G. Larralde, J. Vivas, J. A. Urbina, *Acta Cient. Venez.* **39**, 140 (1988).
18. Statistical analysis of the survival curves, by use of both the log rank (Mantel-Cox) and Peto-Peto-Wilcoxon tests, indicated a significant ($P < 0.0001$) difference between the control (untreated) animals and all those that received the drug treatments, as well as between those that received D0870 at ≥15 mg/kg per day e.o.d. and the group treated with ketoconazole at 30 mg/kg per day daily. Survival analysis was carried out on the StatView program, version 4.5, run on a Power Macintosh 7100/66 computer.
19. We carried out hemocultures by inoculating 2 ml of liver infusion medium with 0.4 ml of blood obtained from experimental mice by cardiac puncture; microscopic examination of the cultures for the presence of proliferative epimastigote forms was done weekly for 4 weeks. Surviving animals were killed, and organs (spleen, liver, heart, and bone marrow) were minced individually in 1 ml of sterile, phosphate-buffered saline with 10 mM D-glucose; 0.4 ml of the suspension was inoculated in juvenile animals (15 to 20 g). Hemoinoculation (50 μl of blood diluted to 100 μl with sterile, phosphate-buffered saline) was done subcutaneously in 10- to 12-day-old mice. Xenodiagnosis was done with 10 second-stage *Rodnius prolixus* nymphs per mouse; after 2 weeks, the feces were analyzed for *T. cruzi* metacyclic forms, and the exam was repeated weekly thereafter for 1 month. The presence of circulating *T. cruzi* antibodies was detected by immunoprecipitation of ^{125}I-labeled total epimastigote surface antigen antigens with experimental sera in the presence of protein A, followed by analysis of the precipitate by SDS–polyacrylamide gel electrophoresis.
20. C. Britto, M. A. Cardoso, P. Wincker, C. M. Morel, *Mem. Inst. Oswaldo Cruz Rio J.* **88**, 171 (1993); P. Wincker *et al.*, *Am. J. Trop. Med. Hyg.* **51**, 771 (1994). The *T. cruzi*–specific primers used in the tests were 5′-AAATAATGTACGGG(T/G)GAGATGCATGA-3′ and 5′-GGTTCGATTGGGGTTGGTGTAATATA-3′.
21. Statistical analysis of the survival curves, by use of both the log rank (Mantel-Cox) and Peto-Peto-Wilcoxon tests, indicated no significant differences between the control (untreated) animals and those that received ketoconazole at 30 mg/kg per day daily or D0870 at 10 mg/kg per day e.o.d., whereas there were significant differences between these groups and those receiving D0870 at 10 mg/kg per day daily ($P = 0.05$) or ≥15 mg/kg/day e.o.d. ($P = 0.005$).
22. S. De Wit, E. O'Doherty, R. P. Smith, R. Yates, N. Clumeck, *Intersci. Congr. Antimicrob. Agents Chemother. Abstracts* **35**, F97 (1995).
23. This work was supported by the UN Development Programme–World Bank–World Health Organization Programme for Research and Training in Tropical Diseases (grant 930161) and the National Research Council of Venezuela (Consejo Nacional de Investigaciones Cientificas y Técnicas, grant RP-IV-110034). We acknowledge technical assistance by R. Lira and G. Visbal. We dedicate this paper to the memory of Jose Witremundo Torrealba.

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Auditory Neurophysiologic Responses and Discrimination Deficits in Children with Learning Problems

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Children with learning problems often cannot discriminate rapid acoustic changes that occur in speech. In this study of normal children and children with learning problems, impaired behavioral discrimination of a rapid speech change (/dɑ/versus/gɑ/) was correlated with diminished magnitude of an electrophysiologic measure that is not dependent on attention or a voluntary response. The ability of children with learning problems to discriminate another rapid speech change (/bɑ/versus/wɑ/) also was reflected in the neurophysiology. These results indicate that some children's discrimination deficits originate in the auditory pathway before conscious perception and have implications for differential diagnosis and targeted therapeutic strategies for children with learning disabilities and attention disorders.

Learning and attention problems occur in many children, often concurrently (*1*). These disorders frequently involve an inability to process complex auditory information that occurs, for example, in speech. In fact, a large subset of children with such disorders cannot process complex auditory signals, even at the most elemental level (*2*, *3*).

A comprehensive study is under way to examine the relation among psychophysical speech discrimination abilities, standardized measures of learning and academic achievement, and neurophysiology in a large population of both normal children and children with learning problems. One aim is to determine whether children with certain auditory processing problems have difficulties that originate from abnormalities in the neurophysiologic encoding of acoustic differences in speech (which occurs after peripheral sensory encoding and before conscious perception) or whether the problems arise from some higher level processing deficit (which may involve, for example, linguistic or cognitive abilities) (*4*). Such information would aid in the diagnosis and treatment of these children, whose learning problems have been difficult to define or categorize.

An important aspect of this work is to establish a neurophysiologic correlate of behavioral discrimination. Fortunately, there is a neurophysiologic response that occurs in response to small (as well as large) acoustic changes in both simple and complex stimuli (*5*). This response, termed the mismatch negativity (MMN), provides an index of the neurophysiologic representation of acoustic contrasts and thus provides a tool for exploring the processing of acoustic differences that underlie speech perception.

The MMN originates in the auditory thalamocortical pathway (*6*, *7*) and demonstrates learning-associated plasticity (*8*). It is elicited by a physically deviant stimulus occurring in a series of homogeneous stimuli. The response can be elicited in a passive paradigm in which attention or behavioral responses are not required (*9*). It has been obtained during sleep in infants and adults and during wakefulness, sleep, and barbiturate anesthesia in animal models (*10*). From a developmental standpoint, the MMN is robust in children and appears to be mature by school age (*11*, *12*). Thus, the MMN reflects with considerable precision the discrimination of acoustic change and can be used to determine which aspects of the acoustic signal are differentiated neurophysiologically and, ultimately, which neuronal pathways are impaired (*7*, *13*).

In this experiment, behavioral discrimination abilities and MMN responses were evaluated in a group of normal children ($n = 90$) and in a group of children with learning problems ($n = 91$). The normal group consisted of children ages 6 to 15 years with no history of learning or attention problems (based on a detailed parent questionnaire) and scores within normal limits (including no discrepancy between ability and achievement) on a psychoeducational test battery (*14*). The group with learning problems consisted of children in the same age range who had been diagnosed clinically as having a learning disability (LD children), attention deficit disorder (ADD children), or both; in some cases, they had scores that were not within the normal limits on two or more of the tests in the psychoeducational test battery and a history of learning or attention difficulties (suspected LD). All children had normal intelligence (scores >85 on the Brief Cognitive Scale) (*14*). The normal group differed significantly from the group with

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learning problems on measures of listening comprehension, visual speed of processing, sound blending, auditory processing, reading, spelling ($P < 0.001$ in all cases), and auditory memory for words ($P < 0.02$).

Using a parameter estimation by sequential tracking (PEST) paradigm (*15*), we obtained just-noticeable differences (JNDs) for two rapid spectrotemporal differences with two continua of synthetic consonant-vowel syllables. The continua varied either in the duration of the formant transition (/bɑ/to/wɑ/) [(bah-wah) to (dah-gah)] or in the spectral content of the formant transition (/dɑ/to/gɑ/) (*16*). There was no correlation between intelligence and JND scores ($r = -0.10$, $P = 0.165$, not significant). To compare discrimination data for the two acoustic contrasts, we converted the JNDs for all participants to JND′ scores to compare results across test conditions and across groups (*17*).

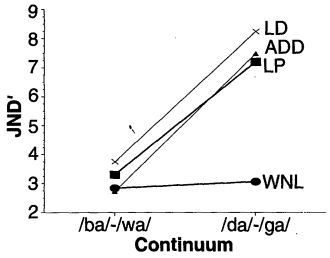

Fig. 1. Mean JND′ scores for normal children (WNL) and children with learning problems (LP) for the /bɑ/-/wɑ/ and /dɑ/-/gɑ/ continua. LD and ADD subgroup data are shown by thin lines (the suspected LD subgroup is not shown).

Figure 1 shows the mean JND′ scores for the normal group and the group with learning problems for both the /bɑ/-/wɑ/ and the /dɑ/-/gɑ/ continua. The JND′ scores indicate that the difference between groups was much smaller for the /bɑ/-/wɑ/ than for the /dɑ/-/gɑ/ stimuli. The normal children performed better than the children with learning problems for both stimuli ($F = 11.54$, $P < 0.001$), and both groups discriminated the /bɑ/-/wɑ/ contrast better than the /dɑ/-/gɑ/ contrast ($F = 13.55$, $P < 0.001$). In addition, a significant group-by-condition interaction indicated a greater difference between the normal group and the group with learning problems for /dɑ/-/gɑ/ discrimination than for /bɑ/-/wɑ/ discrimination ($F = 10.74$, $P < 0.002$).

When subgroups of LD and ADD children were compared to the normal children, and when LD and ADD children were compared to each other, a Scheffé post hoc analysis showed similar group-by-condition differences (all combinations were significant at the $P < 0.01$ level except for normal children versus ADD children for the /bɑ/-/wɑ/ contrast) (Fig. 1). Therefore, even though discrimination was impaired for both stimulus contrasts in the children with learning problems, the perception of those rapid speech contrasts was impaired to a different extent. Moreover, individual JND′ scores suggest that an auditory perception deficit affects a large number of LP children. For example, nearly 35% of them had /dɑ/-/gɑ/ JND′ scores greater than 7, whereas only 10% of the normal children had such poor discrimination scores.

Electrophysiologic MMN responses were elicited by synthetic /dɑ/-/gɑ/ and /bɑ/-/wɑ/ stimulus pairs from the same continua used in the behavioral experiment. The specific stimulus pairs were selected to be difficult for listeners with normal abilities to discriminate (*18*). MMN responses were measured with procedures similar to those previously described (*19*).

MMNs were elicited from 42 children from the group tested behaviorally, all of whom could discriminate the /bɑ/-/wɑ/ contrast well. These children were age-matched and grouped according to their behavioral perception of /dɑ/-/gɑ/ (*20*). Figure 2 shows robust grand-average MMN responses for "good" /dɑ/-/gɑ/ perceivers ($n = 21$) and absent grand-average MMN responses for "poor" /dɑ/-/gɑ/ perceivers ($n = 21$) to the /dɑ/-/gɑ/ stimulus contrast. The MMN area and duration measures for individual children also were significantly smaller in the "poor" group than in the "good" group ($P < 0.003$ for both measures). There was a correlation between /dɑ/-/gɑ/ discrimination scores and both MMN duration and area ($r = -0.40$, $P < 0.01$ and $r = -0.42$, $P < 0.01$, respectively). These data indicate that good perception of /dɑ/versus/gɑ/ is associated with robust MMN responses, and poor discrimination of /dɑ/versus/gɑ/ corresponds to diminished MMN responses.

In addition, 14 "good" and 14 "poor"

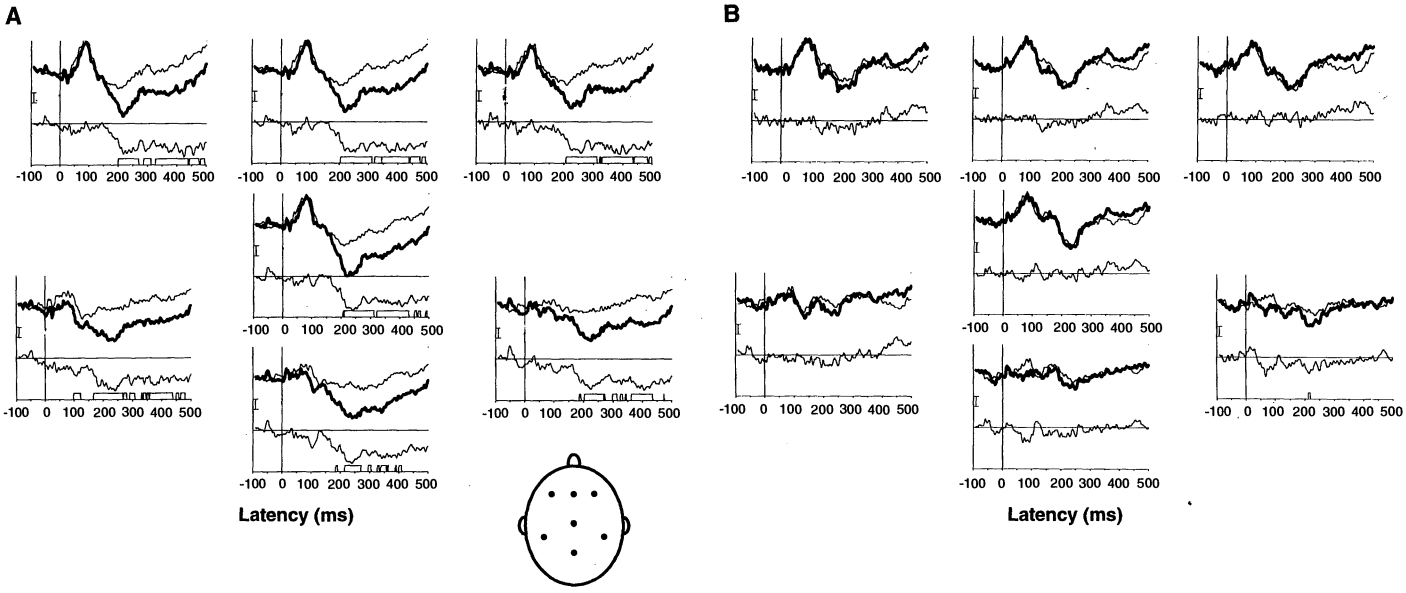

Fig. 2. Grand-average MMN responses elicited by a /dɑ/-/gɑ/ contrast at seven scalp recording locations in (**A**) "good" /dɑ/-/gɑ/ perceivers and (**B**) "poor" /dɑ/-/gɑ/ perceivers. The schematic head indicates electrode positions. The top thin line is the response to the /dɑ/ stimulus when it was presented alone. The thick line is the response to the /dɑ/ stimulus when it signaled an acoustic change in the oddball paradigm. The mismatch response is seen in the difference wave (lower thin line) as a deflection below the zero line. The boxes below indicate the latency ranges over which a significant mismatch response occurs ($P < 0.01$). Scale bars = 0.5 μV.

/dɑ/-/gɑ/ perceivers from the same pool of 42 children were tested neurophysiologically with the /bɑ/-/wɑ/ contrast. Both groups had MMN responses to /bɑ/-/wɑ/ that were consistent with their behavioral discrimination abilities. There was no significant difference in MMN duration and area between the two groups ($t = 0.49$, $P = 0.63$, not significant, and $t = 0.71$, $P = 0.49$, not significant, respectively) (Fig. 3).

Taken together, these psychophysical and electrophysiologic data indicate that the behavioral discrimination exhibited by children with learning problems is mirrored consistently by an electrophysiologic measure that originates specifically in the auditory pathway and does not depend on attention or a voluntary response. The results provide strong evidence that the discrimination difficulties of some children with learning problems occur before conscious perception. Furthermore, the behavioral data show that perception of all rapid spectrotemporal changes may not be impaired to the same extent in children with learning problems. The processing of the two contrasts studied here may tap into separate and distinct neural mechanisms, which is consistent with the view that the encoding of acoustic elements of speech occurs at distinct locations along the auditory pathway (*7*, *13*, *21*).

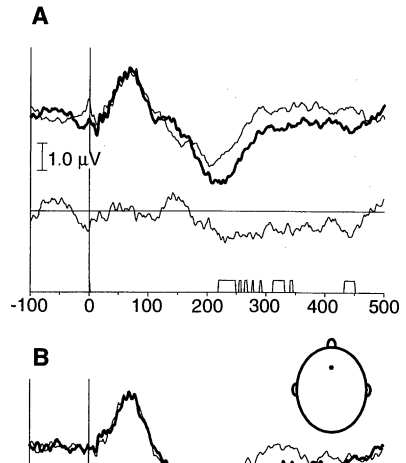

Fig. 3. Grand-average MMN responses elicited by a /bɑ/-/wɑ/ contrast at one scalp recording location (frontal center) for (**A**) 14 "good" /dɑ/-/gɑ/ perceivers and (**B**) 14 "poor" /dɑ/-/gɑ/ perceivers. The mismatch response is seen in the difference wave (lower thin line) as a deflection below the zero line. The boxes below indicate the latency ranges over which a significant mismatch response occurs ($P < 0.05$).

Electrophysiologic responses might be applicable clinically in the differential diagnosis of children with learning problems, to separate individuals who have auditory system–based deficits from individuals who have deficits originating later in the perceptual process. Because previous research shows that speech-sound perception can be modified by training (*3*, *22*) and that the MMN changes after listening training (*7*), it is important to determine which acoustic elements are perceived abnormally by children with learning problems. That information would influence the design of targeted intervention strategies and provide a foundation for the study of neural processes underlying perception problems.

REFERENCES AND NOTES

1. A child with learning disabilities shows a significant discrepancy between mental ability and achievement in one or more academic areas. A child with attention problems exhibits symptoms of inattention, impulsivity, and hyperactivity in amounts significantly greater than those seen in mental-age peers [B. Y. L. Wong, Ed., *Learning about Learning Disabilities* (Academic Press, San Diego, 1991); R. A. Barkley, *Attention Deficit Hyperactivity Disorder: A Handbook for Diagnosis and Treatment* (Guilford, New York, 1990)].
2. J. J. Godfrey, A. K. Syrdal-Lasky, K. K. Millay, C. M. Knox, *J. Exp. Child Psychol.* **32**, 401 (1981); L. Bradley and P. E. Bryant, *Nature* **301**, 419 (1983); R. C. Tees and J. F. Werker, *Can. J. Psychol.* **41**, 48 (1987); W. Weirdt, *Appl. Psychophys.* **9**, 163 (1988); L. L. Elliott and M. Hammer, *J. Speech Hear. Dis.* **53**, 467 (1988); M. A. Reed, *J. Exp. Child Psychol.* **48**, 270 (1989).
3. P. Tallal, *Int. J. Pediatr. Otorhinolaryngol.* **3**, 1 (1981); M. Merzenich *et al.*, *Science* **271**, 77 (1996); P. Tallal *et al.*, *ibid.*, p. 81.
4. D. L. Share, A. F. Jorm, R. Maclean, R. Matthews, *J. Educ. Psychol.* **76**, 1309 (1984); K. E. Stanovich and L. S. Siegal, *ibid.* **86**, 24 (1994); J. M. Fletcher *et al.*, *ibid.*, p. 6; M. Studdert-Kennedy and M. Mody, *Psychon. Bull. Rev.* **2**, 508 (1995).
5. R. Näätänen, A. Gaillard, S. Mäntysalo, *Acta Psychol.* **42**, 313 (1978); R. Näätänen, Ed., *Attention and Brain Function* (Erlbaum, Hillsdale, NJ, 1992), pp. 136–210; N. Kraus and R. Näätänen, Eds., *Ear Hear.* **16** (1995).
6. M. Scherg and T. Picton, in *Psychophysiological Brain Research, Vol. I*, C. Brunia, A. Gaillard, A. Kok, Eds. (Tilberg Univ. Press, Tilberg, Germany, 1990), pp. 94–98; M. Sams, E. Kaukoranta, M. Hämäläinen, R. Näätänen, *Psychophysiology* **28**, 21 (1991).
7. N. Kraus *et al.*, *J. Neurophysiol.* **72**, 1270 (1994).
8. R. Näätänen *et al.*, *Neuroreport* **4**, 503 (1993); N. Kraus, T. McGee, T. Carrell, C. King, K. Tremblay, *J. Cog. Neurosci.* **7**, 27 (1995); K. Tremblay *et al.*, *Assoc. Res. Otolaryngol. Abstr.* **18**, 183 (1995).
9. R. Näätänen, *Behav. Brain Sci.* **13**, 201 (1990).
10. V. Csépe, G. Karmos, M. Molnár, *Electroenceph. Clin. Neurophysiol.* **66**, 571 (1987); K. Alho *et al.*, *ibid.* **77**, 151 (1990); D. Javitt *et al.*, *ibid.* **83**, 87 (1992); C. King *et al.*, *Hear. Res.* **85**, 45 (1995).
11. N. Kraus *et al.*, *Electroencephalogr. Clin. Neurophysiol.* **88**, 123 (1993).
12. V. Csépe, *Ear Hear.* **16**, 90 (1995); M. Cheour-Luhtanen *et al.*, *Hear. Res.* **82**, 53 (1995).
13. P. Paavilainen *et al.*, *Electroencephalogr. Clin. Neurophysiol.* **78**, 466 (1991); N. Kraus *et al.*, *J. Acoust. Soc. Am.* **96**, 2758 (1994); M. H. Giard *et al.*, *J. Cog. Neurosci.* **7**, 133 (1995); T. J. McGee *et al.*, *J. Acoust. Soc. Am.* **99**, 3606 (1996).
14. R. Woodcock and M. Johnson, *Woodcock-Johnson Psycho-Educational Battery: Tests of Cognitive Ability* (W-J PEB) (DLM Teaching Resources, Allen, TX, 1977); ———, *Woodcock-Johnson Psycho-Educational Battery–Revised: Tests of Cognitive Ability* (DLM Teaching Resources, Allen, TX, 1989); G. Wilkinson, *Wide Range Achievement Test-3* (WRAT-3) (Jastak Associates, Wilmington, DE, 1993); G. DuPaul, *The ADHD Rating Scale: Normative Data, Reliability, and Validity* (unpublished manuscript, University of Massachusetts Medical Center, Worcester, MA, 1990; this can be found in R. A. Barkley, *Attention-Deficit Hyperactivity Disorder* (Guilford, New York, 1990). W-J PEB-R tests included Cross Out (a visual measure of processing speed), Sound Blending, Memory for Words, Sound Patterns, Listening Comprehension, and Incomplete Words. WRAT-3 tests included spelling and reading.
15. M. M. Taylor and C. D. Creelman, *J. Acoust. Soc. Am.* **41**, 782 (1967).
16. Five-formant synthetic speech syllables were produced with a Klatt cascade-parallel formant synthesizer [D. Klatt, *J. Acoust. Soc. Am.* **67**, 971 (1980)]. A /bɑ/-/wɑ/ continuum and a /dɑ/-/gɑ/ continuum were created in which the values of the synthesis parameters between the endpoint stimuli were interpolated linearly to generate the intermediate stimuli. Across the /bɑ/-/wɑ/ continuum, the transition durations of the first and second formants changed from 10 to 40 ms in 1-ms steps. Overall spectral content was unchanged across the continuum. Across the /dɑ/-/gɑ/ continuum, the third formant onset frequency changed from 2580 to 2190 Hz in 10-Hz steps, with the transition duration held constant at 40 ms. All syllables were 100 ms in total duration.
17. The JNDs of the 40 best-performing normal children were used to define an optimal performance standard for each continuum. These 40 participants were distributed evenly across the age range, and no age effects were apparent. JNDs were converted to standard scores, termed JND′ scores, on the basis of the mean and SD of these 40 best performers.
18. From the /bɑ/-/wɑ/ continuum, the syllable with a 35-ms formant transition duration served as the standard stimulus and the syllable with the 40-ms formant transition duration served as the deviant stimulus in the MMN experiments. From the /dɑ/-/gɑ/ continuum, the syllable with an F_3 onset frequency of 2500 Hz served as the standard stimulus and the syllable with an F_3 onset frequency of 2580 Hz served as the deviant stimulus. These pairs were discriminated at threshold by normal adult listeners [discrimination index, $d' = 1$, as described by D. M. Green and J. A. Swets, *Signal Detection Theory and Psychophysics* (Krieger, New York, 1974)].
19. The procedures used to measure and analyze the cortical responses were similar to those that have been described (*11*). Speech stimuli were presented to the right ear at 75 dB sound pressure level (SPL) through insert earphones. An oddball paradigm was used in which a deviant stimulus was presented randomly in a series of standard stimuli. Participants watched a videotape of their choice with the free-field soundtrack level less than 45 dB SPL.
20. The difference in /dɑ/-/gɑ/ perception between the "good" and "poor" perceivers was significant ($t = 6.82$, $P < 0.001$). There was no significant difference in the scores for /bɑ/-/wɑ/ between these two groups ($t = 0.65$, $P = 0.517$, not significant), thereby indicating that all children could perform the JND task.
21. S. H. Auerbach *et al.*, *Brain* **105**, 271 (1982); D. P. Phillips and M. E. Farmer, *Behav. Brain Res.* **40**, 85 (1990).
22. D. B. Pisoni, R. N. Aslin, A. J. Perey, B. L. Hennessy, *J. Exp. Psychol.* **8**, 297 (1982); E. W. Ball and B. A. Blachman, *Reading Res. Qtrly.* **26**, 49 (1991); P. K. Kuhl, K. A. Williams, F. Lacerda, K. N. Stevens, B. Lindblom, *Science* **255**, 606 (1992).

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