Research Article

Amplitude Modulation Detection in Children with a History of Temporary Conductive Hearing Loss Remains Impaired for Years After Restoration of Normal Hearing

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Received: 8 April 2018; Accepted: 20 September 2018; Online publication: 17 October 2018

ABSTRACT

Otitis media with effusion (OME) is considered a form of relative sensory deprivation that often occurs during a critical period of language acquisition in children. Animal studies have demonstrated that hearing loss during early development can impair behavioral sensitivity to amplitude modulation (AM), critical for speech understanding, even after restoration of normal hearing thresholds. AM detection in humans with a history of OME-associated conductive hearing loss (CHL) has not been previously investigated. Our objective was to determine whether OME-associated CHL in children ages 6 months to 3 years results in deficits in AM detection in later childhood, after restoration of normal audiometric thresholds. Children ages 4 to 7 years with and without a history of OME-associated CHL participated in an AM detection two-alternative forced-choice task at 8 and 64 Hz modulation frequencies using a noise carrier signal and an interactive touch screen interface. Thirty-four subjects were studied (17 with a history of OME-related CHL and 17 without). Modulation detection thresholds improved with age and were slightly lower (more sensitive) for the 64 Hz modulation frequency for both groups. Modulation detection thresholds of children with a history of OME-associated CHL were higher than control thresholds at 5 years, but corrected to expected levels between ages 6–7. OME-associated CHL results in impaired AM detection, even when measured years after

restoration of normal audiometric thresholds. Future studies may shed light on implications for speech and language development and academic success for children affected by OME and associated conductive hearing loss.

Keywords: amplitude modulation, pediatric hearing loss, otitis media with effusion, neurodevelopmental pediatrics

INTRODUCTION

Auditory sensory deprivation due to common ear disorders in early childhood may have long-lasting effects on the neural processes underlying hearing, speech, and language development. These effects have been referred to as amblyaudia, a term that highlights the far-reaching consequences of sensory deprivation on the nascent auditory system, drawing parallels to amblyopia in the field of vision science (Whitton and Polley 2011; Kaplan et al. 2016). The concept of early sensory deprivation leading to long-term deficits has been well-established in the visual system (Wiesel and Hubel 1963; Qi et al. 2016; Tailor et al. 2017; Wallace et al. 2011), and the time-sensitive nature of these developmental processes comes with increased clinical urgency. Disorders that cause only mild immediate impairment are treated more aggressively when they are recognized to occur within a critical period of brain development that, once past, cannot be recovered. Since the initiation of universal newborn hearing screening in the 1980s, the vast

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majority of infants are now appropriately screened for congenital hearing loss, with the goal of early habilitation to minimize long-term deficits. Hearing loss during early childhood has been shown to have detrimental effects on speech and language, academic achievement, and socio-behavioral functioning (Whitton and Polley 2011; Kaplan et al. 2016). Early treatment of sensorineural hearing loss has been linked with better speech and language outcomes (Yoshinaga-Itano and Apuzzo 1998; Moeller 2000; Yoshinaga-Itano et al. 2001), and extensive research on cochlear implantation has also shown that earlier restoration of sensory input results in improved hearing and language outcomes (Robbins et al. 1999; Connor et al. 2000; Kirk et al. 2002). Unfortunately, children with mild or transient hearing loss, often conductive in nature and not present at birth, may still suffer the long-range consequences of impaired sensory input despite universal newborn screening.

Otitis media with effusion (OME) is one of the most common diseases of childhood, and is by far the most common cause of acquired conductive hearing loss (CHL) in children (Simpson et al. 2007; Zielhuis et al. 1990). OME typically develops in infancy or early childhood, after the newborn hearing screen has occurred, and can cause a CHL of up to 40 dB (Bluestone 1973; Gravel and Wallace 2000). Because the effects on hearing are often fluctuating or transient, they can be easily overlooked. Early studies showed minimal effects on long-term hearing outcomes for children with OME when the presence of hearing loss was not specifically confirmed (Roberts et al. 2004; Jung et al. 2005). When CHL is present in both ears, however, a 20–40 dB impairment is significant enough to impact speech and language development (Tomblin et al. 2014; Silva et al. 1982; Roberts et al. 2004; Shriberg et al. 2000). The long-term effects of these deficits are an area of active debate and investigation (Pillsbury et al. 1991; Bennett et al. 2001; Lous et al. 2005; Paradis et al. 2000; Roberts et al. 2004; Whitton and Polley 2011).

Animal studies have suggested far-reaching effects of even temporary or unilateral hearing loss during early development, with the recognition that negative effects can persist even after the restoration of normal hearing thresholds (Moore et al. 1999; Polley et al. 2013; Caras and Sanes 2015). Polley et al. (2013) induced brief unilateral hearing loss in a mouse model on or before P16, and found that interaural level difference (ILD) sensitivity and frequency tuning were disrupted 1 week after normal hearing was restored. Caras and Sanes (2015) looked at amplitude modulation (AM) detection threshold, a measure of listening ability that depends on time-varying cues that are important for speech understanding (Shannon

et al. 1995; Nelson and Carney 2004; Henry et al. 2016). This task is distinct from measures such as the ILD that involve integration between the two ears. The authors found that gerbils who underwent sensory deprivation during the critical period of cortical development (between P11–23) performed more poorly on an AM detection task compared to controls, even though all gerbils had normal hearing at the time of testing. To our knowledge, AM detection thresholds in humans with a history of transient conductive hearing loss have not been previously investigated.

The purpose of the present study was to investigate whether auditory processing strategies important for speech understanding, specifically AM detection, are impaired in children with a history of OME-related CHL. We hypothesized that temporary hearing impairment occurring between the ages of 6 months and 3 years would result in measurable deficits in AM detection thresholds that persist into later childhood, after restoration of normal audiometric thresholds.

METHODS

Children between the ages of 4 and 7 years with normal audiometric thresholds, with and without a history of bilateral OME-related CHL, were recruited for this study. Initial identification of subjects for the experimental group was from the first author (MMB)'s pediatric otolaryngology clinical practice. Potential experimental subjects were identified by searching billing records for the procedure codes associated with myringotomy and tympanostomy tube placement (CPT 69436). The electronic medical record was reviewed for each potential subject between the ages of 4 and 7. Children with elevated thresholds of 25 dB HL or higher at 500 Hz in at least the better hearing ear between the ages of 6 months and 3 years were eligible to be included in the experimental group. Many of the control subjects were seen for other otolaryngologic problems, such as enlarged tonsils and adenoids. These were typically developing, age-matched children with no history of ear or hearing difficulties. The majority of subjects in both groups were not still in need of ongoing care from an otolaryngologist. Exclusion criteria included a history of sensorineural hearing loss, or non-native English speakers. This study was approved by the Research Subjects Review Board at the University of Rochester.

Potential subjects who met the inclusion criteria for either the experimental or control group were approached by telephone or in person at a subsequent office visit. Eligible subjects were invited to

participate in the study. Informed consent from the parent and verbal assent from the children were both obtained for every subject. A questionnaire was completed by the subject's parent (in person or with a member of the study team by telephone) regarding any medical history of ear infections or hearing loss, as well as the need for any speech language services. This questionnaire did not influence whether subjects were placed in the experimental or control group, but was used to exclude subjects eligible for the control group who may have had an unrecognized history of ear problems not reflected in the medical record.

Each study session consisted of an otoscopic examination, including pneumatic otoscopy when possible; tympanometry to confirm normal Eustachian tube function or patent tympanostomy tubes; and a routine audiogram, to confirm clear ear canals and normal pure tone thresholds in both ears without air bone gap(s). The experimental protocol was then carried out in listening sessions that included about 30 min of active participation. Efforts were made to condense experiments into one efficient listening session in order to balance the time required by the family (for multiple sessions) and the attentional demands on the subject (for long testing sessions). All sessions were conducted in a standard, double-walled audiometric test booth with acoustic stimuli presented diotically through calibrated, audiometric headphones (TDH-50P, 60 Ω).

A graphical user interface consisting of a main display window for presenting feedback to the subject and three touch-activated response buttons was used to estimate detection thresholds for sinusoidal AM of a 500-ms, noise-carrier stimulus (bandwidth 100–5000 Hz) at modulation frequencies of 8 and 64 Hz (Fig. 1). These modulation frequencies were chosen

to approximate the perception of fluctuation (8 Hz), which is close to the average rate at which syllables occur, and that of roughness (64 Hz), which corresponds to envelope structure within syllables (Joris et al. 2004). A two-interval, two-alternative, auditory discrimination task was designed using a two-down one-up adaptive staircase procedure (Levitt 1971). Pilot data in several children confirmed that the program converged successfully on the subject's AM detection threshold in 40–60 trials (2–4 min). Each trial consisted of a modulated test stimulus and an unmodulated standard stimulus, presented in random order, separated by a 200-ms silent interval. Stimuli were normalized for overall energy (65 dB SPL), presented diotically, and gated on and off with 10-ms cosine-squared ramps. The left and right response buttons changed color during the presentation periods of the first and second stimuli, respectively, to reinforce the association between the stimulus sequence and response button locations. Subjects were instructed to press a center green button to start each trial and then respond by pressing the left or right button, depending on whether the modulation occurred during the first or second stimulus interval, respectively. Correct responses were reinforced by presenting an image in the display window from a preselected theme of the subject's choice (e.g., Disney characters, superheroes, minions, etc.), and incorrect responses resulted in presentation of a solid black square. Following the 0.5-s feedback period, the trial ended, and the subject was permitted to start the next trial. If there was no subject response within 7 s of trial initialization, there was no feedback period, and the subject was prompted to move on to the next trial. Trials with no response were ignored in the staircase paradigm.

FIG. 1. **a** Graphical user interface for estimation of amplitude modulation (AM) detection thresholds in children. The green button initiates a single trial consisting of one modulated target stimulus and one unmodulated standard stimulus in random sequence. The left (right) button is the correct response if the target stimulus occurred first (second). Correct responses are reinforced with an image from a theme of the subject's choice.

Incorrect responses result in the display window turning black. **b** Amplitude-modulated noise waveforms used as stimuli. Waveforms show pressure (arbitrary units) as a function of time for the modulation frequency of 64 Hz. Amplitude modulation depth is given in dB to the left of each waveform. 0 dB corresponds to 100 % modulation depth. The lower waveform shows the unmodulated standard stimulus

Test stimuli were initially presented at 0 dB (100 %) modulation depth for several trials to familiarize the subject with the test procedure. Thereafter, the modulation depths of test stimuli were systematically varied from trial to trial based on a two-down one-up tracking procedure (Fig. 2). Step size decreased from 6 to 3 dB modulation depth after 2 reversals, and from 3 to 1.5 dB after 4 reversals. Each test session continued until 13 total reversals were obtained (median 49 trials; interquartile range (IQR) 42–56 trials). The AM detection threshold (~ 70.7 % correct responses) was calculated as the average of the last eight reversal points in stimulus modulation depth. Incorrect responses for the 0-dB stimulus condition produced no change in modulation depth. Consequently, median chance performance based on model simulations was -1.31 dB (IQR -1.88 to -0.94 dB; $n=1000$ simulations). Thresholds were measured in the same order in all subjects, with 1–2-min breaks between sessions during which the subjects rested or watched a short video. Thresholds were measured twice for the 64-Hz condition, twice for the 8-Hz condition, and generally once more for the 64-Hz condition. The 64-Hz condition was tested first because preliminary experiments in younger subjects suggested that this condi-

tion was easier to learn. Repeated threshold estimates in the same subject at the same modulation frequency were generally similar, with a median absolute difference of 2.25 dB. In rare cases for which modulation detection thresholds differed by more than 10 dB (4 of 81 thresholds in control subjects; 6 of 86 thresholds in subjects with a history of CHL), the higher threshold was eliminated from subsequent analyses. Thresholds were not strongly dependent on the number of trials per track but tended to be higher for tracks with more trials (by 0.075 ± 0.048 dB/trial [mean $\pm$ SE]; $r^2=0.015$, $p=0.12$; linear regression analysis). The number of trials per track was similar between control subjects (median 47; IQR 41–56) and those with a history of CHL (median 51; IQR 45–56.5).

Modulation detection thresholds were analyzed in R (version 3.4.1) using a linear mixed-effects model analysis (Bates et al. 2015). The model included age (in months), gender, and CHL history as between-subject fixed effects and modulation frequency as a within-subject factor. Subject intercepts were modeled as a random effect to account for repeated threshold estimates in each subject. Interactions were included between fixed effects and dropped when not significant ($p>0.05$) in order of decreasing p value. Degrees

FIG. 2. Representative behavioral test results used to estimate modulation detection thresholds in children. Repeated two-down one-up behavioral tracks in one subject (CHL group; male; 73 months old) show the modulation depth of the target stimulus as a function of trial number. Modulation frequency was 8 Hz (top) or 64 Hz (bottom). Successive tracks are plotted in different colors

and shifted to the right by 10 trials for clarity. Thick regions of each line indicate the portion of the track used to calculate the modulation detection threshold. Threshold was calculated as the mean of the final eight reversal points. Thresholds were -17.9 and -15.8 dB for the 8-Hz condition and -14.5 , -14.1 , and -18.2 dB for the 64-Hz condition

of freedom for F tests and pairwise comparisons of least-squares means were calculated based on the Satterthwaite approximation. Visual inspection of model results showed that residuals were normally distributed.

RESULTS

Forty subjects were consented to participate in the study. One subject had acute otitis media diagnosed on the day of testing and was excluded from further testing and analysis. Five subjects had elevated pure tone thresholds on the day of testing and were excluded from further analysis. The remaining 34 subjects are included in the remainder of the data analysis. All 34 subjects had auditory thresholds < 20 dB HL, no air bone gap(s), and a normal ear exam (with { $N=6$ } or without { $N=28$ } patent tympanostomy tubes, consistent with tympanometry) on the day(s) of testing. There was no difference in audiometric thresholds between groups on the day of testing. Word discrimination scores were >99 % at 40–45 dB HL and were similar for both groups. There were 17 with a history of OME-associated CHL and 17 with a normal ear and hearing history. Children in the CHL group consisted of 14 subjects with elevated thresholds of 25 dB HL or higher at 500 Hz in at least the better hearing ear between the ages of 6 months and 3 years, and 3 children with onset of symptoms prior to age 3, but audiograms were performed after the third birthday. The analysis was carried out both with and without these additional three children who did not meet strictest criteria, and there was no difference in outcome. The age range for all 34 subjects was 48–95 months (4–7 years); and 21 (61.8 %) were male. The distribution of observed ages was similar between the CHL group (69.9 ± 11.0 months) and the control group (73.7 ± 14.2 months; means $\pm$ SD). Across all subjects, 15 % were 4 years of age, 44 % were 5 years of age, 18 % were 6 years of age, and 23 % were 7 years of age. All subjects in the experimental group underwent tympanostomy tube placement in early childhood, prior to the study period. The average age at the time of tube insertion was 33.4 months (median 29 months, range 16–66 months).

Modulation detection thresholds were consistent within subjects, and generally differed by less than 2–3 dB across repeated measurements at the same modulation frequency (Fig. 2 showing representative tracks). Modulation detection thresholds decreased with increasing age across subjects (age; $F_{1,29.6} = 18.79$, $p = 0.0002$), with older children achieving lower modulation detection thresholds (greater sensitivity) than younger children (Fig. 3). Notably, the analysis

showed a significant main effect of hearing status ($F_{1,29.5} = 10.93$, $p = 0.0025$) that varied with age (hearing status $\times$ age; $F_{1,29.5} = 9.91$, $p = 0.0037$). In the younger age group (<6 years old), children with a history of OME-associated CHL were less sensitive to AM than control subjects (4.24 ± 2.07 dB; least-squared mean difference $\pm$ SE; $t_{30} = 2.05$, $p = 0.050$). By age 6–7 years (72–84 months), most subjects with a history of OME-associated CHL were performing at levels similar to age-matched peers (-2.55 ± 2.49 dB; $t_{30} = -1.02$, $p = 0.32$; Fig. 3). Other significant main effects included modulation frequency ($F_{1,131.5} = 10.94$, $p = 0.0012$) and gender ($F_{1,28.9} = 6.58$, $p = 0.016$). Thresholds were slightly lower for the 64 Hz modulation frequency compared to 8 Hz (-1.84 ± 0.56 dB) and lower in male subjects than females (-3.63 ± 1.42 ; least-squared mean differences $\pm$ SE). Two-way interactions were not significant between hearing status and gender ($F_{1,27.1} = 0.030$, $p = 0.86$), hearing status and modulation frequency ($F_{1,126.3} = 1.11$, $p = 0.29$), modulation frequency and gender ($F_{1,126.6} = 0.97$, $p = 0.33$), modulation frequency and age ($F_{1,126.8} = 1.06$, $p = 0.30$), or gender and age ($F_{1,27.3} = 2.71$, $p = 0.11$).

Children with a history of OME-associated CHL were more likely to have had a speech language evaluation, compared to controls ($X^2_{1,N=34} = 6.10$, $p = 0.013$). Parents were more likely to report concerns regarding their child's hearing and/or speech in the experimental group compared to controls ($X^2_{1,N=34} = 7.77$, $p = 0.005$). The proportion of children receiving speech services was 0.412 in the CHL group compared to 0.176 in the control group ($X^2_{1,N=34} = 2.27$, $p = 0.13$). Finally, there was no difference between experimental subjects and controls in the need for occupational or physical therapy ($X^2_{1,N=34} = 0.37$, $p = 0.55$).

DISCUSSION

The results of the present study in children show that early-onset conductive hearing loss due to OME is associated with deficits in AM detection that persist for years after restoration of normal hearing. We found that children with a history of OME-associated CHL performed more poorly on an AM detection task than controls at age 5. All children in the hearing loss group had ear tubes placed in early childhood (between the ages of 16–35 months), resulting in restoration of normal hearing. In some cases, normal audiometric thresholds were confirmed up to 4 years before experimental testing. Despite this period of normal pure tone thresholds, subjects with a history of OME-associated hearing loss continued to experience

FIG. 3. Modulation detection thresholds of children in control ($N=17$) and CHL ($N=17$) groups. Thresholds are plotted as a function of age at modulation frequencies of 8 Hz (**a**) and at 64 Hz (**b**). Modulation detection thresholds improve in both groups with age as shown by the lower thresholds reached by older children.

Children less than approximately 6 years in age with OME-related CHL have higher thresholds than age-matched children without a history of significant OME-related CHL. Trend lines are predictions from the linear mixed-effects model

difficulty with the AM detection task compared with age-matched controls, lending further support to the idea of a critical period of auditory development during which even mild deficits can have far-reaching consequences.

AM detection is known to be important for speech understanding. There are many cues that the brain uses to distinguish and process speech sounds in the natural environment. Temporal cues, including fine structure and overall envelope structure (amplitude modulations) have been increasingly recognized as key factors that the auditory system responds to at multiple levels along the neural axis (Shannon et al. 1995; Joris et al. 2004). Our study provides a possible explanation for the impact of early hearing loss on speech and language skills, through a lag in the developmental trajectory of this ability to detect temporal cues such as AM. In the present study, although the effect on AM detection appeared to

resolve by age 6–7, those children with a lag in AM detection threshold development were also more likely to be evaluated for speech and language services in the interim. Considering that no other services (occupational or physical therapy) were recommended for these children, this finding lends evidence that the lag in maturation of AM detection is clinically relevant for the development of speech and language.

The current study showing persistent deficits in AM detection for several years following restoration of normal hearing may contribute to a sense of urgency in treating children with OME-related CHL, in order to maximize their developmental potential, in a similar theoretical framework to amblyopia. Surgical placement of tympanostomy tubes is effective at removing middle ear fluid and restoring normal hearing. This procedure requires general anesthesia in the vast majority of children, and has inherent surgical risks, including chronic otorrhea and ear

drum perforation. In children with bilateral middle ear effusions for greater than 3 months (according to current clinical guidelines), the surgical risks are outweighed by the potential benefits, particularly for children with hearing loss and speech delay. Demonstration of a prolonged impairment in modulation detection abilities, coupled with an increased concern about speech and language development, could sway clinicians and families toward earlier surgical management in order to optimize long-term auditory perceptual abilities.

Several studies have shown a maturation effect for AM and FM sensitivity in children with no history of hearing impairment (Banai et al. 2011; Sutcliffe and Bishop 2005; Dawes and Bishop 2008; Hall and Grose 1994; Lorenzi et al. 2000). Adult-like processing appears to be achieved by around ages 8–10, although select measures may be adult-like as young as age 5 (Cabrera and Werner 2017). There is also support in the literature for males maturing faster than females in complex auditory processing (Huyck and Wright 2018), a finding that is consistent with our current results. In studying the developmental trajectory of AM detection, we have shown that control subjects between the ages of 4 and 7 years have a similar maturation pattern to what has been reported in the literature, while subjects with a history of OME-related CHL lag behind their peers in this important development. Our study supports previous findings that these processes are well established by around age 8 years, and those children with a history of impairments due to OME-associated CHL appear to have largely recovered function by this later age. Importantly, the prevalence of speech and language disorders is highest among children ages 3–6 years (Black et al. 2015), the time period when we found the largest difference in AM detection between those with OME-associated CHL and controls.

OME has been considered a form of relative sensory deprivation when it occurs during the critical period of speech and language acquisition (Gravel et al. 1996; Moore et al. 1989, 1991); however, there remains considerable debate in the literature about the long-range importance of these effects (Roberts et al. 2004; Whitton and Polley 2011). Several meta-analyses have attempted to link OM history with speech outcomes, but the degree and duration of associated hearing loss is often unspecified (Shekelle et al. 2003; Casby 2001; Roberts et al. 2004). In a recent review, Whitton and Polley (2011) postulated that it is the degree of associated CHL, and not the presence of OME alone, that results in perceptual and physiological alterations in the auditory system. Studies that focus on the hearing loss associated with OME have shown more long-term effects (Hall and Grose 1994; Gravel et al. 2006; Hogan and Moore 2003;

Graydon et al. 2017). Many of these studies investigated the ability of children to detect properties of complex sounds that are known to be involved in binaural integration and speech encoding, including the masking level difference (MLD) and comodulation masking release (CMR), among others.

Hall and Grose (1994) examined CMR before and after insertion of pressure equalization tubes in children with OME. They found that monotonic CMRs were reduced in children with a history of OME, and remained impaired up to 3 months following tube insertion and restoration of normal hearing. By 6–8 months, there was no longer a difference between children with a history of OME and controls. This is one of the first studies to show a persistent deficit after restoration of normal hearing. Importantly, baseline testing prior to insertion of tubes was done when children had fluid present in the middle ear(s), causing impairments in pure-tone thresholds. There was no information on whether these children experienced any speech and language delays. Most subjects were slightly older (5–10 years) at the time of documented CHL, which may have resulted in a more transient effect, since many of these children are outside of the critical period for speech and language development. In our study, hearing loss that occurred earlier in childhood resulted in long-lasting deficits, years after restoration of normal hearing.

Gravel et al. (2006) prospectively studied two cohorts of children to determine whether OME in the first 3 years of life was associated with higher-order audiometric measures later in childhood, around age 8. They found that the duration of OME-related hearing loss in early childhood was associated with decreased hearing sensitivity (pure tone thresholds) in an extended high-frequency range, higher thresholds for acoustic reflexes, and prolonged wave V latency on auditory-brainstem responses. There was no effect on psychoacoustic outcomes, including MLD, speech in noise, or binaural processing. A similar study by Hogan and Moore (2003) followed a cohort of 31 full-term children over 6 years, and found that those with the highest lifetime prevalence of OME had significantly lower MLD.

A recent study by Graydon et al. (2017) compared binaural integration in children with and without a history of unilateral or bilateral conductive hearing loss using MLD and listening in spatialized noise sentence (LiSNS) tasks. They found a difference between experimental subjects and controls in the LiSNS but not the MLD task. Children with a history of CHL performed more poorly on the LiSNS task compared with children in the control group. In their study, no significant difference was found in tasks that did not involve binaural cues. This allowed the authors to conclude that the differences they found

were not due to deficits in attention, language, or memory in the children with a history of early hearing loss; however, it also points to binaural integration as the main deficit. Our study showed a monaural impairment in auditory development, possibly because the CHL in our cohort was in both ears. This may also be a result of the overall maturation effect, as their mean study age was over 8 years in both groups, compared to our younger population.

The current study is distinct from prior work in several key aspects. Importantly, we were able to document bilateral CHL at a young age in all experimental subjects, lasting long enough to consider surgical placement of tympanostomy tubes (according to current guidelines, at least 3 months duration). This age bracket at the time of CHL also allowed us to investigate the consequences of CHL that occur during the most sensitive period for language development in humans, whereas previous studies have often included older children with OME-associated CHL. In addition, the age of subjects at the time of testing was younger than most other studies, starting at 4 years. Because maturation of AM detection occurs across the age spectrum that we selected, we were able to take advantage of the variability in responses and slope of change to highlight a developmental difference in rate of development between the control and experimental groups. Thresholds were slightly lower (by about 1.8 dB) for the 64 Hz modulation frequency compared to 8 Hz, which differs from prior studies (Viemeister 1979; Hall and Grose 1994). It is possible that test order contributed to this difference. All subjects were tested at 64 Hz (2 tracks) followed by two tracks for the 8-Hz condition and, in most cases, one last track for the 64 Hz condition. While thresholds were not notably more sensitive for this final 64-Hz track compared to the first two, additional experience with the 64 Hz condition may have yielded slightly lower thresholds. Finally, studying AM detection allowed us to expand our concept of the effects of bilateral OME. Monaural sensory deprivation is known to cause significant structural and synaptic changes in the brain (Wiesel and Hubel 1963; Taylor et al. 2017). In the auditory system, these changes are perceptually evident in tasks involving interaural cues, where submillisecond differences between the ears are readily detected. Our study included AM stimuli where fluctuations occurred on the order of tens to hundreds of milliseconds. In addition, animal studies have shown that *binaural* sensory deprivation can also cause disruptions in perception in animals (Rosen et al. 2012; Caras and Sanes 2015), even in the absence of neural competition. This is particularly evident with tasks such as AM detection that do not rely on binaural cues and are therefore less suscepti-

ble to asymmetric input and phase shifts between the two ears. The present study is the first in humans to show a lasting effect of bilateral CHL on AM detection thresholds, and is consistent with prior animal studies that demonstrated changes in binaural coding and perception (Rosen et al. 2012).

Our study is limited by the relatively small number of subjects when stratified by age, making subset analysis difficult. Despite low numbers, the distribution of ages was similar between the control and experimental groups, and the effects were statistically significant. We also faced a possible self-selecting bias, in which parents of children with ongoing hearing and speech concerns may have been more likely to participate in research on hearing and speech. Subjects were not selected based on this measure, and all experimental subjects had an objective history of OME-associated CHL documented in early childhood. It is possible that the children in our experimental group represent the more severely affected based on this self-selection bias, in addition to the bias inherent in the decision-making process to place tympanostomy tubes in the first place. There may be an intermediate group of children who had transient OME-related hearing loss but no long-term deficits. These children are less likely to have received tympanostomy tubes, and would not have been captured in our selection process. There was insufficient information in the medical records to quantify whether the magnitude or duration of hearing loss prior to tympanostomy tube insertion accounted for any of the variability in AM detection thresholds. All subjects in the experimental group underwent surgical tympanostomy tube placement in early childhood, and it is possible that the surgical procedure affected our results. Additional research with subsets of participants may be beneficial in exploring these issues.

Our study found that mild, transient hearing deficits due to OME-associated CHL can affect the time course of AM detection maturation. Children with a history of OME-associated CHL lagged behind their peers in development of this important component of speech and language processing. Additionally, these children were more likely to be evaluated for speech and language deficits. This points to a persistent, long-term effect of sensory deprivation that occurred during the critical period of speech and language development, with potential consequences for language-based learning and academic performance. The clinical implications are powerful, given how common middle ear disease is in children within this age range, and these results may inform the decision about when to consider surgical tympanostomy tube placement. Future studies are needed to clarify the neural processes underlying these effects.

COMPLIANCE WITH ETHICAL STANDARDS

This study was approved by the Research Subjects Review Board at the University of Rochester. Informed consent from the parent and verbal assent from the children were both obtained for every subject.

Conflict of Interest The authors declare that they have no conflict of interest. The project described in this publication was supported by the University of Rochester CTSA award number UL1TR002001 from the National Center for Advancing Translational Sciences of the National Institutes of Health. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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