Novelty Detection in the Human Auditory Brainstem

Lavinia Slabu, Sabine Grimm, and Carles Escera

Institute for Brain, Cognition, and Behavior (IR3C), and Cognitive Neuroscience Research Group, Department of Psychiatry and Clinical Psychobiology, University of Barcelona, 08035 Barcelona, Catalonia-Spain

Auditory deviance detection has been associated with a human auditory-evoked potential (AEP), the mismatch negativity, generated in the auditory cortex 100–200 ms from sound change onset. Yet, single-unit recordings in animals suggest much earlier (~ 20 –40 ms), and anatomically lower (i.e., thalamus and midbrain) deviance detection. In humans, recordings of the scalp middle-latency AEPs have confirmed early (~ 30 –40 ms) deviance detection. However, involvement of the human auditory brainstem in deviance detection has not yet been demonstrated. Here we recorded the auditory brainstem frequency-following response (FFR) to consonant-vowel stimuli (/ba/, /wa/) in young adults, with stimuli arranged in oddball and reversed oddball blocks (deviant probability, $p = 0.2$), allowing for the comparison of FFRs to the same physical stimuli presented in different contextual roles. Whereas no effect was observed for the /wa/ syllable, we found for the /ba/ syllable a reduction in the brainstem FFR to deviant stimuli compared with standard ones and to similar stimuli arranged in a control block, with five equiprobable, rarely occurring sounds. These findings demonstrate that the human auditory brainstem is able to encode regularities in the recent auditory past to detect novel events, and confirm the multiple anatomical and temporal scales of human deviance detection.

Introduction

A large number of auditory-evoked potential (AEP) studies in humans indicate that infrequently occurring deviant sounds reliably elicit a negative cortical EEG potential at 100–200 ms from change onset, named the mismatch negativity (MMN; Näätänen et al., 2011). Recent animal results from single-unit recordings in the primary auditory cortex (Ulanovsky et al., 2003), the thalamus (Kraus et al., 1994; Antunes et al., 2010), and the inferior colliculus (Malmierca et al., 2009) have suggested, however, that the MMN might be preceded by much earlier (20–40 ms) auditory novelty-related activity. This was recently confirmed in human studies showing the existence of deviance-related activity, similar to the MMN, in the middle latency responses (MLR) of the AEP, peaking at ~ 40 ms (Grimm et al., 2011) and even at 30 ms (Slabu et al., 2010) for stimuli differing in their spectral features from the repetitive auditory background. Together, all of these results suggest that novelty detection might be a basic principle of the functional organization of the auditory system at all hierarchical levels along the auditory pathway, and that the generation of the MMN-like responses recorded from the human scalp involves different levels of the auditory system's hierarchy.

To date, no correlate of deviance detection has been shown at the brainstem level in humans by recording the auditory brainstem response (ABR; Slabu et al., 2010). Yet, recent studies have shown the ability of the human auditory brainstem to encode context-dependent information and to undergo plastic changes during short-term auditory exposure to repetitive sounds (Chandrasekaran et al., 2009; Skoe and Kraus, 2010b). These studies took advantage of the frequency-following response (FFR), which, in contrast to the phasic ABR, reflects the tonic brainstem response with bursts of activity matching the repetitive peaks present in the acoustic signal (Galbraith et al., 1995; Skoe and Kraus, 2010a). There is convincing evidence that the FFR is generated in the auditory brainstem, because cooling the inferior colliculus in cats abolishes the FFR recorded from the scalp, whereas the response is still present caudally at the superior olivary complex (Smith et al., 1975). Also, in patients with lesions in the inferior colliculus, no FFR could be recorded from the scalp (Sohmer et al., 1977). However, whether the human auditory brainstem is able to detect novel auditory stimuli remains to be proved. Here, we used the FFR to consonant-vowel (CV) syllables arranged in an oddball paradigm to test the involvement of the brainstem in representing the history of past auditory events and in tracking infrequent violations in the formant transition duration of a repetitive syllable.

Materials and Methods

Eighteen paid volunteers (aged 19–32 years, mean age 21.6 years, 9 females, 5 left-handed) were included in the study. All but one (Romanian) of the participants had Catalan, Spanish, or both as their mother tongues and had been living in a Spanish/Catalan-speaking environment. All participants had normal hearing (hearing threshold < 25 dB SPL from 250 to 8000 Hz) as tested by pure tone audiometry at the beginning of the experimental session. The experimental protocol was approved by the ethical committee of the University of Barcelona, and was in accordance

Received May 23, 2011; revised Nov. 16, 2011; accepted Nov. 23, 2011.

L.S., S.G., and C.E. designed research; L.S. performed research; L.S. and S.G. analyzed data; L.S., S.G., and C.E. wrote the paper.

This work was supported by Grant PSI2009-08063 from the National Program for Fundamental Research, Grant CDS2007-00012 from the Consolider-Ingenio 2010 Program of the Spanish Ministry of Science and Innovation, Grant 2009SGR11 from the Generalitat de Catalunya, and the ICREA Academia Distinguished Professorship from the Institut Català de Recerca i Estudis Avançats, awarded to C.E.

Correspondence should be addressed to Dr. Carles Escera, Department of Psychiatry and Clinical Psychobiology, Faculty of Psychology, University of Barcelona, P. Vall d'Hebron 171, 08035 Barcelona, Catalonia-Spain. E-mail: cesera@ub.edu.

DOI:10.1523/JNEUROSCI.2557-11.2012

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Figure 1. Stimuli and experimental design. **A**, Frequency spectrum of the five different consonant-vowel syllables used in the experiment. **B**, The three experimental conditions. In the oddball condition, the standard stimulus was the /wa/1 syllable, and the deviant stimulus ($p = 0.2$) was the /ba/ syllable. In the reversed oddball condition, the roles of the standard and deviant syllables were switched. In the control condition, five different syllables (/ba/, /wa/1, /wa/2, /wa/3, and /wa/4) were presented randomly, each with a probability of $p = 0.2$. Each square represents the spectrogram of the 170 ms stimulus. The black rectangles frame the transition duration of formants F1 and F2 that differentiated the five different syllables.

with the Code of Ethics of the World Medical Association (Declaration of Helsinki). Written informed consent was obtained from each participant before the experiment.

Stimuli and procedure. Five different CV syllables of 170 ms duration were generated with the Klatt speech synthesizer (Klatt, 1980; Fig. 1A). The fundamental frequency (F0), and the third (F3), fourth (F4), and fifth (F5) formants were set identically for all stimuli at 100, 2900, 3500, and 4900 Hz, respectively. To elicit a large onset response, the first 5 ms of the CV syllables included a rapid glide in the first (F1; from 400 to 1700 Hz) and second (F2; from 1700 to 1240 Hz) formants. After the initial 5 ms, the five syllables differed in the duration of F1 transition from 125 to 800 Hz and F2 transition from 571 to 1200 Hz. These transition duration values were set at 20, 35, 50, 65, and 80 ms for the five different tokens used in the experiment (Fig. 1B). The resulting CV syllables were perceived either as /ba/ for the 20 ms transition of F1 and F2, or as /wa/ of different strengths for the longer transition durations (herein referred to as /wa/1, /wa/2, /wa/3, and /wa/4 for the 35, 50, 65, and 80 ms transition, respectively). The CV stimuli were presented in alternating polarities, via Beyerdynamic DT48A headphones (Beyerdynami) to the right ear at an intensity of 80 dB SPL. The stimulus onset asynchrony was jittered between 256 and 344 ms in steps of 8 ms, equiprobably distributed over the

trials. Three different conditions were used (Fig. 1B). In the oddball condition, the standard stimulus was the syllable /wa/1 and the deviant stimulus ($p = 0.2$) was the syllable /ba/. The stimulus sequence in this condition was constrained so that each deviant stimulus was preceded by at least two standard stimuli. In the reversed oddball condition, the roles of the deviant and standard stimuli of the oddball condition were switched, controlling for stimulus-specific responses. However, whether the brain responses to the deviants were elicited as a result of a memory comparison process or simply reflected probability processing could not be resolved without an additional control block, in which the five different CV syllables, /ba/, /wa/1, /wa/2, /wa/3, and /wa/4, were presented in random order, each with a probability of $p = 0.2$ (cf. Schröger and Wolff, 1996). A total of 31,500 stimuli were delivered in the three conditions, including 2100 deviants per oddball condition and 2100 corresponding stimuli in the control condition. Conditions were split into six different blocks of 5250 stimuli, each lasting ~26 min. The resulting 18 blocks were presented in random order. During the experiment, the participants sat comfortably in a recliner chair in an acoustically and electrically shielded room. They were instructed to relax and to watch a silent movie with subtitles, while ignoring the auditory stimulation. After each block, the participants had a short break allowing for movement.

Figure 2. Grand-average ABRs (**A**) and FFR spectra (**B**) for the /ba/, /wa/1, /wa/2, /wa/3, and /wa/4 syllables in the control condition. **A**, A significant enhancement of the response amplitude in two latency windows (18–22 ms and 27–31 ms) over the temporal transition of F1 and F2 was observed for the /ba/ syllable compared with the /wa/1 syllable (* $p < 0.05$). **B**, The amplitude of the H2 (* $p < 0.05$) harmonic followed the increase of the formant transition duration in the control condition.

Data acquisition. FFRs were extracted from the continuous EEG recording, which was acquired with a Neuroscan SynAmpsRT amplifier and Scan software (Neuroscan) from the Cz electrode. Electrodes placed at the left ear lobe and forehead served as the reference and ground, respectively. All electrode impedances were maintained $< 5 \text{ k}\Omega$. The continuous EEG was online bandpass filtered from 0.05 to 1500 Hz. The data were collected at a sampling rate of 20 kHz with a gain of 5000.

Data processing and analysis. Epochs for deviant, standard, and control stimuli were averaged separately. To obtain a similar number of trials for each type of stimulus, the averages for standard stimuli included only those epochs immediately preceding a deviant stimulus. Before averaging, data were filtered off-line with a bandpass filter from 70 to 1500 Hz and epoched in 196 ms bins. Epochs with any activity exceeding a range of $35 \text{ }\mu\text{V}$ were rejected off-line (Russo et al., 2008). A minimum of 1604 trials was averaged in each condition. The averaged AEPs were baseline-corrected to a 40 ms interval preceding sound onset for the deviant, standard preceding the deviant, and control stimuli.

In the time domain, the mean amplitude of the responses was retrieved in two latency windows, 18–22 ms and 27–31 ms, corresponding to the first two peaks of the FFR during the common temporal span of the format transition for the /ba/ and /wa/ syllables. Also, the latency of the largest peak within each of these two time windows was retrieved for statistical comparison. To analyze the data in the spectral domain, fast Fourier analyses (Dumermuth and Flüher, 1967) encompassing 8192 points (Matlab R2010a, MathWorks) were applied on the ABR averages windowed with a 2 ms on/2 ms off Hanning ramp (Russo et al., 2004) within the 20–85 ms time period corresponding to the CV formant transition, and the mean spectral amplitude was calculated for 10-Hz-wide bins surrounding the F0 (100 Hz) and the subsequent five harmonics: H2, H3, H4, H5, and H6 (Banai et al., 2009). The selection of the harmonics was based on previous studies showing context-dependent

encoding in the human auditory brainstem (Chandrasekaran et al., 2009; Skoe and Kraus, 2010b). Higher harmonic components were not reliably present in all subjects and were therefore not analyzed (Skoe and Kraus, 2010b).

The data were analyzed by means of repeated-measures ANOVA on the mean amplitudes of F0, H2, H3, H4, H5, and H6 separately, including the factor Stimulus Type (deviant, standard, control). Where appropriate, the Greenhouse-Geisser correction was applied in ANOVAs. However, the original degrees of freedom were reported for the ANOVAs together with the correction term ϵ . If appropriate, pairwise differences between single levels of Stimulus Type were tested applying repeated-measures contrasts. The Bonferroni correction was applied to adjust for multiple testing, and significance was defined for values of $p \leq 0.025$.

Results

In the time domain, robust FFRs were elicited by the five different CV syllables in the control condition (Fig. 2). The mean FFR amplitude was larger for the /ba/ syllable than for the /wa/1 syllable as measured in the two latency windows, 18–22 ms ($F_{(1,17)} = 23.398$, $p = 0.00015$) and 27–31 ms ($F_{(1,17)} = 4.958$, $p = 0.04$), corresponding to the temporal span of the formant transitions of the syllables. No statistical differences were found between the latencies of the largest peak within each time window ($F_{(1,17)} = 3.230$, $p = 0.09$; and $F_{(1,17)} = 3.4$, $p = 0.083$, respectively). In the spectral domain, the amplitude of the H2 computed in the 20–85 ms latency window showed a stimulus effect ($F_{(4,69)} = 19.006$, $p = 0.0000011$; $\epsilon = 0.782$), indicating that the second harmonic of the fundamental frequency varied as a function of the CV formant transition. Specifically, *post hoc* repeated-measures contrasts revealed larger amplitudes for /ba/ than for /wa/1 ($F_{(1,17)} = 7.069$, $p = 0.013$), for /wa/1 than for /wa/2 ($F_{(1,17)} = 4.913$, $p = 0.041$), and for /wa/2 than for /wa/3 ($F_{(1,17)} = 10.622$, $p = 0.005$), with no further amplitude decrease for the /wa/4 syllable (Fig. 2).

Grand-average FFRs to deviant, standard, and control stimuli are shown in Figure 3. In the time domain, no significant differences were found for the amplitudes of deviant, standard, and control stimuli. In the spectral domain, the /ba/ syllable elicited significantly smaller amplitudes of H2 ($F_{(2,34)} = 10.241$, $p = 0.001$; $\epsilon = 0.833$) and H4 ($F_{(2,34)} = 4.266$, $p = 0.026$; $\epsilon = 0.920$) in the role of deviant than in the role of either standard or control stimulus (Fig. 4). *Post hoc* repeated-measures contrasts confirmed statistically significant differences in the mean amplitude of H2 and H4 between deviant /ba/ and standard /ba/ (H2, $F_{(1,17)} = 11.047$, $p = 0.004$; H4, $F_{(1,17)} = 8.000$, $p = 0.012$), and between deviant /ba/ and control /ba/ (H2, $F_{(1,17)} = 13.484$, $p = 0.002$; H4, $F_{(1,17)} = 6.291$, $p = 0.023$), while standard /ba/ and control /ba/ elicited responses of similar amplitude (H2, $F_{(1,17)} = 1.411$, $p = 0.251$; H4, $F_{(1,17)} = 0.067$, $p = 0.799$). The repeated-measures contrast for the /wa/1 syllable failed to reveal any significant differences between deviant, standard, and control /wa/1 syllables.

Discussion

Our results show that the human auditory brainstem is able to detect a novel acoustic event occurring among a series of repetitive ones. This is supported by the attenuated human brainstem response to a CV stimulus occurring with a low probability (as “deviant” stimulus) compared with that elicited by the same physical stimulus presented with much higher probability (as “standard” stimulus), or in the context of four, equally rare stimuli, controlling for stimulus probability. The results obtained in this control condition allow us to preclude the possibility that the brainstem neuron populations responding specifically to deviant-stimulus features were in a less refractory state than those responding to standard-stimulus features (May and Tiitinen, 2010). Rather, these results suggest that the human auditory brainstem is able to encode acoustic regularities in a memory trace and to detect deviant events based on a comparison process between the current auditory input and the recent auditory past (Näätänen et al., 2011). Also, our results are in agreement with previous FFR studies showing that the human auditory brainstem encodes stimulus statistics over multiple time scales (Chandrasekaran et al., 2009; Skoe and Kraus, 2010b), as observed also for cortical neurons (Ulanovsky et al., 2004) and human cortical-evoked potentials (Costa-Faidella et al., 2011).

To our knowledge, ours is the first study reporting a neural correlate of auditory deviance detection at the brainstem level in humans. Human auditory change detection has so far been investigated by means of the MMN (Näätänen et al., 2011), usually peaking at 100–200 ms from sound-change onset and with major generators in superior temporal cortex (Alho, 1995; Escera et al., 2000). In addition, recent studies measuring the MLR (Slabu et al., 2010; Grimm et al., 2011) have revealed auditory deviance detection in humans at latency ranges similar to those observed in animal studies of single unit activity (Ulanovsky et al., 2003, 2004), i.e., ~30–40 ms from sound-change onset. Yet, a study using broadband noise bursts of different bands within the 500–3000 Hz range (Slabu et al., 2010) failed to find any correlate of deviance detection in the human ABR, contrasting with the recent studies in animals describing novelty responses in the medial geniculate body (Antunes et al., 2010) and inferior colliculus (Pérez-González et al., 2005; Malmierca et al., 2009). The results reported here, together with the MMN and MLR results in

Figure 3. Grand-average FFRs for (*A*) the /ba/ syllable and (*B*) the /wa/1 syllable when the given syllable served as a deviant stimulus (red line) or standard stimulus (blue line) and when it occurred in the control condition (black line). Note that the responses were elicited by the same physical stimulus (either /ba/ or /wa/1) in different contextual roles in the three different experimental conditions.

Figure 4. Deviance detection in the human auditory brainstem. *A*, Grand-average spectra of the FFRs to the /ba/ (left) and /wa/1 (right) syllables when presented in the role of standard (blue line), control (black line), and deviant stimulus (red line) in the three experimental conditions. Note that for the /ba/ syllable, the FFRs to the standard and control stimuli were remarkably identical, whereas those to deviant stimuli showed attenuated H2 and H4 amplitudes ($*p < 0.025$). *B*, Mean ($N = 18$), SEM, and individual measures (diamonds) of H2 and H4 amplitudes to the /ba/ (left) and /wa/1 (right) syllables when presented in the role of standard (STD, blue), deviant (DEV, red), and control (CON, black) stimulus.

humans and those of stimulus-specific adaptation (SSA) in animals, give support to the emerging view that novelty detection based on regularity encoding is a pervasive property of the auditory system, spanning the whole anatomical hierarchy from the

inferior colliculus upward, and in multiple temporal dimensions. The specific functional roles of the multiple levels of auditory deviance detection in building perceptual auditory objects (Nelken et al., 2003; Winkler et al., 2009) or drawing attention involuntarily (Escera et al., 1998, 2000) remain to be established in future research.

The present study took advantage of the FFR, an AEP response that, contrasting with the phasic nature of the ABR, reflects sustained, phase-locked activity elicited by the incoming stimulus (Galbraith, 1994; Galbraith et al., 1995; Skoe and Kraus, 2010a). A key aspect of the FFR is that it is synchronized with high fidelity to the stimulus F0 and its lower harmonics (Russo et al., 2005). Hence, it was not surprising that the amplitude of H2 elicited by our CV stimuli varied as a function of their formant transition duration, with larger amplitudes for shorter durations. Similarly, deviance-related effects were also observed for H2 and H4 as an attenuation of their amplitude in relation to both the standard and the control conditions for the /ba/ syllable. It is not clear, however, why the deviant stimuli resulted in an attenuated brain response. Previous studies describing spectrally enhanced FFR to a CV token that is repeated over time compared with that occurring in a variable context (Chandrasekaran et al., 2009), and the ability of the brainstem to track on-line stimulus statistics (Skoe and Kraus, 2010b) has implicated top-down influences mediated by feedforward and feedback coupling via the corticofugal system (Suga et al., 2002; Tzounopoulos and Kraus, 2009). This is also in agreement with the current accounts of the MMN based on Dynamic Causal Modeling (Garrido et al., 2009), where higher-order levels generate prediction signals about upcoming auditory events (Bendixen et al., 2009). Yet, recent results showed that reversible deactivation of the auditory cortex does not abolish SSA in the auditory thalamus (Antunes and Malmierca, 2011), and local GABAergic modulation mediates SSA in inferior colliculus (Malmierca et al., 2010). Together, these findings do not allow us to conclude whether the novelty responses at the level of the human brainstem could be intrinsic in nature, i.e., generated by local circuitry dynamics, or whether they resulted from a combination of both bottom-up and top-down mechanisms.

The amplitude of the FFR brainstem response to the /wa/1 syllable was similar regardless of its role as a standard, control, or deviant stimulus, contrasting with the deviance-related effects observed for the /ba/ syllable. While the origin of this asymmetry is not clear, former studies have described similar asymmetries for the MMN elicited by linguistic stimuli (Phillips et al., 2000) including CV syllables (Maiste et al., 1995), particularly when one of the deviant stimuli was at the edge of a continuum. In our study, this was the case at a phonetic level, as the /ba/ syllable is a less ambiguous member of the phonetic category “ba” than the /wa/1 syllable. Yet, a similar argument holds at the acoustic level, because /ba/ has the shortest formant transition duration compared with the /wa/ syllables. Therefore, deviance detection at the brainstem level may be more sensitive to a more salient feature (faster rising formant transition) occurring in the context of less salient ones (slower rising formant transition) than vice versa. This would be partially in agreement with MMN studies showing easier detection of a frequency-modulated tone among unmodulated tones than vice versa (Bishop et al., 2005). Conversely, the FFR is sensitive to temporal stimulus properties, for example, with larger responses to rising than to falling syllables (Krishnan and Parkinson, 2000). Based on such differences in brainstem encoding per se, we may speculate that the /ba/ syllables elicited stronger phase-locked neural activity in general, and when presented among /wa/1 standards would more easily elicit a contrast

in activation than vice versa. Nevertheless, future studies should aim at clarifying these issues.

In summary, our results show that the human auditory brainstem is able to encode the recent auditory past and to track potentially relevant changes in speech input. Together with former studies in animals and humans, our data support the hypothesis that novelty detection is a key principle in the functional organization of the auditory system.

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