Language-specific phoneme representations revealed by electric and magnetic brain responses

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There is considerable debate about whether the early processing of sounds depends on whether they form part of speech. Proponents of such speech specificity postulate the existence of language-dependent memory traces, which are activated in the processing of speech[1–3] but not when equally complex, acoustic non-speech stimuli are processed. Here we report the existence of these traces in the human brain. We presented to Finnish subjects the Finnish phoneme prototype /e/ as the frequent stimulus, and other Finnish phoneme prototypes or a non-prototype (the Estonian prototype /õ/) as the infrequent stimulus. We found that the brain's automatic change-detection response, reflected electrically as the mismatch negativity (MMN)[4–10], was enhanced when the infrequent, deviant stimulus was a prototype (the Finnish /ö/) relative to when it was a non-prototype (the Estonian /õ/). These phonemic traces, revealed by MMN, are language-specific, as /õ/ caused enhancement of MMN in Estonians. Whole-head magnetic recordings[11,12] located the source of this native-language, phoneme-related response enhancement, and thus the language-specific memory traces, in the auditory cortex of the left hemisphere.

Our subjects were Finns and Estonians, who speak closely related languages with very similar vowel structures[13–15] except that only Estonians have the vowel /õ/, which is roughly between /ö/ (as in 'sir') and /o/ (as in 'sore') (Fig. 1a). To determine the phonemes best representing the vowel prototypes /e/ (as in 'net' but longer in duration), /ö/ and /o/ (and also /õ/ for Estonians), we asked subjects to categorize phoneme stimuli varying in the second-formant (F2) frequency while the F1, F3, and F4 frequencies as well as the fundamental frequency were kept constant. Finns and Estonians judged the vowels common to the two languages similarly (Fig. 1b). In addition, the /õ/ category could also be observed in the responses of Estonians (Fig. 1b). Finns had a gap in this position of their response profile, suggesting that they could perceive the stimuli giving rise to the prototype /õ/ perception in Estonians as different from the prototype phonemes of their own language. Thus, although perhaps forming a perceptual category, the Finns did not consider this foreign phoneme prototypical, because they had not experienced it in their own language.

We then presented to 13 normal-hearing Finnish subjects (aged 18–29 years, right-handed, 4 females and 9 males) the prototype /e/ as the standard stimulus, randomly replaced by infrequent deviant stimuli that differed from the standard stimulus only in F2 (Fig. 1a). In further stimulus blocks, simple sinusoidal tones with frequencies

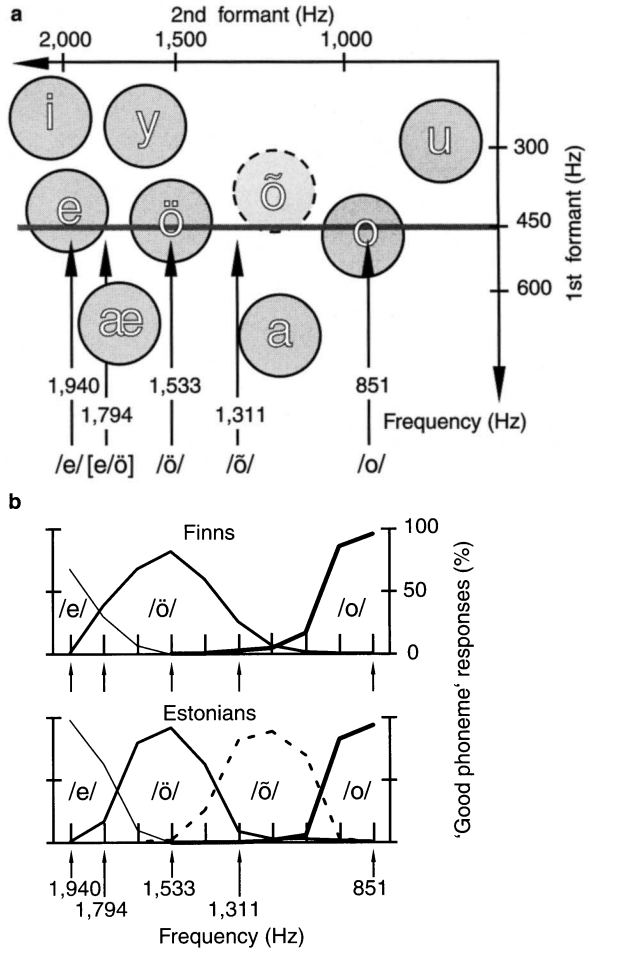

Figure 1 a, The arrows show locations of the vowel stimuli in the F1–F2 space. The standard stimulus was the Finnish and Estonian prototype /e/; the deviant stimulus [e/ö] was an intermediate between /e/ and /ö/; the deviant stimulus /ö/ was a prototype shared by the two languages; the deviant stimulus /õ/ was an intermediate between the Finnish and Estonian prototypes /ö/ and /o/ (and closely corresponded to the Estonian prototype /õ/); the deviant stimulus /o/ was a prototype in both languages. **b**, The percentages of 'good phoneme' /e/, /ö/ and /o/ responses in Finns (top) and of 'good phoneme' /e/, /ö/, /õ/ and /o/ responses in Estonians (bottom) in the behavioural task. The ten stimuli used in the judgement task are indicated with tick marks. The frequency scales are logarithmic.

equal to these F2 frequencies were used in an otherwise identical paradigm. Brain electric responses to these stimuli were recorded while subjects were reading self-chosen text under the instruction to ignore all auditory stimuli.

Responses to the simple tone and its frequency changes are shown in Fig. 2. The standard stimuli elicited a P1–N1–P2 waveform, while the deviant-stimulus response was dominated by the MMN, an auditory response generated by an attention-independent change-detection process[5]. As expected, the MMN amplitude increased as a function of the frequency deviance[7] (Fig. 2). That the present MMN to phonemes occurred independently of attention was supported by the absence of any subsequent slow positivity[6,7] (P3 or P3a; Fig. 3).

Brain responses to phonemes are presented in Fig. 3a. Consistent with results indicating that MMN is enhanced with increasing frequency deviation[7] (Fig. 2), the MMN amplitude was, in general, larger with greater F2 deviation from the standard stimulus /e/ (Figs 3a and 4a). In striking contrast, the deviant /ö/ (prototype) elicited a larger MMN than did the deviant /õ/ (non-prototype), although /ö/

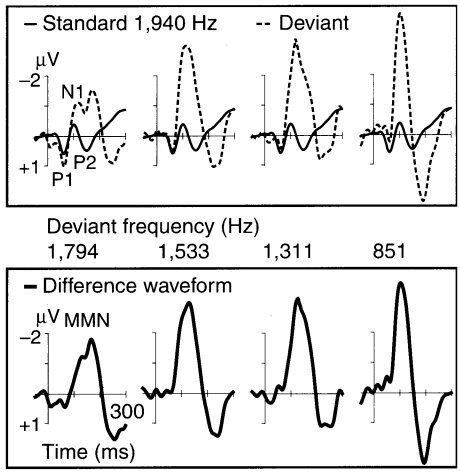

Figure 2 Top, the electric response (from the frontal Fz electrode; grand-average waveforms of Finnish subjects) to the standard sinusoidal tone of 1,940 Hz (solid line; equal to the F2 of /e/ used as the standard stimulus in the present phoneme experiments) and to deviant sinusoidal tones of 1,794, 1,533, 1,311 and 851 Hz (broken line; equal to the F2 of the deviant stimuli [e/o], /ö/, /õ/, and /o/, respectively). The standard-stimulus response shows relatively small P1, N1 and P2 deflections[6]. The negative displacement of the deviant-stimulus response relative to the standard-stimulus response is caused by the mismatch negativity (MMN), which can be seen by subtracting the standard-stimulus trace from that for the deviant stimulus (bottom). MMN steadily increases in amplitude with the increasing magnitude of frequency change.

deviated acoustically less from /e/ than did /õ/. Thus MMN was enhanced in size for prototype deviants from that attributable to the mere acoustic difference. In contrast to the MMN amplitude, the MMN latency was an orderly function of the magnitude of acoustic deviation, with the prototypicality of the deviant stimulus having no effect (Fig. 4b).

The deviant /õ/, although not a phoneme in the Finnish language, is a phoneme in Estonian. Thus, in Estonians, the MMN amplitude should not drop from deviant /ö/ to deviant /õ/. To verify this, 11 normal-hearing Estonian subjects (19–31 years old, right-handed, 6 females and 5 males) were subjected to the same experimental paradigm as the Finns. The drop in MMN amplitude from /ö/ to /õ/ seen in Finns did not occur in Estonians (Figs 3b and 4a), which must be due to /õ/ being a prototype in Estonian but not in Finnish. A two-way ANOVA (language versus deviants /ö/ and /õ/) showed a significant interaction term ($F(1, 22) = 11.16$, $P < 0.005$), indicating that the MMN amplitude as a function of deviance was different in Estonians and Finns. This language-specific prototypicality effect suggests the existence of neural traces of language-specific phoneme representations.

Magnetic responses to the deviant stimuli (MMNM, the magnetic equivalent of the electric MMN) were recorded from 9 of the Finnish subjects[9,11,16]. The pattern of responses over the left hemisphere was the same (the diminished /õ/ response) (Fig. 4c, d) as that shown by the electric responses (Fig. 4a). Furthermore, the magnetoencephalogram showed that MMNM was larger in the left than in the right hemisphere when the deviant stimulus was a prototype (left, 34 fT cm^{-1}; right, 22 fT cm^{-1}; ANOVA, laterality × prototypicality interaction, $F(1, 8) = 6.27$, $P < 0.05$; see Fig. 4d, top). The equivalent current dipole[11,12] of the left-hemisphere response showed that MMNM originated at the left auditory cortex and, further, that its dipole moment (strength) was considerably greater for all prototype deviants than for the non-prototype deviant /õ/ (see Fig. 4c, d). The right-hemisphere responses were not strong enough for us to determine the corresponding equivalent current dipole for each subject. As was the case with the electric MMN, the MMNM latency steadily decreased with increasing acoustic deviation, there being no prototypicality effect.

Thus a vowel prototype of the subject's native language presented as the deviant stimulus elicited a considerably larger MMN (MMNM) than could have been expected on the basis of the acoustic (F2) distance from the frequent, standard phoneme alone. That is, the MMN amplitude was enhanced when the deviant stimulus was a prototype as opposed to an equally complex non-prototype. Furthermore, this MMN-amplitude enhancement pattern reflected the native-language phonology: when the deviant stimulus was a phoneme prototype in Estonian, but not in Finnish, the enhancement occurred in Estonian subjects but not in Finns. We therefore suggest that, in principle, our MMN paradigm could help to unravel the experience-dependent neural memory traces for phonemes of any given language.

We found cortical memory traces of speech sounds. These traces probably serve as recognition patterns[17] for speech sounds, and allow the correct perception of a given language: they are activated by corresponding (and roughly corresponding, the category effect) speech sounds. These recognition patterns presumably develop gradually with exposure to the language; behavioural data suggest they develop within the first year of life[18].

The left-hemisphere dominance of the MMNM enhancement to phoneme prototypes (Fig. 4c, d) suggests that the neural phoneme traces are located in the left auditory cortex. That the locus of the memory trace is indeed indicated by the locus of MMN (MMNM) generation is supported by the feature-specific loci of MMN generation in the auditory cortex[19–21]. In contrast to the left-hemisphere results, in the right auditory cortex both prototypes and non-prototypes elicited a small MMNM of a similar size that resembles the response elicited by non-prototypes in the left auditory cortex. Thus the magnetic results indicate that the left auditory cortex is involved in phonemic discrimination, presumably because the neural phoneme traces are located there, whereas both the left and right auditory cortices serve acoustic discrimination. □

Methods

Stimuli. The F2 frequency for the semi-synthetic standard stimulus was chosen so that it produced the best exemplar representing /e/ (prototype), as judged by the subjects when the F2 frequency was changed in 4% steps. The first (F1), third (F3) and fourth (F4) formants were constant at 450, 2,540 and 3,500 Hz, respectively. The average fundamental frequency (F0) of each semisynthetic vowel was 105 Hz. Vowels were generated by the production of synthetic stimuli from natural glottal excitation in conjunction with a vocal-tract model[22,23]. This method is based on a speech-production model assuming that speech is produced as a cascade of three independent processes: the glottal excitation,

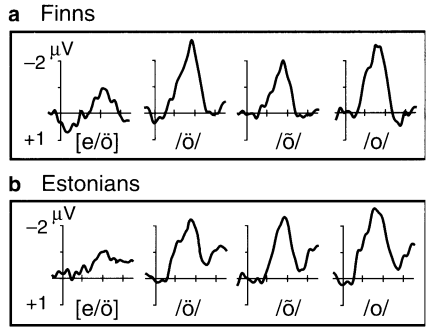

Figure 3 The amplitude of the mismatch negativity (MMN; frontal Fz electrode; grand-average deviant-standard difference waveforms) reflects the language-specific phoneme categories of the Finnish and Estonian languages. Note that the MMN amplitude for the deviant /õ/, a non-prototype in Finnish, is clearly smaller than that for the adjacent prototype deviants with Finnish subjects (**a**) but not with Estonian subjects (**b**) for whom /õ/ was a prototype.

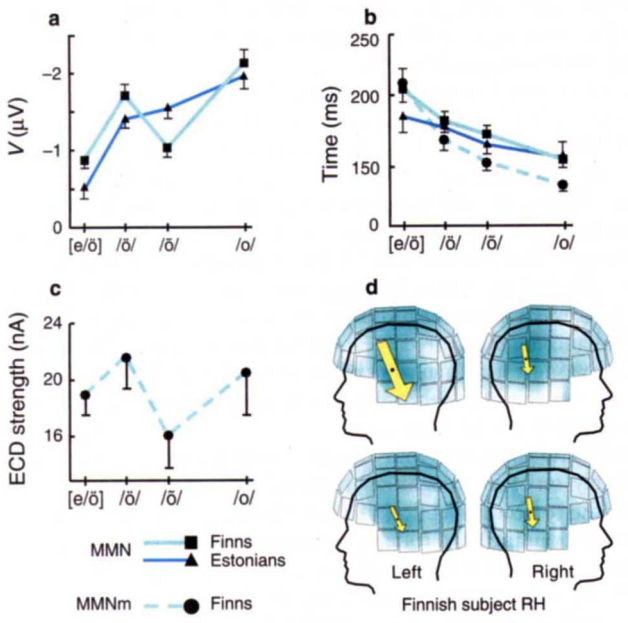

Figure 4 a, MMN peak amplitude (at Fz) in Finns (blue) and Estonians (purple) as a function of the deviant stimulus, arranged in the order of increasing F2 difference from the standard stimulus. Bars indicate s.e.m. **b**, MMN (at Fz) (solid lines) and MMNM (left hemisphere) (broken line) peak latencies as a function of the deviant stimulus for Finns (blue) and Estonians (purple). **c**, Strength of the equivalent current dipole (ECD; average of 9 Finnish subjects) modelling the left auditory-cortex MMNM for the different deviant stimuli. **d**, Left- and right-hemisphere MMNMs of one typical Finnish subject for deviants /ö/ and /õ/ presented in contour (spacing 2 fT cm^{-1}) maps of the magnetic field-gradient amplitude at the MMNM peak latency. The squares indicate the arrangement of the magnetic sensors. The arrows represent ECDs indicating activity in the auditory cortex; the black dots in these arrows show the centres of gravity of MMNM. Note that the prototype /ö/ elicits a much larger MMNM in the left than in the right hemisphere, whereas non-prototype /õ/ responses in both hemispheres are small and quite similar in amplitude.

the vocal tract, and the lip-radiation effect[22]. In this way we could accurately adjust the formants of the stimuli without making sound quality too artificial. The excitation process was computed from a male voice (vowel /a/, normal phonation) using an automatic inverse filtering technique[23]. The vocal tract was modelled using an eighth-order all-pole filter with coefficients adjusted to shift the second formant. The lip-radiation effect was modelled with a fixed differentiator.

Behavioural task. The stimuli, presented at 1,400-ms onset-to-onset intervals, were 75 dB in intensity and 400 ms in duration (with rise and fall times of 10 ms each). Each stimulus was presented about 30 times. Finnish subjects were instructed to press the /e/, /ö/ or /o/ button when the stimulus sounded as a good representative of that category. For Estonians, there was also a response button for their /õ/.

Electric measurements. Measurements were performed in an acoustically and electrically shielded room. Blocks of the vowel /e/ were binaurally presented (75 dB, with a duration of 400 ms including 10-ms rise and fall times) through headphones as the standard stimuli, 15% of the stimuli were randomly appearing deviant sounds (one type per block). The onset-to-onset inter-stimulus interval was 900 ms. The nose-referenced electroencephalogram (EEG, sampling rate 250 Hz) was averaged and digitally filtered (passband 1–30 Hz). Epochs with artefacts exceeding 100 μV at any electrode or with an electro-oculogram (EOG) response exceeding 150 μV were discarded. The baseline for the waveforms was defined as the mean amplitude between −50 and 0 ms relative to stimulus onset. The MMN amplitude was determined from the Fz electrode (where it was usually largest) separately for each subject as the mean amplitude of the 150-ms period centred at the largest peak between 100 and 240 ms.

Magnetic measurements. The experimental paradigm was the same as for the electric measurements. The magnetic responses were measured using a helmet-shaped, whole-head Neuromag-122 magnetometer[24] (sampling rate 397 Hz). The stimuli were delivered through plastic tubes and earpieces at 60 dB above the individual hearing level. Epochs with an electro-oculogram or magnetoencephalogram change exceeding 150 μV or 1,500 fT cm^{-1}, respectively, were omitted from subsequent analysis. The locus of the neuronal activity was estimated by determining the equivalent current dipole at the MMNM peak latency using 40–44 channels separately over the left and right frontotemporal cortices.

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1. Kuhl, P. K. *Percept. Psychophys.* **50,** 93–107 (1991).
2. Liberman, A. M., Harris, K. S., Hoffman, H. S. & Griffith, B. C. *J. Exp. Psychol.* **54,** 358–368 (1957).
3. Kuhl, P. K. *J. Phonet.* **21,** 125–139 (1993).
4. Näätänen, R., Gaillard, A. W. K. & Mäntysalo, S. *Acta Psychol.* **42,** 313–329 (1978).
5. Näätänen, R. *Ear Hear.* **16,** 6–18 (1995).
6. Näätänen, R. *Attention and Brain Function* (Lawrence Erlbaum, Hillsdale, NJ, 1992).
7. Tiitinen, H., May, P., Reinikainen, K. & Näätänen, R. *Nature* **372,** 90–92 (1994).
8. Aaltonen, O., Eerola, O., Hellström, Å., Unispaikka, E., & Lang, A. H. *J. Acoust. Soc. Am.* (in the press).
9. Aulanko, R., Hari, R., Lounasmaa, O., Näätänen, R., & Sams, M. *NeuroReport* **2,** 1356–1358 (1993).
10. Kraus, N. *et al. Science* **273,** 971–973 (1996).
11. Hari, R. in *Auditory Evoked Magnetic Fields and Electric Potentials. Advances in Audiology* Vol. 6 (eds Grandori, F., Hoke, M. & Romani, G. L.) 222–282 (Karger, Basel, 1990).
12. Hämäläinen, M., Hari, R., Ilmoniemi, R. J., Knuutila, J. & Lounasmaa, O. V. *Rev. Mod. Phys.* **65,** 413–497 (1993).
13. Wiik, K. *Ann. Univ. Turku.* **94,** 1–192 (1965).
14. Iivonen, A. *Phonetica* **52,** 221–224 (1995).
15. Liiv, G. & Remmel, M. *Sov. Fenno-Ugric Studies VI* **1,** 7–23 (1970).
16. Näätänen, R., Ilmoniemi, R. J. & Alho, K. *Trends Neurosci.* **7,** 389–395 (1994).
17. Näätänen, R. & Alho, K. *Electroenceph. Clin. Neurophysiol.* (suppl.) **44,** 179–185 (1995).
18. Kuhl, P. K., Williams, K. A. & Lacerda, F. *Science* **255,** 606–608 (1992).
19. Giard, M. H. *et al. J. Cogn. Neurosci.* **7,** 133–143 (1995).
20. Alho, K. *et al. Psychophysiology* **33,** 369–375 (1996).
21. Levänen, S., Ahonen, A., Hari, R., McEvoy, L. & Sams, M. *Cereb. Cortex* **6,** 288–296 (1996).
22. Fant, G. *The Acoustic Theory of Speech Production* (Mouton, Hague, 1960).
23. Alku, P. *Speech Commun.* **11,** 109–118 (1992).
24. Knuutila, J. E. T. *et al. IEEE Trans. Magnet.* **29,** 3315–3320 (1992).

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Bcl-2 promotes regeneration of severed axons in mammalian CNS

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Most neurons of the mammalian central nervous system (CNS) lose the ability to regenerate severed axons *in vivo* after a certain point in development[1]. At least part of this loss in regenerative potential is intrinsic to neurons[2–4]. Although embryonic retinal ganglion cells (RGCs) can grow axons into tectum of any age, most RGCs from older animals fail to extend axons into CNS tissue derived from donors of any age, including the embryonic tectum[2]. Here we report that the proto-oncogene *bcl-2* plays a key role in this developmental change by promoting the growth and regeneration of retinal axons. This effect does not seem to be an indirect consequence of its well-known anti-apoptotic activity. Another anti-apoptotic drug, ZVAD, supported neuronal survival but did not promote axon regeneration in culture. This finding could lead to new strategies for the treatment of injuries to the CNS.