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The relationship between mismatch response and the acoustic change complex in normal hearing infants

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Abstract

Objective—To examine the utility of the mismatch response (MMR) and acoustic change complex (ACC) for assessing speech discrimination in infants.

Methods—Continuous EEG was recorded during sleep from 48 (24 male, 20 female) normally hearing infants aged 1.77 to 4.57 months in response to two auditory discrimination tasks. ACC was recorded in response to a three-vowel sequence (/i/-/a/-/i/). MMR was recorded in response to a standard vowel, /a/, (probability 85%), and to a deviant vowel, /i/, (probability of 15%). A priori comparisons included: age, sex, and sleep state. These were conducted separately for each of the three bandpass filter settings were compared (1-18, 1-30, and 1-40 Hz).

Results—A priori tests revealed no differences in MMR or ACC for age, sex, or sleep state for any of the three filter settings. ACC and MMR responses were prominently observed in all 44 sleeping infants (data from four infants were excluded). Significant differences observed for ACC were to the onset and offset of stimuli. However, neither group nor individual differences were observed to changes in speech stimuli in the ACC. MMR revealed two prominent peaks occurring at the stimulus onset and at the stimulus offset. Permutation t-tests revealed significant differences between the standard and deviant stimuli for both the onset and offset MMR peaks ($p < 0.01$). The 1-18 Hz filter setting revealed significant differences for all participants in the MMR paradigm.

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Conflicts of Interest

The authors have no additional conflicts to report.

Conclusion—Both ACC and MMR responses were observed to auditory stimulation suggesting that infants perceive and process speech information even during sleep. Significant differences between the standard and deviant responses were observed in the MMR, but not ACC paradigm. These findings suggest that the MMR is sensitive to detecting auditory/speech discrimination processing.

Significance—This paper identified that MMR can be used to identify discrimination in normal hearing infants. This suggests that MMR has potential for use in infants with hearing loss to validate hearing aid fittings.

Keywords

Acoustic change complex; mismatched response; infant; hearing loss; speech discrimination; sleep

1. INTRODUCTION

The importance of exposure to quality spoken language during the first year of life has been highlighted in studies of normal hearing (NH) infants and toddlers (Kuhl, 1991; Strange and Jenkins, 1978; Werker and Tees, 1984) and in studies of the later implications of this exposure on word learning and syntactic abilities (Graf Estes et al., 2007; van Leeuwen et al., 2008; Mueller et al., 2012). Research in infants with hearing loss (HL) has shown improved language outcomes when infants are fit with amplification and enrolled in early intervention by six months of age (Yoshinaga-Itano et al., 1998). In infants, speech discrimination has been assessed primarily utilizing behavioral measures, which can be less effective in young infants or infants with motor or other types of behavioral dysfunction. The advancement of non-behavioral, clinical assessments of speech discrimination has the potential to improve early amplification optimization and thus long-term language outcomes. This manuscript reports on an initial effort utilizing two evoked potential (EP) measures, Mismatch Response (MMR)¹ and Acoustic Change Complex (ACC) as potential approaches for assessing early infant speech discrimination.

Auditory evoked responses to acoustic deviance, including the MMR and ACC responses, likely are generated bilaterally in auditory cortex with contributions from frontal cortex (Giard et al., 1990; Alho, 1995), and appear to be lateralized to the left hemisphere when processing speech (Näätänen et al., 1997; Tervaniemi et al., 2000). MMR is presumed to be an automatic, pre-perceptual change-detection response (Näätänen and Alho, 1995) which can be elicited by concrete changes in stimuli, such as tone, frequency, pitch, duration, continuity, or interstimulus interval, as well as abstract changes, such as grammatical errors or errors in sentence structure (for a review see (Näätänen et al., 2008). MMR is measured by comparing evoked responses to repeated or familiar stimuli to those generated to the change and has been well defined in adults (Näätänen and Alho, 1995, 1997; Näätänen and Winkler, 1999) and children (Cheour et al., 1998; Kushnerenko et al., 2002; Kushnerenko et al., 2007; Mueller et al., 2012). It has also been correlated with behavioral measures of

¹The standard terminology for this response is the mismatch negativity (MMN). However, in very young infants this response may appear as a positivity at the scalp vertex (Kopionien et al., 2002; Trainor et al., 2003). Therefore, we use the term mismatch response (MMR) to highlight this difference and avoid potential confusion over the polarity/orientation of the observed responses.

discrimination in young children (Kraus et al., 1993) and later reading abilities (Leppänen et al., 2012).

The ACC is elicited when a change in one or more stimulus features is detected in a steady stream of information (Kaukoranta et al., 1989; Ostroff et al., 1998; Small and Werker, 2012; Tremblay et al., 2001, 2004, 2003). The ACC is analyzed by measuring P1-N1-P2 peaks of the EP in response to an acoustic transition such as /ah/ to /ee/ or from silence to sound onset. Characterization of the ACC in infants is limited. A recent study (Cone, 2015) utilized a paradigm that blended components of MMR and ACC methodologies to examine the relationship between EPs to a variety of vowel stimuli and a behavioral head turn in normal hearing infants aged 4-12 months of age. The EPs revealed neural encoding of the vowel stimuli; however, a clear relationship between the EPs and the behavioral response was not always detectable. Correlations were observed between the EP and conditioned head turn paradigm most robustly for /a-u/ presentation, likely due to the pronounced differences in acoustic saliency.

Several factors, including physiological and methodological, contribute to the detectability, measurement and, ultimately, the clinical utility of the MMR and ACC responses. Previous studies of infants have reported MMR waveform morphologies that are sensitive to variations in developmental age. These age-related morphological variations are reflected by changes in the spectral content of the MMR signals and by changes in the optimal scalp location for detecting the signals. For example, Trainor and colleagues (2003) reported observable deviations in a frontal, slow-wave positivity of the MMR beginning at age two months accompanied by a slower developing, parietal negativity that appears through age six months. Those deviations were revealed by comparing MMR waveform morphologies in two different bandpass filter conditions, 0.5-20 Hz and 3-18 Hz, supporting the notion that oscillatory brain activity generated from different brain regions may also reflect differences in the development of those regions.

Filtering settings during analysis of MMR and ACC also vary across types of stimuli used during testing. If we focus on studies that employed speech stimuli (the focus of the current study), settings employed have included: bandpass filtering 0.3-20 Hz (Friedrich and Friederici, 2011) and 1-30 Hz (Cone, 2015; Small and Werker, 2012); and low-pass filtering of 35 Hz (Cranford et al., 2003) and 40 Hz (Kraus et al., 1993). The high pass filter commonly used during sleep is 1 Hz (Holinger et al., 2000; Luck, 2005). Due to the different low-pass filter settings employed in the literature, the current study examined three different low-pass cutoffs (i.e., 18, 30, and 40 Hz) in combination with a high-pass filter of 1 Hz.

While differences in filter settings account for some differences in the detectability of MMR and ACC, detectability also varies based on age and stimuli type, highlighting the importance of methodological considerations to improve the clinical utility of such responses in individuals. For example, the type of stimuli used in testing is critical for the elicitation of detectable responses, particularly in early stages of development. Changes in speech sounds (Cheour et al., 2002, 1998) and pitch (Kushnerenko et al., 2002) elicit detectable responses earlier in life more reliably than do interstimulus gaps such as those used by Trainor and colleagues (2003). Additionally, rapid developmental changes of

anatomy and physiology can influence waveform morphology of the contributing EPs (He et al., 2009; Kushnerenko et al., 2002). The inherently dominant spectral power of the lower frequency, frontal slow-wave component can also diminish the detectability of higher frequency components that occupy smaller regions of space-time. These differences are exacerbated by the Brownian motion of the underlying EEG signals and influenced further by choices of recording and reference electrodes for signal analysis.

As MMR and ACC are elicited passively and in the absence of directed attention (Eponiemi et al., 2000; Leppänen et al., 1997; Näätänen et al., 2005), they have considerable potential as measures of early speech discrimination in infants. Although the MMR is considered a pre-attentive response, there has been debate on the modulatory effects of attention on it (Sussman, 2007). Studies with adults attempt to control attention by having participants attend a visual stimulus during testing, but controlling attention in awake/alert infants may be more problematic. “Sleep is the penultimate behavioral state of the fetus, neonate, and young infant” (Grigg-Damberger, 2016, p. 432). Infants under the age of six months spend up to 18 hours per day sleeping, and approximately 50% of that time is spent in rapid eye movement (REM) sleep. Studies of the MMR recorded from infants report stability in EP waveforms (latency, amplitude, *etc.*) across various states of alertness, including sleep (van den Heuvel et al., 2016; Kushnerenko et al., 2002; Kushnerenko et al., 2001) ability to assess ACC during sleep in young infants is unknown to the best of our knowledge at the time of writing this manuscript. Testing during sleep reduces the possible influence of attentional effects and has the added benefit of reducing data loss associated with movement artifacts. However, it is also possible that a change in EEG spectral power during different sleep states influences the overall detectability of concurrent auditory responses with overlapping spectra.

A physiological marker of speech discrimination in infants would provide a means to assess adequate amplification in children with hearing loss during the crucial early months of development. Ideally, we would like to employ a signal processing algorithm that is indifferent to changes in sleep state contributions and other non-experimental irregularities, or that at least accounts for such variation when testing for acoustic deviance responses. We defined three goals for this study: **1.** To examine whether speech-evoked auditory potentials (MMR and ACC) reveal responses to acoustic feature changes in sleeping infants, **2.** To examine the sources of variance most likely to affect the detectability of MMR and ACC deviance features, and **3.** To identify and describe experimental effects that may facilitate or impede the development of a physiological clinical marker of infant speech discrimination.

2. METHODS

2.1. Participants

Forty-eight (28 male, 20 female) typically developing infants aged 1.77 to 4.57 months ($M = 2.96$, $SD = 0.85$) participated in this study. Four were excluded due to poor recordings that rendered the data unusable. Thus, data from 44 infants (24 male, 20 female) are included in the analyses. This age range was selected based on the age at which infants are fit with hearing aids and the age at which clinical utility would be optimal. All infants had passed their newborn hearing screening, as measured by a click-evoked auditory brainstem response

(ABR) screening. Data analyzed in this study were drawn from a larger, ongoing project in which different experimental stimuli are assigned randomly to each participant upon enrollment. The infants included in this study were selected because they were assigned a common vowel contrast (/i/ and /a/) in both the MMR and ACC conditions. All infants were given written consent by a parent to participate in the study as approved by the Colorado Multiple Institutional Review Board.

2.2. EEG Procedure

Infants were placed in a comfortable rocker or held by a parent in a quiet, dim room to induce or aid sleeping during the test session. The rocker's motion was not active during the EEG recordings, but was active during EEG preparation or during breaks if the infant appeared to be waking. Eleven Ag/AgCl electrodes were placed on the scalp according to the International 10-20 system (F5, Fz, F6, C5, Cz, C6, P5, Pz, P6, M1, and M2) and were referenced to the nasion (Nz) for online signal acquisition. An additional bi-polar recording channel (EOG) was placed on the lateral canthus of the right eye and referenced to the superior orbit to monitor eye movement and waking. When a child was held by a parent, an additional ground electrode was placed on the parent's forearm. Continuous EEG was recorded with a sampling rate of 1000 Hz and filtered from DC-100 Hz during each experimental block using a Synamps2 EEG amplifier (Compumedics-Neuroscan, Charlotte, NC). During each experimental session, the infants' states of wakefulness and sleep were monitored and documented via behavioral observation of the infant and by continuous monitoring of the ongoing EEG for signs of wakefulness: increased motor activity concurrent with large, noisy signals across all channels, with exceptional activity in the frontal and ocular channels. Experimental stimuli were presented only when the infant was determined to be in a sleep state (i.e., there were no observable movements or behaviors to indicate wakefulness, and the ongoing EEG was judged by the researcher as sufficiently "calm").

2.3. Stimuli

Two naturally produced vowel sounds, /i/ ("ee" as in "bee") and /a/ ("ah" as in "law") were recorded from a female talker (Uhler et al., 2011, 2015) and used as the contrasting stimuli in both the MMR and ACC preparations (Figure 1). Speech stimuli were digitally edited and pitch-matched using the Adobe Audition CC 2015 (Adobe Systems Inc., San Jose, CA) and Melodyne (Celemony Software, Munich, Germany) audio editing platforms. Specifically, each sound was edited to a duration of 500 ms by deletion and/or insertion of the periodic vowel components in the center of the production, and then normalized to a root-mean-square (RMS) amplitude of 0.707 to approximate an equivalent perceived loudness and to minimize peak clipping in the digitally stored waveform. The two sounds were then pitch-matched by shifting each F0 (fundamental) frequency to a common frequency of 204 Hz and by shifting all other frequency information to match the original distances from F0. Pitch matching was performed via the default matching parameters in the Melodyne software environment. Melodyne is an audio editing platform used by professional audio engineers for vocal and other audio corrections with natural sounding results, as reported by adults in the laboratory who were also able to identify the speech stimuli correctly.

The use of pitch matching ensures that responses to acoustic changes occur because of differences in the distinguishing vowel features (i.e., the vowel formant frequencies) rather than some other distracting or otherwise learned feature, such as a slight variation in F0.

2.3.1. Stimulus Presentation—The same two speech sounds (/i/ and /a/, described above) were used as stimuli for both the MMR and ACC protocols, which were presented in separate experimental blocks for each preparation. Figure 2 shows a schematic representation of the stimulus presentation parameters for both ACC (Figure 2A) and MMR (Figure 2B). Although a wide variety of stimulus parameters can be manipulated for experimental comparison, the parameters for both the MMR and ACC in this study were selected under the constraints of maximizing the available testing time during the infants' sleep state, while being able to collect a sufficient number of test trials under multiple experimental conditions. The advantages and some consequences of this limited parameter manipulation are addressed in the discussion, below. All stimuli were presented from a sound field speaker at a level of 70 dBA measured at the location of the infant's head. If an infant awoke during testing or was restless, the trial count was suspended until the infant returned to a sleep state, and additional trials were then collected to ensure a minimum of 225 ACC trials or 60 deviant MMR trials per block after excluding trials from the sleep-wake and wake-sleep transition periods.

For each ACC block, stimuli were presented in trials consisting of three consecutive speech sounds: /i/ - /a/ - /i/, presented with periodic stimulus onset asynchronies (SOA, time from stimulus onset-to-onset) of 0.5 s for a total trial duration of 1.5 s. Throughout the block, trials were presented with periodic trial onset asynchronies (TOA, time from trial onset-to-onset) of 2.996 s. An average of 445 ($SD = 114$) trials was collected in each ACC block, comprising a total of about 1335 stimulus presentations per block.

For each MMR block, stimuli were presented in pseudo-randomly ordered trials consisting of a single speech sound, either /a/ (standard) or /i/ (deviant). For any given MMR trial, the probability of selecting the standard /a/ was 0.85, and the probability of selecting the deviant /i/ was 0.15 with the constraint that the deviant stimulus could not appear more than twice in succession. An average of 636 ($SD = 162$) trials was collected in each MMR block, comprising an average of 551 ($SD = 140$) standard trials and an average of 86 ($SD = 22$) deviant trials per block.

2.4. Data Processing

All data pre-processing and analyses were completed using the Matlab computing environment with tools from Matlab's Statistics, Machine Learning, and Signal Processing toolboxes, as well as from open-source EEGLAB (Delorme) and AORtools (Gilley) toolboxes for Matlab.

2.4.1 EEG Pre-Processing—The continuous EEG data from each participant and each experimental block were treated independently to a common pre-processing algorithm:

A linear detrending correction was applied separately to each channel's data to remove DC components.

Data from each channel were bandpass filtered with a high-pass cutoff of 1 Hz and each of three low-pass cutoffs (40, 30, and 18 Hz), and stored as three separate files (one for each low-pass cutoff). For the remaining analyses, all steps were performed separately on each of the three filtered data sets. This filter range was selected in order to encompass the range of frequencies to be included in later analyses, e.g., frequencies commonly associated with sleep and other slow-wave activity (<1 Hz) and the major EEG frequency bands: delta (1-3 Hz), theta (3-8 Hz), alpha (8-12 Hz), and beta (12-22 Hz).

The integrity of each channel was tested using two criteria: **a.** voltage thresholding and **b.** kurtosis probability thresholding.

- a.** Regions of continuous EEG containing voltage amplitudes of $\pm 150 \mu\text{V}$ and all points ± 0.25 s around those amplitude points were marked as containing voltage artifacts. If more than 20% of a channel's data points were artefactual AND the total number of artefactual points was greater than $2\times$ the number of artefactual points in the concurrent time range of all other channels, then that channel's data were excluded from further analysis.
- b.** The kurtosis of all non-artefactual points was computed separately for each channel, and any channel with a kurtosis exceeding 3 standard deviations from the mean of all channels' kurtoses was excluded from analysis.

By the above criteria, 14 of the 44 participants had one channel that was excluded from analysis (F5, 1; F6, 3; C6, 2; P5, 2; Pz, 2; P6, 4), one participant had two channels (C6 and P6) excluded from analysis. The most common channels to be excluded were parietal electrodes, most likely being the location closest to where the infant's head was laying during sleep. All group averaging procedures account for the actual number of participants' channels that are included in the average.

All data were re-referenced to the average of all channels (i.e., the average reference). Our ultimate goal of developing a clinical measure likely will depend on the extended use of differential amplification via fixed, bi-polar recording channels (e.g., channels commonly found in clinical diagnostic systems used for audiological measures such as the ABR). However, as the goal of the current study is to assess the sources of variance that contribute to response detectability, the average reference provides a best approximation of a "reference-free" or "bias-free" comparison between channels. Because the re-referencing transform is a linear operator, we can then determine the optimal differential montage as the combination of any two electrodes with the largest difference at points in which a significant amplitude displacement is expected (e.g., the latency of a known EP peak will have the largest difference between channels on opposite poles of a dipolar distribution).

After re-referencing, the data were downsampled to a sampling rate of 250 Hz.

Data were then "pre-epoched" by creating a copy of the data and segmenting each channel's data into trials with time epochs defined by the stimulus period of the trial and the inter-stimulus intervals (ISI, time from stimulus offset-to-onset) flanking that period. For ACC blocks, a pre-epoched trial was defined as -1.496 to 2.996 s relative to the onset of the trial. For MMR blocks, a pre-epoched trial was defined as -1.06 to 1.506 s relative to the onset of

the trial. The pre-epoch trials were marked for inclusion or rejection by two criteria: **a.** RMS voltage probability thresholding, and **b.** kurtosis probability thresholding. To ensure that deviant MMR trials were not rejected inadvertently due to experimental effects, the inclusion and rejection criteria were performed separately for all standard MMR trials and for all deviant MMR trials (acknowledging the inherent differences in inter-trial variances due to the different number of trials).

- a.** The RMS voltage amplitude for each pre-epoch trial was computed as the square root of the mean of the squared values in the epoch. Trials with RMS amplitudes exceeding 3 standard deviations from the mean of the RMS amplitudes of all trials were marked for rejection.
- b.** The kurtosis was computed separately for each trial. Trials with a kurtosis exceeding 3 standard deviations from the mean kurtosis of all trials were marked for rejection. The indices for all rejected trials were stored for each pre-processed block and, during the data analysis steps, any sequence of trials containing a rejected trial was excluded from analysis.

Finally, the pre-epoch RMS voltages retained from step 6 (i.e., not rejected) were used to compute the volume normalization coefficient as the mean of all RMS trial amplitudes across all channels. All EEG data in the set were then normalized by dividing each point by the volume normalization coefficient for that experimental block. Normalizing each experimental block improves analysis and interpretation of *relative effects* in the EEG voltage potential rather than to variations due to *global effects* such as differences in EEG frequency band power generated during periods of different active brain states (e.g., sleep vs. wake). From this point, we refer to each pre-processed, normalized block of EEG as an “EEG volume.”

2.4.2 Sleep State Analysis—To categorize sleep state during the recordings, a copy of each continuous EEG volume was transformed into a three-dimensional time-frequency (TF) representation (i.e., a “hypnoscogram”) separately for each channel for the entire recording session. Each TF analysis was performed via the continuous wavelet transform (CWT) using 64 log-spaced, 6-cycle Morlet wavelets with center frequencies (F) from 1 to 20 Hz. We note that each wavelet scale is described by its center frequency, because it cannot be defined explicitly by a single Fourier period; however, we simply refer to each scales’ “Frequency” with the implication that the true nature of the wavelets’ spectra is assumed. Each scale was normalized by dividing by its RMS amplitude, and then smoothed over a 15-second window (+/- 7 seconds from each point) to mimic the time binning used in standard sleep scoring. Each period in the recording was then assigned to a sleep state category of “REM” or “NREM” defined by the overall ratio of REM to NREM periods. High REM periods were defined as periods with increased theta and beta activity at the frontal electrodes concurrent with large amplitude eye movements, whereas low REM periods were defined by relatively diminished amplitudes across all spectral components. Blocks of trials where REM periods accounted for >50% of the block were then categorized as High REM blocks, while blocks where REM periods accounted for <50% of the block were categorized as Low REM blocks. These categories were then used in planned comparisons (described below) to test for the

effects of sleep state on the ERP waveforms. Representative hypnoscagrams from two subjects are shown in Figure 3.

2.4.3. Trial Sequences—To better understand the underlying processes that generate both ACC and MMR responses, we chose wide, overlapping analysis windows that represent sequences of the experimental stimuli. A summary of the sequences and analysis frames for both ACC and MMR is represented schematically in Figure 2. Analysis epochs were defined as –2.006 to 2.510 seconds for MMR, which includes three full trial periods and the ISI periods flanking them. For the ACC trials, analysis epochs were defined as –1.496 to 5.936 seconds, which includes two full trial periods and the ISI periods flanking them. Additional constraints were placed on the MMR epochs, in which we defined a sequence of trials as a “standard sequence” or as a “deviant sequence”. A standard sequence was defined as a series of three consecutive standard trials, (i.e., /a/ - /a/ - /a/), and a deviant sequence was defined as a series of three alternating standard and deviant trials (i.e., /a/ - /i/ - /a/).

The selection of a stimulus in the MMR paradigm is dependent on a probability function that inherently gives rise to differences in the inter-trial variances between standard and deviant sequences. To control for these variances, a subset of the standard MMR sequences was chosen randomly from the set of all MMR sequences such that the number of retained standard sequences matched the number of retained deviant sequences after trial rejection. The random selection of standard sequences was applied separately for each analysis of the data. Replication statistics for this procedure were performed to test the probability that a random selection of trials could result in a selection that misrepresents the true variability. The replication statistics are further described below.

2.4.4. Mean Responses and Global Field Power—The cortical auditory evoked potential (CAEP) responses were computed as the mean of all valid trial sequences, resulting in three mean sequences per channel: ACC, standard (S), and deviant (D). The MMR difference waveform was computed as the deviant minus the standard sequences (D-S). All means were computed using a non-parametric bootstrapping procedure ($n=10007$, random sub-sampling (80%) without replacement), which minimizes the influence of spurious trials in the mean estimation. Lastly, the global field power (GFP) was computed as the RMS magnitude at each point across all channels for the ACC, S, and D waveforms, and the GFP-MMR difference was computed as the deviant GFP minus the standard GFP.

2.5. Statistical Analyses & Results

In order to address our study goals, the data were analyzed in four stages: 1. *A priori* group effects comparisons, 2. Variability and replication tests, and 3. Experimental analyses. All statistical analyses were performed as a series of point-wise or pair-wise, non-parametric permutation t-tests (n -permutations = 10,007, random sampling with replacement), with p -values corrected for multiple comparisons using the false discovery rate (FDR) (Benjamini and Hochberg, 1995; Benjamini and Yekutieli, 2001; Groppe et al., 2011). All reported p -values represent FDR corrected values.

2.5.1 A Priori Comparisons—Prior to conducting experimental analyses, we tested for differences in the CAEP sequences for three comparison conditions: age (<3m vs. >3m), sex (female vs. male), and sleep state (High REM vs. Low REM). Each test was conducted separately for each of the three low-pass filter conditions (40, 30, and 18 Hz). These tests were conducted in order to determine whether additional factors should be included as covariates in the experimental analyses. For each comparison, we conducted three separate tests:

1. Point-wise permutation t-tests of the ACC, standard (S), deviant (D), and MMR (D-S) waveforms between each comparison group, separately for each channel,
2. Point-wise permutation t-tests of the GFP waveforms between each comparison group, and
3. Permutation t-tests of the total RMS sequence magnitudes for each channel, with each channel treated as observations for a subject.

Results of the a priori comparisons revealed no significant differences for any of the three comparisons from either of the two tests (point-wise or RMS). *P*-values for the RMS sequence differences are reported in Table 1, and group-mean GFPs for the ACC, deviant sequence, and MMR are plotted for each comparison in Figure 4a-c. GFPs are shown for the 1-18 Hz condition, as results were comparable for all three filter conditions.

2.5.2. Variability and Replication Tests—A common concern in EEG research is the presence of “bogus effects”, effects that result from extraneous factors such as random group effects, analysis methods, electrode preparation, etc. (for a thorough review, see Luck and Gaspelin, 2017). We performed two analyses in order to assess the probability of finding bogus effects in these results:

1. We assessed the probability of a random group effect by performing a series of comparisons using the same statistical procedures described for the *a priori* comparisons, above. In this case, comparison groups were chosen by randomly dividing the subjects into two groups ($n = 22$ per group). We repeated this test 10,007 times in order to compute the probability that any two randomly selected groups of subjects would yield significantly different MMR or ACC sequence waveforms. Results of this test suggest that the probability that two randomly selected groups will yield significantly different response waveforms is less than 1% for both MMR and ACC. The 95% confidence intervals for the response means of all selected groups ($2 \times 10,007$) are plotted in Figure 4d.
2. We assessed the probability that the variability represented by a randomly selected sub-set of standard MMR sequences was different than
 - a. The variability represented by the corresponding set of deviant sequences, and
 - b. The variability represented by some other randomly drawn subset of standard sequences.

For each subject, the normalized kurtosis of each available trial sequence (after artifact rejection) was computed separately for each channel. Non-parametric bootstrap aggregating (“bagging”) with sub-space sampling (n -boots = 10,007, n -bags = 1,009, sub-space proportion = 0.8) was used to estimate the means and 95% confidence intervals for a series of bags (sub-samples of the sequences) with sub-sample sizes equal to the number of deviant MMR sequences in the set. Probability (PDF) and cumulative (CDF) density functions were computed separately on the set of kurtosis values selected for each bag to estimate the probability that a set of selected sequences will contain a sequence with some known kurtosis (or greater). PDFs and CDFs were computed via kernel density estimation (Botev et al., 2010). Figure 4e shows the estimated PDF of sequence kurtosis for each subject and for the group average for both deviant and standard MMR sequences.

The probability of selecting a subset of standard sequences with variability that exceeds the set of deviant sequences (2a) was computed by the proportion of bags with kurtosis means greater than the upper 95% confidence interval of the deviant set. Results of that test suggest a probability of $p = 0.1551$ (~15% chance) that the mean kurtosis for a random subset of standard sequences will be greater than the mean kurtosis for the deviant sequences. Additionally, the mean of all upper 95% confidence intervals never exceeded a kurtosis value of 4 for either the deviant or standard sequences.

The probability of selecting a subset of standard sequences with variability that exceeds that of some other randomly selected subset (2b) was computed as the proportion of bags with kurtosis means greater than the mean upper 95% confidence interval of all bags. Results of that test suggest a probability of $p = 0.0337$ (~3% chance) that the mean kurtosis for a random subset of standard sequences will be greater than the mean of all upper 95% confidence intervals computed from the standard bags. Taken together, these results suggest that any differences in variability between a subset of standard and deviant sequences are likely to be within an acceptable range for further comparison, and are not likely to skew or bias any observed statistical differences between sequence types.

2.5.3. Experimental Analyses—The experimental analyses were designed to address our two primary questions:

1. Does the CAEP (i.e., the MMR or ACC) provide reliable responses for assessing whether a stimulus has been detected?
2. Does the CAEP provide reliable responses for assessing whether two different stimuli have been discriminated?

To address these two questions, we performed a series of pointwise permutation t-tests between pairwise segments of the CAEP responses. Comparisons were performed at the subject-level by permuting the available sequences and at the group-level by permuting the mean responses of each subject. An alpha threshold of $p < 0.05$ was used to threshold the p-values for all experimental comparisons. For subject-level analyses, we report the percentage of subjects with p-values less than the threshold. For group-level analyses we report the p-values for all p-values below the threshold. Pairwise segment comparisons used to address the experimental questions above were considered planned comparisons, and are described

in the results section below. All other pairwise comparisons were considered as post-hoc comparisons for further discussion.

3.0 Results

3.1. ACC

3.1.1. ACC Detection—Each ACC sequence was divided into five segments of 0.5 seconds: one segment in the pre-stimulus baseline period, one segment from the onset of each vowel (i.e., three “stimulus-on” segments), and one segment from the offset of the last vowel in each sequence. Planned comparisons for ACC stimulus detection (question 1) included comparisons between the pre-stimulus baseline period and each of the three stimulus-on periods (/i/-/a/-/i/). Results of that analysis revealed 100% of subjects with a significant difference ($p < 0.05$) between each of the stimuli and the pre-stimulus baseline period. Significant group differences ($p < 0.05$) were also observed between the pre-stimulus baseline period and each of the stimulus-on periods (see Figure 5). There were no significant differences between the three low-pass filter conditions for these responses. These results suggest that the ACC response is adequate for assessing stimulus detection in this population at both the individual and group levels of analysis.

3.1.2. ACC Discrimination—Planned comparisons for ACC stimulus discrimination (question 2) included comparisons between the intermediate /a/ stimulus-on period and each of the adjacent /i/ stimulus-on periods. Results of that analysis revealed only three participants with significant differences in any of the comparisons ($p < 0.05$). Further, those significant differences were inconsistent between the comparisons, such that the /i/-onset vs. /i/ comparison was found to be different as often as either of the comparisons including the /a/ stimulus. Similarly, there were no group-level differences for any of the comparisons including the /a/ stimulus. The only consistent group differences occurred between the two /i/ stimuli, or at the edges between stimuli (i.e., stimulus transition periods). There were no significant differences between the three low-pass filter conditions for these responses. These results suggest that the ACC response is not adequate for assessing stimulus discrimination in this population, at least for this vowel series, during sleep.

3.2. MMR

3.2.1. MMR Detection—For the MMR, segment sizes and comparisons were different for each of the experimental questions. To test for stimulus detection (question 1), each MMR sequence was divided into nine segments of 0.5 seconds around each of the three stimuli in the sequence: one segment in each pre-stimulus baseline period, one segment from the onset of each stimulus, and one segment from the offset of each stimulus. Planned comparisons for MMR stimulus detection (question 1) included comparisons between each of the stimulus-on periods and the preceding baseline periods for each of the stimuli in the deviant MMR sequence. Results of that analysis revealed 100% of subjects with a significant difference ($p < 0.05$) between each of the stimuli and the pre-stimulus baseline periods for both the standard and deviant sequences. Significant group differences ($p < 0.05$) were also observed between the pre-stimulus baseline period and each of the stimulus-on periods. There were no significant differences between the three low-pass filter conditions for these responses.

These results suggest that the MMR response is adequate for assessing stimulus detection in this population at both the individual and group levels of analysis.

3.2.2. MMR Discrimination—To test for stimulus discrimination (question 2), two sets of segment comparisons were performed. First, each MMR sequence was divided into three segments of 1.5 seconds around each of the three stimuli. Each segment contained the 0.5 second pre-stimulus baseline interval, the 0.5 second stimulus-on interval, and the 0.5 second offset interval for each of the stimuli in the sequence. Planned comparisons for MMR stimulus discrimination (question 2) included comparisons for the deviant MMR sequences the target deviant response (/i/) and each adjacent standard response (preceding /a/ or subsequent /a/). Second, pointwise comparisons between the full epoch of standard and deviant sequences were treated as planned comparisons for stimulus discrimination.

3.2.3. MMR Group Results—Group average MMR waveforms of the standard and deviant waves for each electrode for the 1-18 Hz bandpass filter setting for all participants for long and short windows can be seen in Figure 4. All marked peaks are based on MMR difference values that are significant ($p > 0.05$), then the peak amplitudes and latencies were marked after significance was determined. In order to facilitate comparisons between group and individual MMR response, the peak amplitudes and latencies were averaged across the individual frontal, central, and parietal electrodes to create regions of interest. The significant values are reported in order of latency. The mean latency and amplitude was 78 ms and 2.02 μV for the parietal region, 244 ms and 3.09 μV for the central region, 296 ms and $-5.847 \mu\text{V}$ for the right mastoid, 304 ms and $-3.937 \mu\text{V}$ for the left mastoid 366 ms, and 2.585 μV , respectively, for the frontal region.

We then performed a group-level analysis using permutation t-tests (standard vs. deviant, n -perms = 10,007) of the averaged MMR waveforms (Figure 6). Results of that analysis revealed a pattern of significant differences between both stimuli at about 250 to 500 ms. Additional differences occurred at 733 ms and 1007 ms, which may be similar to the offset responses reported by (Baltzell and Billings, 2014).

3.2.4. MMR Individual Results—For each subject, we performed a permutation t-test (n -perms = 10,007) between the standard and deviant trials at each time point (Figure 5). Tests were performed separately for each MMR condition (vowel contrast). Results of that analysis revealed statistically significant differences for all 44 participants at the individual level for the vowel contrast ($p < 0.05$, FDR corrected). However, peak latencies for these significant differences were highly variable and may reflect the effects of different sleep states. We also looked at the effect of the three bandpass filter settings (i.e., 1-18, 1-30, and 1-40 Hz) and two epoch settings (“long,” -2.006 to 2.5010 and “short,” -500 to 1506 ms) on the detectability of significant individual MMR responses. We first wanted to characterize the effect of these filter settings on the proportion of significant data points across the entire trial window. For each of the bandpass filter settings, data were separated into bins, the size of which was determined by multiplying the inverse of the low pass filter (e.g., 18 Hz) by $\frac{1}{2}$ (e.g., 28ms for the 1-18 Hz filter setting). Table 2 shows the mean proportion of significant data points for each bin across all participants for the long (a) and short (b) epochs. The

results of binning for the 1-40 Hz and 1-30 Hz long and short epochs are provided in Supplementary Table S1.

Additionally, in order to characterize individual MMR responses and facilitate comparison across existing literature, we looked specifically at the responses occurring between -100 ms and 450 ms relative to the onset of the stimulus. Requirements for verification within each subject included activity at frontal and/or central electrode sites AND activity at the mastoid in the bins encompassing the stimulus presentation. Those results are presented in Table 3. All of the infants showed significant responses for the 1-18 Hz bandpass filter in both the long and short epochs. However, the proportion of infants with significant MMR responses for the 1-30 Hz bandpass filter setting was 79.5% for the short epoch and 84.1% for the long epoch. Similar results were obtained for the 1-40 Hz bandpass (79.6%, short epoch; 84.1%, long epoch).

4. Discussion

4.1 Speech discrimination responses

These experiments assessed the feasibility of using ACC and MMR stimulus paradigms to detect speech discrimination responses in the EEG of sleeping infants. Prior barriers to the detection of such responses in a clinical population stemmed from experimental, analytical, and physiological variability that are inherent to EEG data collection and analysis. ACC was present to the onset of each vowel sound, but there was no difference between the two vowel sounds (i.e., /i/ vs. /a/) at an individual or group level ($p > 0.05$). From this, we conclude that the ACC alone is not adequate for differentiating responses from different speech sounds in sleeping infants. The oscillatory response pattern in the ACC, which included four pseudo-periodically spaced peaks, is interesting enough that it warrants further research. At this time its meaning is unclear. Taken with the results of the MMR experiment, it is possible that combining the ACC with a MMR-like paradigm (e.g., standard and deviant stimuli) would provide information about discrimination within an entrained auditory pattern; information that would be both clinically and experimentally useful (e.g., see Cone, 2015).

Figure 6 illustrates responses across electrode sites, which allows comparison of changes by in voltage responses to the standard stimuli and deviant stimuli. MMR response is shown below each standard and deviant response. In addition to the MMR response, there is an additional peak following the MMR peak; it is unclear what this third peak represents. One possibility might be that the initiation of a response from any given stimulus sets up a spatial-temporal oscillation containing information about the stimulus properties, and that the absence of a stimulus that would follow causes a rapid dampening of that oscillation resulting in what appears to be an off-set peak (Freeman and Vitiello, 2006; Gilley et al., 2017). This is further supported by the findings in the ACC results in which a fourth peak appears after the offset of a periodic stimulus sequence (as described above). Another explanation may be that this peak represents the stimulus offset responses and is, perhaps, generated by a different group of neurons that are in the same general region (Baltzell and Billings, 2014). Therefore, this cannot be resolved with low resolution EEG.

4.2. Sources of Variance

MMR results showed group differences ($p < 0.001$) for the vowel contrast, and for 100% of participants at the individual level for the vowel contrast ($p < 0.05$, FDR corrected) for the 1-18 Hz bandpass filter setting. Whereas this percentage was 79.5% for 1-30 Hz, and 84.1% for 1-40Hz for the long epoch. However, peak latencies for these significant differences were highly variable. These sources of variability may reflect the effects of different sleep states or simply individual variability. The frequency spectrum of the human EEG, and to a lesser extent in averaged ERPs, follows a general 1/f pattern such that low frequencies contribute more overall power to the EEG than higher frequencies. During sleep, EEG in young children contains more low frequency power in the delta and theta frequency bands compared to older children and adults (Kurth et al., 2013). However, the exact contributions of these frequency bands also varies by sleep stage (Portas et al., 2000), and some infants (~35%) may exhibit transient theta-alpha bursts in the EEG (Hayakawa et al., 1987). Although auditory ERPs reveal normal auditory processing during sleep and through the sleep-wake cycle (Otte et al., 2013; Portas et al., 2000), detecting ERP differences in higher frequency bands (e.g., as in the MMR response) can be challenging given the smaller contributions to the EEG at those frequencies and to the unknown variability in the center frequency or “characteristic operating frequency” (COF) of each band (Gilley et al., 2014). For example, auditory responses likely represent combined activity in the theta and beta bands (Gilley et al., 2014, 2016), which overlap in frequency with the changes in theta power that occur during sleep. Wide variations in theta power would likely bias any analysis that relies on amplitude comparisons or band-power comparisons. While it is possible that implementing a dynamic filter to the individual responses may improve MMR signal detection, such a filtering scheme would require a wider variety of experimental stimuli to ensure robustness.

Based on the findings reported here, MMR shows promise as a tool to assess speech discrimination during early infancy at an individual level once sources of variability are more clearly identified.

4.3. Study Limitations

Given the significant group and individual differences in the MMR for /a/-/i/ contrast, we conclude that the MMR has potential as a biomarker for speech discrimination. However, at the individual level these differences may be difficult to identify because of the large variability in individual participants (Bishop and Hardiman, 2010).

4.3.1. Experimental effects that may impact outcomes—Sources of individual variability likely are driven and constrained by experimental effects, analysis effects, and physiological differences in the population. For example, when designing an MMR task a decision is made regarding the proportion of deviant trials that will appear during the task. When designing this protocol, we considered outcomes from pilot data and the results of previous studies, and the effects of this decision may impact the size of the ERP response during deviant trials due to changes in stimulus expectancy (Lieder et al., 2013). To avoid an orienting response, we assessed MMR during sleep, and careful consideration was made to

acquire enough deviant trials (Sokolov, 1963), but not so many that would lead to no difference if the proportion is too high.

As with any oddball paradigm, the number of stimulus permutations for an experiment likely exceeds the amount of time that can be spent in any one recording session. Extended from this, one major limitation of this study is the lack of comparison conditions for both the ACC and MMR in which the same vowel sounds were alternated as standards or deviants. In the case of the ACC paradigm, a stimulus sequence with no vowel change would provide additional support for the present findings. Here, given the unpredictability of infant sleep cycles (especially when being monitored in a strange laboratory), we chose to focus on comparisons from two different types of evoked responses, the MMR and ACC. While other comparisons are certainly just as interesting, we feel that these results provide valuable insight to our questions about speech discrimination.

5. Conclusion

Speech discrimination is necessary for the development of spoken language, yet at this time a clinical tool is not available to validate hearing aid fittings in early infancy. While this paper reports findings in normal hearing infants, the use of MMR has potential for use in infants with hearing loss to validate hearing aid fittings. Identifying a tool to assess infant speech perception shortly after hearing aids are fit would be valuable to establish that the hearing aids are providing infants with the ability to discriminate speech.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

1. Acoustic change complex (ACC) and mismatch response (MMR) can be assessed during sleep in infants.
2. ACC is not sensitive to measuring speech discrimination in sleeping infants.
3. MMR is sensitive to measuring speech discrimination in individual sleeping infants.

Speech Sounds

Figure 1.

Waveform and spectrogram for /a-i/ stimuli.

Top panels illustrate the amplitude waveform and bottom panels illustrate the frequency spectrogram for the experimental stimuli.

Figure 2. ACC and MMR sequence and segment analyses. Parameters for presentation sequences for the ACC (2A) and MMR (2B) stimuli representing the SOA and ITI. Below the presentation sequence parameters analysis periods (time in seconds) are shown. The overlapping time windows allow two full ISI trials flanking, with “Pre” representing the time prior to the initiation of the trial, followed by the stimulus onset (“Stim”) and offset (“Off”). Additionally, for the MMR (Panel b), sequence parameters (“S” = Standard stimulus Sequence, “D” = Deviant stimulus sequence, and “D-

S” = MMR response) as well as segment (“s” = standard stimulus, “d” = deviant stimulus; “d-s” = MMR response) are shown.

Figure 3.
Relative sleep hypnoscogram.
Representative low (<50% REM) and high (>50%) REM states for frontal and parietal electrodes from two participants. Classification was based on oscillatory patterns represented by the center frequency (1-20 Hz).

Figure 4.

Comparison of ACC and MMR sources of variance.

Panels a-c show comparisons of GFP for the 1-18 Hz condition for age (a), sex (b), and sleep state (c). Panel d shows 95% Confidence Intervals for response means for all randomly selected groups. Panel e presents the estimated probability (PDF) of sequence kurtosis for individuals and groups.

– comparisons that provide information about stimulus discrimination – and are represented by green shading for statistical plots. The panel in the lower left corner (outlined in red) shows the mean GFP (upper sub-panel) for each of the filter conditions, and the point-wise comparisons for the GFP responses between each of the bandpass filter conditions (lower sub-panel; comparison labels indicate the low-pass cutoff in Hz; n.s.=not significant). The panel in the upper left corner (outlined in red) shows the stacked GFP waveform segments for the 1-18 Hz bandpass condition. The ordinate axis represents relative magnitude and the abscissa represents relative segment time. Each segment has been baseline shifted to the minimum relative magnitude within the segment. Colors corresponding to each of the segments are shown below the axis in the same panel. The panels in the upper and lower right corners of the figure (outlined in light blue) contain the plot keys and other visual information for interpreting the channel plots.

Figure 6.
Mismatched Response.

Group averaged MMR responses for the 1-18 Hz bandpass filter conditions for individual electrodes. In each channel plot, the blue line represents the standard stimulus, orange represents the deviant stimulus, and the purple represents the MMR (deviant-standard). The ordinate axis of each upper sub-panel represents the relative amplitude of the waveform normalized across all channels, and the abscissa represents trial time in seconds with time 0 marking the onset of a trial and vertical dotted lines drawn in 0.5 second intervals aligned to the onset of each stimulus in the trial. The lower sub-panel of each channel plot represents a segment-wise and point-wise comparison matrix for each of the labeled segments in the MMR waveform for the 1-18 Hz bandpass condition and plotted as a distance matrix. The columns of each comparison matrix are aligned in time along the abscissa such that each column has a width of 0.5 seconds (segment-1 time), and the time within each cell of the matrix represents a pointwise comparison between two segments relative to the segment onset times. The upper triangle of the comparison matrix represents the group-level comparisons and shows significant p-values ($p < 0.05$) as vertical shaded bars (darker color indicates lower p-values), while the lower triangle of the matrix shows the percentage of subjects with significant individual differences ($p < 0.05$) for each segment comparison. The ordinate axis of each cell in the lower triangle represents percentage, and a dotted horizontal line in each of these cells shows the 50% mark. Cells in the outer rectangle of the matrix represent comparisons to the standard and deviant – comparisons that provide information about stimulus detection – and are represented by purple shading for statistical plots. Cells in

the inner rectangle of the matrix represent comparisons between each of the change stimulus segments – comparisons that provide information about stimulus discrimination – and are represented by green shading for statistical plots. The panel in the lower left corner (outlined in red) shows the mean GFP (upper sub-panel) for each of the filter conditions, and the point-wise comparisons for the GFP responses between each of the bandpass filter conditions (lower sub-panel; comparison labels indicate the low-pass cutoff in Hz; n.s. = not significant). The panel in the upper left corner (outlined in red) shows the stacked GFP waveform segments for the 1-18 Hz bandpass condition. The ordinate axis represents relative magnitude and the abscissa represents relative segment time. Each segment has been baseline shifted to the minimum relative magnitude within the segment. Colors corresponding to each of the segments are shown below the axis in the same panel. The panels in the upper and lower right corners of the figure (outlined in light blue) contain the plot keys and other visual information for interpreting the channel plots.

Table 1

Planned comparisons for Sex, Age, Sleep Status, and Random Grouping for 1-18 Hz, 1-30 Hz, and 1-40 Hz Band-pass Filters.

Variable	Comparison Group 1	Comparison Group 2	ACC		
			1-18 Hz	1-30 Hz	1-40 Hz
Sex	Female (N=24)	Male (N=20)	0.276	0.298	0.320
Age	< 3 mo (N=20)	3 mo (N=24)	0.106	0.097	0.090
Sleep	AS > QS (N=21)	AS < QS (N=23)	0.182	0.189	0.200
Random	R1 (N=22)	R2 (N=22)	0.147	0.136	0.143

Variable	Comparison Group 1	Comparison Group 2	MMR		
			1-18 Hz	1-30 Hz	1-40 Hz
Sex	Female (N=24)	Male (N=20)	0.215	0.233	0.201
Age	< 3 mo (N=20)	3 mo (N=24)	0.092	0.089	0.100
Sleep	AS > QS (N=19)	AS < QS (N=25)	0.189	0.223	0.201
Random	R1 (N=22)	R2 (N=22)	0.161	0.175	0.234

Table 2

a. Proportion of Significant Points per Bin^{*} by Cortical Region^{} for the 4.5-second Sample using the 1-18 Hz Band-pass Filter.**

Start Time	Time	Frontal	Central	Parietal	Left Mastoid	Right Mastoid
-2.006	-1.730	17.63	13.93	13.43	5.52	5.94
	-1.446	20.78	15.24	15.96	3.81	4.12
	-1.162	15.46	12.01	13.70	3.59	5.29
	-0.878	16.56	14.17	12.42	5.17	4.48
	-0.594	20.29	13.82	8.60	3.46	4.77
	-0.310	17.49	10.68	11.04	2.92	6.33
	-0.026	14.16	13.87	15.55	2.92	4.51
	0.258	19.36	22.90	18.31	9.84	11.53
	0.542	25.59	25.62	19.3	15.4	14.35
	0.826	17.42	16.04	11.39	8.25	9.58
	1.110	12.08	13.30	11.38	5.21	3.99
	1.394	14.76	15.73	12.13	5.65	1.82
	1.678	14.94	20.41	19.25	7.14	5.26
	1.962	15.62	20.03	12.04	3.46	6.62
	2.246	14.30	15.98	14.95	5.11	7.05
	2.500	11.73	10.50	11.68	3.33	4.80

b. Proportion of Significant Points per Bin^{*} by Cortical Region for the 2-second Sample using the 1-18 Hz Band-pass Filter.

Start Time	Time	Frontal	Central	Parietal	Left Mastoid	Right Mastoid
-.502	-0.230	14.90	11.72	13.05	3.8	7.08
	0.056	14.03	14.51	15.49	3.31	3.67
	0.340	23.47	24.74	17.82	15.03	17.5
	0.624	22.37	22.44	16.49	15.16	12.44
	0.908	17.05	15.81	9.25	6.75	7.27
	1.192	11.40	13.60	11.20	6.10	3.83
	1.500	15.97	16.75	15.61	5.92	2.24

Notes:

Cortical regions were defined as follows: Frontal: F5, FZ, F6; Central: C5, CZ, C6; Parietal: P5, PZ, P6

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