencies of the V, Na, Pa and Nb waveforms of the AEPs elicited by the control, deviant and standard stimuli

Wave forms	Mean peak latency (Standard error)					
	S1 (500–1000 Hz)			S2 (1000–1500 Hz)		
	Control	Deviant	Standard	Control	Deviant	Standard
V	7.71 (0.069)	7.59 (0.073)	7.76 (0.089)	7.94 (0.077)	7.88 (0.057)	7.94(0.078)
Na	20.22 (0.137)	20.28 (0.166)	20.50 (0.116)	20.22 (0.125)	20.78 (0.154)	20.83 (0.142)
Pa	30.39 (0.167)	30.22 (0.174)	30.39 (0.172)	30.17 (0.173)	30.72 (0.145)	30.56(0.158)
Nb	41.39 (0.172)	41.11 (0.161)	40.94 (0.164)	40.78 (0.183)	41.28 (0.127)	41.06(0.143)

Standard errors of mean are given in parentheses.



through multi-unit activity recordings to consonant–vowel contrasts in the medial geniculate body of the guinea pigs, questioned the cortical origin of MMN. Furthermore, the single-unit recording studies by Perez-Gonzalez et al. (2005) and Malmierca et al. (2009) have found units in the inferior colliculus of the rat that exhibit similar novelty responses to those found by Ulanovsky et al. (2003) in the cat’s primary auditory cortex, supporting the subcortical origin of some novelty responses in the auditory system. Up to now, the inferior colliculi (IC) novelty neurons expressed a response to novel stimuli that depended on stimulus repetition rate, the frequency contrast between standard and deviant stimuli, and the probability of the deviant stimulus occurring (Ulanovsky et al., 2003; Malmierca et al., 2009). For individual neurons, the response was greatest at the largest frequency contrast, the lowest probability of the oddball stimulus, and a repetition rate of 4 Hz. At a higher stimulus rate, many IC neurons failed to respond entirely.

In the present study, the response to deviant stimuli was enhanced in the time range of MLR, in agreement with a similar observation by our group (Grimm et al., 2010). In particular, the Pa component peaking at about 30 ms showed significant larger amplitudes in response to the deviant as compared with the standard stimulus for the two frequency bands under study. The increased Pa amplitude might reflect that the repetition of a specific standard frequency has been represented in a form of memory, and the brain’s neurophysiological response to the rare stimuli reflects the outcome of a comparison with the memory trace of the preceding repetitive frequency (Naatanen & Winkler, 1999). Alternatively, it may suggest that the difference in frequency of the deviant stimuli, which occur with a much smaller probability than

Fig. 3. Mean amplitudes and the standard errors of the means of the grand-average V, Na, Pa and Nb waveforms ($P < 0.05$) elicited by the deviant, control and standard stimuli. The ‘*’ symbol denotes a significant deviant enhancement compared with standard or control stimuli.

the standard ones, finds frequency-specific neural populations on a less refractory state than those responding to the standard stimuli (Ja"askela"inen et al., 2004). However, our research data showed an increased Pa response also to the deviant stimuli as compared with that elicited to control stimuli, which were physically identical and occurred with the same low probability. By using this control block, the AEP differences between the deviant stimuli occurring in the oddball sequence and the same stimuli occurring in a non-regular acoustic context cannot reflect the consequences of different states of refractoriness. Therefore, our results strongly support a memory comparison-based mechanism and index an early process of true novelty detection in the auditory system. Alternatively, such early effects could be explained by the involvement of an auditory predictive system that preactivates neuronal populations for the upcoming acoustic events (Grimm & Schro"ger, 2007; Widmann et al., 2007; Bendixen et al., 2009).

In the ABR time range, our results failed to show any statistical significant difference between deviant compared with standard and control stimulus responses for the V component. The amplitude of V wave decreased when the frequencies cutoff of the band-pass-filtered was raised from 15 to 250 Hz and from 250 to 1500 Hz. Considering the animal studies mentioned above, even though we can not perform a straightforward analogy with AEP in humans, the most likely reason why in this study no novelty-related activity was observed in the ABR time range was probably caused by a combination of factors, such as stimulus repetition rate, the frequency contrast between standard and deviant stimuli, and the probability of the deviant stimulus (Malmierca et al., 2009). For single-neuron recordings in subcortical structures, the repetition rate typically used to study SSA is of the order of 4 Hz, with the greatest response at the largest frequency contrast, and the lowest probability of the oddball stimulus. It should be kept in mind that establishing the present experimental design was a compromise between the repetition rate, the number and duration of stimuli for recording a reliable ABR. Moreover, it should be noted that, although possibly similar in origin to novelty units in animals, the ABR responses are much earlier, i.e. 20–30 vs. 1–10 ms, respectively. Therefore, from the present observations we may speculate that early auditory deviance detection of simple features could act through top-down mechanisms. As a matter of fact, a recent study has shown that the human IC is sensitive to the top-down modulations related to behavioural goals (Rinne et al., 2008).

The anatomical neural origin of the human MLR, like the ABR, is not yet well understood, and there is still uncertainty on the neural correlates of each of its waveforms. Similar sources of ABR and MLR origin in animals were identified in humans. Thus, the anatomical neural origins of the V component are likely from lateral lemniscus and inferior colliculi (Fischer et al., 1994, 1995). In the MLR time range, recent studies could identify the earliest cortical activity (16–19 ms) to be localized in the medial portion of Heschl's sulcus and Heschl's gyrus (Yvert et al., 2005), with the Pa component supposedly originating from the primary auditory cortex (Yvert et al., 2001). However, there are findings suggesting that Na and Pa components have additional contributions from the thalamus (Buchwald et al., 1981). The Nb wave is suggested to be initiated more in the anterior part of the superior temporal gyrus, corresponding to secondary auditory cortices (Yvert et al., 2005).

Our findings support the idea of a new electrophysiological marker of auditory novelty detection that indicates the auditory response to novel stimuli in the Pa latency range, supposedly originating in the primary auditory cortex.

In agreement with previous animal studies reporting novelty detection on multiple stages along the auditory pathway, and with a

recent human AEP study of us (Grimm et al., 2010) our results confirm the multi-stage hypothesis of human auditory novelty detection. Whether these processes are complementary, hierarchical, interactive or redundant (Chechik et al., 2006; Malmierca et al., 2009) can not be decided on the basis of the present experimental design.

While traditionally change detection has been indexed by the MMN AEP, the present results show the existence of a deviance detection response in the MLR range of the AEP, at about 30 ms. More generally, the results support the notion that novelty detection is a basic property of the functional organization of the auditory system that acts at different hierarchical levels along the auditory pathway, and that the generation of the MMN recorded from the human scalp might involve different levels of the auditory system's hierarchy, at least when deviance detection occurs in regard to a single physical attribute of the acoustic input.

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Abbreviations

ABR, auditory brainstem; AEP, auditory-evoked potential; EEG, electroencephalogram; IC, inferior colliculi; MLR, middle latency responses; MMN, mismatch negativity; SSA, stimulus-specific adaptation.

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