Cortical Auditory Dysfunction in Childhood Epilepsy: Electrophysiologic Evidence

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Abstract: Children with epilepsy are at increased risk for language impairments. Recent studies have suggested that abnormal cortical processing of complex sounds, including speech, may be a contributing factor. Cortical auditory evoked potentials provide an objective, non-invasive method for assessing auditory function in children. We begin with an overview of the cortical auditory system, cortical auditory evoked potentials, and childhood epilepsies. This overview provides a framework for reviewing recent studies using auditory evoked potentials to evaluate sound processing in children with epilepsy. Clinical implications, methodological considerations, and directions for future research are discussed.

Key Words: Auditory evoked potentials, auditory cortex, epilepsy.

INTRODUCTION

The cortical auditory system mediates perception of complex sounds, including speech, in the listener's environment. Cortical processing underlies many human auditory behaviors such as speech sound perception, sound localization, and pitch perception [1-3]. Cortical processing of speech sounds is of particular interest to clinicians due to its role in language development. A child's ability to discriminate and recognize speech sounds is considered pre-requisite for normal language development [4,5]. Moreover, it is increasingly recognized that impairments in speech perception, resulting from cortical auditory dysfunction, contribute to abnormal language development in children with neurodevelopmental disorders, including autism and dyslexia who have no history of hearing loss or structural brain lesions [6-9].

Children with epilepsy are at increased risk for developmental language disorders [10-14]. Both receptive and expressive language difficulties have been identified, as children with epilepsy often have difficulty processing and understanding spoken speech, especially in everyday listening situations that include background noise (e.g. classrooms, restaurants). Behavioral studies have reported speech perception impairments in children with even mild forms of epilepsy [12,15]. However, because attention disorders are also common in children with epilepsy, behavioral measures may not be reliable [16,17].

Cortical auditory evoked potentials (CAEP) offer an objective, non-invasive method for assessing auditory function in children. Many recording paradigms do not involve behavioral responses and can be implemented while children are watching a movie or reading a book. CAEP also offer excellent temporal resolution and, since many acoustic speech cues occur in the millisecond (msec) scale, they are well suited for studying speech perception. The purpose of this review is to discuss recent findings from CAEP studies in children with epilepsy. The topic of this review will be of particular interest to pediatric neurologists, audiologists, and speech-language pathologists, as well as clinical neurophysiologists.

We begin with a primer on the cortical auditory system (section 1) and CAEP methods (section 2). The next section provides an overview of childhood seizure and epilepsy syndromes (section 3). We then discuss findings from recent CAEP studies in children with epilepsy and their clinical implications (section 4). The last three sections cover methodological considerations, our summary and conclusions, and directions for future research (sections 5-7).

1. AUDITORY CORTEX: STRUCTURE AND FUNCTION

In this section, we briefly review the structure and function of human auditory cortex (Fig. **1**). Auditory cortex mediates sound perception and is involved in sound discrimination, localization, and recognition, as well as auditory learning, attention, and memory. Sound information is transmitted from the ear to the cortex by a complex series of parallel and crossing pathways. In normal-hearing adults, sound information is transmitted to auditory cortex in less than 25 msec. Transmission rates are generally longer in children under 11 years of age, reflecting the immature status of the central auditory pathways [18].

The subcortical auditory system interfaces directly with cortex through white matter fiber tracts that project unilaterally from the ventral nucleus of the medial geniculate complex of the thalamus. The first cortical region to receive auditory input is located inside the Sylvian fissure of each hemisphere on the supratemporal plane and includes Heschl's

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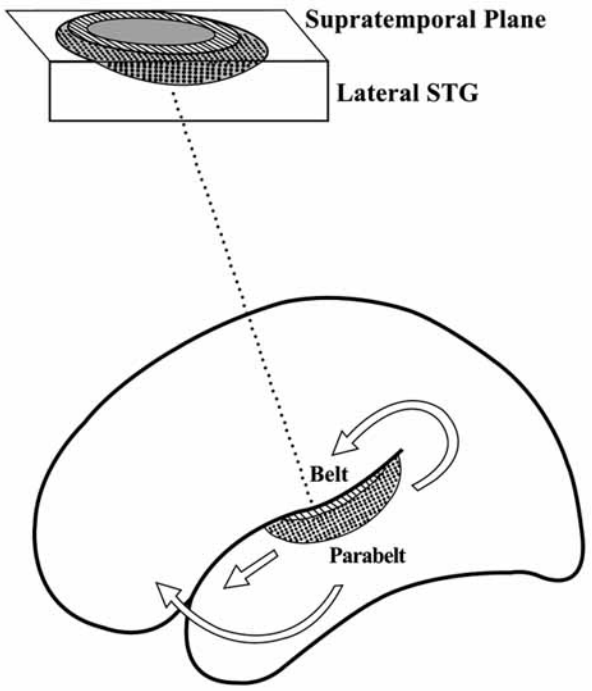

Fig. (1). Schematic lateral view of the left hemisphere showing locations of the auditory core (solid black), auditory belt (striped), and auditory parabelt (checked) on the supratemporal plane and superior temporal gyrus. Arrows indicate direction of projections from auditory cortex.

gyrus (Brodmann areas 41, 42). The functional area associated with Heschl's gyrus is the primary or core auditory field (AI). Core auditory areas in each hemisphere are connected through the corpus callosum [19]. Human neuroimaging and microelectrode studies have demonstrated that the response properties of the primary auditory field are tonotopically-organized, with high frequencies represented medially and low frequencies laterally [20-22]. Animal studies using single-frequency tones have shown that neurons in the primary auditory field respond preferentially to a limited range of frequencies, centered on a characteristic frequency [23]. However, recent studies have found that AI neurons are also responsive to pitch in harmonically complex sounds [24] and are modulated by non-auditory stimuli, including somatosensory and visual inputs [25,26]. Auditory information is distributed laterally from core areas to non-primary auditory areas for higher-level processing.

Two non-primary auditory fields have been identified: the belt and parabelt. The auditory belt is a narrow region that surrounds and receives input from the primary auditory field and overlays the intermediate aspect of Heschl's gyrus, as well as the planum temporale and planum polare, auditory structures located posterior and anterior, respectively, to Heschl's gyrus. At least eight subdivisions have been identified within the auditory belt, all of which show weaker tonotopic organization than the primary auditory field [27,28]. Recent human neuroimaging studies have suggested that the planum temporale and planum polare mediate sound localization and pitch perception [1,29].

A second non-primary auditory area, the parabelt, is located lateral to the primary auditory and belt regions on the posterior superior temporal gyrus. The parabelt receives input from the medial aspect of Heschl's gyrus [30], the auditory belt, and the medial pulvinar of the thalamus [31]. Neurons in the parabelt respond preferentially to complex sounds, including noise bursts and species-specific vocalizations [32-34]. The auditory parabelt in the dominant (usually left) hemisphere is associated with the functional region known as Wernicke's area (Brodmann area 22) and is involved in speech perception and comprehension. The auditory parabelt projects to multiple cortical areas within the temporal lobe, including the anterior superior temporal gyrus and middle temporal gyrus, and to the parietal and frontal lobes that mediate other auditory functions including working memory, sound localization, phonological processing, and auditory attention [35-39].

2. CORTICAL AUDITORY EVOKED POTENTIALS

Cortical auditory evoked potentials (CAEP) are synchronized, low voltage, low frequency electrical signals recorded from the brain in response to sounds (Fig. **2**). CAEP are time-locked to the auditory stimulus and recorded non-

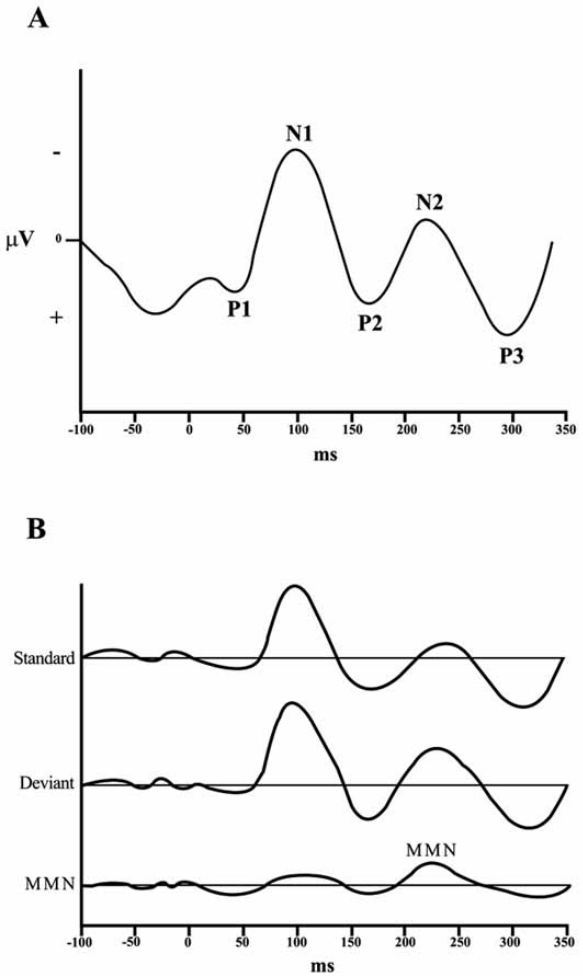

Fig. (2). Schematic representation of cortical auditory evoked potentials. (A) Waveform with identified components: P1, N1, P2, N2, and P3. (B) Three waveforms corresponding to the averaged response to repeated frequent stimulus (top), averaged response to an infrequent stimulus (middle), and the computed difference waveform (bottom).

invasively in children using electrodes affixed to the scalp. CAEP latencies are measured in msec and their amplitudes in microvolts (μV). Due to their relatively low amplitude, CAEP waveforms are averaged to identify individual component peaks (positive, negative). The three earliest peaks in the long-latency CAEP waveform are the P1, N1, and P2. Later cortical auditory responses include the N2, mismatch negativity, and P3.

The P1 is a vertex-positive deflection and one of the earliest of the long-latency auditory responses to be recorded from cortex, occurring in adults between 40-60 msec after stimulus onset. The neural generators of P1 have been localized lateral to the primary auditory field (Heschl's gyrus) on the supratemporal plane and may also include contributions from the subcortical auditory system [40]. Developmentally, the P1 is evident as early as 5 years of age and undergoes age-related decreases in both latency and amplitude, reaching adult-like values by approximately 15 years of age [41].

The N1 is a vertex-negative potential that peaks in adults between 90-110 msec following the onset of a sound. Although multiple cortical generators have been identified, intracranial studies have localized the main sources of the N1 to the supratemporal plane, including Heschl's gyrus and the planum temporale [42-46]. The N1 is an automatic, transient response to the onset of a sound. Acoustic changes within a sound, including frequency changes, can elicit a second, smaller N1 termed the acoustic change complex [47]. The N1 is affected by stimulus parameters, including sound intensity and presentation rate. With a decrease in sound intensity, the N1 latency increases and amplitude decreases. Similarly, the N1 amplitude decreases at higher stimulus rates, with repetition, and in sleep [48].

Developmentally, the N1 response emerges between 5-6 years of age [49], although an N1 may be elicited as young as 3 years with very slow stimulus rates [50]. The N1 latency shows age-related decreases similar to the P1. However, in contrast to the P1, the N1 amplitude increases through childhood, reaching adult-like values between 13-15 years of age [49,51,52].

The P2 is a vertex-positive peak that follows the N1 and occurs around 140-170 msec after sound onset. Multiple neural generators within and outside the temporal lobe have been identified for the P2 including the reticular activating system and insular cortex [49,53]. An interesting property of the P2 is that its amplitude can be enhanced with perceptual training and spectral complexity [54,55]. In contrast, the N1 does not show similar enhancement effects. The differential effects of perceptual training and spectral complexity on the N1 and P2 have been attributed to differences in their underlying neural generators and functional roles [55].

The P2 response develops earlier than the N1, reaching adult-like latencies by 3 years of age in parallel with maturation of the brainstem pathways [56]. This difference in the developmental time course of the N1 and P2 has been attributed to maturational differences in their underlying neural generators: the N1 generator is the lemniscal pathway that terminates in primary auditory cortex and develops more slowly than the non-lemniscal pathway, which generates the P2 [49].

The N2 is a processing negativity with adult latencies of 220-270 msec post-stimulus that is associated with detection of an auditory target and is sensitive to stimulus features, including intensity [57]. The N2 is thought to have multiple components and neural generators within and outside the temporal lobe. In contrast to earlier cortical auditory responses, the N2 shows an age-related increase in latency and does not reach adult values until approximately 17 years of age.

The mismatch negativity (MMN) is a pre-attentive, modality-specific index of acoustic change detection [58] occurring 150-250 msec after stimulus onset. The two main neural generators of the MMN are non-primary auditory areas and pre-frontal cortex [59]. The MMN is elicited using tones or speech in a passive odd-ball paradigm in which one stimulus (standard) is presented sequentially in a series with a second stimulus (deviant) interspersed infrequently (15-20%). The MMN is identified on a difference waveform computed by subtracting the averaged response waveform of the standard (frequent) stimulus from the averaged waveform of the deviant (infrequent) stimulus. The MMN is best seen at midline electrodes and is often largest at frontal midline electrode Fz. The MMN is thought to reflect a pre-attentive stage of auditory processing in which an incoming novel stimulus (deviant) is compared with a short-term memory trace of the more frequent stimulus [60]. The MMN is sensitive to acoustic changes, including changes in frequency, intensity, and duration [61,62]. The amplitude of the MMN increases as the size of the stimulus difference increases. The MMN is well suited for studying children because it does not require a behavioral response and is typically elicited when subjects are distracted visually by watching a movie or reading.

Developmentally, an MMN-like response, called the "auditory discriminative potential" has been identified in newborns and infants [63,64]. This large frontal negativity peaking around 700-800 msec is considered the precursor to the adult MMN. An age-related decrease in MMN latency occurs until approximately 10 years of age [65].

The P3 is a composite, vertex-positive peak occurring at approximately 300 msec post-stimulus in adults. Multiple cortical generators have been identified including non-primary auditory fields, the parietal lobe, and pre-frontal cortex. In contrast to the other CAEP components discussed in this section, the P3 is elicited by asking subjects to detect a rare, unpredictable target stimulus that occurs in a series of standard (frequent) stimuli. The P3 is elicited using an active odd-ball paradigm that requires subjects to respond. The two main components of the P3 are the P3a and the P3b. The earlier P3a is thought to reflect an alerting process in the frontal lobe and may represent an initial cortical response to an incoming signal [66], while the later P3b reflects attentional and memory-related mechanisms required to process the signal [67].

Developmentally, a longer-latency P3-like positivity has been identified in 1 year olds around 500-600 msec post-stimulus [68]. However, it has not yet been determined whether this is the developmental precursor to the adult P3. Studies of children ages 7-10 years have identified reliable P3 responses, although the topography differed from that

seen in adults [69]. P3 latencies undergo a rapid decrease of approximately 20 msec/year from childhood to adolescence, a developmental change that has been associated with cognitive maturation [70,71].

3. CHILDHOOD EPILEPSY

Epilepsy is defined as a neurological disorder characterized by recurrent (e.g. ≥2), unpredictable abnormalities in brain activity that manifest clinically as seizures [72,73]. A seizure refers to a transient clinical event with signs and/or symptoms that are caused by abnormal, excessive, hypersynchronous neuronal activity [72,74]. Various approaches to the issue of epilepsy and seizures in children have been taken in the evoked potential literature. While some studies focus on specific seizure types (e.g. generalized tonic-clonic, absence, or partial seizures), others have investigated broad categories of epilepsy syndromes (e.g. idiopathic generalized epilepsy) or individual epilepsy syndromes (e.g. childhood absence epilepsy, Benign Rolandic epilepsy). These differences are potentially important. For example, a child with "absence seizures" could have a variety of different epilepsy syndromes, such as childhood absence epilepsy, juvenile myoclonic epilepsy, or others. Due to the inter-study differences in approach, a brief discussion of the classification of seizures and epilepsy syndromes is warranted. Following this, we review several epilepsy syndromes with particular attention to those in which auditory evoked potential studies have been performed. The classification of seizures and epileptic syndromes is based on consensus reports from the International League against Epilepsy and the International Bureau for Epilepsy [72-74].

Seizure Classification

The purpose of seizure classification is to provide a clinical description of ictal features and behaviors. The primary dichotomy in seizure classification is between generalized and partial seizures. Generalized seizures have clinical and EEG data that indicate initial involvement of both hemispheres. These include tonic-clonic, absence, and myoclonic seizures, among others. Conversely, partial seizures are focal, beginning in a particular brain region, and further subdivided into those that impair consciousness (complex) and those that do not (simple).

Epilepsy Classification

Epilepsy syndromes are defined by characteristic epileptic patterns, seizure type, EEG, age of onset, history, and prognosis. Similar to seizure classification, epilepsy syndromes are categorized as either generalized or localized (partial). These two broad categories may be subdivided into idiopathic epilepsies, which are age-dependent syndromes that occur in otherwise normal children and are without a clear cause (although many are genetic), and symptomatic epilepsies that stem from specific brain lesions and are often accompanied by other neurological deficits.

Generalized Epilepsies

Of the generalized epilepsies, the two most common fall within the idiopathic subgroup, and are childhood absence epilepsy and juvenile myoclonic epilepsy. Childhood absence epilepsy is characterized clinically by absence seizures, which are brief (5-15 seconds) staring spells that often occur multiple times per day and are accompanied by a generalized 3-Hertz spike and wave pattern on EEG. Children are usually not aware of the events and resume normal behavior after the seizure, without a post-ictal phase. Approximately 20-40% of children with absence seizures also develop generalized tonic-clonic seizures. Onset is usually 5-8 years of age, and the syndrome is outgrown by puberty in approximately 80% of children.

Juvenile myoclonic epilepsy begins between 12 and 18 years of age, typically with early morning myoclonic seizures characterized by bilateral jerking of arms and shoulders without alteration of consciousness. Generalized tonic-clonic seizures are also seen in 80% of patients and absence seizures in 20%. Cognition and language are considered unaffected, although executive dysfunction, reflecting frontal lobe involvement, is common. The EEG in this syndrome is characterized by fast spike and wave and poly spike and wave discharges. Remission is unlikely and these patients require lifetime treatment with anti-seizure medications.

The symptomatic generalized epilepsies include West syndrome and Lennox Gastaut syndrome and are associated with various pathologies. These syndromes are characterized by medically refractory epilepsy and a variety of seizure types. Mental retardation and severe language impairments are common.

Partial Epilepsies

Partial epilepsies have been the primary focus of previous CAEP studies. Partial epilepsies are further subdivided into idiopathic epilepsies and symptomatic epilepsies. Idiopathic epilepsies include Benign Rolandic epilepsy, also known as benign childhood epilepsy with centrotemporal spikes (BECTS), childhood epilepsy with occipital paroxysms and the recently identified Panayiotopoulos syndrome. Symptomatic epilepsies include temporal lobe epilepsy and unusual epileptic syndromes, such as Landau-Kleffner syndrome, that have partial and generalized features.

Benign Rolandic epilepsy is characterized by unilateral focal motor seizures that involve the face and arm, and occur mostly during sleep. The onset is between 3 and 13 years of age and the seizure prognosis is good with spontaneous remission by adolescence. The EEG is characterized by a normal background with spikes and sharp waves in the centrotemporal (Rolandic) area, which tend to be more frequent in sleep. It is often not treated medically, since seizures occur mostly at night and traditionally there have been no associated cognitive or language impairments. However, recent studies have identified subtle cognitive and language deficits that can affect academic performance in these children [12,75,76].

Childhood epilepsy with occipital paroxysms is similar to Benign Rolandic epilepsy, except that 1) the seizure focus is in the occipital or posterior temporal region, 2) the seizures commonly start with visual symptoms, and 3) the clinical course is typically less benign. A number of occipital epilepsy syndromes, presenting in childhood or adolescents, have been recently identified [77,78]. Another recently identified form of idiopathic focal epilepsy is Panayiotopoulos syndrome which is characterized by autonomic seizures,

Table 1. CAEP Studies of Children with Generalized Epilepsy

Study	Age (yrs)	Stimuli	Epilepsy Subtype	Results
Celebisoy et al. 2005[a]	9-18	tones	*	**P3:** normal latency
Chen et al. 1996[b]	7-15	tones	*	**P3**: prolonged latency on phenobarbital, normal latencies on CBZ/valproate; decreased amplitudes
Enoki et al. 1995[c]	5-20	tones	Tonic-Clonic, Absence	**N2**: slightly prolonged latency with CBZ, *ns* **P3**: slightly prolonged latency with CBZ, *ns*
Henkin et al. 2003[d]	11-16	tones, speech	Tonic-Clonic, Absence	**N1**: normal latency; normal amplitude **N2**: normal latency; normal amplitude **P3**: normal latency; normal amplitude
	11-16	difficult speech, semantics	Absence	**N1**: normal latency; normal amplitude **N2**: normal latency; sig. increased amplitude **P3**: normal latency (difficult speech), sig. prolonged latency (semantics); normal amplitude
	12-16	difficult speech, semantics	Tonic-Clonic	**N1**: normal latency (difficult speech), sig. prolonged latency (semantics); normal amplitude **N2**: sig. prolonged latency; normal amplitude **P3**: sig. prolonged latency; normal amplitude
Konishi et al. 1995[e]	$\bar{X}$=13.7	tones	Absence, Juvenile Myoclonic	**P3**: prolonged latency in children 13 years or older
Sunaga et al. 1994[f]	6-15	tones	*	**P3**: sig. prolonged latency
Turkdogan et al. 2003[g]	7-20	tones	*	**N2**: sig. prolonged latency **P3**: sig. prolonged latency; normal amplitude

CBZ: carbamazepine, ***ns***: not significant, **sig.**: significant, $\bar{X}$: mean, *****not specified
Footnotes: *a:*[97], *b:*[102], *c:*[91], *d:*[88], *e:*[96], *f:*[94], *g:*[90]

multifocal interictal spikes, and an earlier age of onset than either Benign Rolandic or occipital epilepsy [79].

Temporal lobe epilepsy is characterized by either simple or complex partial seizures with temporal lobe onset that begin in childhood and extend into adulthood. This symptomatic epilepsy is associated with language and cognitive impairments [80], especially when seizures lateralize to the left hemisphere [81]. Patients frequently report auras and have structural brain abnormalities on MRI, including mesial temporal sclerosis, especially with early onset.

Landau-Kleffner syndrome occurs typically in children 5-9 years after seemingly normal early development. It is associated with regression in speech and language functions. One of the characteristic early clinical signs is a rapidly developing auditory agnosia for speech and non-speech sounds, despite normal hearing [82,83]. Nocturnal, simple partial motor seizures are the most common, especially with the onset of clinical symptoms. EEG findings associated with this rare, regressive syndrome include bilateral independent, multifocal spike discharges, maximal over the temporal lobe, and 1-3 Hz slow waves [84]. Despite considerable variability in the EEG, involvement of the posterior temporal lobe is a consistent finding in Landau-Kleffner syndrome. Although the clinical seizures generally resolve by adolescence, residual language impairments are common. Landau-Kleffner syndrome is sometimes considered part of a broad spectrum that includes Benign Rolandic epilepsy and the continuous spike-waves during slow wave sleep syndrome (CSWS), all three of which are associated with language impairments, diffuse and continuous 1-3 Hz spike-waves during much of the slow wave sleep period, and an EEG pattern known as electrical status epilepticus in sleep [85,86].

4. CORTICAL AUDITORY EVOKED POTENTIALS IN CHILDREN WITH EPILEPSY

Cortical auditory evoked potentials (CAEP) are increasingly used to study auditory function in children with epilepsy. This likely reflects greater recognition of speech perception and receptive language impairments in children with epilepsy and availability of CAEP recording paradigms that do not require overt behavioral responses or attention. Additional information about the studies reviewed in this section is presented, by epilepsy type, in Table **1** (generalized epilepsies) and Table **2** (partial epilepsy).

Early Cortical Auditory Evoked Responses (P1-N1-P2)

A study of children ages 6-12 years with Benign Rolandic epilepsy reported normal P1 and N1 latencies [87].

Table 2. CAEP Studies of Children with Partial Epilepsy

Study	Age (yrs)	Stimuli	Epilepsy Subtype	Results
Celebisoy et al. 2005[a]	9-18	tones	Benign Rolandic, Temporal Lobe	**P3**: sig. prolonged latency
Chen et al. 1996[b]	7-15	tones	*	**P3**: prolonged latency on phenobarbital, normal latencies on CBZ/valproate; decreased amplitudes
Enoki et al. 1995[c]	5-20	tones	*	**N2**: slightly prolonged latency with CBZ, *ns* **P3**: slightly prolonged latency with CBZ, *ns*
Gokcay et al. 2006[d]	5-17	tones	Occipital Paroxysms	**P3**: sig. prolonged latency; normal amplitude
Konishi et al. 1995[e]	$\bar{X}$=11.0	tones	Benign Rolandic, Occipital Paroxysms	**P3**: slightly prolonged latency
	$\bar{X}$=10.7	tones	Temporal Lobe	**P3**: sig. prolonged latency in ages 9-15
Liasis et al. 2006[f]	6-12	speech	Benign Rolandic	**P1**: normal latency; sig. increased amplitude **N1**: normal latency; normal amplitude N1-P2 **P2**: normal latency; sig. increased amplitude P2-N2 **N2**: sig. shortened latency **MMN**: absent response
Naganuma et al. 1994[g]	7-16	tones	Benign Rolandic	**P3**: sig. prolonged latency in ages 12-13
Naganuma et al. 1995[h]	5-16	tones	*	**P3**: prolonged latency
Naganuma et al. 1997 [i,j]	5-16	tones	Benign Rolandic, Occipital Paroxysms	**P3**: slightly prolonged latency
			*	**P3**: sig. prolonged latency with CBZ
Seri et al. 1998[k]	6-7	tones	Landau-Kleffner Syndrome	**N1**: normal latency & amplitude for tones applied in absence of spike activity (used as comparison) **N1**: prolonged latency & sig. decreased amplitude for tones applied 4 sec post spike activity
Sunaga et al. 1994[l]	6-15	tones	Temporal Lobe	**P3**: normal latency
Turkdogan et al. 2003[m]	7-20	tones	Temporal Lobe, Benign Rolandic	**N2**: sig. prolonged latency **P3**: sig. prolonged latency; normal amplitude
Wioland et al. 2001[n]	9-19	tones	Landau-Kleffner Syndrome	**N1**: normal latency; slightly increased amplitude **N2**: normal latency; sig. increased amplitude

CBZ: carbamazepine, ***ns***: not significant, **sig.**: significant, $\bar{X}$: mean, *****not specified
Footnotes: *a:*[97], *b:*[102], *c:*[91], *d:*[98], *e:*[96], *f:*[87], *g:*[101], *h:*[100], *i:*[99], *j:*[95], *k:*[89], *l:*[94], *m:*[90], *n:*[15]

A study of children ages 11-16 years with idiopathic generalized epilepsy also observed normal N1 latencies and amplitudes, as compared with age-matched normal controls, when simple tones were used, but prolonged latencies for complex speech stimuli [88]. These results are consistent with behavioral findings in children with Benign Rolandic epilepsy and idiopathic generalized epilepsy who typically have no difficulty processing simple tones, but do have difficulty processing speech, especially under adverse (e.g. real-world) listening conditions [12,75]. A study of children ages 6-7 years with Landau-Kleffner syndrome and severe auditory impairments reported prolonged N1 latencies for tones, suggesting adverse effects of interictal activity on early cortical auditory processing in the temporal lobe [89]. This view is supported by a study of children (9-19 years) with clinically resolved Landau-Kleffner syndrome who showed normal auditory N1 latencies [15]. There have been relatively few studies of the auditory P2 response in children with epilepsy. One study of children ages 6-12 years with Benign Rolandic epilepsy reported normal P2 latencies [87].

Taken together, these findings suggest that early cortical auditory responses to simple tones are normal in children

with epilepsy disorders unless a severe auditory impairment (e.g. auditory agnosia) is present, as in Landau-Kleffner syndrome. However, when speech stimuli are used, early cortical auditory responses are more likely to be prolonged even in children with traditionally benign epilepsies.

Late Cortical Auditory Evoked Potentials (N2, MMN, P3)

A consistent finding in CAEP studies is that N2 responses are prolonged in children with epilepsy, especially when speech stimuli are used. Abnormal N2 latencies for speech have been observed in children with a variety of seizure types, including absence and generalized tonic-clonic seizures [88,90]. In contrast, N2 latencies for simple auditory stimuli, such as tones, may be normal [88,91] or prolonged [90]. N2 latencies are prolonged in children with Landau-Kleffner syndrome, regardless of stimulus type, but appear to normalize with clinical resolution of seizures [15,89]. Of note, one study reported abnormally short N2 latencies in children with unilateral or bilateral spiking [87].

The mismatch negativity (MMN) has not been studied systematically in children with epilepsy.

In one of the few published studies, MMN responses were largely absent in children with Benign Rolandic epilepsy [87]. The finding was attributed to impairment in the ability to form memory traces of the standard stimulus [87].

The auditory P3 has been the focus of numerous studies in children with epilepsy due, in part, to its association with cognitive functions, including attention and memory. The auditory P3 occurs approximately 300 msec post-stimulus and has two main components: the P3a and the P3b. The P3a is thought to reflect automatic shifting of attention and is seen as a large positivity occurring after the MMN response with a predominantly frontal lobe distribution [92,93]. The P3b occurs during active task participation, such as counting or pressing a button when target sounds are detected, and is associated with temporal-parietal areas mediating memory and attention [92]. Although many of the P3 studies reviewed in this section did not distinguish between P3a or P3b response measurements, most of these studies used active auditory task paradigms most suitable for eliciting the P3b. Therefore, unless otherwise specified, we infer that the P3 findings reported in these studies refer to the P3b.

A consistent finding in CAEP studies of children with epilepsy is that P3 latencies are prolonged but with normal amplitudes [88,90,91,94-100]. This pattern holds across studies of children with idiopathic generalized epilepsy [94,96,99], idiopathic partial epilepsies including Benign Rolandic epilepsy [95,96,99-101], occipital paroxysmal discharges [95,97-99], and symptomatic partial epilepsies [95-97,99,100].

One CAEP study of 5-16 year olds found the most prolonged latencies to tones in children with symptomatic partial epilepsy and moderately prolonged latencies in children with idiopathic partial epilepsy, including Benign Rolandic epilepsy [96,99]. Significantly, the most abnormal prolongations of P3 occurred in children older than 9 years, while minimal abnormalities were seen in younger patients between 5 to 8 years. This was particularly true among idiopathic generalized epilepsies where prolongation was reported in children only if they were 13 years or older [96].

A small number of studies, however, conflict with the generally consistent findings of prolonged P3 latencies among children with epilepsy. It has been reported that children newly diagnosed with epilepsy between the ages of 7-15 years show no prolongation of P3 [102]. One CAEP study reported that children ages 9-18 years with generalized seizures had normal P3 latencies [97], which had also been seen in 7-15 year olds with temporal lobe epilepsy [94]. Henkin and colleagues found normal P3 latencies for tones and simple speech in children with idiopathic generalized epilepsies, but prolonged latencies for more complex, meaningful speech in children with generalized tonic-clonic or absence seizures [88].

Studies have consistently reported normal P3 amplitudes across seizure types in children, including generalized tonic-clonic and absence seizures [88], occipital paroxysms [98], symptomatic partial and generalized epilepsies, cryptogenic partial and generalized epilepsies, and idiopathic partial epilepsies [90].

To summarize, CAEP studies report largely normal early cortical auditory responses (P1-N1-P2) in children with epilepsy disorders, with the exception of Landau-Kleffner syndrome. In contrast, later cortical auditory responses (N2, P3) are often prolonged, especially in children with partial epilepsies. This suggests abnormalities in higher-level auditory perceptual functions, including discrimination and identification of complex sounds such as speech. The potential effects of anticonvulsant medications on CAEP latencies have yet to be studied systematically and warrant further investigation. Absent MMN responses have also been reported in children with partial epilepsies. Prolonged CAEP latencies have been associated with the presence of spikes [90] or increased spike frequency [95,100]. However, prolonged latencies have also been observed in the absence of spikes [87], suggesting that the underlying epileptic brain regions may be responsible. Although there are several reports of abnormal CAEP amplitudes, with decreased amplitudes ipsilateral to the side of spiking, this is not a consistent finding. The CAEP findings reviewed suggest that cortical auditory function is disrupted in children with epilepsy consistent with growing behavioral evidence for perceptual impairments of complex auditory information, including speech, in this population. The presence of cortical auditory dysfunction and associated speech perception impairments likely contribute to the language impairments frequently observed in children with epilepsy.

5. METHODOLOGICAL CONSIDERATIONS

A number of methodological factors can affect CAEP results, including differences in recording paradigms and stimuli, individual variation, and, of particular concern in studies of children with epilepsy, medication effects.

Methodological Differences

Across-study differences in paradigms and stimuli used to elicit CAEP are common and may account, in part, for the

conflicting results in the literature. For example, differences in stimulus presentation rates are known to affect the latency and amplitude of both early and late CAEP [18,50,103-105]. It is also difficult to directly compare findings from studies that use pure tones with those that use complex auditory stimuli, such as speech, due to known differential stimulus effects on CAEP [106,107]. Differences in the number and locations of recording electrodes used in CAEP studies have introduced another source of inter-study variability. CAEP latencies and amplitudes can vary between recording sites in the same child, reflecting differences in the maturation rates of distinct cortical sites [49]. Such methodological differences preclude comparison of results across studies and efforts to replicate findings, thereby adversely affecting the potential clinical utility of CAEP in children with epilepsy. It will be important for future studies to use standardized methodologies, thus allowing across-study comparisons and validation of findings.

Individual Variation

Across-subject differences in cortical auditory structure and function also affect CAEP findings. Individual differences in location, size, and volume of cortical auditory structures within and between the two hemispheres are increasingly well documented [108,109]. Such differences have led to increased use of standardized brain maps for comparing results across subjects. Individual differences in the functional organization of the cortical auditory system are also increasingly well characterized [3,110]. If not identified, individual differences in functional organization can impact results leading to potentially erroneous conclusions. This is most likely to occur with group analyses because they are generally based on averaging results across subjects, potentially obscuring individual differences. This underscores the need for both individual and group analyses in CAEP studies.

Medication Effects

Antiepileptic medications can also affect cortical evoked potentials. Studies of antiepileptic medication effects in humans and animals have reported prolonged CAEP latencies [100-102,111-116]. For example, carbamazepine was found to increase P1 latencies to visual stimuli in children [114]. Oral administration of diazepam has been associated with prolonged P3 latencies, with no affect on amplitude [117]. P3 latencies were also found to increase in children receiving phenobarbital [102,115], carbamazepine [100,101,116], and with high-dose phenytoin [116]. Furthermore, P3 latencies decreased following discontinuation of phenobarbitol, while P3 amplitudes increased following discontinuation of carbamazepine, phenobarbitol, and valproate [115]. These results suggest that antiepileptic medications may confound results of CAEP studies and warrant particular attention.

6. SUMMARY AND CONCLUSIONS

Four main conclusions may be drawn from the CAEP studies reviewed. First, early cortical auditory evoked responses (P1-N1-P2) to simple tones are typically normal in children with epilepsy and seizures. The one exception is children with Landau-Kleffner syndrome who typically have the most severe auditory impairments (e.g. auditory agnosia). Second, early cortical auditory responses to speech stimuli are often prolonged (abnormal) even in children with benign epilepsies. Third, later cortical auditory responses (N2, MMN, P3) are consistently abnormal (prolonged, absent) across different epilepsy disorders regardless of stimulus type. Fourth, the prolonged CAEP latencies observed in children with epilepsy do not appear to be a characteristic of other neurodevelopmental disorders with associated language impairments, such as autism. CAEP studies in children with autism spectrum disorder report normal latencies, but abnormal (decreased or increased) amplitudes.

In conclusion, findings from the studies reviewed suggest that cortical auditory function is disrupted in children with epilepsy, consistent with behavioral evidence of speech perception impairments in this population. The presence of cortical auditory dysfunction and associated speech perception impairments likely contribute to the language impairments frequently observed in children with epilepsy. These findings underscore the importance of using CAEP methods to evaluate auditory function in children with epilepsy and seizures.

7. FUTURE DIRECTIONS

The application of CAEP methods to study cortical auditory function in children with epilepsy has yielded important new insights. However a number of issues remain unsolved. For example, it is not known whether particular seizure disorders have characteristic, or signature, CAEP patterns. Similarly, the effects on CAEP responses of seizure onset age, duration, and type remain poorly understood and warrant further investigation. Well-designed studies, using appropriate methodological controls, are needed to address these issues. Finally, longitudinal studies are needed to determine the long-term effects of epilepsy and seizures on cortical auditory function in children.

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