INVITED REVIEW

Auditory Mapping With MEG: An Update on the Current State of Clinical Research and Practice With Considerations for Clinical Practice Guidelines

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Summary: Auditory evoked fields (AEFs) are well suited for studies of auditory processing in patients. Their sources have been localized to Heschl's gyri and to the supratemporal auditory cortices. Auditory evoked fields are known to be modulated by peripheral and central lesions of auditory pathways and to reflect group-level pathophysiology of neurodevelopmental and psychiatric disorders. They are useful in lateralization of language processes for planning neurosurgery and for localization of language-related cortex. The recently developed artifact rejection and movement compensation methods will enhance and extend the use of AEFs in studies of clinical patients and pediatric groups. New pediatric magnetoencephalography systems will facilitate clinical AEF studies of developmental disorders. In addition to their established use in planning neurosurgery, AEF findings in several new clinical patient groups suffering, e.g., from developmental, neurodegenerative, or psychiatric disorders have been reported. Several recent investigations report the correlations with clinical symptoms and sensitivity and specificity profiles of AEFs in studies of these disorders; this development is mandatory in gaining wider clinical approval for the use of AEFs in clinical practice dealing with individual patients. Most promising future research lines of clinical applicability of AEFs focus on developmental and psychiatric disorders.

Key Words: MEG, AEFs, Clinical applications, Hearing disorders, Developmental disorders.

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Magnetoencephalography (MEG) is well suited for non-invasive investigation of brain regions embedded within cortical sulci, such as the auditory cortices within Sylvian fissures. Magnetoencephalography permits high temporal (<1 ms), spectral (<1 Hz), and spatial (<1 cm) resolutions, making it particularly well-suited to investigate auditory processing, speech perception, and language comprehension. Both MEG and EEG can be used to follow dynamics of cortical activation at (sub) millisecond timescale, providing an excellent opportunity to study latencies of brain activation relative to stimulation. It is easier, however, to estimate sources of auditory evoked fields (AEFs) than auditory evoked potentials from the measured signals. This is mainly due to the anterosuperior orientation of the induced currents in the auditory areas within the Sylvian fissures generating auditory evoked potential signal maximum in the head midline, whereas the amplitude maxima in AEFs reside over each activated hemisphere. Moreover, the skull and scalp are transparent to magnetic fields, but electric fields are somewhat distorted by them. Techniques that have been used in clinical and research studies include auditory transient, task-related, and steady-state responses (SSRs), and oscillatory brain activity.[1] A brief introduction to these is presented below (for reviews, see Refs. 2 and 3). As defined by ACMEGS guidelines, in current clinical practice, AEFs are indicated for localization of the auditory cortex on the superior temporal gyrus.[4,5]

TRANSIENT RESPONSES

An abrupt sound evokes a sequence of AEF deflections in the auditory cortices of each hemisphere. Detection of magnetic counterparts of the earliest activation of auditory pathways, auditory brainstem responses, is difficult because the response generators are located deep in the brain. Wide recording passband and a high number of averaged responses are needed to detect magnetic auditory brainstem responses, but their data-driven source analysis is possible from magnetometer signals.[6] The earliest cortical AEFs appear 11 ms after the stimulus onset.[7] Deflections at 8 to 13 ms after the stimulus onset have been detected in direct cortical recordings from the medial tip of the Heschl's gyrus, harboring the primary auditory cortex.[8,9] The middle-latency responses begin at 19 ms,[10] whereas the more widely studied middle-latency AEF deflections peak around 30 to 50 ms.[11] In intracerebral recordings, they appear to be generated in the Heschl's gyri[12] or by propagating activity from the Heschl's gyri to planum temporale and the superior temporal gyrus.[9]

There are several ways to identify the AEF deflections. In one, the labels are given according to the coinciding electric evoked potential, adding a suffix "m" to refer to magnetic signals. For example, the prominent AEF at 100 ms is called N100m because it coincides with the vertex-negative electric evoked potential N100. The next deflection of opposite polarity at about 200 ms is called P200m. This nomenclature is used for the remainder of the article.

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The most prominent AEF response peaking at about 100 ms (N100m) is generated in the supratemporal auditory cortex. The first N100m mapping studies suggested that the signals are generated within the Sylvian fissure in the upper surface of the temporal lobe, and MEG-MRI coregistrations supported this interpretation (Fig. 1). Intracerebral evoked potential recordings in humans have suggested that deflection at N100 ms is generated in the intermediate and lateral parts of the Heschl's gyri and in the planum temporale[9,12]; thus, the source areas of N100m probably include both primary and association cortices.[13] The N100m properties depend, in part, on the ear of stimulation (with contralateral dominance), features of the sound stimulus, and interstimuli interval. The N100m displays a strong individual variation, which is significantly correlated across siblings, indicating high heritability linked to chromosomes 2, 3, and 8.[14] This interindividual and intraindividual (between hemispheres) variability of N100m results in a wide range of normal values of latencies and response amplitudes, making identification of pathological values difficult in clinical practice. The replicability of N100m responses is good.[15] Some problems related to between-hemisphere variability of N100m may be diminished by studying N100m responses within one hemisphere to stimulation of ipsilateral and contralateral ears; possible effects of peripheral hearing differences, however, need to be taken into account in this approach.[16] Figure 1 displays an averaged AEF waveform and the magnetic field contour map elicited by a monaurally presented tone, and a source of the response modeled with an equivalent current dipole.

The N100m response is followed by P200m, N250m, and, when the stimulus is a long one, by a sustained field, ending with an off response. In children younger than 10 years, an AEF at about 100 ms after the stimulus onset but with an opposite orientation to that of N100m (P100m) and a subsequent N200m are the most prominent deflections. The response latencies are changing across childhood and mature toward adult values in early puberty.[17,18]

SSRs

When the stimulus rate increases up to about 1 to 2 Hz, the responses to successive stimuli overlap and form sinusoid-like "steady-state" responses at the stimulation frequency. The strongest SSRs in the auditory system are induced at about 40-Hz stimulus rate. Source analysis implies that SSRs (at modulation or repetition rates <70 Hz) are generated in the auditory cortex,[19] mainly by concatenation of middle-latency responses to successive stimuli.[20] The responses can be analyzed both in frequency and time domain, and can be used for tagging stimulus features by a specific frequency. For example, an input to each ear can be labeled with a specific frequency during binaural stimulation to study features of binaural suppression.[21] This approach revealed developmental function of specific genes for axonal crossing between auditory cortices.[22] The test–retest reliability of the SSRs, particularly their phase consistence, was good. An MEG

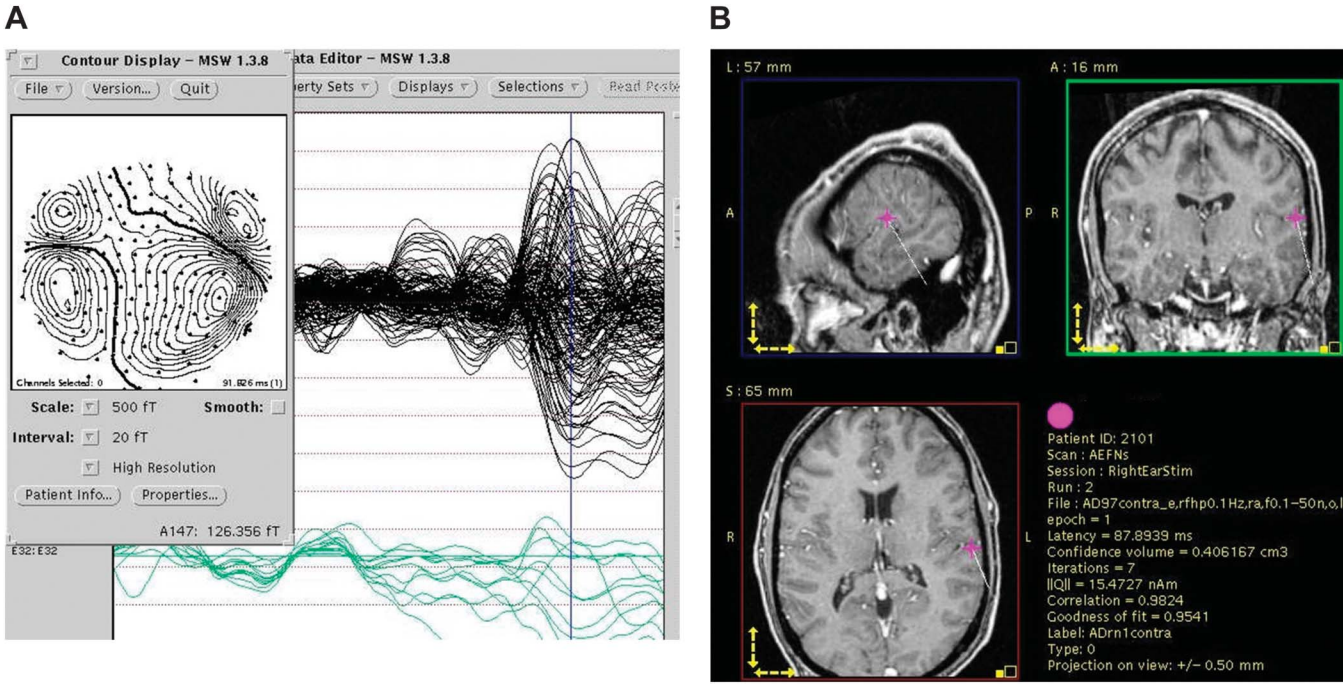

FIG. 1. Auditory evoked fields (AEFs) to left-ear stimuli in a 29-year-old right-handed man with suspected focal epilepsy and no interictal epileptiform activity either on EEG or MEG studies. **A**, Auditory evoked fields with contour plot of the magnetic field. **B**, Equivalent current dipole (ECD) mapped on the patient's brain MRI localizes to the ipsilateral Heschl's gyrus (Courtesy of Susan Bowyer). MEG, magnetoencephalography.

reconstruction of the SSR sources with the Loreta beamforming method has been postulated to enhance signal-to-noise estimates for 40-Hz ASSR.[23]

TASK-RELATED RESPONSES

Task-related modifications of evoked activity such as mismatch responses elicited by oddball deviations of a repeating sound sequence, speech-related N400 responses, or effects of attention are used to probe human information processing strategies. The mismatch negativity (MMN for the EEG-based recordings) and mismatch field (MMF for the MEG-based investigations) are methods to investigate the effects of transitions within stimulus sequences. The techniques emphasize the difference between one repeated stimulus that becomes standard and a second stimulus presented occasionally that becomes a deviant. Mismatch paradigm elicits a clear MEG deflection over the auditory cortices. In intracranial recordings, the deviant responses are generated in a wide area of the lateral Heschl's gyri and supratemporal plane.[24] Mismatch fields have been extensively used as markers of various cognitive properties in innovative and elaborate experiments. Mismatch negativity and MMF display a large interindividual variability and occasionally intraindividual variability between hemispheres as well. Their replicability in healthy subjects is less than optimal, and the reliable dipole modeling of the MMFs cannot be performed in both hemispheres in about 20% of the subjects.[25] Mismatch fields are smaller in amplitude in aged subjects than those in young healthy subjects.[26]

The N400m response has been used to test perception of speech components as well as phonologic and semantic language structure and is generated in multiple cortical areas[27] including the posterior aspects of the middle temporal gyrus. It has been observed as early as 12 to 18 months of life. Dipole modeling localizes N400m sources to superior temporal cortices, whereas distributed current-source modeling points to middle and anterior temporal sources.

OSCILLATORY BRAIN ACTIVITY

Oscillatory brain activity is one of the mechanisms that underlies auditory perception and comprehension of spoken language. The data are usually analyzed in time-frequency space and topographical frequency maps. In auditory processing of language-type stimuli, it appears that 4-Hz MEG oscillations represent syllables, whereas words formed from these syllables are coded with 2-Hz activity and sentences with 1-Hz activity. Similar oscillatory activities can be recorded from subdural grids with the same stimuli from broad cortical areas, including the temporal and frontal lobes in both hemispheres.[28] Features of syllables may be determined by mechanical units of language apparatus defining natural oscillatory rhythms; natural mandibular cycles occur at about 4 Hz.[29] Stimulus-locked and stimulus-induced oscillatory activity are increasingly used also in studies of different patient groups.[30,31]

CURRENT CLINICAL ROLE OF AEFs

The current clinical use of AEFs targets patients whose auditory cortex is affected by direct or indirect pathological processes.[4] N100m latencies are delayed by brain tumors in the posterior temporal lobe[32] or in patients with focal epilepsy localizing to the auditory cortex.[33] The functional localization of the auditory cortex by using sources of N100m AEFs has been considered useful for planning surgery in the left temporal lobe because the left auditory cortex is often surrounded by the language-related cortex.[32] Language lateralization can be achieved by calculating hemispheric ratio of sequential single dipole source clusters accounting for responses elicited by audible words in a recognition memory task. The method combines speech lateralization and activation of short-term memory processes, both provide useful information in planning of temporal lobe surgery. An agreement with the Wada test has been reported in 87% of the patients. The results are considered useful for preoperative planning.[34,35]

UPDATE OF THE CLINICALLY PERTINENT RESEARCH

This summary is intended to review recent data from research studies and clinical trials that used MEG to investigate normal and aberrant functions of auditory pathways in humans. Authors examined both clinically and research-oriented techniques using AEFs that might be at a threshold of a wider application. Particular attention was given to potential nuances of data acquisition and interpretation in pediatric patient population. We did not chart the utilization of AEFs to lateralize or localize speech-eloquent areas for surgical planning, as this is already a well-established clinical use in individual patients. A number of reviewed studies were included to highlight present directions of preclinical research.

IMPROVEMENTS IN DATA ACQUISITION AND PROCESSING

Distinct patient populations pose specific challenges during clinical MEG studies. These include fetuses, children, patients exhibiting a high degree of involuntary movements, and subjects with preexisting hearing loss. Specialized equipment and post-processing techniques may improve clinical data acquisition in these patients. In addition, time collection and reliability of MMN responses can be improved with a novel paradigm.

Use of the specialized MEG equipment for pediatric populations has been advocated by a number of investigators. A 64-channel and 151-channel whole-head axial gradiometer MEG systems for children (Yokogawa/KIT, Kanazawa, Japan) have been constructed and tested with AEFs in healthy children[36] and in children with autistic spectrum disorder,[37] demonstrating that it is feasible to measure AEFs using a customized sensor configuration in a helmet size to accommodate children's heads and necks. Recently, additional whole-head systems designed specifically for pediatric studies have been described.[38,39]

Specific MEG devices with sensor arrays designed to fit the shape of pregnant women's abdomen have been available from the early 2000s for studies of fetal AEFs. It is also feasible to study neonates by attaching a cradle to these devices. This results in the neonates lying on one side, enabling a study of AEFs in one hemisphere. A recent study compared AEFs from fetuses and newborns in two laboratories and found that although newborns have stronger AEFs to white noise than tone stimuli, the fetuses do not display this difference. This was, at least in part, attributed to dampening the white noise sounds in the passage through the amniotic fluid and different environmental noise in the two conditions. It should be noted that although the newborns were studied in a quiet environment, the fetuses are surrounded by the maternal heartbeat, bowel movement sounds, and the maternal voice. Reliable AEFs were obtained from 59% of the fetuses and from 53% of the newborns.[40] The good replicability of the basic results between laboratories is encouraging. The need for specifically designed MEG devices for fetal studies and high number of rejected test subjects may, however, limit the development of this approach toward general clinical applications.

Particular subsets of patients present very unique challenges for data acquisition and processing. Airaksinen et al. examined patients with advanced Parkinson disease during subthalamic nucleus deep brain stimulation (DBS). Spatiotemporal signal space separation (tSSS) effectively removed strong magnetic artifacts generated by DBS from recorded MEG data in the majority of patients (Fig. 2). Ipsilateral auditory N100m responses in the right hemisphere were enhanced with DBS.[41] This enhancement, however, did not correlate with the clinical improvement induced by DBS. The results demonstrate that even very severe artifacts do not necessarily prevent the use of AEFs in patients, and that pathophysiology of different clinical conditions treated by DBS is amenable to AEF studies.

Both voluntary and involuntary movements during AEF recording could pose a significant difficulty for data postprocessing by smearing the recorded field patterns. Nenonen et al. processed AEFs of 20 healthy adults in stationary head position as well as while performing continuously tracked, controlled head movements with tSSS and SSS-based movement correction. The recorded AEFs were similar in amplitude to the reference recordings after movement correction. Source localization

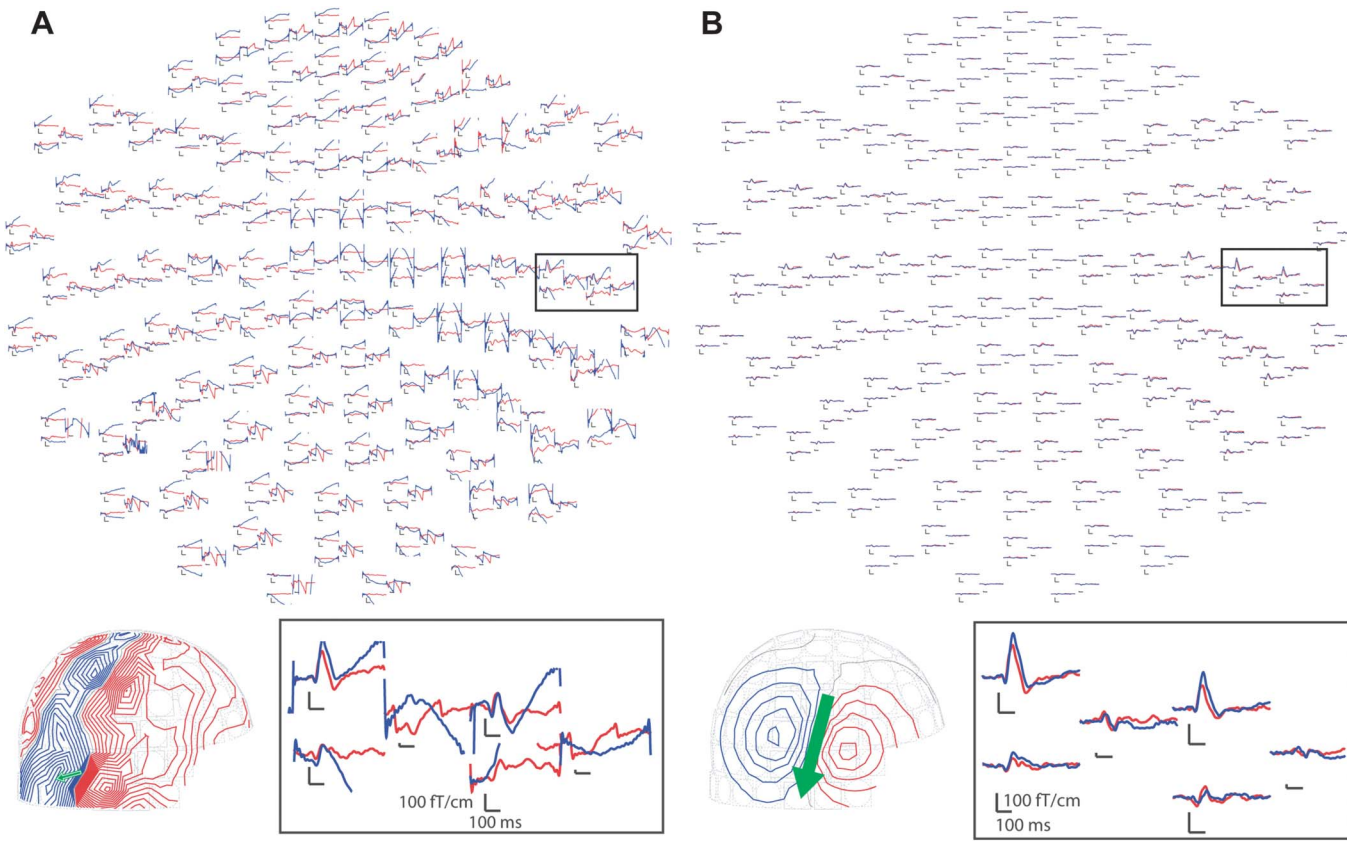

FIG. 2. Auditory evoked fields (AEFs) to right-ear stimuli in one patient before (**A**) and after (**B**) applying tSSS. The responses are viewed from above; the nose points upward. Auditory evoked fields in the squares are shown in enlarged form in the insets. Deep brain stimulation device (on: blue line and off: red line) produces very strong magnetic artifacts, particularly when switched on; the artifacts are effectively removed by tSSS. The filtered responses reveal an enhanced ipsilateral N100m during DBS on. In magnetic field patterns, red lines indicate flux out and blue lines into the head. The contour step is 50 fT. The arrow indicates the equivalent current dipole, estimated from the corresponding field pattern. Modified from Airaksinen et al. (2011), with permission. DBS, deep brain stimulation.

differed by 5 to 8 mm when tSSS and movement correction methods were combined, comparing with tSSS alone.[42] The methodology enhances applicability of AEFs particularly in children.[43]

Arithmetic averaging relies on the assumption of the additive model, requiring homogeneity of the variances of responses between the averaged conditions. Single-trial AEFs within the subjects usually fulfill this condition and justify the use of the arithmetic mean of the single trial responses as an efficient estimate of single-subject responses. When the AEFs across subjects are evaluated, it is apparent that the SD varies across time; thus, creating an averaged grand mean of single-subject responses does not fulfill the conditions of arithmetic averaging. This can be taken into account by mathematical transformation of individual single-subject responses.[44] This may produce a more accurate way to make comparisons of AEFs between groups of patients and healthy controls. Because the AEFs in single subject are precise when arithmetic averaging is used, the mathematical transformation of variance is not needed when sources of the AEFs are used for functional mapping in individual patients.

Hearing loss may affect AEF amplitudes and latencies. In the study conducted by Alain et al., AEFs were elicited in 17 hearing impaired and 17 normal-hearing seniors with complex tones that had either all harmonics in tune or had the third harmonic mistuned by 4% or 16% of its original value. The tones were presented without, with low, or with moderate Gaussian noise. The P50m amplitude was larger in the hearing impaired subjects than that in the normal-hearing subjects, whereas the AEF latencies were not systematically different. Similar noise-induced increases in N100m source strength were present in both groups. The enhanced P50m amplitude in the hearing impaired subjects suggests that hearing loss increased neural excitability in auditory cortices, which could be related to deficits in inhibitory control.[45] Thus, age and hearing impairment need to be taken into account in analysis of patient populations.

Inability to persist through or comply with the testing regiment has been frequently reported in the pediatric patients. Pihko et al. tested two groups of newborns, one with tactile stimulation only and another with alternating tactile and auditory stimuli. This approach improves the signal-to-noise ratio of the evoked fields, as the longer interstimulus interval within one modality enhances the amplitudes. The equivalent current dipole parameters of the somatosensory responses measured with and without the alternating auditory stimulation were equivalent and had expected source localizations in the contralateral postcentral gyrus and in the secondary somatosensory cortex around the Sylvian fissure, indicating that the intervening auditory stimuli do not interfere with the somatosensory responses. This study also demonstrated that auditory and tactile MEG responses in newborns can be obtained in one measurement session.[46]

The MMN requires long recording times and relies on the use of offline subtraction procedures. Both factors may diminish the signal-to-noise ratio of the MMN. The multifeature paradigm has been developed to speed up collection of MMN responses. The standard tone is composed of three sinusoidal partials. The five deviant tones differed from the standard by frequency band, intensity, duration, side of sound source (left- or right-sided rather than bilateral), and a silent gap. After each standard tone, one of the 5 deviants was presented in a pseudorandom order, such that in a sequence of 10 tones each deviant type was presented once, but the same deviant type was never immediately repeated.[47] This paradigm is naturally applicable to MMF studies as well,[30,48] and it speeds up considerably the collection of MMFs to various sound deviations. This feature is particularly important in studies of clinical patients.

Test–retest reliability of MMFs elicited by duration deviants and stimulus omissions was recently evaluated in 16 healthy subjects. The authors found good intraclass correlations of MMF amplitudes for duration and omission deviants (intraclass correlations 0.8–0.9); peak latencies were less replicable. Sensor- and source-level replicabilities were similar. Duration MMF was missing from one of the two measurements in two subjects, and MMF amplitudes were small in three. Omission MMFs were significant in five subjects in both sessions, and the MMF amplitudes were highly variable.[49] These results resemble previous replicability estimates[25] and emphasize that although MMFs are replicable in group-level analysis, individual variability is considerable and may produce difficulties when individual patients are evaluated in clinical practice.

DATA INTERPRETATION

The auditory cortex is, on average, more convoluted in the left than right hemisphere. This anatomical difference may produce stronger cancellation of electric currents underlying AEFs in the left than right hemisphere and result in a rightward bias in measured AEF amplitudes.[50] This needs to be considered when interpreting the hemispheric differences of AEFs in clinical patient studies.

POSSIBLE NOVEL CLINICAL INDICATIONS

Background: Some Previous Studies of AEFs in Patient Groups

Auditory evoked field studies have indicated plasticity of the central nervous system neural representations in unilateral deafness.[51,52] In children, unilateral sensorineural hearing loss appears to generate bilateral delay of N100m maturation, paralleling findings in patients with prelingual deafness after cochlear implantation.[53] Early AEF studies in patients with tinnitus reported enhanced N100m responses suggesting hyperexcitability of the auditory cortex,[54] but this finding was not replicated in other studies.[55] Steady-state response has also been reported to be enhanced in patients with tinnitus.[56] Auditory evoked fields to monaural stimulation in patients with strokes in the temporal region have demonstrated that N100m is modulated by cerebrovascular insults and completely abolished only by very large hemispheric strokes.[57] The N100m elicited by auditory transients is weaker in dyslexic adults than normal-reading adults.[58] Differences of the source locations of N100m between hemispheres seem to be aberrant in patients with schizophrenia (for a review, see Ref. 59).

Mismatch field may index cognitive impairment observed in a large number of different brain disorders, such as schizophrenia, chronic alcoholism, Parkinson disease, and Alzheimer's disease. Irrespective of their very different etiologies and symptoms, these disorders appear to converge at the functional deficiency of the auditory-frontal cortical network generating MMFs. This functional deficiency seems to index cognitive impairment shared by these brain disorders, along with normal aging.[60] N400m responses have been used to probe the pathophysiology of specific language impairment (SLI) and dyslexia.[61]

In the past decade, these conditions, as well as some additional neurological and psychological disorders, have been investigated using AEFs. Some of the findings are compelling to consider as new clinical indications for AEFs' utilization. Table 1 presents the suggestions of usefulness of AEFs in various clinical conditions arranged according to the AEF deflections.

New Studies in Hearing Disorders

The AEF index of hemispheric asymmetry in terms of ipsilateral/contralateral ratio at the acute stage was suggested to predict the 1-month hearing outcome of acute unilateral idiopathic sudden sensorineural hearing loss (ISSNHL).[62] In probing the predictive relevance of AEF hemispheric asymmetry to the hearing at the chronic stage, healthy-side dominance of N100m was observed initially and remained in groups of patients with complete, partial, and no recovery of hearing. This hemispheric asymmetry pattern did not predict hearing improvement at 1 year. The initial I/C amplitude ratio on affected-ear stimulation, probably reflecting the severity of the hearing loss, strongly correlated with the hearing level of the final stage in the ISSNHL. Because a restored hearing status did not necessarily lead toward a normal functional organization, the dynamics of hemispheric asymmetry was suggested to index a central reorganization in the brain for sound processing in the ISSNHL.[16] Lateralization of N100m and SSR has also been used to evaluate mechanisms of the ISSNHL recovery with "constraint-induced sound therapy," unilateral prolonged delivery of spectrally modified music to the affected ear. The hearing-level difference between the affected and intact ear improved more with the therapy than by traditional treatment. In a subgroup of patients, the amplitude difference between contralateral and ipsilateral N100m and SSR, absent in the acute phase, normalized during the therapy. This difference was considered to indicate that maladaptive neuroplasticity, favoring more symmetric auditory representations, was prevented by the sound therapy.[63] Thus, the AEFs are useful in pathophysiological studies of the ISSNHL, but they do not yet produce predictive information to estimate individual recovery.

Auditory evoked fields can be used to objectively evaluate hearing in patients with absent auditory brainstem responses due to auditory neuropathy. Bihemispheric AEFs were detected in these patients for both left- and right-ear stimulus. Although the latencies of N100m were severely prolonged and amplitudes were considerably decreased compared with the normal range, N100m latency was shorter in the hemisphere contralateral to the stimulated ear, as usually found in normal subjects, despite the abnormal delay in N100m latency. Auditory evoked fields were suggested to be useful to evaluate residual hearing in patients with auditory neuropathy.[64]

Several recent studies have probed the role of AEFs in studies of tinnitus. N100m changes observed in patients with tinnitus seem to be explained better by tinnitus-associated hearing loss than by tinnitus itself.[65] Despite this, AEFs have

TABLE 1. Suggested Future Clinical Applications for Different AEF Deflections

Recorded Parameter	Localization	Possible Future Clinical Applications
P50m	Heschl's gyri and planum temporale	Language development: most prominent component Autistic spectrum disorder: less leftward lateralization
SSR	As P50m	Schizophrenia: abnormal asymmetry Bipolar disorder: interhemispheric asymmetry ADHD: amplitude decrease
N100m	Lateral Heschl's gyri, planum temporale, and superior temporal gyrus	Autism: delayed latencies Autosomal dominant lateral temporal lobe epilepsy (ADLTE): increased amplitude Landau–Kleffner syndrome: increased amplitude Unilateral idiopathic sudden sensorineural hearing loss: ipsilateral/contralateral amplitude ratio correlated with the hearing level in the final stage Auditory neuropathy: prolonged latency and decreased amplitudes Acute stroke: prolonged latency and decreased source strength Subcortical ischemic vascular dementia (SIVD): delayed latency Schizophrenia: absence of normal hemispheric asymmetry Bipolar disorder: absence of normal hemispheric asymmetry Tinnitus: amplitude decrease with rehabilitation
MMF	Lateral Heschl's gyri, planum temporale, and superior temporal gyrus	Refractory epilepsy: decreased amplitudes Behavioral variant of frontotemporal dementia: reduced amplitudes Fibromyalgia: smaller amplitude in the right hemisphere; leftward asymmetry Risk of depression: amplitude increase
N400m	At least posterior superior and middle temporal gyri	Impaired language development: absent repetition effect in the left hemisphere

ADHD, attention-deficit hyperactivity disorder; AEF, auditory evoked field; MMF, mismatch field; SSR, steady-state response.

been used to elucidate the possible pathophysiological mechanisms of the tinnitus and to evaluate the rehabilitative procedures, such as tailor-made notched music training[66] or transcutaneous vagus nerve stimulation.[67] A recent detailed and critical review of the MEG in tinnitus research is available.[68]

New Studies in Ischemic Events

In patients during an acute phase of stroke, the N100m latency was significantly prolonged and its source strength was significantly smaller in the lesioned than nonlesioned hemisphere. In addition, the 3D interhemispheric difference of the source locations was larger in patients than in normal controls. Moreover, the N100m source strengths were stronger in the nonstroke hemisphere of the patients than those in the control subjects.[69] Auditory evoked fields of patients with subcortical ischemic vascular dementia had delayed N100m latency compared with the control group, likely reflecting impairment in the auditory pathways. These results suggest that AEF could be a sensitive and objective indicator for monitoring the course of subcortical ischemic vascular dementia.[70] It is apparent that AEFs will not be used in diagnostics of ischemic events in the near future. Prognostic information, not available from the general clinical picture but apparent in AEFs, would be important in clinical terms.

Monitoring Normal Development and Developmental Disorders

In pediatric studies, precise age group needs to be taken into consideration. In children between 2 and 5 years of age, P50m was the most prominent AEF deflection and its source strength in the left hemisphere was a significant predictor of language performance. The synaptic density in the auditory cortex reaches a plateau at about 10 years of age, followed by a rapid decrease. The same developmental trajectory was reported in P50 amplitudes.[71] The P100m is the most prominent AEF deflection in older children. Typically developing (TD) children (3–7 years old) were studied longitudinally over the next 3 years by AEFs elicited by human vocal stimuli. A significant relationship between language development and increased P100m amplitude was observed in the left hemisphere.[72]

Mismatch fields induced by varying stimulus frequency and language (native vs. non-native speech syllables) were recorded in 6-month-old infants, 12-month-old infants, and adults. The 6-month-old infants displayed increased relative theta power for frequent syllables, regardless of their status as native or non-native syllables, reflecting young infants' attention and cognitive effort to highly frequent stimuli ("statistical learning"). In adults, increased relative theta power for non-native stimuli was observed regardless of their presentation frequency, reflecting increased cognitive effort for non-native phonetic categories. The 12-month-old infants showed a pattern more similar to adults than to the 6-month infants. Speech perceptual narrowing may be governed by an implicit learning process involving a shift in attention from frequent events in infants to learned categories in adults.[43]

Language experience shapes infants' abilities to process speech sounds, with universal phonetic discrimination abilities narrowing in the second half of the first year. Brain measures reveal a corresponding change in neural discrimination, as the infant brain becomes selectively sensitive to its native language(s). In the study conducted by Ramirez et al., AEFs were elicited by Spanish and English syllables, presented in a double oddball paradigm to elicit MMFs in Spanish-English bilingual and English monolingual 11-month-old infants. In monolingual infants, English deviants produced stronger late MMFs, whereas in bilingual infants both late MMFs were similar. An equally strong late MMF response to Spanish and English can be interpreted as signaling equal phonetic sensitivity to both languages, as one would predict based on infants' dual language exposure.[73]

Auditory evoked fields of children with normal and impaired language development (SLI) elicited by spoken real words and pseudowords presented only once or two times in a row displayed group-level differences. In TD children, the N400m in the bilateral superior temporal cortices was attenuated to the second presentation of the same word. In the SLI children, the repetition effect was practically absent in the left hemisphere. The N400m was as strong to words as to pseudowords in the SLI children, whereas in the TD children the left hemisphere N400m was longer for pseudowords than words. The results suggest that the short-term maintenance of linguistic activation required for spoken word recognition is defective in the SLI, particularly in the left language-dominant hemisphere.[74]

Mixed findings of auditory response properties have been reported previously in patients with autism spectrum disorders (ASDs; for a review, see Ref. 75). Children with ASD exhibited significantly less leftward lateralization in their P50m source strength compared with the TD children. Furthermore, a shorter P50m latency in both hemispheres was correlated with higher language-related performance in the TD children, whereas this latency was not correlated with nonverbal cognitive performance or chronological age. The children with the ASD did not show any correlation between P50m latency and language-related performance; instead, increasing chronological age was a significant predictor of shorter P50m latency in the right hemisphere.[37]

In a carefully executed study of 25 ASD and 17 TD children in the age of about 10 years, the ASD group had prolonged N100m latency in the right hemisphere. The sensitivity of 75%, specificity of 81%, and positive predictive value of 86% were obtained for individual classification of ASD versus TD using the AEFs elicited by most distinctive stimulus frequency of 500 Hz.[75] The delayed AEFs in younger ASD children have been demonstrated as well.[76] In a longitudinal study, ASD and TD children were measured twice at 2- to 5-year intervals. Bilateral N100m and spectrotemporal measures (gamma-band power and intertrial coherence) were examined. N100m latencies were delayed in the ASD group versus the TD group at the initial examination and at follow-up, and were associated with clinical ASD severity. In addition, gamma-band evoked power and intertrial coherence were reduced in the ASD cohort versus the TD group. N100m latency and gamma-band maturation rates did not differ between ASD and TD groups. Despite evidence for AEF maturation in the ASD, the neural abnormalities in the ASD persisted across time. Magnetoencephalography measures were also separately analyzed for five children who exhibited "optimal outcome," being initially on the ASD spectrum but no longer

meeting diagnostic criteria at follow-up. They exhibited N100m latency and gamma-band activity values in-between the TD group and the ASD group. Data from the five "optimal outcome" children, although not statistically significant, suggest that such clinical outcomes may be associated with AEF values intermediate between the TD and the ASD groups. Larger cohorts are needed to determine whether the AEFs have prognostic utility.[31]

Auditory evoked fields may assist in separating subgroups of patients with dyslexia, attention-deficit hyperactivity disorder (ADHD), and attention-deficit disorder. Neuroauditory profiles of one hundred forty-seven 11-year-old children (37 with dyslexia, 37 with ADHD, 36 with attention-deficit disorder, and 37 TD) were charted with morphometry of the Heschl's gyri and planum temporale, with AEFs evoked with different instrumental sounds and synthetically generated harmonic tones, and with several psychoacoustic auditory tests. The patient groups had clearly larger planum temporale in the left hemisphere. The sources of the P100m were located in the planum temporale in the patients but in the Heschl's gyri in control subjects. Auditory evoked field peak latency differences between hemispheres were clearly larger in the patient groups than in the controls. The 3 disorder groups could be separated by 80% to 90% accuracy and control subjects could be identified from the 3 disorder groups with 80% to 100% specificity when all neuroimaging and behavioral tests were taken into account. The authors suggested that the measured parameters could be used as biomarkers of auditory-related developmental disorders.[77]

New Studies in Neurodegenerative Diseases

Patients with Alzheimer's disease appear to lack a frontal source component, apparent in AEFs of healthy age-matched controls both to standard tones and frequency deviants. This approach had a high accuracy, sensitivity, and specificity in identifying spontaneous Alzheimer's disease patients.[78] The research sample was relatively limited: only five patients with Alzheimer's disease were studied.

In patients with behavioral variant of frontotemporal dementia, the AEF amplitudes to standard tones were normal, but MMF amplitudes, induced with multifeature paradigm, were reduced. Network connectivity, in terms of coherence among frontal, temporal, and parietal dipole sources, was also abnormal in these patients. In the beta-frequency range, left frontotemporal coherence was reduced. In the gamma-frequency range, frontal interhemispheric coherence was reduced, whereas parietal interhemispheric coherence was enhanced. The results suggest impaired change detection resulting from dysfunctional frontotemporal interactions in these patients.[30]

New Studies in Psychiatric Disorders

Diagnosis of psychiatric disorders and monitoring of their pharmacological treatments depend on subjective interpretation of the patient's clinical signs by the treating physician. Ability of the MEG to demonstrate both normal and aberrant neuronal processing may contribute additional objective measures for clinical use. In patients with schizophrenia, 20- to 80-Hz SSR MEG recordings revealed bilaterally reduced SSR power and dipole moments specific to the 40- and 80-Hz frequencies, and less right-greater-than left 40-Hz SSR power and phase-locking factor compared with healthy subjects, indicating that patients with schizophrenia may be characterized by abnormal asymmetry of the 40-Hz SSR. Moreover, severity of global hallucinatory experiences was significantly associated with smaller left 80-Hz MEG SSR in patients with schizophrenia.[79] A recent meta-analysis of 14 EEG and 6 MEG SSR studies in schizophrenia suggested that 40-Hz SSR spectral power and phase-locking deficits are robust in schizophrenia, and that these measures could be useful probes for assessing circuit dysfunctions in the disorder. Large-scale studies of the longitudinal expression in patients with schizophrenia and at-risk populations to further validate the 40-Hz SSR as a potential biomarker were considered necessary. The source-level data in most MEG studies were considered particularly useful, as the underlying generators of the 40-Hz responses could yield insights into the underlying brain regions and networks involved in the SSR deficits in patients with schizophrenia.[79]

Euthymic bipolar patients and matched controls were evaluated with SSRs, and failed to demonstrate normal laterality (left–right interhemispheric asymmetry) of SSR.[80] In patients with schizophrenia or with bipolar disorder, a typical N100m asymmetry (more anterior sources in the right than left superior temporal gyrus) was not seen. The results may challenge the current nosological dichotomy between schizophrenia and bipolar disorder.[81] These limited findings suggest that the specificity of SSR changes for separating schizophrenia from bipolar disorder is not high.

Mismatch fields elicited with a variant of the multifeature paradigm of a 4-tone pattern called Alberti Bass were analyzed in 88 healthy subjects with different musical backgrounds and tendency for reporting depression. Risk of depression, assessed by clinically validated depression scales, was correlated with MMFs elicited by deviations in timbre and sliding pitch of a note. The authors attributed the result to unfamiliarity, mistuning, and unpleasantness of the deviant chords, as depressed patients appear to be more sensitive to negative and unpleasant stimuli.[82]

Novel Applications in Epilepsy

Analysis of AEFs may provide a more detailed understanding of aberrant neural networks in patients with epilepsy. Patients with autosomal dominant lateral temporal lobe epilepsy have recurrent auditory auras that are presumed to emanate from the auditory cortex or its association areas. In the study conducted by Usui et al., 3 of 5 autosomal dominant lateral temporal lobe epilepsy patients exhibited large N100 ms, exceeding the mean + 2.5 SDs of N100m in control subjects. The enhanced N100m was present in the patients having seizures provoked by auditory stimuli. Thus, a large N100m may be one indicator of the epileptogenic cortical area in this patient group.[83]

Patients with Landau–Kleffner syndrome demonstrate verbal auditory agnosia or impairment suggesting bilateral dysfunction of auditory- and language-related cortex. Twenty-eight children with Landau–Kleffner syndrome were evaluated. Twelve patients had normal AEFs, four patients lacked the response in one hemisphere, and seven patients had no AEFs at all. In 5 patients, 1% to 38% of tones evoked a typical spike at

a constant latency between 50 and 120 ms. Auditory stimulation can thus be used to enhance epileptiform activity in some of these patients. Sources of AEFs were located in supratemporal surfaces but were quite scattered. The topology of the AEFs overlapped the spike sources in the perisylvian cortex, indicating that the disease process modifies the auditory cortical organization. The six patients with a unilateral pacemaker of epileptiform activity (21% of all) were considered good surgery candidates.[84]

Ten patients with intractable epilepsy and matched healthy controls were studied with a multifeature MMN paradigm. All AEF amplitudes for standard stimuli were significantly decreased, and MMFs were smaller in the patient cohort than those in the control subjects. Although N100m amplitude associated significantly with neuropsychological processing speed index, the MMF latencies correlated with age of onset and duration of the epilepsy. Auditory evoked fields thus demonstrated a widespread impairment in patients with drug-resistant epilepsy.[48]

New Studies in Other Clinical Conditions

Patients with fibromyalgia often exhibit affective and cognitive symptoms including deficits in attention, executive function, and working memory. The amplitude of MMF in the right hemisphere was smaller in patients with fibromyalgia than that in healthy control subjects. The directional asymmetry coefficient of MMF amplitude was lower in patients with fibromyalgia, indicating more leftward asymmetry than in healthy controls. Smaller right MMF amplitudes were associated with lower pressure pain threshold at the thenar muscle. The results indicated that preattentive auditory processing is compromised in fibromyalgia.[85]

The SSRs induced by 40-Hz click trains are smaller in adult patients with ADHD than in their non-ADHD peers. This difference is diminished by amphetamine used as a psychostimulant in ADHD treatment.[86] The 40-Hz SSR may thus provide a tool to analyze effects of medication in these patients.

Mean AEF latencies of ten 3–5-year-old children with fetal alcohol spectrum disorder (FASD) displayed about 10-ms delay in the temporal activation when compared with age-matched TD controls. The mean values ranged from 110 to 150 ms in patients with FASD and from 95 to 130 ms in TDs and overlapped with the TD range in the majority of patients with FASD.[87] Auditory evoked fields in a larger group of adolescent FASD patients had significantly shorter P50m and N100m latencies in the left hemisphere than TD controls; no differences were observed in the right hemisphere. The changes did not correlate with the psychological profiles of the patients. The main difference was a widespread sex-specific differential activation of the frontal, temporal, and medial cortices in FASD patients compared with TD controls. The authors concluded that auditory processing delays may have potential as markers of functional disorders in very young children with FASD, but these measures may not be useful for older children.[88]

CONCLUSIONS AND RECOMMENDATIONS

The novel artifact rejection and movement compensation methods have improved the applicability of AEFs in studies of clinical patient and pediatric groups, so they can be recommended for use when AEFs are needed for clinical purposes. New MEG systems designed specifically for children will probably enhance the clinical studies of developmental disorders in the near future. New ways of stimulus presentation to elicit AEFs may speed up data collection and increase the possibilities of faster patient flow. Faster data analysis methods and new ways to integrate AEF results into clinical decision making, such as automated integration of the data into hospital digital archiving systems, would further enhance possibilities of clinical use of AEFs by making the data quickly available for clinical use.

Novel research has described AEF findings on the group level in several cohorts of clinical patients (Table 1). Correlating AEFs with clinical symptomatology, validation of AEFs against standard diagnostic methods, as well as estimations of their sensitivity, specificity, and positive and negative predictive values would speed up acceptance of new clinical indications and use of AEFs in individual patients. Evaluation of such parameters is delightfully observed in recent studies.[16,31,76,78,89] Objective assessment of the effects of AEFs on clinical decision making or relation to patient outcome would be highly useful as well. The reported patient cohorts are often small, and confirmation of findings by recordings of similar patient groups from other MEG units is rare. This is not surprising, as the number of laboratories studying clinical applications of AEFs is limited.

The present data on new clinical applications, although highly interesting, are not yet sufficient to support expanding the indications in the current American Clinical Magnetoencephalography Society's Clinical Practice Guidelines.[4,5] In the near future, auditory MEG studies will probably provide useful clinical data particularly in management of the patients with developmental disorders, in individual tailoring of rehabilitation in adults, and in establishing a diagnosis of psychiatric disorders.

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