

Research report

Impaired gap detection in juvenile microgyric rats

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Abstract

Previous research with adult animal models links the presence of cortical neuromigrational anomalies (i.e., microgyria similar to that found in brains of dyslexics) with rapid auditory processing (RAP) impairments. RAP impairments are in turn found in children with specific language impairment (SLI) and also in individuals with dyslexia. Gap detection, a simple measure of auditory temporal acuity, appears to be impaired in children with SLI but not in dyslexic adults, even though both groups exhibit impaired processing on more complex, rapid auditory tasks. In the current study, juvenile rats with bilateral microgyria, but not their adult counterparts, exhibited impaired detection of short duration silent gaps in white noise when compared to age-matched sham littermates. Results lend further support to: (1) an association between neuromigrational anomalies and RAP impairments; and (2) the validity of an animal model of RAP impairments associated with language disturbances in humans. Current results also support the view that auditory processing disturbances associated with cortical malformations may be evident early in development at a relatively “low” level (e.g., simple gap detection), but may require “higher-order” auditory discrimination tasks (e.g., tone sequences, phonemic discriminations) to be elicited later in life.

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1. Introduction

Children identified as having specific language impairment (SLI) develop language late for no medically diagnosed reason (e.g., hearing impairment, general intelligence deficit, physical abnormality). Researchers have repeatedly found that children with SLI exhibit deficits in processing quickly changing and/or brief auditory stimuli, including verbal and non-verbal tasks (see Refs. [1,25,26,32]). Tallal has suggested that an inability to integrate two or more pieces of sensory information arriving in the central nervous system in rapid succession may comprise a basic impairment associated with and/or underlying cascading deleterious effects on

receptive comprehension and emergent language skills (and contributing to the emergence of SLI) [27].

In a longitudinal study, rapid auditory processing (RAP) thresholds measured in infancy were found to predict language comprehension and production at 16–36 months [2–4]. In this study, infants with lower RAP thresholds (which indicate greater auditory acuity) were found to exhibit better language ability at the later ages. Similarly, Trehub and Henderson [29] found that infants (6 or 12 months), who performed above median on a gap detection task, later had larger productive vocabularies, longer and more complex sentences, and greater numbers of irregular word forms (at 16–24 months). Finally, as one might expect, RAP thresholds (as measured by gap detection) decrease between infancy and adulthood as auditory acuity matures [30,31].

Interestingly, developmental dyslexics also show impairment on RAP tasks (such as tone sequences, phonemic discriminations, etc.) [13]. Since children with SLI have an

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increased incidence of dyslexia in elementary school (estimated to be as high as 80% [24]), it becomes interesting to consider the nature and expression of RAP deficits across the developmental lifespan (from children with SLI to adults with dyslexia). In fact, children with SLI are found to have higher gap detection thresholds than controls [15]. However, when gap detection thresholds are tested in adults, dyslexics show similar thresholds to controls [16,20]. Thus, it may be that temporal acuity is somewhat delayed in individuals with RAP impairments, but given enough time, these individuals may no longer be impaired at simple temporal acuity tasks (such as detecting gaps in white noise). Interestingly, these same individuals (adult dyslexics) show evidence of a rapid processing impairment when tested on more complex auditory discriminations (i.e., sequential tones, phonemic stimuli). This suggests that the task difficulty required to elicit deficits within an “impaired” system may increase with developmental maturation.

Using rodent models, rapid auditory processing impairments have been linked to neuromigrational anomalies (including ectopias and microgyria), similar to those found in the brains of human dyslexics [6,8,10,18,19]. In the current study, we compared auditory acuity in two groups of rats with induced microgyria against sham-operated littermates. The first group of littermates was tested on a silent gap detection task during the juvenile period, while the second group was tested in adulthood. Results for microgyric and sham littermates were then assessed within each study.

2. Methods

A total of 66 male Wistar rats born at the University of Connecticut to purchased dams (Charles River Laboratory, MA) were used in these studies (31 juveniles and 35 adults). Juvenile findings are from Group 1A, and adult findings are from Group 1B.¹ No methodological differences (e.g., housing, handling, test battery) existed between any of these groups other than the age at testing (i.e., juvenile or adult). Pups were weaned on P21 to pair-housing by treatment. Juvenile testing began on P24, and adult testing began at P53 following the move to individual housing on P50. All procedures were approved by the University of Connecticut’s Institutional Animal Care and Use Committee (IACUC) and conducted in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals, including adequate measures to minimize pain or discomfort to the animals.

¹ We specifically did not retest juvenile subjects (Group 1A) at an adult age for direct age comparison, since pilot data from our lab (unpublished findings) suggest prior experience on this task influences performance. Accordingly, juveniles in Group 1A and adults in Group 1B were naïve at the start of testing.

2.1. Induction of focal microgyria

Following birth on postnatal day 1 (P1), litters were culled to 10 pups (8 male; 2 female). Male pups were randomly assigned to receive sham surgery or focal freezing induction of bilateral microgyria, balancing treatment within litter (described in detail in Ref. [21]). Briefly, pups received cryogenic anesthesia, and a cooled steel probe was placed on the exposed skull for 5 s, approximately 2 mm lateral of the sagittal suture and 2 mm caudal of bregma. Following the initial lesion (applied in a randomly determined hemisphere), an identical lesion was placed in the opposite hemisphere with a second probe. Sham-operated controls received similar treatment except that the probe was kept at room temperature. Pups were sutured, marked with footpad injections for identification, warmed under a lamp, and returned to the dam.

2.2. Behavioral testing—startle reduction

The reflex modification paradigm consists of the presentation of a benign pre-stimulus prior to a startle-eliciting stimulus (SES). The SES is a 50-ms 105-dB white noise burst that elicits the acoustic startle reflex (ASR). When the pre-stimulus is detected, the amplitude of the whole-body ASR is reduced (also called pre-pulse inhibition). The magnitude of pre-pulse inhibition is related to the overall detectability of the pre-stimulus. By comparing reflex amplitudes when a pre-stimulus is present (i.e., a cued trial) versus not present (i.e., an uncued trial), an objective measure of sensory detection can be obtained. The inter-trial interval for all procedures was variable but averaged 20 s (range 16–24 s). All subjects were tested on a Single Tone procedure (where a 7-ms, 11-kHz tone served as the cue) at the beginning of testing, to assess base-line hearing and acoustic startle for all treatment groups.

2.2.1. Apparatus

During testing, each subject was placed on a load-cell platform (MED Associates, Georgia, VT). The platform’s output voltage was passed through a linear amplifier (Med Associates Model 250-60) and into a Biopac MP100WS Acquisition system connected to a Power Macintosh 7200 to record the amplitude of the subject’s acoustic startle response. Maximum peak values were extracted during the 150-ms epoch directly following the onset of the SES, representing the subject’s response amplitude for that trial (dependent variable). Auditory stimuli were generated on a Power Macintosh 6100 and presented through powered Yamaha YHT-M100 speakers.

2.2.2. Silent Gap procedure

A single test session consisted of 300 trials. Continuous 78-dB broad-band white noise served as background with breaks of silence 50 ms prior to the SES as cues. During week 1, gaps ranged from 0 (uncued) to 100 ms in length (0, 2, 5, 10, 20, 30, 40, 50, 75, and 100 ms), and during week 2, gaps ranged from 0

to 10 ms (0, 2, 3, 4, 5, 6, 7, 8, 9, and 10 ms). A week of testing consisted of 5 consecutive days with one test session per day. Trials were presented in a pseudo-random order so that no more than three similar trials occurred in a row.

To ascertain gap detection, the averaged absolute response to uncued (0-ms gap) trials was compared to each individual averaged cued response. If the gap duration was detected, the cued response should be significantly reduced from the uncued response ($p < 0.05$). To compare between lesion and sham performance, an attenuated response was calculated by taking each averaged cued response divided by the averaged uncued and multiplied by 100 ($[\text{cued}/\text{uncued}] \times 100$) for each subject on each gap each day. This produced an index from 0% to 100%, with 100% indicating no detection (cued = uncued response). Since Juvenile and Adult results were from separate studies, Absolute and Attenuated Response analyses were performed separately within each age.

2.3. Brain analysis

Following behavioral testing, subjects were weighed, anesthetized, and transcardially perfused with fixative (10% Buffered Formalin Phosphate). Heads were removed, placed in formalin, and shipped to GDR for anatomical analysis. The brains were removed, lesions confirmed, and location visually assessed.

3. Results

3.1. Brain analysis

Postmortem analysis confirmed similar sized bilateral microgyria in all subjects exposed to the P1 freezing lesion treatment (located in the sensorimotor cortex including regions Par1, Par2, HL, and FL [33]). No malformations were seen in any sham subject.

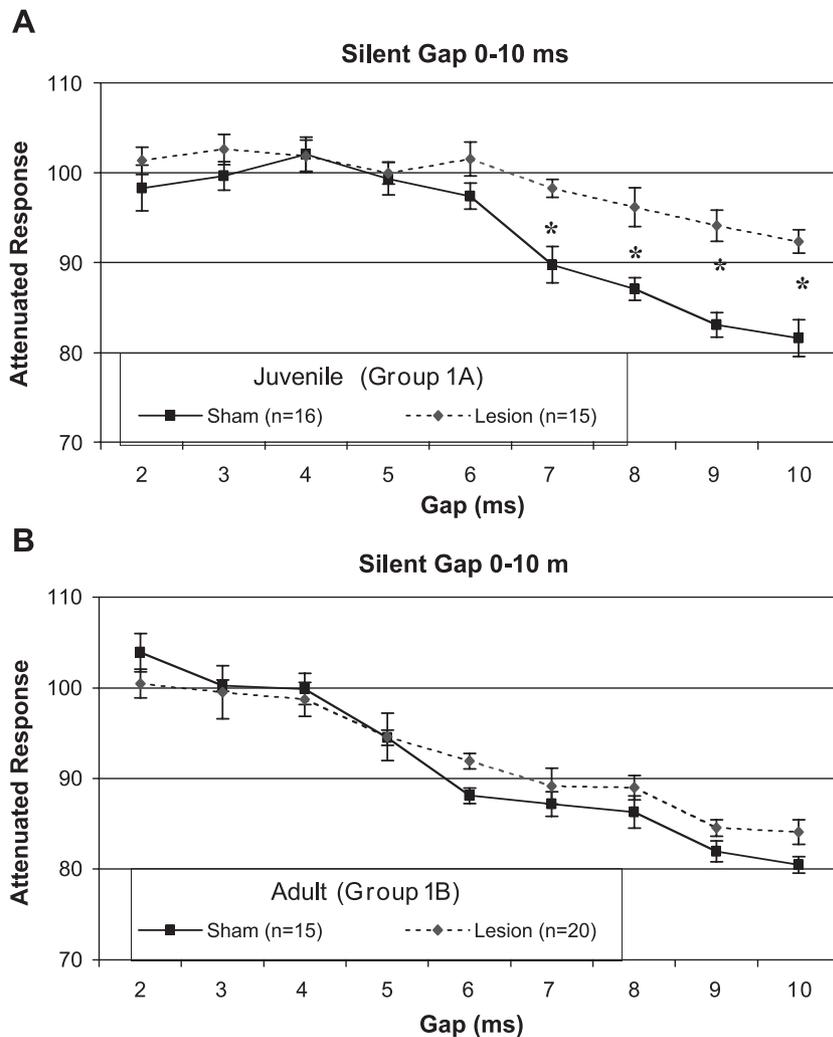


Fig. 1. Attenuated Response performance for week 2—Silent Gap 0–10 ms {Attenuated Response = (averaged cued response/averaged uncued response) \times 100}. (A) Group 1A: Juvenile shams performed better than lesion littermates at the 7–10-ms gaps ($F_{1,29}$; $*p < 0.03$). (B) Group 1B: Adult lesion (microgyric) and sham subjects perform similarly.

3.2. Single Tone and Silent Gap procedures

Initial ANOVAs of all measured scores indicated no significant Litter effects at either age (Group 1A or Group 1B), and therefore, subjects were treated as individual observations for further analyses. Comparison of the Attenuated Response Scores on the Single Tone procedure also indicated no significant effects of Lesion at either age ($F_{1,27} < 1$, $F_{1,33} < 1$; respectively). That is, treatment groups at both ages showed highly significant detection of the single tone cue, but no acoustic startle response differences across treatment. Therefore, any differences on the silent gap procedure do not reflect differences in hearing or basic acoustic startle attenuation between sham and lesion subjects. Finally, where appropriate, Huynh–Feldt correction of sphericity was applied for repeated measures statistics.

3.2.1. Gap detection assessed via Absolute Response measures

For the Silent Gap 0–100 ms, Juveniles (Group 1A) could not detect the 2- or 5-ms gap, but did significantly detect the other gaps tested ($F_{1,29}$; $p < 0.05$). Adults (Group 1B) significantly detected gaps of 5, 10, 20, 30, 40, 50, 75, and 100 ms ($F_{1,33}$; $p < 0.05$), but not the 2-ms gap. These results are consistent with previous lab results (see Ref. [26]). Again, there were no differences in detection between sham and lesion groups at either age for these longer gap durations.

For the shorter gap set of 0–10 ms (week 2), Adults were found to significantly detect gaps of 5–10 ms ($F_{1,33}$; $p < 0.05$) with no differences between sham and lesion groups. The Juvenile group, however, did show sham/lesion detection differences in that sham juveniles detected gaps of 6–10 ms ($F_{1,29}$; $p < 0.05$), but lesion juveniles detected gaps of 7–10 ms ($F_{1,29}$; $p < 0.05$) and did not detect the 6-ms gap. It is important to note that upon individual analysis, only 2 of the 16 lesion juveniles were able to detect the 6-ms gap.

3.2.2. Sham/lesion comparison assessed via Attenuated Response scores

Comparison of Attenuated Response scores supplements the Absolute Response analysis by more easily comparing group performance across a between variable (such as sham/lesion). For the 0–100-ms gap analysis, juvenile results (Group 1A) showed no main effect of Lesion ($F_{1,29} < 1$), nor interaction with Gap ($F_{3,16,91.71} < 1$). Better performance across days and at longer gaps was also found, with significant Day and Gap effects ($F_{3,86,111.97} = 42.6$; $p < 0.001$, $F_{3,16,91.71} = 321.9$; $p < 0.001$, respectively). However, for Silent Gap 0–10 ms, a marginal effect of Lesion ($F_{1,29} = 3.05$, $p < 0.1$) and Lesion \times Gap interaction ($F_{2,46,71.33} = 2.28$, $p < 0.1$) was found. Performance was better at longer gaps, as indicated by a significant Gap effect ($F_{2,46,71.33} = 26.8$; $p < 0.001$). Specifically, a post hoc analysis revealed that juvenile shams performed significantly better than juvenile lesions at gaps of 7–10 ms (see Fig. 1A).

Adult results (Group 1B) for Silent Gap 0–100 ms showed no main effect of Lesion ($F_{1,33} < 1$), nor interaction with Gap ($F_{8,264} < 1$), indicating similar performance between adult sham and lesion groups at all gaps. Significant effects of Day and Gap ($F_{3,13,103.40} = 39.37$; $p < 0.001$, $F_{2,27,74.80} = 142.2$; $p < 0.001$, respectively) were found, indicating improved performance over days and at longer gaps. Similarly, Adult results for Silent Gap 0–10 ms showed no main effect of Lesion ($F_{1,33} < 1$), nor interaction with Gap ($F_{2,05,67.7} < 1$; see Fig. 1B). A significant Gap effect ($F_{2,05,67.7} = 10.2$; $p < 0.001$) was again found, indicating better performance at longer gaps. Although not reported here, this adult group (1B) comprises part of a larger group demonstrating significant deficits for microgyric as compared to sham male rats on a short duration two-tone sequencing discrimination task (see Ref. [19]). Importantly, these findings confirm the consistency of rapid auditory processing deficits on tasks of sufficient temporal demand in the current adult group with previously reported findings [6,8,18].

4. Discussion

We report better gap detection in adult as compared to juvenile rats during weeks 1 and 2, consistent with previous findings (see Refs. [7,9,23]). We also report that our adult rat group did not show any detection or performance differences between sham and lesion animals for either gap detection task, results that are consistent with multiple prior null findings for sham versus lesion adult rats on simple silent gap detection tasks (e.g., Refs. [6,18,19]). Notably, we have in these same studies shown consistent evidence of RAP deficits in adult microgyric rats using more complex acoustic tasks. This suggests that in the adult microgyric rat model, more temporally demanding acoustic discrimination tasks are required to elicit the deleterious effects of microgyria.

Juvenile rats also failed to show sham/lesion differences during week 1 (using longer silent gaps of 0–100 ms). However, these same subjects *did* show detection and performance differences with the shorter gap conditions during week 2 (silent gaps of 0–10 ms). Specifically, sham juveniles could detect a 6-ms silent gap, while lesion juveniles could not. Further, significant attenuated response differences were found between sham and lesion performance at the 7–10-ms gaps, with shams performing significantly better than lesion littermates.

These convergent findings mirror data from humans with RAP impairments. Specifically, as auditory acuity develops, an initial impairment in gap detection seen in language impaired children (e.g., SLI) is no longer seen in language impaired adults (e.g., dyslexics) [15,16,20]. Nevertheless, other temporally demanding acoustic tasks continue to elicit a RAP deficit in dyslexic adults [13].

Previous studies have associated microgyria, a neuro-migrational anomaly, with aberrant cortical connectio-

changes including thalamo-cortical, inter- and intra-hemisphere cortico-cortical connections (see Refs. [11,12,22]). These connectional changes, possibly triggered at the time of injury (P1) as a compensatory mechanism, may also lead to a shift in cell size in the medial geniculate nucleus of the thalamus (auditory nucleus), an effect observed in microgyric rats as well as dyslexic adults [14,18]. These connectional changes may also be related to the impaired processing of quickly occurring or changing sensory stimuli. When tested early in development, as in the current study, there appears to be some developmental delay in simple auditory acuity in individuals with early injury. Perhaps due to the development of the cortical network responsible for auditory processing, this delay is not evident in adult testing with the same simple acuity tests (i.e., when cortical processing has matured and auditory acuity has improved; see Refs. [16,20,29,30]). However, a RAP impairment persists and can still be detected in adult microgyric rats with more difficult auditory tasks (see Refs. [6,18,19,21]). Since the temporal task demand has increased beyond that compensated for by cortical maturation, the processing deficit, presumably due to the aberrant cortical connectivity still present in the system, remains in adult microgyric animals compared to sham littermates.

This early auditory delay and subsequent processing impairment may reflect a developing network that includes fundamental disruptions in auditory representation. Applied to the human condition, individuals with RAP impairments (such as children with SLI) may fail to clearly define early speech phoneme representations due to initially poor auditory acuity. This early disruption of a critical building block of the language system may put these individuals at greater risk for developing consequent, higher-order language problems. Thus, if early intervention is applied, the auditory network might be trained to hear the quickly changing components of speech. This early RAP impairment in SLI children could be potentially ameliorated, and later language problems avoided or significantly reduced (see Refs. [17,28]). For example, kindergarten children with language impairments were found to be at high risk for reading disabilities in second and fourth grades, except when language impaired children received assistance and showed an improvement in their spoken language abilities [5]. If language impaired children improved their spoken language abilities, their subsequent reading outcomes were better than for those children with persistent language impairments.

In conclusion, we report that juvenile microgyric subjects have poorer gap detection and auditory acuity as compared to sham littermates. This early impairment in auditory acuity is not seen in adult animals, although more temporally demanding tasks have consistently been shown to elicit a RAP deficit in these same adult microgyric animals. Current results parallel the human literature regarding individuals with RAP impairments. Specifically, children with RAP impairments show poorer gap detection

than controls, but impaired adults do not, even though more complicated tasks elicit a RAP deficit. Current results also confirm the view that an early fundamental temporal acuity problem is associated with the occurrence of neuro-migrational anomalies.

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