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# Developmental changes in refractoriness of the cortical auditory evoked potential

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**Abstract**

**Objective**: This study examined morphological changes in the cortical auditory evoked potential (CAEP) waveform as a function of varying stimulation rate. Stimuli were presented in a paradigm which indirectly assesses the refractory properties of the underlying neuronal generators.

**Methods**: CAEPs were recorded in 50 normal-hearing children (3–12 years) and 10 young adults (24–26 years). A speech sound was presented in a stimulus train with sequentially decreasing inter-stimulus intervals (ISIs) of 2000, 1000, 560, and 360 ms. Latencies and amplitudes of the P1, N1, and P2 components at the Cz electrode were examined as a function of stimulus rate and age.

**Results**: Results revealed significant changes in the CAEP as a function of age and stimulation rate. At younger ages the N1–P2 component was elicited only at the slowest stimulation rates, and was more clearly apparent at successively faster stimulation rates as age increased.

**Conclusions**: We have described a stimulus paradigm that allows examination of the development of refractoriness by highlighting the interaction between age and rate on CAEP morphology.

**Significance**: Complex maturational patterns of CAEP components are best understood when the effects of both age and stimulus rate on the CAEP waveform are considered.


*Keywords:* Refractoriness; Development; Auditory evoked potentials; Central auditory system; Stimulation rate

## 1. Introduction

In a series of papers, we have investigated aspects of maturation of the human central auditory pathways (Sharma et al., 1997, 2002a–c). Our measures of central auditory system maturation are the age-related changes in the morphology, latency, and amplitude of the P1, N1, and P2 components of the cortical auditory evoked potential (CAEP). P1, N1, and P2 are obligatory components of the CAEP that are generated with input from auditory thalamo-cortical and cortico-cortical pathways, primary auditory cortex, and various association cortices (Ceponiene et al., 1998; Naatanen and Picton, 1987; Ponton et al., 2002).

Several studies have examined the development of the P1, N1, P2 CAEP components with widely varying results (Albrecht et al., 2000; Ceponiene et al., 2002; Eggermont and Ponton, 2003; Musiek et al., 1988; Ponton et al., 1996b, 2000, 2002; Sharma et al., 1997; Surwillo, 1981). For example, the development of P1 latency has been shown to vary anywhere from 14 to 26 years and beyond (Eggermont, 1988; Ponton et al., 1996b, 2000; Sharma et al., 1997, 2002a). Similarly, the age of first appearance of the N1 and P2 components in young children is debated with some authors noting that it first appears around 3–8 years, while others have suggested that the N1 component is absent in young children

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(Ceponiene et al., 1998; Pang and Taylor, 2000; Sharma et al., 1997; Tonnquist-Uhlen et al., 2003).

It is likely that variations in stimulation rate underpin some of the differences in outcome. Only a handful of studies have examined the development of the P1, N1, and P2 responses in childhood as a function of stimulation rate (Ceponiene et al., 1998, 2002; Surwillo, 1981; Wible et al., 2002). Surwillo reported that a systematic decrease in the latency of the N1 component occurred with an increase in inter-stimulus interval (ISI) (from 250 to 1000 ms) for children aged 9–13 years, but not for adults. Surwillo suggested that the refractory properties of the underlying neural components involved in the N1 response may not be fully developed in children since cortical processing of stimuli at faster rates revealed a less robust CAEP response in children.

Ceponiene et al. (1998) examined CAEPs in 7–9 year old children at 3 different ISIs of 1400, 700, and 350 ms. As the ISI was decreased, the latency of the P1 and N1 increased. Interestingly, the authors observed that the N1 component was not present at the fastest stimulation rate (350 ms). The N1 component began to emerge as the ISI was slowed from 350 to 700 ms, and was more robust at the slowest rate (1400 ms ISI). Based on this finding, the authors suggested that the indiscernible N1 response at rapid stimulation rates indicates that the neural generators of the N1 response undergo significant developmental changes in refractoriness in early childhood.

As described by Naatanen and Picton (1987), the N1 wave of the CAEP has at least 3 distinct generators giving rise to 3 obligatory components. Component 1 of the N1 wave is thought to be most sensitive to amplitude changes as a result of differences in stimulation rate, particularly when the ISI is relatively short (Naatanen and Picton, 1987). Components 2 and 3 of the N1 wave are less likely to be affected by changes in ISI, and are thought to represent processes of attention (component 2) or an orienting response (component 3) (Naatanen and Picton, 1987). The changes in the CAEP waveform described above are likely driven by changes in refractoriness of component 1 generators.

Only a few studies in adults have attempted to differentiate the effects of refractoriness (the time needed for a neural population to recover after generating a response to a stimulus) from long-term habituation (a decrease in waveform amplitude with continuous, repeated stimulation) on CAEP waveform morphology (Budd et al., 1998; Roeser and Price, 1969; Roth et al., 1976). Roth et al. (1976) examined CAEP responses to stimuli presented in different combinations of ISIs (3, 1.5, and 0.75 s) and showed that amplitude changes were dependent only on the stimulus *immediately preceding* the stimulus used to elicit the CAEP response and not other preceding stimuli. The amplitude changes were attributed to refractoriness in the N1 and P2 components rather than to effects of long-term habituation. Habituation would have resulted in continuous amplitude decrements over the course of all the stimuli preceding the one used to elicit the CAEP response (Roeser and Price, 1969). These results were later replicated by Budd et al. (1998) who used stimulus blocks differing in ISI and containing a randomly interleaved deviant sound. They compared the amplitude of responses immediately following the deviant sound to the responses not following the deviant. The authors reported that the changes in N1 amplitude were specific to the ISI condition and were not affected by the deviant stimulus. In their study, the authors concluded that N1 amplitude decrements reflect a refractory process from the preceding stimulus rather than habituation. Taken together, these studies suggest that a stimulation paradigm in which the ISI just preceding the stimulus used to elicit the CAEP response is varied (e.g. a 'stimulus train') can be used to study the effects of neuronal refractoriness on CAEP morphology separate from the effects of long-term habituation.

We examined the development of the CAEP response morphology in a paradigm which examines the effects of refractoriness separate from long-term habituation. We used a train of brief vowels [uh] presented at sequentially decreasing inter-stimulus intervals (2000, 1000, 510, and 360 ms) to elicit CAEPs. In this manner, the ISI just preceding the stimulus used to elicit the CAEP was varied to better examine the effects of refractoriness on CAEP components (Budd et al., 1998; Roth et al., 1976). Responses were recorded from Cz to highlight refractory changes in component 1 of the N1 response. Our aim was to examine the developmental pattern of changes in CAEP morphology as a function of age and stimulation rate in normal-hearing children aged 3–12 years and young adults.

## 2. Methods

### 2.1. Subjects

CAEPs were recorded in 50 normal-hearing children ranging in age from 3 to 12 years, and from 10 normal-hearing young adults ranging from 24 to 26 years of age. All subjects and parents of subjects under the age of 18 years received informed consent prior to participation in any of the experimental procedures. All procedures and protocols, including informed consent procedures used in the present study, received prior approval by the University of Texas at Dallas and its Institutional Review Board. Subjects had no reported history of neurological pathology or severe head injury, and no reported speech, language, or learning impairments. Subjects were divided into 6 groups based on age. Table 1 provides a summary of these age groups.

### 2.2. Stimulus paradigm

Cortical auditory evoked responses were recorded in response to a natural speech syllable [uh]. The duration of