Visual stimulation enhances auditory processing in 3-month old infants and adults

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Behavioral work demonstrates human infants are sensitive to a host of intersensory properties and this sensitivity promotes early learning and memory. However, little is known regarding the neural basis of this ability in infants. Using event-related potentials (ERPs) with infants and adults, we show that during passive viewing auditory evoked brain responses are increased with the presence of simultaneous visual stimulation. Results converge with previous adult neuroimaging studies, single-cell recordings in non-human animals, and behavioral studies with human infants to provide evidence for an elevated status of multisensory stimulation in infancy. Furthermore, these results may provide a neural marker of multisensory audio-visual processing in infants that can be used to test developmental theories of how information is integrated across the senses to form a unitary perception of the world.

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Most objects and events can be simultaneously explored in a variety of sense modalities. Since the 1960’s researchers have demonstrated that human infants are sensitive to those properties of objects and events that can be redundantly presented in more than one sense modality (see Bahrick, Lickliter, & Flom, 2004; Lewkowicz, 2000a; Lickliter & Bahrick, 2004; for reviews). Between 2- and 5-months of age, for example, human infants perceive the rhythm, tempo, and synchrony common to visible and audible stimulation from events such as an object striking a surface (e.g., Bahrick, 1988, 1992; Bahrick, Flom & Lickliter, 2002; Bahrick & Lickliter, 2000). Likewise, infants detect the temporal synchrony uniting audible and visible speech (e.g., Lewkowicz, 1996; 2000b) and detect expressions of affect across faces and voices (Walker-Andrews, 1986). Infants’ sensitivity to the redundant and synchronous bimodal auditory and visual stimulation characterizing a bouncing ball, for example, specifies that the two sources of stimulation “go together” and constitute a unitary event (e.g., Bahrick, 1983, 1988; Bahrick & Lickliter, 2002; Bahrick & Pickens, 1994; Lewkowicz, 1992, 1996, 2000b; Spelke, Born, & Chu, 1983). Thus, infants’ sensitivity to redundant and synchronous multimodal information is important because it promotes early learning about various objects and events. While a growing body of research exists regarding infants’ behavioral capacity for intersensory perception and their perceptual sensitivity to redundant multimodal stimulation (see Lewkowicz, 2000a; Lickliter & Bahrick, 2004; Walker-Andrews 1997 for reviews), little to no research has examined human infants’ neurophysiological response to multimodal stimulation. The purpose of the current experiment is to provide a first step in examining infants’ neurophysiological response to multimodal and unimodal stimulation.

Much of what we do know about the neural basis of multisensory perception, however, comes from work using non-human animals and often reveals an “elevated” status of multimodal
stimulation compared to unimodal stimulation. For instance, single cell recordings from neurons within the deep layers of the superior colliculus in 30-day old cats reveals that firing rates during bimodal audio-visual (AV) stimulation are exponentially greater (i.e., superadditive) than during unimodal auditory (A) and visual (V) stimulation (Wallace & Stein, 1997). Similar patterns of superadditivity have been demonstrated with monkeys (e.g., Jay & Sparks, 1984; Wallace, Wilkinson, Stein, 1996) as well as guinea pigs, mice, hamsters and rats (see Stein, Jiang, Stanford, 2004 for a review).

Research with human adults also shows a similar elevated response to multimodal stimulation compared to unimodal stimulation. For example, when adults are asked to identify objects based on auditory information, visual information, or concurrent auditory and visual information, the amplitude of early sensory evoked potentials elicited by bimodal AV stimulation are larger than the sum of the responses elicited by unimodal A and V stimulation (e.g. Giard & Peronnet, 1999; Santangelo, Van der Lubbe, Olivetti-Berlardinelli, & Postma, 2008). Specifically, increased electrophysiological activity in the sensory-specific auditory and visual regions, as well as the non-sensory specific cortical response of the right fronto-temporal regions, were observed when stimuli were presented audio-visually compared to the sum of responses to unimodal auditory and visual presentation (Fort, Delpuech, Pernier, & Giard, 2002a; 2002b; Giard & Peronnet, 1999; Santangelo et al., 2008). Recent fMRI studies have confirmed the pattern of ERP results in human adults. Specifically, adults show enhanced processing in both sensory specific areas and non-specific association areas in the presence of bimodal stimulation compared to sum of the unimodal stimulation (Calvert, 2001; Calvert, Hansen, Iversen, & Brammer, 2001; Beauchamp, Lee, Argall, & Martin, 2004; Kayser, Petkov, Augath, & Logothetis, 2007; Alpert, Hein, Tsai, Naumer, & Knight, 2008). Together ERP and fMRI
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studies in human adults show enhanced activation in visual and auditory cortex, as well other areas such as the superior temporal sulcus (STS), inferior frontal cortex, and the superior colliculus (SC) during multisensory processing and integration (Ghazanfar & Schroeder, 2006; Belardinelli et al., 2004; Hein et al., 2007; Calvert, Campbell, & Brammer, 2000).

To date, no work has systematically investigated the effects of bimodal compared to unimodal stimulation on human infants’ neural responses; yet, infants’ neural responses to modality-specific stimulation have been extensively studied (see Wunderlich & Cone-Wesson, 2006 for a review). For example, even a few days after birth rapidly presented auditory stimuli reliably elicit prominent auditory evoked potentials over central and fronto-temporal scalp locations (Kushnerenko, Ceponiene, Balan, Fellman, Huotilainen, & Naatanen, 2002). Importantly, the auditory evoked components observed in young infants, albeit more latent, can be directly compared to auditory evoked components elicited in adults (see Wunderlich & Cone-Wesson, 2006 for a review). In addition, it is known that adults auditory ERPs are enhanced by the simultaneous presence of visual stimuli (e.g. Giard & Peronnet, 1999). An unanswered question, however, is if auditory-elicited activity in infants is modulated by the presence or absence of sensory information in another modality, namely visual information.

In order to better understand the neural processes associated with infants’ processing of multimodal stimulation we assessed 3-month-olds’ and adults’ event-related-potential (ERP) response to unimodal (auditory or visual) and bimodal (audio-visual) stimulation. Three-month olds were chosen because behavioral work demonstrates between 2- and 5-months of age infants are sensitive to and learn from cues that are redundant across multiple senses (Bahrick, 1988, 1992; Bahrick, Flom & Lickliter, 2002; Bahrick & Lickliter, 2000). In addition, the auditory system is sufficiently developed at 3-months of age to reliably and consistently elicit stable and
defined electrophysiological sensory components that can be compared to those in adults (Wunderlich & Cone-Wesson, 2006). Since an explicit task (e.g. stimulus identification or categorization) could not be given to infants, adults were instructed to passively view images, in an attempt to equate the conditions under which infants and adults viewed the stimuli. Importantly, recent research examining multisensory processing in adults has shown that passive viewing evokes similar effects to those observed when subjects perform an explicit categorization or identification task (Vidal, Giard, Roux, Barthelemy, & Bruneau, 2008).

In the current experiment it was predicted, based on neuroimaging and ERP work with human adults (Calvert, 2001; Calvert et al., 2001; Beauchamp et al., 2004; Kayser et al., 2007; Alpert et al., 2008), single cell recordings in animals (see Stein et al., 1994 for a review), and behavioral work with infants (Bahrick et al., 2002; Jordan, Suanda, & Brannon, 2008), that the synchronous presentation of bimodal (auditory-visual) stimulation would evoke an amplified auditory response compared to unimodal auditory stimulation in infants. A group of adults was also included to allow for a comparison of the infant ERP response to that of the mature ERP in response to the same stimuli.

**Method**

**Subjects**

Sixteen healthy full-term 3-month old infants (6 females; $M = 99.94$ days, $SD = 4.20$ days) participated. Infants were recruited from local birth announcements. Fourteen healthy adults also participated (6 females; $M = 24.14$ years, $SD = 3.61$ years) and were recruited from other research labs within the University. Data from 26 additional infants were excluded. Nineteen infants did not complete the experiment because they became fussy and seven infants were excluded for failure to attend to the events. This attrition rate is comparable to previous
ERP studies of young infants (e.g. Izard, Dehaene-Lambertz, & Dehaene, 2008; Quinn, Westerland, & Nelson, 2006).

*Stimuli and Procedure*

Infants viewed unimodally and bimodally presented auditory and visual events. Visual events consisted of a single large (10.5 cm) or small colored circle (2.5 cm) presented in the middle of a white screen. The auditory event consisted of either a high-pitched pure tone (2000 Hz) or a low-pitched pure tone (150 Hz) presented between 60-65 decibels. Using E-Prime software (Psychology Software Tools, Pittsburgh, PA), events were presented for 1000 milliseconds with an inter-stimulus interval between 1000-1200 milliseconds. Spectral analysis of the high pitch tone demonstrated sound wave features between 2000 and 10,800 Hz with intense components anchored around both 2,400 and 6,300 Hz giving it a “ping” sound quality. Spectral analysis of the low pitched tone demonstrated sound wave features between 150 to 2000 Hz with the most intense features of the sound wave between 150 and 200 Hz giving it a “bong” sound quality. Two sizes of circles, different colors, and two tones were presented to reduce the likelihood that observed effects were due to specific sensory properties of a particular event.

During the bimodal condition, the large circle was paired with the low pitched auditory tone while the small circle was paired with the higher pitched tone. The remaining trials consisted of auditory or visual events presented unimodally. Auditory, visual, and audio-visual trials were presented 30 times each in a pseudo-random order with the constraint that all three experimental conditions were presented before re-randomization occurred. Events were presented via computer screen and speakers approximately 50cm. from the infant while sitting on the parent’s lap as we recorded the ongoing EEG using a 64-channel HydroCel Geodesic Sensor Net (Electrical Geodesics Inc., Eugene, OR). To ensure infants attended equally to both bimodal
and unimodal conditions, stimuli were only presented when the infant was looking at the computer screen and stimulus presentation was paused when the infant looked away from the screen.

Data Processing and Reduction

EEG recordings were band-pass filtered online from 0.1- to 100-Hz and digitized at a rate of 250 Hz. Continuous electrophysiological data was then processed off-line using NetStation 4.2.3 software (EGI, Eugene Oregon). Data were subjected to a 30-Hz low-pass filter, segmented into epochs (−200 ms to 1200 ms), and baseline corrected for the 200-ms pre-stimulus recording interval. Each segment was then visually inspected for artifacts (eye blinks, eye movement, and electrode drift). Segments of infant data were excluded if more than 10 channels contained off-scale amplitudes of over 200 µV and/or if eye blinks, eye movements, or electrode drift occurred at any time during the segment (−200—1200 ms). Segments with less than 10 bad channels were included; however, bad-channel data were replaced using spherical interpolation of neighboring channel values. Adult segments were excluded by computer algorithm if more than 10 channels exceeded signal amplitudes of over 200 µV, or if the segment contained eye blinks (max-min > 140 µV over moving average over 80 ms) and/or eye movements (max-min > 55 µV over moving average of 80 ms). Following artifact rejection, an average was computed for each infant across each stimulus condition (unimodal A, unimodal V, and bimodal AV) and the data were then re-referenced to the average reference for each participant. No significant differences were observed in the number of good trials retained for each experimental condition. Infants retained, on average, 14.56 segments for the visual alone condition, 14.93 segments for the auditory alone condition, and 15.88 segments for the auditory-visual condition after artifact rejection (all p’s > .1). All subjects included in the final analysis retained at least 10 segments for
each experimental condition. Adult subjects retained, on average, 24.14 visual trials, 23.43 auditory trials, and 23.14 audio-visual trials after artifact rejection by computer algorithm. Individual artifact-free trials were combined to compute a grand average waveform and topographical map for each condition across all participants in each age range for visualization and inspection purposes (see Figure 1).

Data Analysis

We used a subtraction method to isolate the auditory response during the bimodal audio-visual presentation and compared it to the unimodal auditory response. Specifically, we compared the unimodal auditory condition (A) to the bimodal audio-visual (AV) condition minus the unimodal visual (V) condition. Both infants and adults elicit a prominent auditory evoked P2-N2 complex over mid-line and lateral scalp sites. In 3-month-olds, researchers often observe a division of the P2-N2 complex: the P2 is comprised of two separate positive components peaking around 150 and 350 ms divided by a small negative trough around 200-250 ms (Kushnerenko et al., 2002; Novak, Kurtzberg, Kreuzer, & Vaughan, 1989; Molfese, 2000) and is followed by a large negative deflection peaking around 450 ms over central and fronto-temporal scalp locations (Kushnerenko et al., 2002). Since we were interested in comparing the effects of bimodal presentation on auditory processing, our analysis was restricted to scalp sites and time windows that best characterized auditory-related potentials. We further limited our analysis to scalp sites that best characterized the electrophysiological activity isolated by the difference comparison ((AV-V)-A) in infants and used those same sites to make comparisons in adults. Specifically, with the infants we analyzed the P2-N2 complex by comparing conditions on the P150 (125-175 ms), P350 (250-400 ms), and N450 (400-550 ms) over bilateral fronto-temporal scalp groupings (64 channel EGI Hydrocel GSN: left = 7, 15, 16, 20, and 21; right = 41, 50, 51,
Auditory processing in adults is typically reflected in the auditory N1, P2, and N2 ERP components (see Wunderlich & Cone-Wesson, 2006 for a review). Although adults showed more midline activity than infants, we compared ERPs (A versus (AV- V) on the auditory N1 (75-125 ms), P2 (160-400 ms), and N2 (240-290 ms) in adults over the same sites that best characterized the components in infants. For all time windows of interest, a repeated measures ANOVA was conducted on the mean amplitude in adults and infants separately.

Results

3-Month-olds

Auditory and audio-visual events for the 3-month-olds elicited prominent P150, P350, and N450 components over fronto-temporal sites (Figure 1). A repeated measures ANOVA with the within subjects factors of stimulation (bimodal or unimodal) and hemisphere (left and right fronto-temporal groupings) was performed on the mean amplitudes of the P150, P350, and N450. No significant differences were observed between the responses to the unimodal auditory (A) and bimodal auditory-visual (AV-visual) stimulation on the P150 or the P350 (all p’s > .2). However, a significant effect of stimulation was observed on the N450 over fronto-temporal sites, with the AV events (AV-visual) eliciting more negative potentials during this time frame compared to the unimodal events ($F(1,15) = 5.12, p = .03, \eta^2_p = .25$). No significant differences were observed between hemispheres ($F(1, 15) = 1.57, p >.2$). These results show an increased auditory response (N450) to bimodal compared to unimodal stimuli after subtracting out the unimodal visual response.

Adults

In adults both unimodal and bimodal conditions elicited an auditory N1, P2, and N2 response (see Figure 2). A repeated measures ANOVA with stimulation (unimodal and bimodal)
and hemisphere (left and right) were run using the mean amplitudes of the auditory N1, P2, and N2 responses over fronto-temporal sites. A significant hemispheric difference was observed on the N1 ($F(1,13) = 6.47$, $p = .02$, $\eta^2 p = .33$) with the left fronto-temporal grouping showing more negative amplitude potentials compared to the right fronto-temporal grouping (Figure 2). No other significant effects were observed on the N1 or the P2 components ($all \ p’s > .1$). A significant difference between stimulation conditions, however, was observed on the N2 component, with the bimodal (AV-visual) condition eliciting more negative amplitudes compared to the unimodal auditory condition ($F(1,13) = 4.75$, $p = .04$, $\eta^2 p = .26$). No other significant effects or interactions were observed on the N2 component ($all \ p’s > .3$). These results show an increased auditory response (N2) to bimodal stimuli (AV-V) compared to unimodal stimuli in adults, comparable to that observed in infants.

Discussion

The purpose of this experiment was to examine 3-month-olds’ and adults’ neural responses to bimodal and unimodal stimulation. Results revealed systematic differences in auditory processing between unimodal and bimodal stimulation in both infants and adults. The mid-latency auditory evoked N2 (N450 in infants) component was more negative in response to bimodal stimulation compared to the unimodal auditory stimulation after electrophysiology associated with unimodal visual processing was subtracted out. These results suggest that increased auditory processing with the simultaneous presentation of visual stimulation is present from the first few months of life and continues to be present in adulthood.

We did not observe early auditory processing differences between bimodal and unimodal conditions in infants nor in adults. Previous studies with adults, however, have reported differences in early sensory processing between bimodal and unimodal conditions (Calvert et al.,
2001; Foxe et al., 2002) including modulation of the auditory N1 and P2 with adults (Vidal et al., 2008). However, these previous studies presented adults with hundreds of trials per condition. Given we were primarily interested in the infant brain response, we were limited in the number of trials that could be successfully presented to the infants without increasing subject fatigue and attrition. It is likely the limited number of trials (30 per condition) reduced our ability to detect differences in these early components. We suspect that more trials per condition may produce early differences comparable to those observed at middle-latencies.

Nonetheless, the current ERP waveforms for the A, V, and AV conditions (Figure 1) are consistent with previous adult ERP work comparing the sum of unimodal A and V responses to the bimodal AV response with adults (Fort et al., 2002a; 2002b; Giard & Peronnet, 1999; Vidal et al., 2008). Likewise, using a conceptually similar analysis method as previous studies, we observed differences between bimodal and unimodal auditory processing on the N2 auditory component in both infants and adults (Figure 2). Electrical activity during the P2-N2 complex is suspected to arise from a number of sub-regions within the primary and/or higher-order auditory association areas in the superior temporal region in adults and infants (Novak et al., 1989). Studies using fMRI have identified the superior temporal region, in addition to a number of other cortical and subcortical regions, as important to intersensory processing (see Calvert, 2001 for a review). Specifically, these studies identify superior and middle temporal regions as “multisensory” or “heteromodal” where these regions receive converging projections from different sense modalities and respond to input from multiple senses. Studies of primate neuroanatomy confirm that the superior temporal sulcus (STS) and a number of other cortical and subcortical structures, in fact, receive information from multiple senses (see Calvert, 2001 for a review). Source localization estimates of the auditory evoked potentials seat brain activity
during the P2-N2 complex within this general area and the observed differences in our study plausibly reflect activation in such multisensory areas (Novak et al., 1989). The application of source localization algorithms with realistic head models of infants, however, would be required to confirm this speculation.

Another open question is how neural activity associated with intersensory perception may be related to attention. No explicit task was required of infants or adults, yet we observed increased auditory processing with bimodal compared to unimodal presentation, reducing the probability that “task parameters” cued subjects to attend to one type of stimulus more than another. These findings converge with recent work showing multisensory interactions in adults under similar passive viewing conditions (Vidal et al., 2008). However, it is still unclear how the magnitude of the observed effect might differ between passive viewing and active tasks used in other studies of adults (e.g. Giard & Peronnet, 1999). In the visual domain, for example, early sensory components such as the posterior visual P1 and N1 are influenced by covert attention (see Hillyard & Anllo-Vento, 1998; Hillyard, Mangun, Luck, & Heinze, 1990; Hillyard, Teder-Sälejärvi, & Münte, 1998; Luck, 2005 for reviews). Furthermore, research examining attention and orienting in infants between 4- and 7-months of age have repeatedly found a negative central (Nc) component that peaks around 600-700 ms over central and fronto-central scalp locations to be associated with increased attention or orienting towards more interesting or novel stimuli (deHaan, 2007; Nelson & Collins, 1991; 1992; Nelson & deRegnier, 1992; Reynolds & Richards, 2005; Richards 2003; Rothbart, Posner, & Rosicky, 1994). Future research is needed that investigates the role of attention in modulating intersensory neural interactions during early development.
On a related note, we employed static, non-naturalistic sensory events as stimuli, similar to those used in previous studies of adults (Fort et al., 2002a; 2002b; Giard & Peronnet, 1999). We predict that the use of more engaging, or dynamic face/voice pairings would elicit greater intersensory effects. However, adding a dynamic social nature to the stimuli increases the possibility of producing exponentially more complex data because such stimuli might recruit other brain systems related to social, emotional, and/or face processing that were not observed in our study. Work in our lab is beginning to address these issues.

A number of neuroimaging and electrophysiological studies with adults report a “superadditive” response to bimodal stimuli (Calvert, 2001; Calvert, Campbell, & Brammer, 2000; Calvert, Hansen, Iversen, & Brammer, 2001; Giard & Peronnet, 1999; Santangelo, Van der Lubbe, Berlardinelli, & Postma, 2008). Such a response is proposed as a homologue to the “superadditive” response observed during single-cell recording with non-human animals, where multisensory cells in non-human animals often show an exponentially greater firing rate (i.e., 150 to 260%) during multimodal stimulation compared to unimodal stimulation (e.g., Wallace, Wilkinson, & Stein, 1996; Wallace & Stein, 1997). Adult human studies, however, typically report a superadditive brain response to AV that is simply greater than the sum of the response to the unimodal A and V (e.g. Giard & Peronnet, 1999). Single cell recordings in non-human animals are conducted with very little noise, fMRI and EEG are a summation of the response of millions of cells combined with noise from other brain and non-brain sources (see Laurienti, Perrault, Stanford, Wallace, & Stein, 2005 for a review). Thus, comparisons between “superadditive” responses in humans and other non-human animals using different methodologies must be made with caution. Nonetheless, both non-human animal electrophysiology and human brain imaging show an amplified brain response to bimodal
compared to unimodal information. In these cases, the brain responds in an elevated way to multimodal stimulation and does more than linearly combine responses from the separate sense modalities. The current results add to this literature by documenting an “elevated” auditory response to bimodal stimulation in infants.

The current ERP findings with infants provide a neural foundation to test psychological theories on the development of intersensory perception, specifically addressing issues such as the role of synchrony or perceptual binding of featural information from multiple senses. Specifically, it would be of key importance to ask if the N2 is enhanced for synchronous compared to asynchronous stimulus presentation or if redundant properties such as rhythm modulate the N2 differently compared to non-redundant stimulus properties.

Finally, auditory evoked potentials have been used in clinical settings to identify or flag propensities towards abnormal development (e.g. Molfese, 2000). A better understanding of the neural markers of intersensory processing may prove useful to clinicians and researchers interested in understanding atypical development in cases such as autism where difficulties arise in tasks such as social orienting or language learning that require integration of information from multiple senses. The results of the current investigation provide a first step in examining the neurophysiological basis of infants’ sensitivity to multimodal stimulation and demonstrate that bimodal stimulation produces a greater evoked response compared to unimodal stimulation in the infant brain.
References


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Figure Captions

Figure 1
Summary of ERPs to unimodal audio, unimodal visual, and bimodal audiovisual stimulation.
(A.) Average infant ERP waveform between -200 and 800 ms for each experimental condition.
(B.) Infant scalp topography at each component of interest for each experimental condition.
(C.) Average adult ERP waveform between -200 and 800 ms for each experimental condition.
(D.) Adult scalp topography at each component of interest for each experimental condition

Figure 2
Summary of ERP results for infants and adults.  A. Difference map of the (AV-visual) minus Auditory for infants at 475 ms  White items represent electrode sites used to calculate the average waveforms.  B. Average waveforms for the bimodal (AV-visual) and unimodal conditions over fronto-temporal scalp locations from -200-800 ms for infants.  The gray boxes highlight components of interest.  The * indicates a significant difference between conditions.  C. Difference map of the (AV-visual) – Auditory for adults at 250 ms  White items represent electrode sites used to calculate the average waveforms.  D. Average waveforms for the bimodal (AV-visual) and unimodal conditions over fronto-temporal scalp locations from -200-800 ms for adults.  The gray boxes highlight components of interest.  The * indicates a significant difference between conditions.
Figure 1.
Figure 2.