Induced Microgyria and Auditory Temporal Processing in Rats: A Model for Language Impairment?

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Studies have shown the existence of minor developmental cortical malformations, including microgyria, in the brains of dyslexics. Concomitant studies have shown that language-impaired individuals exhibit severe deficits in the discrimination of rapidly presented auditory stimuli, including phonological and nonverbal stimuli (i.e., sequential tones). In an effort to relate these results, male rats with neonatally induced microgyria were tested in an operant paradigm for auditory discrimination of stimuli consisting of two sequential tones. Subjects were shaped to perform a go/no-go target identification, using water reinforcement. Stimuli were reduced in duration from 540 to 249 msec across 24 d of testing. Results showed that all subjects were able to discriminate at longer stimulus durations. However, bilaterally lesioned subjects showed specific impairment at stimulus durations of 332 msec or less, and were significantly depressed in comparison to shams. Right- and left-lesioned subjects were significantly depressed in comparison to shams at the shortest duration (249 msec). These results suggest a possible link between the neuropathologic anomalies and the auditory temporal processing deficits reported for language-impaired individuals.

Developmental language disorders, including developmental dyslexia, are characterized by discrepant or unusually low language ability despite normal intelligence, motivation, and instruction. Investigations of potential biologic substrates underlying language impairment (LI) have focused on both anatomical and physiological differences between language-impaired and control individuals. For example, developmental neuropathologic anomalies have been seen in the brains of dyslexics (Galaburda and Kemper, 1979; Galaburda et al., 1985; Humphreys et al., 1990). These anomalies, although present bilaterally, are found predominantly in frontal and perisylvian regions of the left hemisphere, and include ectopic collections of neurons in the molecular layer, dysplasias, myelinated scars, and polymicrogyria. Although the relationship between these anomalies and the behavioral deficits seen in dyslexia cannot be tested directly in humans, experiments with autoimmune strains of mice, 15–40% of whom spontaneously develop molecular layer ectopias (Sherman et al., 1985, 1987), have demonstrated some clear correlations between behavior and anatomy. For example, left-pawed ectopic mice perform better than their right-pawed counterparts on a water escape task, but worse on a discrimination learning paradigm (Denenberg et al., 1991). Ectopic mice in general perform worse in Morris maze and black–white discrimination learning tasks, although these deficiencies can be ameliorated by postweaning enrichment (Schrott et al., 1992).

Other research has probed the substrates of language impairment by focusing on the functional underpinnings of LI, hypothesizing that dysfunction at a sensory processing level may have cascading developmental effects, and hence lead to higher-order language problems. These studies have demonstrated that a large subgroup of language-impaired children exhibit severe deficits in the ability to perform auditory discriminations of information presented sequentially within a brief time window (300 msec or less). Although this deficit is profoundly evident when children with LI are asked to discriminate speech stimuli characterized by brief temporal components (e.g., consonant–vowel syllables) (Tallal and Piercy, 1975; Tallal, 1977, 1980), the presented material need not be linguistic in order for the deficit to be observed. While normal children are able to discriminate two 75 msec tones separated by as little as 8 msec, language-impaired children require over a 350 msec in-

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terval to perform this same basic discrimination (Tallal and Piercy, 1973). These and other findings (Bakker, 1971; Tallal, 1980; Shucard et al., 1984; Byring and Jarvilehto, 1985; Obrzut et al., 1987; Pinkerton et al., 1989; Reed, 1989; Ortiz Alonso et al., 1990; Watson, 1992) strongly suggest a fundamental dysfunction of the basic ability to perform rapid auditory discriminations in individuals with LI. Subsequent studies have demonstrated similar temporal integration deficits in the visual and tactile modalities, as well as in the performance of sequential motor functions (Johnston et al., 1981; Tallal et al., 1981, 1985; Katz et al., 1992). These results suggest that a fundamental sensory/motor deficit in temporal integration may characterize LI, although Tallal (Tallal et al., 1993) has hypothesized that it is specifically deficits in the auditory modality that disrupt phonological processing and speech perception and, consequently, result in abnormal language acquisition.

In addition to these processing deficits observed in language-impaired children, defects in the processing of rapid information in the visual system have been observed in developmental dyslexics who also do poorly on tests requiring rapid visual processing (Lovegrove et al., 1990; Slaghuis et al., 1992). Several recent studies have reported that dyslexics exhibit diminished visual evoked potentials to rapidly changing, low-contrast stimuli, but normal responses to slowly changing or static, high-contrast stimuli (Livingstone et al., 1991). Similar response differences between controls and dyslexics were observed using stimuli of differing spatial frequency (Lehmkuhle et al., 1993). This response pattern is consistent with impaired functioning of the magnocellular, but not the parvocellular, division of the visual pathway. Such an interpretation is supported by the fact that neurons of the magnocellular layers of the lateral geniculate nucleus (LGN) were found to be, on average, 27% smaller in dyslexic brains (Livingstone et al., 1991). Interestingly, these same dyslexic brains exhibited neuropathologic anomalies as described above.

The relationship between developmental neuropathologic anomalies and functional deficits in "rapid processing," both of which characterize language-impaired individuals, has never been directly tested. The purpose of the present experiment was to merge these two approaches to the study of developmental LI via an experimental animal model. It has previously been shown that both molecular layer ectopias and microgyria can be induced in otherwise normal rats by neonatal damage (stab wounds and freezing lesions, respectively), and that these induced anomalies are neuroanatomically similar to those appearing spontaneously in both dyslexic humans and immune-disordered mice (Humphreys et al., 1989; Rosen et al., 1992a,b; Sherman et al., 1992). In the present study, male rats that had received neonatal microgyric lesions to either left, right, or both neocortices, as well as sham-operated controls, were assessed for performance on an auditory discrimination task in which the temporal parameters of the stimulus were manipulated. Our hypothesis was that microgyric lesions of the neocortex might specifically impair the ability of subjects to perform auditory discriminations at shorter stimulus durations. Further, we wished to investigate whether the left hemisphere specialization for auditory temporal processing observed in a variety of species, including humans (Halperin et al., 1973; Papcun et al., 1974; Dewson, 1977; Natale, 1977; Petersen et al., 1978; Divenyi and Efron, 1979; Leek and Brandt, 1983; Heffner and Heffner, 1986; Ehret, 1987; Gaffan and Harrison, 1991), and specifically for intact male rats tested in a paradigm similar to that described here (Fitch et al., 1993), would be evident using this preparation.

Materials and Methods

Induction of Focal Necrotic Lesions

Six time-mated female Wistar rats (Charles River Laboratories, Wilmington, MA) were delivered to the laboratory of G.D.R. and A.M.G. on days 16–18 of gestation. On the day after birth (P1), litters were culled to 10, maximizing for males (range = 4–8), and the male pups randomly assigned to one of four groups: left, right, or bilateral freezing lesions or sham surgery. Focal necrotic lesions were then induced based on a modification of the technique employed by Dvorák and colleagues (Dvorák and Feit, 1977; Dvorák et al., 1978), and reported in detail elsewhere (Humphreys et al., 1989; Rosen et al., 1992a). Briefly, pups were anesthetized via induction of hypothermia, and a small incision was made in the anteroposterior plane of the skin over the left or right cerebral hemisphere, exposing the skull. For bilateral lesions, a midline incision was made. A cooled ($\approx -70°C$) 2-mm-diameter stainless steel probe was placed on the skull of lesion subjects, approximately midway between bregma and lambda, for 5 sec. For bilateral lesions, the first hemisphere to receive the freezing lesion was randomly assigned. Sham subjects were prepared as above, except that the probe was maintained at room temperature. After placement of the probe the skin was quickly sutured and the subjects were uniquely marked with ink injections to the footpads, warmed under a lamp, and returned to the mother. Assignment of subjects to one of the four treatment groups was balanced within a litter, so that each litter had at least one member of each group.

Litters were weaned on P21 and the subjects group-housed (two or three per cage) with littermates until P45, when 24 males (six subjects from each treatment group, four subjects from each litter) were individually marked with picric acid and shipped to R.H.F.

Behavioral Testing

Upon receipt, subjects were individually housed in tubs. The behavioral testing was performed blind with respect to group. At approximately P70, subjects were put on a water-restricted schedule, and received ad libitum access to water for only 15 min/d.

Subjects were then introduced to a modified operant conditioning apparatus for training sessions of 30–40 min/d. The test apparatus consisted of a Plexi-

glas box, modified by the attachment of a Plexiglas tube of sufficient diameter to accommodate the head of an adult rat. The face of the tube was affixed to a plate containing a mechanical switch that the rat could operate with his nose, and a drinking tube below the switch. Miniature Sony speakers were affixed bilaterally (via O-rings) over holes drilled in the Plexiglas tube. This apparatus was custom designed to allow shaping of subjects through a series of phases controlled by a Macintosh IIci computer. Subjects were trained to insert their head into the tube in a relatively straight position (breaking an emitter-detector beam), and to hold this position for a period of 1000 msec before pressing the illuminated nose button to obtain a water reward. Subjects received white-noise feedback (via the speakers affixed to the tube) to indicate correct positioning. Once able to perform this task consistently (48 trials/session), subjects were introduced to the auditory discrimination paradigm.

Testing consisted of a go/no-go target identification task. Once in position, the subject was exposed to an auditory stimulus that consisted of a two-tone sequence. The subject was required to assess whether this stimulus was his "target" (reinforced) or a nontarget sequence (not reinforced). The full presentation of the stimulus was contingent upon proper head placement of the subject; removal of the head during stimulus presentation resulted in an aborted trial, and a 5 sec time-out (all lights extinguished). The same tone sequence was then presented on the next trial. If proper head position was maintained for the duration of stimulus presentation, then the nose button was illuminated for a 3 sec response interval. A press following the subject's target resulted in the presentation of water, while a press following a negative sequence resulted in a time-out of 45 sec.

The stimuli were generated by a Macintosh IIci computer, and were composed of two sine-wave tones 20 msec in duration, separated by an interstimulus interval (ISI) of 500 msec. The low tone was 1100 Hz and the high tone was 2300 Hz, presented at a suprathreshold intensity of 75 dB; these stimuli were identical to those that had previously been used to show a right ear advantage for auditory discrimination in adult male rats (Fitch et al., 1993). Only Hi-Lo or Lo-Hi sequences were assigned as targets, and these were counterbalanced across animals and remained constant for each subject across testing sessions. Negative sequences included Lo-Lo, Hi-Hi, and the opposite mixed pair. Presentation of target and nontarget stimuli in a test session was random with the constraint that half of the presentations be target (to maintain motivation), and that no more than three target or nontarget sequences occur in succession. Right and left audio speakers were alternated daily to prevent bias via differences in speaker properties. Each daily session consisted of 48 trials.

After 6 d of testing at the above stimulus parameters, the ISI for all sequences (including targets and nontargets) was reduced to 350 msec. All other parameters, including the assignment of each subject's target, remained constant. At the end of 6 d, the duration of the tones within the stimulus sequence was reduced from 20 to 16 msec each, and the ISI was reduced from 350 to 300 msec. After another 6 d of testing the tone durations were reduced to 12 msec and the ISI was reduced to 225 msec, for the final 6 d of testing. There were a total of 24 d of testing, with 6 d at each of four conditions defined by incrementally decreased stimulus duration.

For each test session the sequence of presentation on each trial, and the corresponding response type (hit, false alarm, correct rejection, or miss) and latency to respond were recorded by a Macintosh IIci computer. All phases of training were controlled by programs written in the software program LABVIEW specifically for this purpose.

Histology

After the completion of testing subjects were deeply anesthetized with ketamine and xylazine, and were transcardially perfused with 0.9% saline and 10% formalin. The skulls were extracted, placed in 10% formalin, and shipped to G.D.R. There, the brains were removed from the skulls and were placed into fresh 10% formalin for 7 d, before being dehydrated in a series of graded alcohols and embedded in 12% celloidin (cf. Sherman et al., 1987). Serial sections were cut coronally at 40 μm and a series of every 10th section was stained for Nissl substance with cresylecht violet. Using a drawing tube attached to a Zeiss Universal photomicroscope, both neocortical hemispheres were drawn from the frontal to occipital pole. In addition, the damaged area was traced starting from the first section that showed any architectonic distortion and proceeding until the distortion had unambiguously disappeared. Previous research (Humphreys et al., 1989; Rosen et al., 1992a) had demonstrated that the appearance of the area of damage with Nissl stains correlated quite well with assessment of damage as seen with various immunocytochemical stains (i.e., glial fibrillary acidic protein, glutamate, and 68 kDa neurofilament). The area of the neocortical hemispheres, and that of the damaged area were measured from these drawings using a Zeiss MOP-3 Electronic Planimeter interfaced to a Macintosh Plus computer. Total neocortical volume and microgyric volume were determined using Cavalieri's estimation (Rosen and Harry, 1990). In rare situations where, because of missing or damaged sections, the equispaced criteria required for Cavalieri's estimator were not met, a measurement method involving piecewise parabolic integration was employed (Rosen and Harry, 1990). The architectonic location of the lesion was also quantified by overlaying the topographic location on a normalized flattened map of the neocortex derived from Zilles (1985).

Results

Histology

Histology confirmed the expected location of cortical injury in 22 of the 24 subjects (Fig. 1). However, it

was determined that two subjects (a sham and a left lesion) had been interchanged at some point during the study. Since the exchange could have occurred either before or after behavioral testing, these two subjects were dropped from further analyses. Thus, the final n per group was sham = 5, right lesion = 6, left lesion = 5, bilateral lesion = 6.

The degree of neocortical damage was equivalent in all surgical groups. Thus, the percentage of damage in the neocortical hemispheres did not differ between right-lesioned and left-lesioned subjects ($\bar{x} \pm$ SEM = 5.04 ± 0.64 vs 7.16 ± 1.52, respectively; $F_{1,9} = 1.88$, NS). Repeated-measures ANOVA demonstrated no difference in the percentage of damage between the right and left hemispheres of bilaterally lesioned animals ($\bar{x} \pm$ SEM = 4.79 ± 0.65 vs 5.43 ± 0.81, respectively; $F_{1,5} = 3.61$, NS). The range of topographic location of the lesions, shown in Figure 2, demonstrates the relative symmetry of damage in bilaterally injured animals. The distribution of the lesion location of those sustaining unilateral left hemisphere lesions, however, was more medial than their unilateral right hemisphere–lesioned counterparts, and their regions of overlap were quite small. Whereas the microgyria in the right hemisphere involved some frontal, hindlimb, and forelimb regions of the somatosensory cortex, the left hemisphere locations were mostly confined to lateral portions of the somatosensory cortex.

Behavior

It has previously been shown that while rats trained in this paradigm do not withhold responses to negative sequences (the incidence of correct rejections and misses combined being less than 1% of responses), response latencies following the presentation of target versus nontarget do show significant differences (O'Connor et al., 1992; Fitch et al., 1993). Specifically, latencies to respond to the target (hits) have been shown to be significantly shorter than latencies for incorrect responses to nontarget sequences (false alarms) when discrimination occurs. This effect has also been demonstrated for human babies tested in an operant discrimination paradigm using similar auditory stimuli (Benasich and Tallal, 1993). Since a stimulus-specific difference in response latencies can only exist where subjects actually differentiate the stimuli, a significant false alarm/hit difference validates subject discrimination (Fitch et al., 1993).

Based on this method, response latencies for hits and false alarms (FA) were analyzed across days (6 d of testing), treatment groups (right, left, bilateral, or sham), and stimulus conditions (four stimulus conditions), in a multifactorial ANOVA. In addition, the FA/hit latencies were analyzed across conditions within each treatment group separately, to delineate the pattern of discrimination for each individual group. Finally, mean FA/hit differences for individual subjects were examined, to verify that the observed effects were not sample dependent or the result of outlier values.

Discrimination between Groups

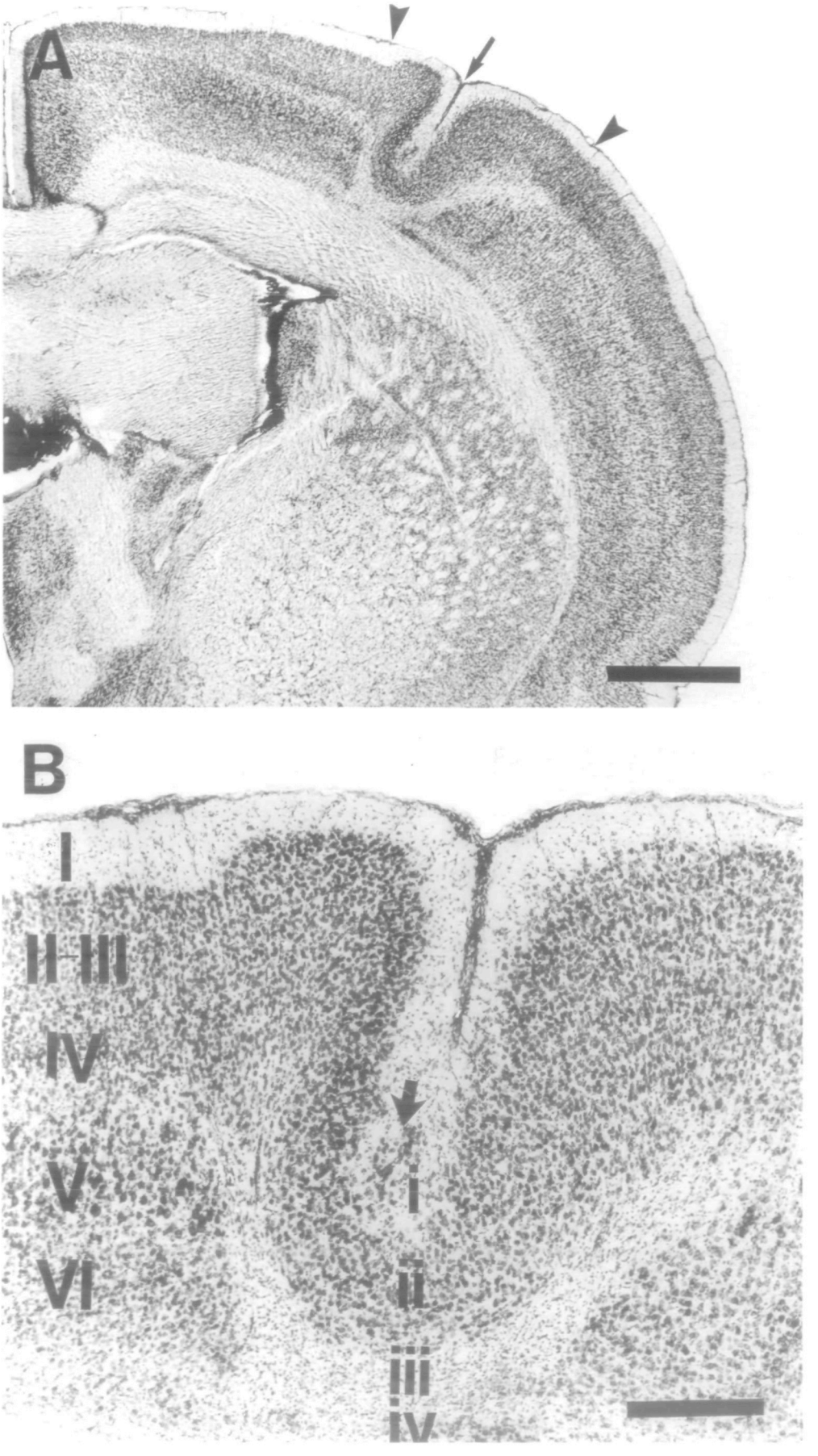
Sham versus lesioned subjects. An ANOVA was performed, using the mean response latency for false alarms and hits for each subject on each day as the dependent measure. Group was treated as a between variable with two levels, sham ($n = 5$) and lesioned (combining right, left, and bilateral lesions, $n = 17$). Condition was treated as a within variable with four levels (condition 1, tone 1 = 20 msec/ISI = 500 msec/tone 2 = 20 msec; condition 2, 20/350/20; condition 3, 16/300/16; and condition 4, 12/225/12). Day and response type (FA vs hit) were treated as within variables with six and two levels, respectively.

There was a highly significant effect of response type ($F_{1,20} = 55.8$, $p < 0.001$), confirming that FA latencies were significantly longer than hit latencies. As discussed above, this FA/hit difference represents significant discrimination of the stimuli. An interaction between group × response type ($F_{1,20} = 7.2$, $p < 0.02$), however, demonstrated that the FA/hit difference was significantly larger for shams as compared to lesioned subjects. Furthermore, a condition × group × response type interaction ($F_{3,60} = 2.8$, $p < 0.05$) indicated that this treatment effect on discrimination was specific to the shorter stimulus durations. Figure 3 depicts this effect by plotting discrimination indices (FA/hit differences in msec) as a function of condition and group. At conditions 1 and 2, simple effects of group on discrimination index were nonsignificant, showing that both groups performed the discrimination equally well. However, as stimulus duration was further reduced (conditions 3 and 4), a significant sham advantage emerged ($F_{1,20} = 5.0$ and $F_{1,20} = 7.4$, respectively; $p < 0.05$).

Shams versus right, left, and bilateral lesion subjects. To determine the influence of lesion site on these effects, an ANOVA was performed as above but with a breakdown of all four treatment groups: sham ($n = 5$), right lesion ($n = 6$), left lesion ($n = 5$), and bilateral lesion ($n = 6$). Thus, group was a between variable with four levels, and condition, day, and response type were within variables with four, six, and two levels, respectively.

As above, response type was found to be highly significant ($F_{1,18} = 53.4$, $p < 0.001$). In addition, the group × response type interaction was near significance ($F_{3,18} = 3.1$, $p = 0.055$), reflecting the fact that the FA/hit difference was largest for shams, and smallest for bilaterally lesioned subjects. Also, a near-significant condition × group × response type interaction was found ($F_{9,54} = 2.0$, $p = 0.064$), consistent with group differences only at the shorter stimulus durations (see Fig. 4).

Further assessment of this interaction via simple effects analyses of FA/hit differences (i.e., discrimination indices) between each group revealed the following. First, discrimination indices were significantly larger (indicating better discrimination) for shams as compared to bilaterally lesioned subjects at the shorter stimulus durations, condition 3 ($F_{1,9} = 8.68$, $p < 0.02$) and condition 4 ($F_{1,9} = 6.7$, $p < 0.05$). Interestingly, the discrimination indices were also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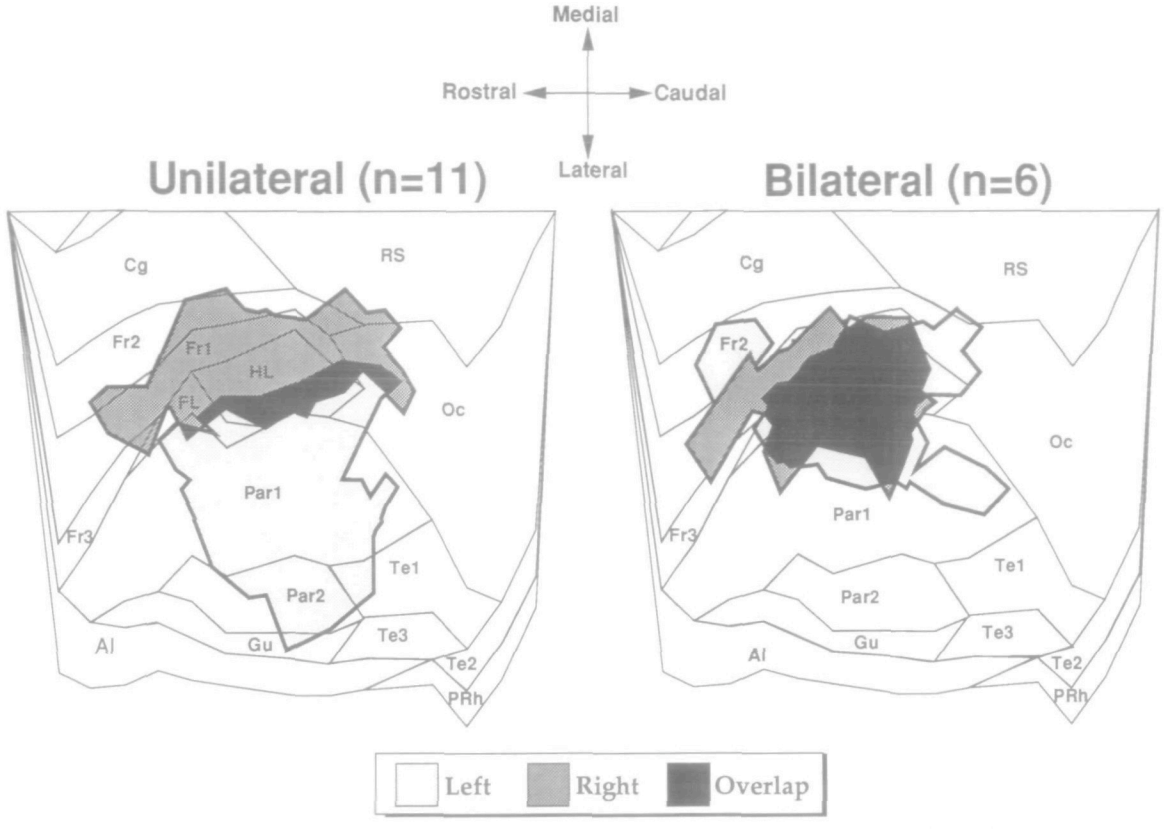

Figure 2. Overall topographic location of microgyria (*shaded areas*) from the left and right hemispheres of unilaterally and bilaterally lesioned animals placed over a flattened map of the neocortex derived from Zilles (1985). The unilateral portion of the figure represents the five left-lesioned and six right-lesioned rats. *Al*, agranular insular (includes dorsal, posterior, and ventral part); *Cg*, cingulate cortex (included Cg1–3); *FL*, forelimb area; *Fr1–Fr3*, frontal cortex areas 1, 2, and 3, respectively; *Gu*, gustatory cortex; *HL*, hindlimb area, *Oc*, occipital cortex (includes all subdivisions of Oc1 and Oc2); *Par1* and *Par2*, primary and secondary somatosensory cortices, respectively; *PRh*, perirhinal area; *RS*, retrosplenial cortex (includes granular and agranular subdivisions); *Te1–Te3*, primary auditory cortex, and temporal areas 2 and 3, respectively.

significantly larger for right-lesioned subjects as compared to bilaterally lesioned subjects at condition 3 ($F_{1,10} = 5.05$, $p < 0.05$). In addition, discrimination indices were significantly larger for shams as compared to right-lesioned subjects ($F_{1,9} = 6.2$, $p < 0.05$), and were near significance for the sham/left-lesion comparison ($F_{1,8} = 5.2$, $p = 0.052$), at the shortest stimulus duration, condition 4.

Discrimination within Each Group

To determine whether subjects within each group were discriminating significantly at each stimulus duration, FA versus hit latencies were analyzed via ANOVA within each group separately. Since it has been shown in similar paradigms that FA latencies are significantly longer than for hits (O'Connor et al., 1992; Fitch et al., 1993), one-tailed analyses were used to assess main effects of response type. Condition was again treated as a repeated measure with four levels. In addition, the 6 d of testing at each condition were broken into two subblocks of 3 d, to extract the effect of "initial" versus "experienced" performance at each condition. Thus, block was a repeated measure with two levels, and day was a repeated measure (within block) with three levels.

Shams. The main effect of response type was highly significant ($F_{1,4} = 20.4$, $p < 0.01$), reflecting discrimination of the target within the sham group. The condition × response type interaction was also significant ($F_{3,12} = 3.9$, $p < 0.05$), with discrimination indices (FA/hit differences) increasing for this group across conditions (see Fig. 4). This appears to reflect a general learning curve for shams across the 24 d of testing, despite the decreasing duration of stimuli used across conditions.

Simple effects of discrimination (FA vs hit latency) were examined at each of the four conditions. The FA/hit difference was not significant at condition 1, but was significant thereafter at condition 2 ($F_{1,4} = 6.9$, $p < 0.05$), condition 3 ($F_{1,4} = 13.7$, $p < 0.02$), and condition 4 ($F_{1,4} = 36.9$, $p < 0.005$; see Fig. 4), indicating that shams were able to discriminate at each of these conditions. There were no day or block effects for this group.

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Figure 1. *A*, Low-power photomicrograph of Nissl-stained section showing hemisphere with microgyria with microsulcus (*arrow*) induced by a P1 freezing lesion. Note the focal nature of the cortical damage (*arrowheads*). *B*, High-power photomicrograph of same microgyria in at *A* (*arrow in*) contrasting the undisturbed six-layer cortex medial to the damaged area (*I–VI*) with the four-layer microgyria (*i–iv*). *Large arrow* denotes ectopic neurons in layer i of the microgyria. Scale bars: *A*, 1 mm; *B*, 250 μm.

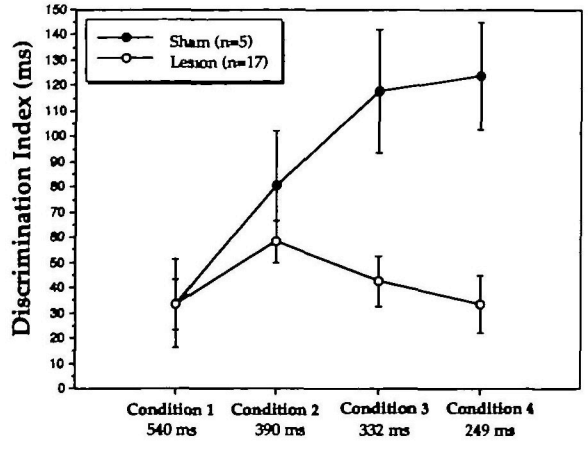

Figure 3. Mean discrimination indices, as calculated by false alarm minus hit latency (in msec), for sham and lesion groups at the four stimulus duration conditions. The *numbers under each condition* are total stimulus time (pretone/ISI/posttone). Discrimination indices are mean scores over 6 d of testing at each condition.

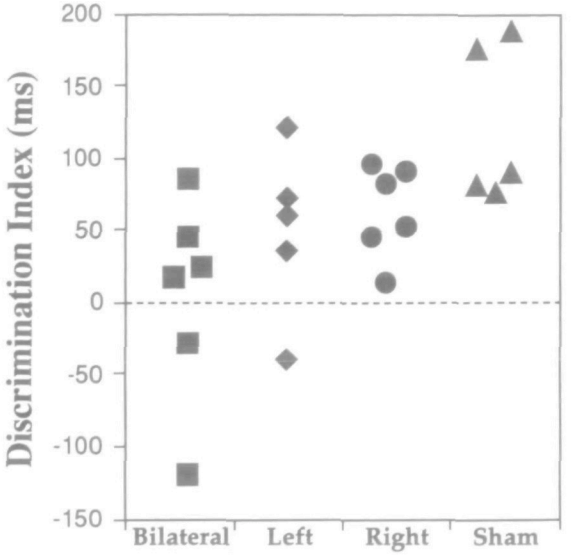

Figure 5. Distribution of discrimination indices for individual subjects by treatment group, across days 13–24 (conditions 3 and 4)

Right lesions. The main effect of response type was significant ($F_{1,5} = 18.7$, $p < 0.005$), reflecting discrimination of the target within the right lesion group. The condition × response type interaction was not significant, reflecting the fact that the discrimination index stayed relatively constant across conditions (see Fig. 4). Simple effects of discrimination at each of the four conditions showed that, like shams, the FA/hit difference was not significant at condition 1, but was significant thereafter at condition 2 ($F_{1,5} = 14.2$, $p < 0.01$), condition 3 ($F_{1,5} = 13.61$, $p < 0.01$), and condition 4 ($F_{1,5} = 9.2$, $p < 0.02$; see Fig. 4). There were no day or block effects for this group.

Left lesions. The main effect of response type was again significant ($F_{1,4} = 28.07$, $p < 0.005$), reflecting significant discrimination of the target within the left lesion group. Simple effects analysis of discrimination at each of the four conditions revealed that the FA/hit difference was near significance at condition 1 ($F_{1,4} = 4.1$, $p = 0.057$), and was significant at condition 2 ($F_{1,4} = 19.7$, $p < 0.01$) and condition 3 ($F_{1,4} = 5.5$, $p < 0.05$), but was not significant at condition 4 ($F_{1,5} = 0.9$, $p = 0.38$; see Fig. 4). These results indicate that subjects with left lesions were able to discriminate at the longer durations, but were specifically impaired at the shortest stimulus duration. There were no day or block effects for this group.

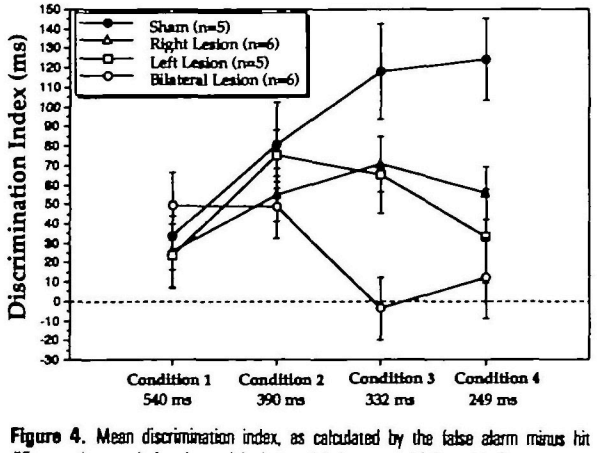

Figure 4. Mean discrimination index, as calculated by the false alarm minus hit difference (in msec), for sham, right lesion, left lesion, and bilateral lesion groups at the four stimulus duration conditions. The *numbers under each condition* are total stimulus time (pretone/ISI/posttone) Discrimination indices are mean scores over 6 d of testing at each condition.

Bilateral lesions. The pattern of discrimination for subjects having received bilateral lesions was clearly distinct from the other three groups. First, the effect of overall response type was only marginal ($F_{1,5} = 2.7$, $p = 0.08$). Examination of simple effects of response type within each condition showed that FA latencies were significantly longer than for hits at conditions 1 ($F_{1,5} = 7.8$, $p < 0.02$), and 2 ($F_{1,5} = 22.78$, $p < 0.01$), but were nonsignificant at conditions 3 and 4 ($F_{1,5} = 0.02$ and 0.11, respectively; see Fig. 4). These results also indicate that bilaterally lesioned subjects were able to discriminate at the longer stimulus durations, but exhibited specific impairment at the shorter stimulus durations.

Interestingly, a highly significant block × response type interaction ($F_{1,5} = 23.44$, $p < 0.01$) was found for this group, reflecting the fact that bilaterally lesioned animals averaged a discrimination score close to zero (chance) for the first 3 d of testing at all four conditions, and then showed marked improvement by the final 3 d at each condition (although not sufficient improvement to attain significant discrimination at the second block in conditions 3 and 4). Such a pattern of "step" learning contrasted the relatively stable patterns of discrimination observed across days for sham and right-lesioned subjects at each condition.

Distribution of Discrimination Scores within Groups

Figure 5 demonstrates that there was almost no overlap between mean discrimination scores of bilaterally lesioned and sham subjects, and minimal overlap be-

tween left-lesioned subjects and shams, when individual discrimination indices across conditions 3 and 4 (where group differences emerged) were plotted. There were no apparent outlier values in any group.

Discussion

Auditory Discrimination and Microgyria

The results can be summarized as follows: (1) All groups showed significant discrimination at the longer stimulus durations as measured by latency differences between FA and hits (cf. Fitch et al., 1993). (2) Lesion subjects (combined) demonstrated depressed discrimination as compared to shams, specifically at the two shorter stimulus durations (conditions 3 and 4). (3) This effect was most marked for subjects with bilateral lesions, who failed to discriminate significantly at the two shorter stimulus durations. Subjects with unilateral lesions of the left or right hemisphere were also depressed as compared to shams at the shortest stimulus duration, and left-lesioned subjects showed no significant discrimination at this duration. (4) Bilaterally lesioned subjects discriminated at chance levels during the first few days at all conditions, and improved to show overall significant discrimination only for the longer stimulus durations, conditions 1 and 2.

These results support the hypothesis that neonatal microgyric lesions of neocortex specifically impair the ability of subjects to perform rapid auditory discriminations in adulthood. Furthermore, subjects showed the most marked impairment if these lesions were bilateral. Left or right hemispheric lesions depressed discrimination at the shortest stimulus duration, although subjects with right hemisphere lesions still showed some significant discrimination while left-lesioned subjects did not. This suggestion of left hemisphere–specific effects is consistent with evidence that intact adult male rats exhibit a right-ear advantage for discriminating identical auditory stimuli (Fitch et al., 1993). However, it should be noted that (1) lesion location for subjects with left and right lesions was not identical (see Fig. 2), and (2) discrimination indices for left- and right-lesioned groups did not differ significantly at any condition in the present study. Consequently, any interpretations regarding hemispheric specialization demonstrated by this paradigm will require further assessment.

The fact that discrimination deficits due to microgyric lesions emerged when the total stimulus duration dropped to 332 msec or less (condition 3 = 332 msec, two 16 msec tones and a 300 msec ISI; condition 4 = 249 msec, two 12 msec tones and a 225 msec ISI; see Fig. 3, 4) is particularly interesting in light of comparable data obtained from human clinical populations on similar auditory tasks. Specifically, when language-impaired and matched-control children were asked to perform a two-tone sequence discrimination similar to the present task, both groups performed at or near 100% correct as long as the total stimulus duration was at or above 578 msec (two 75 msec tones and a 428 msec ISI). However, group differences became evident when the total stimulus duration was reduced to 500 msec or less, and at stimulus durations of 300 msec or less (two 75 msec tones and a 150 msec ISI), control children performed near 100% correct while language-impaired children performed the discrimination only slightly above chance levels (Tallal and Piercy, 1973). In a related study, adults with acquired lesions of the right or left hemisphere, as well as matched controls, were tested on the same auditory task administered to language-impaired children. Discrimination deficits were found only for the left-lesioned group, again at stimulus durations of 300 msec or less (Tallal and Newcombe, 1978).

The results of the present animal study form an exciting parallel to data obtained from clinical studies of language-impaired individuals. The results of such clinical research provided the basis for asserting that specific deficits in auditory temporal processing, in the time range of 300 msec or less, may interfere with primary speech perception and have cascading effects leading to language and reading dysfunction (see Tallal et al., 1993). The present results further suggest that neonatally induced anomalies in neocortical development, as found in the postmortem pathology of diagnosed dyslexics, may be a significant causal factor in this temporal dysfunction.

Anatomic Substrates of Auditory Temporal Discrimination

Early studies on auditory cortical lesions in adult cats showed that such lesions resulted in specific impairment of discrimination for sequences of tones differing only in temporal pattern (for review, see Diamond and Neff, 1957; Elliot and Trahoitis, 1972). More recent studies have shown similar effects following auditory cortical lesions in adult monkeys (Dewson, 1977; Heffner and Heffner, 1986; Gaffan and Harrison, 1991). Studies on the effects of auditory cortical lesions in rats are limited, but some recent research has shown that such lesions impaired the ability of adult rats to discriminate patterns of a 4 kHz tone (Wakita, 1993). Given these findings, which strongly suggest that functions relating to auditory temporal discrimination are "localized" in auditory cortical regions in mammalian species, one must question the mechanisms underlying the present results, since the majority of microgyric lesions were induced in somatosensory–somatomotor (SM) cortices and not auditory cortex.

It is likely that lesions of developing SM cortex resulted in profound reorganization of intercortical and cortical–subcortical connections, including projections critical to auditory temporal discrimination functions. Consistent with this interpretation, researchers have shown that neonatal damage to developing neural structures leads to profound and sometimes pervasive reorganization of the brain (Schneider, 1981; Goldman-Rakic and Rakic, 1984). Similarly, anomalous connectivity has been shown following spontaneous (Rosen et al., 1989b) and induced (Rosen et al., 1989a; Innocenti and Berbel,

1991) microgyria. Innocenti and Berbel (1991) reported that microgyria induced by ibotenic acid injections in the visual cortex of cats resulted in the maintenance of transient auditory projections (i.e., maintenance of projections normally pruned during development). An increase in callosal connectivity associated with a region of microgyria, as well as more pervasive disturbances, has also been reported (Rosen et al., 1989a,b). Similarly, Finlay has shown that induction of cerebral hypoxia by carotid ligation in neonatal cats results in a marked increase in efferent projections from visual cortex to the opposite hemisphere (Finlay et al., 1990). These findings support the notion that the hypoxic-ischemic freezing injury resulting in microgyria might cause profound and pervasive disturbances in cortical connectivity. These effects may be mediated by the maintenance of otherwise transient connections. Such effects would parallel the reorganization observed following unilateral removal of the vibrissae, which results in the maintenance of a transient auditory projection from the magnocellular portion of the medial geniculate to the barrel field (Nicolelis et al., 1991).

In a more general vein, the notion that developmental neuropathologic anomalies such as induced microgyria may be associated with subtle yet pervasive reorganization of neural connectivity patterns is appealing. Such as assertion is consistent with observations that despite the lack of profound, gross anatomical disturbances (i.e., frank lesions or anatomical malformations) in individuals with LI, more subtle anomalies have been demonstrated in a variety of systems, at both the neocortical and subcortical levels (Galaburda and Kemper, 1979; Galaburda and Eidelberg, 1982; Galaburda et al., 1985; Jernigan et al., 1991; Livingstone et al., 1991). Given the existence of these concomitant anomalies, one might suggest that both induced and spontaneous developmental cortical lesions result in disruption of retrograde or afferent patterns of thalamocortical connectivity, in turn disrupting local thalamic organization. Consistent with this hypothesis, induced freezing lesions of the cortical plate occur at a time point corresponding to the arrival of thalamocortical projections beginning to arborize (Catalano et al., 1991). Furthermore, Rosen et al. (1992a) have demonstrated that neurons from layers V and VI, from which cortical efferents to the thalamus normally arise, are specifically destroyed by P0 freezing injury. Additional anatomic research will be needed, however, to assess the effect on thalamic afferent neurons of early cortical lesion and microgyria.

The notion of pervasive neural reorganization is further consistent with reports that the temporal processing difficulties experienced by individuals with LI are multimodal, again suggesting pervasive and/or subcortical anomalies (Johnston et al., 1981; Tallal et al., 1981, 1985; Katz et al., 1992). In conclusion, the mechanisms whereby developmental pathologies lead to dysfunction of rapid temporal processing in rats and individuals with LI may involve pervasive reorganization through cortical and subcortical regions, leading in turn to the specific behavioral deficits observed.

Summary and Conclusions

Individuals with LI, including dyslexia, show deficits in the "rapid processing" of information in both the auditory and visual modalities. In addition, the brains of developmental dyslexics show a wide variety of minor cortical and subcortical focal anatomical malformations, some of which are the result of injury occurring during development. The goal of the present experiment was to examine, in a rat model, whether such minor anatomical malformations could affect "rapid processing" in an auditory discrimination task similar to that which had previously been shown to differentiate language-impaired from control individuals. Our present results demonstrate that the presence of focal developmental neuropathologic lesions disrupted performance of an auditory discrimination task in rats. This deficit appeared to be specific to the discrimination of rapidly presented stimuli (total stimulus duration at or below 332 msec)—a finding remarkably similar to results obtained from children with LI. Rats that received bilateral damage had the most profound disruption of performance on the discrimination task, although subjects with unilateral lesions also exhibited significant disruption at the shortest duration. We hypothesize that this deficit in "rapid processing" may be related to the profound changes in connectivity associated with developmental neocortical damage.

Notes

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