

**Auditory Neurophysiologic Responses and Discrimination Deficits in  
Children with Learning Problems**



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*Science*, New Series, Vol. 273, No. 5277 (Aug. 16, 1996), 971-973.

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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  $\geq 15$  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  $\mu$ l of blood diluted to 100  $\mu$ l 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.
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  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  $\geq 15$  mg/kg/day e.o.d. ( $P = 0.005$ ).
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8 April 1996; accepted 12 June 1996

## 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 (/da/versus/ga/) 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 (/ba/versus/wa/) 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 chil-

dren 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 (/ba/to/wa/) [(bah-wah) to (dah-gah)] or in the spectral content of the formant transition (/da/to/ga/) (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).

Figure 1 shows the mean JND' scores for the normal group and the group with learning problems for both the /ba/-/wa/ and the /da/-/ga/ continua. The JND' scores indicate that the difference between groups was much smaller for the /ba/-/wa/ than for the /da/-/ga/ 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 /ba/-/wa/ contrast better than the /da/-/ga/ 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 /da/-/ga/ discrimination than for /ba/-/wa/ discrimination ( $F = 10.74$ ,  $P < 0.002$ ).

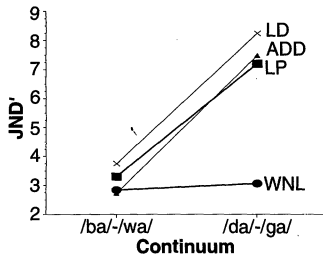
When subgroups of LD and ADD children were compared to the normal children, and when LD and ADD children were compared to each other, a Scheffé post hoc analysis showed similar group-by-condition differences (all combinations were significant at the  $P < 0.01$  level except for normal children versus ADD children for the /ba/-/wa/ 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

/da/-/ga/ JND' scores greater than 7, whereas only 10% of the normal children had such poor discrimination scores.

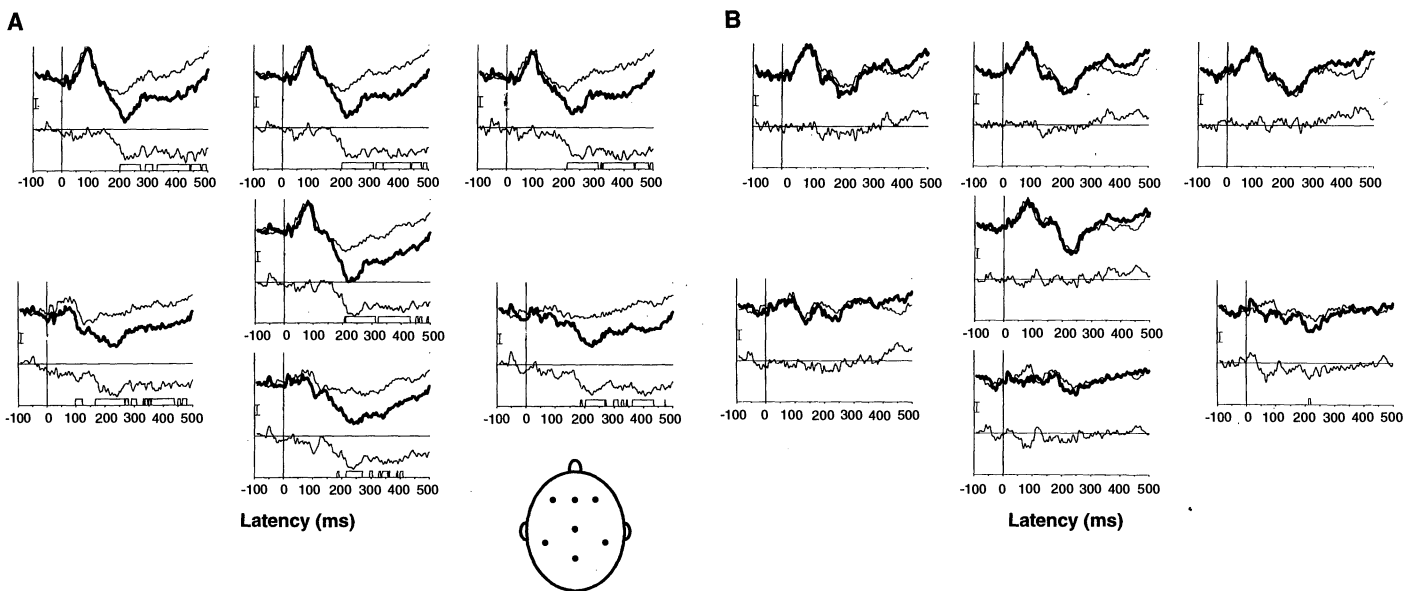
Electrophysiologic MMN responses were elicited by synthetic /da/-/ga/ and /ba/-/wa/ stimulus pairs from the same continua used in the behavioral experiment. The specific stimulus pairs were selected to be difficult for listeners with normal abilities to discriminate (18). MMN responses were measured 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 /ba/-/wa/ contrast well. These children were age-matched and grouped according to their behavioral perception of /da/-/ga/ (20). Figure 2 shows robust grand-average MMN responses for "good" /da/-/ga/ perceivers ( $n = 21$ ) and absent grand-average MMN responses for "poor" /da/-/ga/ perceivers ( $n = 21$ ) to the /da/-/ga/ 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 /da/-/ga/ 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 /da/versus/ga/ is associated with robust MMN responses, and poor discrimination of /da/versus/ga/ corresponds to diminished MMN responses.

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



**Fig. 1.** Mean JND' scores for normal children (WNL) and children with learning problems (LP) for the /ba/-/wa/ and /da/-/ga/ continua. LD and ADD subgroup data are shown by thin lines (the suspected LD subgroup is not shown).



**Fig. 2.** Grand-average MMN responses elicited by a /da/-/ga/ contrast at seven scalp recording locations in (A) "good" /da/-/ga/ perceivers and (B) "poor" /da/-/ga/ perceivers. The schematic head indicates electrode positions. The top thin line is the response to the /da/ stimulus when it was presented alone. The thick line is the response to the /da/ 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 =  $0.5 \mu\text{V}$ .

/da/-/ga/ perceivers from the same pool of 42 children were tested neurophysiologically with the /ba/-/wa/ contrast. Both groups had MMN responses to /ba/-/wa/ 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

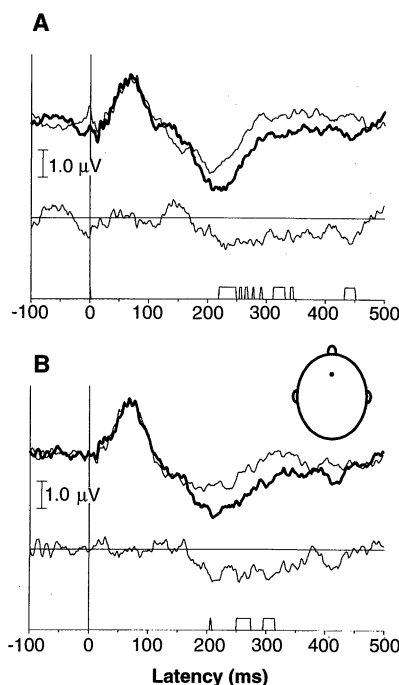
the auditory pathway (7, 13, 21).

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.

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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 /ba/-/wa/ 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 /da/-/ga/ 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 /da/-/ga/ perception between the "good" and "poor" perceivers was significant ( $t = 6.82$ ,  $P < 0.001$ ). There was no significant difference in the scores for /ba/-/wa/ between these two groups ( $t = 0.65$ ,  $P = 0.517$ , not significant), thereby indicating that all children could perform the JND task.
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23. This work was supported by NIH-National Institute on Deafness and other Communicative Disorders (grant DC 01510) and the Foundation for Hearing and Speech Research. We thank A. Cameron, J. Cunningham, J. Hoepfner, K. Tremblay, and B. Trommer for their contributions.

1 May 1996; accepted 21 June 1996



**Fig. 3.** Grand-average MMN responses elicited by a /ba/-/wa/ contrast at one scalp recording location (frontal center) for (A) 14 "good" /da/-/ga/ perceivers and (B) 14 "poor" /da/-/ga/ 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 ( $P < 0.05$ ).