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The Effect of Amplification on Cortical Synchrony in Children with Auditory Neuropathy Spectrum Disorder (ANSD)

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Abstract:

The benefit of hearing aids as a clinical intervention strategy for children with Auditory Neuropathy Spectrum Disorder (ANSD) remains controversial. The goal of this study was to determine whether amplification through hearing aid use increases cortical phase synchrony in children with ANSD. Using inter-trial coherence (ITC) of the EEG signal as our measure of cortical phase-locking, we examined differences in cortical phase synchrony in children with ANSD using a cross-sectional design (n=58) and a longitudinal design (n=16). Results in the cross-sectional portion of the study revealed no significant difference in ITC between unaided and aided children. The longitudinal data revealed no significant increase in ITC over time with hearing aid use. Interestingly, half of the subjects in the longitudinal sample showed a significant decrease in ITC from the unaided to the aided conditions. Overall, our results suggest that hearing aids are not a beneficial intervention strategy for increasing neural synchrony in ANSD and that amplification may actually reduce cortical phase-locking in some children with ANSD.
**Keywords:** Auditory Neuropathy Spectrum Disorder (ANSD), cortical auditory evoked potentials (CAEP), cortical phase synchrony, Inter-trial coherence (ITC), hearing aids

**Abbreviations:** Auditory Neuropathy Spectrum Disorder (ANSD), inter-trial coherence (ITC), sensorineural hearing loss (SNHL), inner hair cells (IHC), auditory brainstem response (ABR), cochlear microphonic (CM), otoacoustic emissions (OAE), Visual Reinforcement Audiometry (VRA), cortical auditory evoked potentials (CAEP)
1. SPECIFIC AIM AND HYPOTHESES

For individuals with Auditory Neuropathy Spectrum Disorder (ANSD) the benefit of hearing aids as a clinical intervention strategy remains uncertain. As ANSD is characterized by neural dys-synchrony, and the direct effect of hearing aids on neural synchrony is relatively unknown, the usefulness of amplification within this population remains ambiguous. Inter-trial coherence (ITC) is a direct measurement of cortical phase synchrony, which has been used to evaluate cortical phase-locking to auditory signals in children with ANSD and sensorineural hearing loss (SNHL; Nash-Kille and Sharma, 2014).

The Specific Aim of this study was to use ITC to measure cortical phase-locking in individuals diagnosed with ANSD, before and after hearing aid fitting, in order to determine the effect of amplification on cortical synchrony. We hypothesized that neural activity would be more synchronous in individuals with ANSD after hearing aid fitting relative to before hearing aid fitting. Furthermore, we conjectured that cortical phase synchrony would increase over time with hearing aid experience. The results of our study may carry clinical implications for audiological practice.

2. INTRODUCTION

Auditory Neuropathy Spectrum Disorder (ANSD) is a type of hearing loss in which the transmission of sound from the inner ear to the brain is disrupted due to dys-synchronous firing of the VIII nerve, which can be caused by abnormalities in the inner hair cells (IHC) within the cochlea, the synapse between the IHC and the VIII nerve, and/or the VIII nerve itself (i.e., fewer than normal nerve fibers or demyelination) (Starr et al., 1996). This dys-synchrony leads to
clinical findings such as absent or atypical auditory brainstem responses (ABR), including a robust cochlear microphonic (CM) that becomes inverted with reversal of the polarity of the stimulus, normal otoacoustic emissions (OAE), and absent acoustic reflexes (Starr et al., 1991; Berlin et al., 1998, 2003, 2010). Behaviorally, auditory nerve dys-synchrony results in differing levels of speech perception deficiencies, especially in the presence of background noise (Kraus et al., 2000; Sininger and Oba, 2001; Rance et al., 2012).

In infancy (i.e., prior to a child’s ability to perform behavioral audiometric tasks), auditory threshold estimates can be derived from ABR measurements (Hecox and Galambos, 1974). Audiologists use threshold estimations to determine the amplification needs of infants with sensorineural hearing loss (SNHL; Bagatto et al., 2005). However, for individuals with ANSD, ABR results are absent or abnormal (Berlin et al., 1998, 2003), and for this reason, the practice of hearing aid fitting in young children with ANSD has proven to be difficult (Berlin et al., 2010; Sharma et al., 2011).

In many clinics, it is customary for audiologists to fit individuals with ANSD with hearing aids as a first line of intervention, even though the issue of hearing aid fitting in ANSD remains somewhat controversial. That is, while some researchers advocate the use of hearing aids as a useful intervention for children with ANSD, others discourage this practice. For example, Rance et al. (2002) found that amplification provided benefit to approximately 50% of participants with ANSD, as measured by a significant increase in speech perception abilities. In contrast, Sharma et al. (2011) found that only approximately one third of children with ANSD in their study showed good cortical development and behavioral outcomes with amplification.
provision. Conversely, a study from Berlin et al, (2010) using speech and language development as the outcome measure, found that only 15% of children with ANSD benefitted from amplification. Thus it appears that while some children with ANSD may demonstrate benefit from hearing aid use, many clearly do not.

Starting at 6-7 months of age, clinical practitioners can use Visual Reinforcement Audiometry (VRA) to obtain behavioral auditory threshold estimates from infants. Because ANSD is hallmarked by abnormal or absent ABR results (Berlin et al., 1998, 2003), professionals may refrain from amplification provision until behavioral test results become available. Even then, auditory thresholds in those with ANSD are often more difficult to ascertain due to co-morbid developmental handicaps and fluctuating thresholds (Starr et al., 1996; Sininger and Oba, 2001; Cone-Wesson, 2004; Wolfe and Clark, 2008; Doyle et al., 1998). As a result, clinicians may take more time than typical to obtain several sets of thresholds to determine stability prior to fitting. An infant with ANSD may therefore remain unaided for one-year or longer before being fit with appropriate amplification, with detrimental consequences for auditory cortical development and plasticity (Sharma et al., 2011; Cardon and Sharma 2013).

Due to the lack of an ABR response, cortical potentials have proven useful in examining development of the central auditory system in children with ANSD (Kraus et al., 2000; Rance et al., 2002; Sharma et al., 2002). For example, using time-waveform EEG analyses, Sharma et al. (2011) and Cardon and Sharma (2013) have reported that ANSD children with normal P1 auditory cortical response latencies were more likely to show better development of behavioral auditory skills compared to children with delayed latency or abnormal P1 responses. Newer
studies using time-frequency analyses in EEG have reported that when resting cortical oscillations are interrupted by a stimulus event (such as a sound), the distribution of EEG phase becomes “phase-locked” to that event and such phase synchronization of brain oscillations can be determined by computing phase relations across single EEG trials using a measure called inter-trial coherence (Makeig et al., 2004). Inter-trial coherence (ITC), which reflects underlying cortical phase synchrony, has proven to be a sensitive indicator of the extent of the deficit in neural dys-synchrony in children with ANSD (Nash-Kille and Sharma 2014; Nash-Kille et al., 2014).

Because the underlying disorder in ANSD is neural dys-synchrony, it is reasonable to conjecture that intervention methods should increase synchronous activity of the auditory nervous system. Thus, if hearing aids are, in fact, a beneficial form of intervention for those with ANSD, auditory cortical synchrony should increase with their use. In this study, we employed ITC as a measure of cortical phase synchrony in order to determine whether amplification through hearing aids increases synchronous neural activity in the auditory cortex in children with ANSD. We hypothesized that peak ITC values would be greater in children with ANSD after hearing aid fitting as opposed to before intervention with amplification. In addition, we conjectured that ITC values would increase over time with continued hearing aid experience. Given our hypothesis, we performed ITC analysis to measure changes in cortical phase synchrony as a function of intervention with amplification in children with ANSD. Results of this study will provide brain-based evidence as to whether or not amplification increases cortical phase synchrony in pediatric ANSD populations.
3. METHODS

3.1. Participants
This study was performed as part of a retrospective review, of cortical auditory evoked potential (CAEP) data previously collected in Brain and Behavior Laboratory over a 15-year time period. CAEP data from a total of 58 children with ANSD were analyzed. First, a cross-sectional analysis was performed and participants were divided into two groups: 1) those who had not been fit with hearing aids at the time of testing (unaided group; n=28; mean age=2.58 years) and 2) those who had been fit with hearing aids at time of testing (aided group; n=30; mean age=3.15 years mean aided experience =1.35 years). In addition to a cross-sectional analysis, we examined results from 16 children with ANSD in whom we had longitudinal data. For this group of children, data were compared in the following test conditions: 1) prior to hearing aid fitting (unaided condition; mean age=1.57 years); 2) the first available test date following hearing aid fitting (first aided condition; mean age=1.95 years); 3) the last available aided test date (final aided condition; mean age=2.67 years). All participants were clinically diagnosed with ANSD using clinical measures (OAE, ABR, acoustic reflex testing) and referred for additional cortical auditory evoked potential testing in our laboratory.

3.2. Data Collection
CAEPs were recorded while participants watched a movie (on mute) while seated in a sound-treated booth in a chair or on the lap of their parents’. A synthesized speech stimulus /ba/ was presented to participants at 75 dB HL. The presentation of stimulus was consistent with other studies published by our group (Sharma et al., 1997; Sharma et al., 2011; Cardon and Sharma, 2013). CAEPs were recorded using a Compumedics Neuroscan evoked potential recording
system. Ag/AgCl electrodes were placed at CZ (active), which was referenced to an electrode placed on the mastoid, the forehead (ground), and an eye channel – superior orbit referenced to lateral canthus – used for artifact rejection. The specifications of this procedure are explained in previous studies by our group (Sharma et al., 1997; Sharma et al., 2011). Enough CAEP data were collected to ensure that a minimum of 250 CAEP sweeps would remain following artifact rejection for each CAEP recording.

3.3. Data Analysis
CAEP waveforms were segmented into epochs of 700 ms (100-ms pre-stimulus interval) and data were baseline corrected. Following baseline correction, epochs containing artifactual data (i.e., eye blinks, excessive muscle activity; ±100 microvolts) were removed. The remaining epochs were then imported into MATLAB using the EEGLAB toolbox for time-frequency analysis. Once in EEG lab, Inter-trial coherence (ITC) analysis was performed on the concatenated CAEP epochs for each participant using the parameters described in previous publications by our group (Nash-Kille and Sharma, 2014; Nash-Kille et al., 2014). Finally, the peak ITC value from the post-stimulus interval was recorded within each participants’ ITC plot.

3.4. Statistical Analysis
3.4.1. Cross-Sectional Analysis
A one-way analysis of variance (ANOVA) was used to compare the peak ITC values for the unaided and aided groups in the cross-sectional portion of the study.
3.4.2. Longitudinal Analysis

For the longitudinal portion of the study, a repeated-measures ANOVA was used to compare ITC results across the unaided, first-aided and last-aided conditions. In addition, observation of the data revealed two distinct patterns of ITC over time in the longitudinal group. That is, in half of the participants in this group, ITC decreased between the unaided and aided conditions (ITC-decreasing subgroup; n=8), while in the remaining participants ITC stayed the same or increased between the unaided and aided conditions (ITC-same or increasing subgroup; n=8). Given this observation, we divided the longitudinal group into two subgroups that reflected these patterns for further analysis. Thus, two additional repeated measures ANOVAs were used to compare the ITC results for the unaided, first-aided and last-aided conditions for the ITC-decreasing subgroup (unaided condition: mean age=1.03 years; first aided condition: mean age=1.38 years; last aided condition: mean age=2.17 years) and ITC-same or increasing subgroup (unaided condition: mean age=2.11 years; first aided: mean age=2.52 years; last aided: mean age=3.15 years) groups.

4. RESULTS

4.1. Cross-Sectional Results

One-way ANOVA performed to assess the differences in mean peak ITC values in the cross-sectional group revealed no significant difference between the aided and unaided conditions (F = 0.134; p = 0.716). In other words, cortical phase synchrony was essentially similar between the aided and unaided conditions in this group (see Figure 1).
Figure 1: Mean ITC peak values are shown for children with ANSD in the unaided (n=28) and aided (n=30) cross-sectional groups. The mean ITC values were not significantly different between the groups.

4.2. Longitudinal Results
A repeated measures ANOVA revealed no significant differences between the overall mean peak ITC values for the unaided, first aided, and last aided testing conditions in the longitudinal group (F = 0.938; p = 0.398; Figure 2). In contrast, the ITC-decreasing subgroup showed a significant main effect for mean peak ITC values (F = 8.812; p = 0.016; Wilks’ Lambda). Additional
pairwise comparisons yielded appreciable differences in mean peak ITC values between the unaided and both the first and last aided conditions (p < 0.01; Figure 3). Representative ITC plots from one subject from the ITC-decreasing group can be seen in Figure 4. In contrast to the ITC-decreasing subgroup, no significant difference was found between any of the test conditions for the ITC-same or increasing subgroup (p>0.05).

Figure 2: Mean ITC peak values are shown for children with ANSD in the longitudinal portion of the study (n=16) for the unaided, first-aided and last-aided test conditions. The mean ITC values were not significantly different between the conditions.
Figure 3: Mean ITC peak values are shown for a subgroup of 8 children in the *ITC-decreasing* subgroup of the longitudinal study, for the unaided, first-aided and last-aided test conditions. The first aided and last aided conditions were significantly different from the unaided condition ($p<0.01$).

Figure 4:
Figure 4: Inter-trial Coherence (ITC) plot for a representative subject in the ITC- decreasing subgroup of the longitudinal study. In each ITC plot the x-axis represents time, while the y-axis displays frequency. ITC strength is coded by color, with red being the strongest (i.e., most statistically significant) ITC and green representing the time-frequency regions with no significant coherence (see color bar to the right).

5. DISCUSSION
To determine whether hearing aid use may possibly increase synchronous neural activity in the auditory cortex, we examined differences in cortical phase synchrony across single trials of the EEG using inter-trial coherence (ITC), in unaided and aided conditions in children with ANSD. Our study yielded the following results: (i) we found no significant difference in mean peak ITC values between aided and unaided conditions in the cross-sectional group (n=58); (ii) data from the longitudinal portion of the study showed no significant difference in ITC values with hearing aid experience (n=16); (iii) half of the individuals from the longitudinal portion (n=8) showed a significant decrease in cortical synchrony from the aided to the unaided conditions.

ITC although a relatively new measure in EEG analyses, is considered a reliable measure of cortical phase-locking within the EEG signal (Makeig et al., 2004). Recent studies have also suggested that ITC is an important index of cortical phase synchronization in children with ANSD (Nash-Kille et al., 2014; Nash-Kille and Sharma, 2014). For example, Nash-Kille and Sharma (2014) compared ITC in a large group of 91 children with ANSD with age-matched children with sensorineural hearing loss (SNHL) and typical hearing. Using procedures identical to those used in the present study, Nash-Kille and Sharma reported that children with ANSD showed lower ITC values compared to children with normal hearing and SNHL. Furthermore,
Nash-Kille and Sharma reported that children with ANSD who had normal latency aggregate P1 cortical responses, showed significantly lower than normal ITC values, suggesting that ITC is a more sensitive measure of the neural synchrony deficit (relative to the averaged cortical response waveform) in children with ANSD.

In the present study, our results revealed no significant increase in ITC values after hearing aid fitting. The cross-sectional portion of the study revealed no significant difference in mean peak ITC values between unaided and aided children (Figure 1). The overall longitudinal mean peak ITC values for the unaided, first aided, and last aided testing conditions remained revealed no significant increase in ITC over time (Figure 2). This finding suggests that amplification through hearing aids does not appear to improve cortical phase synchrony in the majority of individuals with ANSD. Furthermore, a significant decrease in ITC values from the unaided to the aided points in half the longitudinal sample (Figures 3 and 4) suggests that in at least some children, cortical phase-locking may be decreased as a result of amplification. Overall, our results suggest that amplification does not appear to be a useful intervention strategy for children with ANSD as a whole. Our results are consistent with other reports in the literature, which generally discourage amplification as an effective intervention strategy for children with ANSD (Rance, et al., 2002; Berlin et al., 2010; Sharma et al., 2011).

A significant decrease in ITC values from the unaided to the aided points in half the longitudinal sample suggests that in at least some children, cortical phase-locking may be decreased as a result of hearing aid fitting. This decrease may be explained in several possible ways. For example, in ANSD, it is generally believed that lack of synchronous neural firing results in a
perceptually distorted auditory signal. This is reflected in the low speech perception scores (especially in noisy environments) typically seen in children with ANSD. Therefore, it is possible that hearing aids may serve to amplify the already distorted signal. Amplifying a degraded signal could increase the overall level of distortion at the level of the cortex, resulting in a decrease in the ability of cortical neurons to phase lock to the amplified distorted signal, further reducing auditory discrimination. This speculation is supported by anecdotal clinical reports of children with ANSD who dislike and often refuse to wear their hearing aids, presumably because amplification makes the already distorted signal sound worse to them.

A second possibility for the reduced coherence levels seen in some participants may be related to the different etiologies that underlie the neural dys-synchrony in patients with ANSD. These etiologies include, demyelination, axonal loss, and varying rates of neural firing throughout the fibers of the VIII nerve (Starr, Picton and Kim, 2001). Given the deviation in these causes of dys-synchrony, it is reasonable to believe that the auditory nervous systems of people with different etiologies may be differentially affected by amplification. That is, it is possible that for children with a particular etiology (such as neural demyelination), amplification could adversely affect cortical coherence; while for other underlying etiologies, amplification may not prove as harmful.

Thirdly, it is possible that under-amplification rather than amplification itself is causing this decrease in cortical phase synchrony. Fitting young ANSD children with amplification presents an enormous challenge for clinicians as: 1) ABR thresholds cannot be used to guide amplification selection; and 2) behavioral thresholds, when they can be obtained, are often
unreliable (Sharma et al., 2011). In clinical practice, we have observed that young children with ANSD may therefore be under-fitted with amplification. As a result of under-amplification, hearing aids may prove detrimental by acting as an earplug, simply occluding the ear and decreasing intensity of the incoming signal. Such a possible scenario may also explain our results of significantly decreased ITC values as a function of hearing aid fitting. Such a result would be consistent with a recent report showing that ITC decreases as a function of audibility in children with hearing loss (Nash-Kille and Sharma, 2014) and that increasing the amplitude of auditory signals results in increases in synchronous firing in the central auditory system (Javel, 1986).

Finally, it should be noted that not all children showed unchanged or decreased cortical phase-locking after amplification. Of the 16 longitudinal participants, two children showed an increase into normal ranges of cortical synchrony after hearing aid fitting (12% of the complete longitudinal dataset; 25% of those in the ITC-increasing subgroup within the longitudinal dataset). This finding is consistent with studies by both Berlin et al. (2010) and Sharma et al. (2011) who found that 15% and 33% of children with ANSD may benefit from amplification respectively. Thus, it is possible that a minority of children with ANSD may show an improvement in cortical synchrony and benefit in behavioral perception of sound when appropriately fit with amplification.

5.1 CLINICAL IMPLICATIONS
The present study adds to previous research literature (Berlin et al., 2010; Sharma et al., 2011) that suggests that benefit via amplification is limited in children with ANSD. Despite these findings, hearing aid fitting continues to be the first intervention strategy employed in most cases
of ANSD. While the literature indicates that some children with ANSD receive benefit from amplification, many do not. The current study provides evidence that neural synchrony may be worsened by hearing aid fitting in some cases. Given these results, there are at least two clinical areas that need to be targeted in future studies: improved hearing aid fitting techniques for children with ANSD; and alternative interventions that target the underlying dys-synchrony in children with ANSD as a first line of intervention.

6. CONCLUSION AND SUMMARY
The goal of this study was to determine whether amplification through hearing aids increases cortical phase synchrony in those with ANSD. Overall, we found no significant difference in cortical phase coherence between aided and unaided subjects, and no significant increase in cortical synchrony with hearing aid use over time. However, a subgroup of individuals showed a significant decrease in overall cortical phase synchrony following amplification provision. The underlying cause of the observed decreased cortical phase synchrony is unknown and warrants further investigation.
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disorder fitted with hearing aids and cochlear implants. *Clin Neurophysiol*, 125, 1459-1470.


