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Research report

Rapid auditory processing and MGN morphology in microgyric rats reared in varied acoustic environments

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Abstract

Adult male rats with induced microgyric lesions exhibit significant deficits in rapid auditory processing, as well as morphological alterations in the medial geniculate nucleus (MGN) of the thalamus. These findings are considered striking in light of similar anatomical and auditory processing anomalies in language disabled humans. Given evidence from clinical and animal studies that acoustic experience may alter sensory processing at behavioral and neurophysiological levels, the current study examined effects of developmental exposure to auditory stimulation on behavioral and anatomical indices in microgyric and sham rats. Stimulation (E7–P70) included: (1) chronic white noise (80 dB) with standard housing; (2) 3 h/day of 78 dB filtered light classical music with social housing; or (3) standard acoustic environment (control) with standard housing. Microgyric effects on auditory processing and thalamic morphology were evident regardless of environmental condition. In sum, the effects of microgyria on brain and behavior appear to be robust, and largely orthogonal to any main effect of acoustic stimulation on auditory processing. These findings suggest that a more active form of acoustic stimulation (e.g., training) may be required to ameliorate the deleterious behavioral and anatomical consequences of focal microgyric lesions.
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1. Introduction

The environment plays an essential role in the development of language abilities—a child's exposure to language in the first months of life sets the stage upon which the infant builds his/her phonetic representations of language [18,26]. Up to 20% of children, however, exhibit difficulty in acquiring language [1,25]. Some of these children have hearing impairments or other physical limitations that impede normal speech acquisition and/or production, such as chronic otitis media, which degrades auditory input and is associated with delayed language and subsequent learning impairments [15,19,23].

Another sub-population (between 6 and 10% of children) exhibit delayed language for no apparent diagnosable reason and are labeled as language impaired (LI). Research has shown that LI children are characterized by rapid auditory processing deficits—defined as an inability to correctly process and comprehend quickly changing or occurring acoustic stimuli [27]. Tallal et al. [28] suggest that this auditory processing deficit may be one causal factor in disrupting language acquisition and may impose cascading effects on the development of other language-related skills including reading. This view is supported by the observation that up to 80% of LI children go on to be diagnosed with dyslexia in grade school [26]. Further, adult dyslexics show evidence of auditory processing impairments (see Ref. [10] for review).

Post-mortem analysis of brains from dyslexic humans reveal a predominance of cortical neuromigrational anomalies (e.g., ectopias, microgyria; [13]). These brains also show a shift in cell size distribution, to more small

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and fewer large cells, in the auditory thalamic nucleus (MGN, medial geniculate nucleus; [14]). A similar MGN effect has been seen in an animal model where microgyria is induced via a focal freezing technique [16]. Further, the rapid auditory impairment seen in LI and dyslexic subjects has also been observed in this animal model. Specifically, studies found that male rats with microgyria were impaired in their ability to discriminate two-tone sequences separated by short but not long inter-stimulus intervals [3,4,11,12]. Male microgyric subjects also have difficulties in discriminating between synthetic speech syllables (e.g., /ba/ versus /wa/) characterized by quickly changing acoustic components [5,6]. Interestingly in pilot tests, when microgyric rats receive active auditory training, their auditory discrimination improves to be comparable to sham littermates [2,6].

Environment has also been shown to influence the relationship between auditory processing and language ability in humans. For example, Cohen et al. [7] showed that differences in auditory discrimination account for a correlation between apartment level noise from expressway traffic and reading deficits in children, with children from noisier apartments having poorer auditory discrimination and more severe reading deficits. This correlation was stronger the longer the child had lived in the noisy apartment. Auditory experience has also been shown to improve children's auditory discrimination and language skills. For example Tallal and co-workers [21,29] utilized computer games that lengthen or exaggerate the quickly changing acoustic cues in speech to markedly improve the discrimination ability and language comprehension of children with LI. Similarly, fMRI studies found that acoustic training produces activation in the left prefrontal cortex to rapidly changing nonlinguistic stimuli in dyslexic patients, although no prefrontal area response to rapid stimuli was evident prior to training [30]. Anecdotal evidence, though controversial, also exists for improvements in auditory discrimination and Performance IQ associated with passive listening to classical music (e.g., the 'Mozart Effect'; see Ref. [31] for review).

Based on these convergent data, we used microgyric male rats known to exhibit auditory processing impairments to investigate the effects of passive exposure to varied acoustic environments during development (prenatal through adulthood) on subsequent auditory discrimination and thalamic morphology compared to sham littermates. Acoustic environments included (1) an Enriched environment with nightly exposure to varied acoustic stimuli and social (group) housing in an enriched facility, (2) a chronic White Noise environment (to mask auditory input, as a model of otitis media) with standard housing, and (3) a Control environment with standard acoustic and housing conditions. Our hypothesis was that microgyric subjects in the Enriched environment would show improvements in auditory discrimination, while both sham and microgyric subjects in the White Noise environment might show poorer discrimination when compared to controls. Similarly, we hypothesized that thalamic morphology would shift in parallel to any auditory discrimination changes.

2. Methods

2.1. Subjects

Subjects include a total of 40 male Wistar rats born from time-mated dams (Charles River Laboratories, Wilmington, MA) at the University of Connecticut. Upon arrival (embryonic day 7; E7), dams were placed in one of three acoustic environments—Enriched, White Noise, or Control. All groups received similar treatment for the induction of the focal microgyric lesion on postnatal day 1 (P1; see below). Pups were weaned on P21, and housed using a 12-h light/dark cycle with food and water available ad libitum. Environmental interventions were maintained through P70, when all subjects were moved to standard single-housing for testing. 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 with adequate measures to minimize pain or discomfort to the animals. Body weight was assessed at weaning (P21), at the conclusion of environmental manipulation (P70), and at perfusion (P118).

2.2. Environment groups

The three environmental groups consisted of the following: (1) an Enriched group (seven lesion and six sham subjects) reared with 3 h of non-vocal, light classical music exposure (75–78 dB) when the dark period began. Subjects were group housed at weaning in an enriched social housing condition. (2) A White Noise group (six lesion and seven sham subjects) reared in a separate room with 24 h exposure to broadband white noise (80 dB inside housing tubs). Subjects were pair housed by treatment at weaning. (3) A Control group (seven lesion and seven sham subjects) reared in the normal housing area (average room noise 45–55 dB). Subjects were pair housed by treatment at weaning. All acoustic interventions began at E7 and continued through P70.

2.3. Induction of focal microgyria

On P1 litters were culled to 10 pups. Pups were collected and randomly designated to receive bilateral freezing lesion or sham surgery, balancing treatment groups within litters. Based on a modification of the technique employed by Dvorák and co-workers, focal microgyric lesions were induced [8,9] (explained in detail

elsewhere [17,24]). In brief, pups assigned to the lesion condition received hypothermic anesthesia followed by a small midline incision over the skull. A cooled 2-mm diameter stainless steel probe was placed on the skull cap, approximately 2-mm lateral of the sagittal suture and 2-mm caudal of bregma, for 5 s. Following the initial lesion, an identical lesion was placed in the opposite hemisphere, with the first lesion side randomly determined. With the exception that the steel probe was maintained at room temperature, sham surgeries were identical. The skin was rapidly sutured following treatment, and subjects marked with ink footpad injections, warmed under a lamp, and returned to the dam.

2.4. 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 105-dB white noise burst that elicits an 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 extent 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 [20]. The inter-trial interval for all procedures was variable but averaged 20 s.

2.4.1. Apparatus

During testing, each subject was placed on a movement transducer platform (MED Associates, Georgia, VT). The platform's output voltage was passed into a Biopac MP100WS Acquisition system connected to a Power Macintosh 7200 to record the amplitude of the subject's ASR. Maximum peak values were extracted during the 150-ms directly following the onset of the SES and represents the subject's response amplitude for that trial (dependent variable). Auditory stimuli were generated on a Power Macintosh 6100 using custom programmed software with programmable frequency output. Stimulus files (one file per session) were played using SoundHack 0.881NF and presented through powered Yamaha YHT-M100 speakers. Sound intensity levels were checked at subject level before testing using a hand-held sound level meter (Radio Shack).

2.4.2. Single tone procedure

A single test session consisted of 104 trials. Trials were either cued or uncued (Fig. 1A) and presented in a pseudo-random order (no more than three similar trials in a row). On cued trials, the 105-dB SES was preceded by 50 ms with a 7-ms, 2300-Hz tone cue. Uncued trials consisted of only the silent background and a SES.

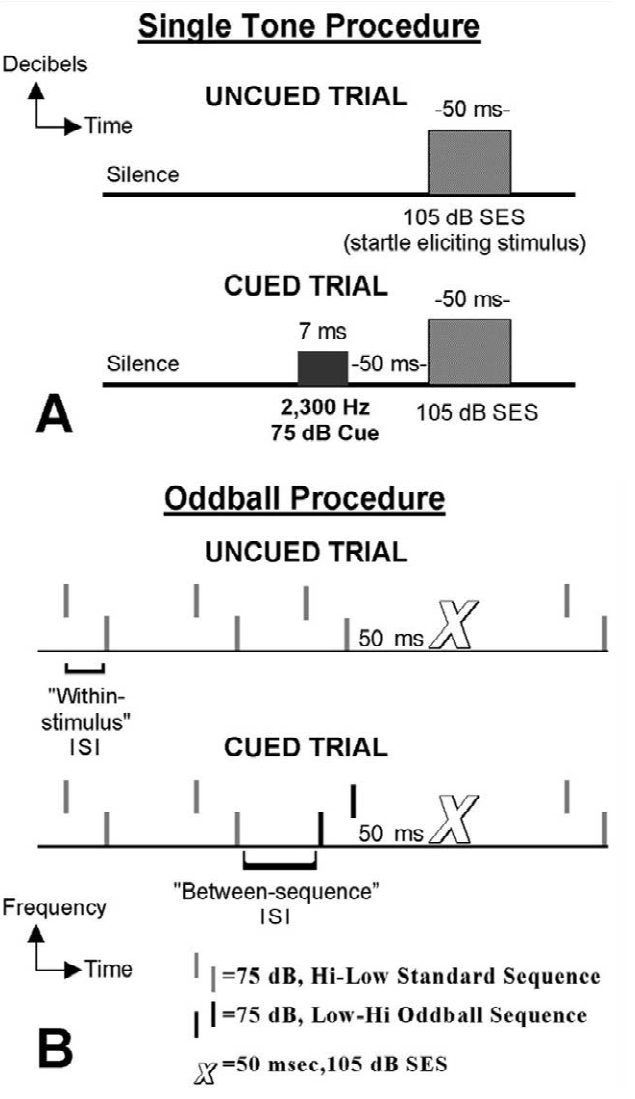

Fig. 1. Sample trials for startle reduction: (A) depicts cued and uncued trials in the single tone procedure, and (B) depicts those in the oddball procedure. Both tasks utilized a variable duration inter-trial interval with the SES occurring on average every 20 s. Test sessions included 104 trials with pseudo-random presentation of uncued and cued trials.

2.4.3. Oddball procedure. Again test sessions included 104 trials. Repeated presentation of a standard stimulus, consisting of a 75-dB, high/low two-tone sequence (2300 and 1100 Hz, respectively), served as background. Tones (7 ms) were separated by a within-stimulus inter-stimulus interval (ISI) of 225, 75, 40, or 10 ms duration, which remained constant within a test session. Each sequence was separated by a between-sequence ISI, which was always 200 ms greater than the within-stimulus ISI in order to maintain the perceptual contiguity of the tone pair. On uncued trails, the standard stimulus preceded the 105-

dB SES by 50 ms. For cued trials, an 'oddball' stimulus, comprised of the same tones used in the standard sequence but in reverse order (low/high), was presented 50 ms before a SES (see sample trials in Fig. 1B).

2.5. 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 at Beth Israel Deaconess Medical Center for anatomical analysis. The brains were removed, weighed, lesions confirmed and location visually assessed. Brains were placed in fresh 10% formalin for 7 days prior to dehydration via graded alcohols, embedded in 12% celloidin and serially sectioned in the coronal plane at 30 μm. Every fifth section was stained with cresyl violet, mounted on glass slides and coverslipped with Permount.

2.5.1. Morphometry

Utilizing the procedure set forth by Herman et al. [16], MGN cell measures were assessed. In brief, cell-packing densities and cross-sectional cell areas were measured in the MGN of all rats using the modified dissector method and software of Williams and Rakic [32]. Three fields on each of three slides were measured; samples were taken from the rostral to caudal extent and in the ventral, medial and dorsal portions of the nucleus of both hemispheres for a total of 18 fields per brain. Images taken at ×500 were projected onto a Sony GVM 1311Q monitor connected to a Macintosh Centris 650. Overlaid on these images was a counting square (95×85 μm). A Heidenhain MP-25 photoelectric micrometer interfaced to a National Instrument NB-GPIB card in the Centris 650 read *z*-axis movement. The base of the section was set to a *z*-axis of zero. An opaque overlay prevented counting below or above the confines of the 20-μm optical box. The screen became transparent when the plane of focus was moved to 5 μm above the base and again became opaque at 25 μm. The neurons within this range that had focused nucleoli were traced on a digitizing tablet. Neurons that touched the top and right sides of the counting box were omitted. Cell-packing density and neuronal area measurements were then output to the computer.

3. Results

Post mortem analysis confirmed bilateral microgyria in all subjects exposed to the P1 freezing lesion treatment (see Fig. 2). These malformations were located in sensorimotor cortex (SM-I) including regions Par1, Par2, HL, and FL [33]. No malformations were seen in any sham subject.

3.1. Behavioral tests

3.1.1. Single tone procedure

Significant effects of Cue were found for all subjects, indicating significant discrimination of the tone. Analysis of Attenuated Response (calculated by taking the cued response amplitude/the uncued response amplitude and multiplying by 100) indicated no significant effect of Environment ($F(2,34)<1$), Lesion ($F(1,34)=1.38$; $P=$ns), nor interaction of Environment and Lesion ($F(2,34)<1$). Since no base-line startle differences were evident between

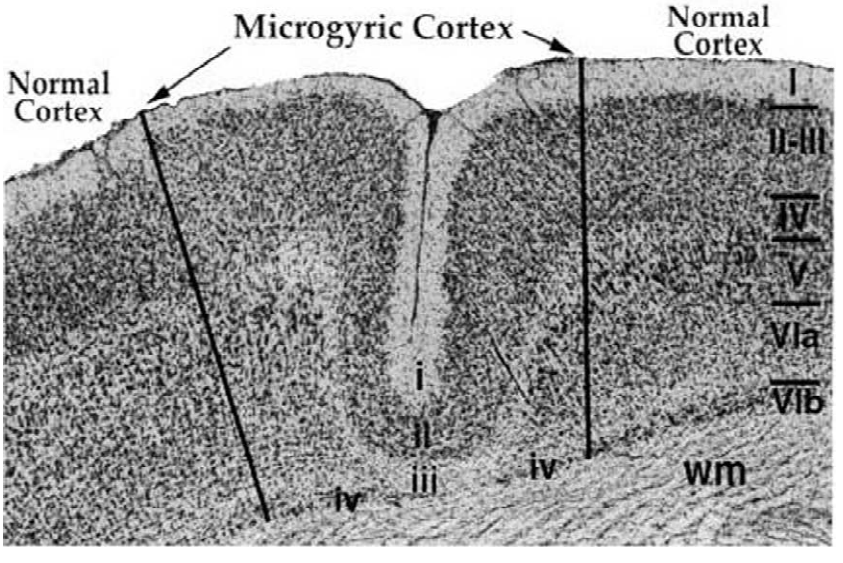

Fig. 2. An example of a microgyric lesion in rat sensorimotor cortex produced from a P1 focal freezing lesion treatment. The six normal cortical layers are denoted with the Roman Numerals I–VIb, and wm denotes cortical white matter. Microgyric cortex is composed of cortical layers i–iv and shows a distinct fold in otherwise smooth cortex.

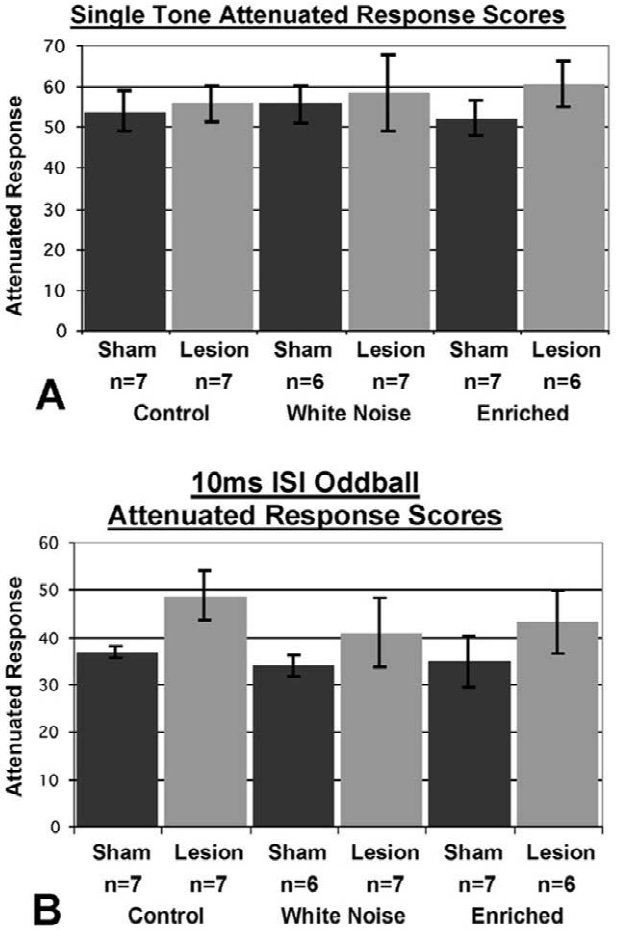

Fig. 3. Behavioral test results. Attenuated Response is calculated by dividing the response to cued trials by the response to uncued trials and multiplying by 100. A lower score indicates better attenuation to the cue, and thus superior auditory perception. (A) Single Tone results showed no base-line startle differences between the groups with no significant main effect of Lesion ($F(1,35)=1.38$; $P=$ns), Environment ($F(2,34)<1$), nor interaction ($F(2,34)<1$). (B) The 10-ms ISI Oddball results showed a significant main effect of Lesion ($F(1,34)=8.98$; $P<0.005$) with no main effect of Environment ($F(2,34)=1.1$; $P=$ns) nor interaction ($F(1,34)<1$).

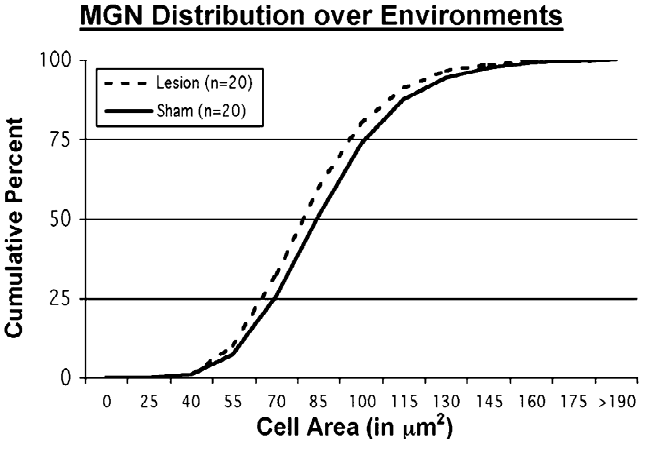

Fig. 4. Overall, lesion subjects had significantly more small and fewer large cells than sham littermates ($\chi^2=123.14$, df=11, $P<0.0001$). There was no significant Main Effect of Environment nor interaction.

the different groups (Fig. 3A), we can infer that auditory environment and lesion manipulations did not impact baseline hearing or general startle response.

3.1.2. Oddball procedure

Significant effects of Cue were found for all subjects at all ISI, indicating significant discrimination of the oddball. Analysis of Attenuated Response across the four ISI conditions showed that at the 10-ms ISI (Fig. 3B), a significant main effect of Lesion ($F(1,34)=8.98$; $P<0.005$) indicated poorer performance (higher attenuated response score) in microgyric subjects compared to sham littermates. There was no Environment main effect ($F(2,34)=1.1$; $P=$ns) nor Environment by Lesion interaction ($F(1,34)<1$).

3.2. Body weight

A significant effect of Environment ($F(2,34)=23.32$; $P<0.001$) was observed with no significant effect of Lesion ($F(2,34)=1.73$; $P=$ns) nor interaction ($F(2,34)=1.73$; $P=$ns). A significant effect of Age was seen ($F(2,68)=3274.02$; $P<0.001$) reflecting increasing body weight as subjects became older. At all age points, White Noise subjects were significantly heavier than Controls, who were in turn significantly heavier than Enriched subjects (probably reflecting activity differences between groups). Interestingly, these body weight difference were seen even at P21 when subjects were housed and treated identically except for acoustic environment.

3.3. Brain weight

As presented elsewhere [22], a highly significant effect of Lesion ($F(1,33)=29.13$; $P<0.001$) on brain weight was seen, with no interaction ($F(2,33)<1$) nor main effect of ($F(2,33)=1.10$; $P=$ns) Environment. (Analyses were performed using P118 body weight as a covariate.) The presence of microgyric lesions uniformly resulted in a decreased brain weight compared to sham littermates.

3.4. MGN morphology

ANOVA performed on the cell packing density of the MGN indicated no significant effect of Environment ($F(2,31)=1.16$; $P=$ns), Lesion ($F(1,31)<1$), nor an Environment by Lesion interaction ($F(1,31)=1.60$; $P=$ns). Further, an ANOVA analysis on cell area showed no significant effect of Environment ($F(2,31)<1$), Lesion ($F(1,31)=2.66$; $P=$ns), nor an Environment by Lesion interaction ($F(1,31)=1.96$; $P=$ns). However, distribution analysis indicated that lesion subjects had more small and fewer large cells overall than sham littermates ($\chi^2=123.14$, df=11, $P<0.0001$; Fig. 4).

4. Discussion

Results in the single tone task indicate that our environmental interventions produced no visible impairment or change in auditory startle response (ASR), or pre-pulse inhibition. Lack of a baseline group difference allows us to freely compare the ASR between groups in order to evaluate differences in more complex auditory perception.

As seen in previous research, the 10-ms ISI Oddball results showed a significant Lesion effect, indicating lesion subjects had poorer discrimination at the short duration ISI than sham littermates. Interestingly, neither a main effect of Environment nor an interaction between Environment and Lesion were significant. When we look at the morphology of the MGN, prior findings are again replicated. We found a significant Lesion effect, reflecting a shift to more small and fewer large cells in lesion subjects as compared to sham littermates. Environment did not show a significant main effect or interaction with Lesion. As such, our results indicate that: (1) rapid auditory processing deficits previously shown in microgyric rats on a two-tone oddball detection task as well as the occurrence of MGN anomalies have been replicated in Controls; (2) a main effect of Lesion on behavior, brain weight, and MGN morphology suggests that the lesion effects were consistent across environment groups (and thus surprisingly resilient to intensive auditory interventions during development).

As an aside, the apparent lack of environmentally mediated behavioral improvement in this study should not be taken as evidence that microgyric effects cannot be ameliorated. In our study we employed passive auditory stimulation, but in studies where training (an interactive form of auditory exposure) has been employed, significant improvements in auditory discrimination in LI children have been observed (e.g., Refs. [21,29,30]). Pilot data in impaired microgyric rats also suggests that auditory training may improve auditory discrimination (e.g., Refs. [2,6]), and further testing will address this issue.

In conclusion, the results of the current study indicate that the consequences of bilateral microgyria (e.g., reorganization associated with brain weight reduction, alterations in thalamic morphology and rapid auditory processing deficits) are surprisingly robust. These effects do not appear to be ameliorated by passive acoustic stimulation, even when provided daily from birth to adulthood and despite the fact that these interventions have sufficient impact to significantly alter body weight. More active engagement in a task (e.g., auditory training) may be required to ameliorate the effects of microgyria.

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