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INVITED REVIEW

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

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Summary: Using visual evoked fields (VEFs) to differentiate healthy, normal brain function from dysfunctional cortex has been demonstrated to be both valid and reliable. Currently, VEFs are widely implemented to guide intracranial surgeries for epilepsy and brain tumors. There are several areas of possible future clinical use of VEFs, including early identification of disorders, such as multiple sclerosis, Parkinson's disease, stroke, and human immunodeficiency virus–associated neurocognitive disorders. These studies have suggested that VEFs could be used to study disease pathophysiology or as a biomarker for early identification of a disorder. The current clinical practice guidelines of the American Clinical Magnetoencephalography Society for VEFs are sufficient. At this time, VEFs should be used clinically to identify visual cortex and potentially tailor surgical resections.

Key Words: Magnetoencephalography, Magnetic evoked fields, Visual evoked fields, Visual processing, Presurgical mapping.

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Visual evoked fields (VEFs) have been reliably used in clinical practice since the late 1990s. This is a standard clinical tool for tailoring a surgical resection in the occipital cortex.[1] In 2011, the American Clinical Magnetoencephalography Society (ACMEGS) published clinical practice guidelines (CPGs) detailing the analysis of spontaneous cerebral activity, presurgical functional brain mapping using evoked fields, magnetoencephalography (MEG) reporting, and the qualifications of MEG personnel.[2–5] Even more recently, the ACMEGS published a second position statement specifically detailing the value of MEG as a noninvasive diagnostic tool in the presurgical mapping of eloquent cortices and supported, "The routine clinical use of MEG in obtaining noninvasive localizing or lateralizing information regarding eloquent cortices (somatosensory, motor, visual, auditory, and language) in the presurgical evaluation of patients with operable lesions preparing for surgery."[6]

Although the "gold standard" for mapping eloquent cortices has been through direct cortical stimulation, MEG as a noninvasive diagnostic tool has established its effectiveness in identifying these regions.[1–3,6] This article will focus on utility of MEG in localizing eloquent visual cortex. It will begin by providing an overview of the current clinical role of VEFs in clinical practice. After this, an update of research and clinical developments that have followed the publication of the ACMEGS CPGs in 2011 will be reviewed. Finally, recommendations for clinical practice, based on previous studies and current research, will be outlined.

CURRENT CLINICAL ROLE OF MEG IN VISUAL MAPPING

Magnetoencephalography is a noninvasive methodology that directly measures neuronal signaling by recording the magnetic field created from dendritic, intracellular, electrical currents of the neuron at the surface of the head.[1–3,6–10] In EEG, the different conductivities of brain, cerebrospinal fluid, skull, and scalp lead to smearing of potential distribution on the scalp and therefore compromised localization accuracy. In contrast, magnetic fields are not significantly distorted by biologic tissues, which allows for superior spatial resolution of MEG compared with EEG. Finally, MEG exhibits a distinct sensitivity to tangential sources arising from sulci.[8,10] This is extremely useful in localizing primary visual cortex, as the triangular shape of the occipital lobe is composed of numerous sulci.[11] The clinically most accepted and used MEG source model is the single equivalent current dipole (ECD).[1–3,6–10] With the implementation of various acceptance parameters (e.g., confidence volume and goodness of fit),[12] the single ECD result is displayed on the patient's structural MRI, revealing the estimated source localization (thus called, magnetic source imaging).

Between 1968 and 1972, David Cohen demonstrated the ability to noninvasively measure and analyze magnetic fields produced from electrical currents of synchronous neuronal activity.[13,14] Throughout the 1980s and 1990s, many basic science VEF articles were published that supported the use of MEG to detect visual processing. These research studies are not included here because this article is limited to clinical studies that used VEF.

In this regard, Brenner published the first documented VEF study in 1975.[15] In three subjects, a reproducible response

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(P100m) was obtained 5 to 8 cm above the inion, and the authors concluded these results were, "… clearly localized in the vicinity of the visual areas of the brain".[3] After this, in 1991, Harding et al.[18] described topographic localization of the P100m response using half field and full field stimulation in four subjects. Then, in 1996, Nakasato et al.[16] outlined the clinical application of VEFs with coregistration of the VEF dipoles to a structural brain MRI. A robust P100m response was present in all healthy subjects, and this differed from four individuals with bitemporal hemianopsia and five people with occipital lobe lesions and hemianopsia. In the latter cases, only a P100m response was present in the unaffected occipital lobe.[16] A second VEF study in 1996 evaluated P100m response in five healthy subjects and revealed dipole localization within the bottom of the calcarine fissure.[17] In 1998 Ikeda et al.[19] demonstrated a VEF consisting of a large deflection with a latency of 100 to 120 milliseconds (P100m) that localized around the calcarine fissure. Finally, in 1998, the origin of the N75m, P100m, and N145m was studied in six healthy young adults.[20] The reliability of the dipole estimation was highest for the P100m response, and this dipole mapped to the calcarine fissure. Furthermore, the results were in agreement with the retinotopic organization in humans that was described by Holmes in 1945.[20] The authors concluded, "The presence of the retinotopic organization of the P100m thus suggests that its generator may be located in the cortex around the calcarine fissure."[20]

These studies have provided evidence that VEFs yield consistent results across different neuromagnetism laboratories, indicating reliability and external validity.[3,16–20] As detailed below, other studies have demonstrated internal validity in so far as occipital lobe lesions abolish or displace VEFs.[16,22] In a case study from 2004, VEFs were evaluated in conjunction with visually evoked potentials and electrocorticography.[21] The authors explained the differences between electrocorticography and MEG modalities, specifically outlining the differences in sensitivity to neuronal sources (e.g., sulcal compared with gyral sources) and spatial resolution. In this report, the authors stated, "… the magnetic field distribution for the VEF response clearly demonstrates the accuracy of the direction of the ECD." Moreover, by integrating electrocorticography, visually evoked potential, and VEF, the visual motion complex was accurately mapped.[21] Taken together, the reproducibility of VEFs and single ECD localization across different centers in conjunction with abolishment or displacement of VEFs in occipital cortex lesions and concordant results between VEFs and electrocorticography suggests that VEFs are both reliable and valid measurements of eloquent visual cortex.[3,16–21]

As the technique for acquiring VEFs became refined, many MEG centers have found it relatively easy to acquire, analyze, and report VEFs. Figs. 1A–1F illustrates normal VEFs in a 19-year-old right-handed young man with drug-resistant focal epilepsy undergoing an epilepsy presurgical evaluation. For a review of the minimum requirements for VEFs, please refer to Table 1.

AN UPDATE ON CLINICAL RESEARCH WITH VEFs

As detailed above, several studies have demonstrated VEFs yield reasonable, and consistent, results with the P100m localization within the calcarine fissure. Using VEFs to differentiate healthy, normal brain function from dysfunctional cortex was first documented by Nakasato et al.[16] when healthy subjects and individuals with pituitary adenomas compressing the optic chiasm and structural occipital lobe lesions were studied. The ability to differentiate normal and abnormal cortical function has been widely implemented to guide intracranial surgeries.

Our MEG center published one of the early series demonstrating the utility of VEFs in tailoring surgical resections. Grover et al.[22] reported a case series of 21 patients with temporoparieto-occipital lesions where VEFs guided the resection strategy. In this study, a black and white hemifield checkerboard pattern reversed at 1 Hz. A single ECD model was used to locate the VEF locations on the patient's brain MRI. In this series, 15 of 21 patients exhibited preoperative visual field deficits, and the VEFs altered the surgical treatment plan in 3 cases. In 1 case (patient #15), the patient had a complete homonymous hemianopsia, and the surgery was changed from a complete resection of the tumor, cyst, and margins to a limited resection of the tumor only. The VEFs indicated that the occipital cortex could detect the visual stimuli, even though the subject was unable to see the reversing pattern. All VEF latencies were delayed (the N75m had a latency of 155 milliseconds, the P100m had a latency of 189 milliseconds, and the N145m had latency of 242 milliseconds). The P100m was located just mesial to the wall of the cystic lesion in the right occipital lobe. The N145m was also along the mesial wall of the cystic lesion. Following this tailored resection, the patient experienced near total resolution of the hemianopsia[22] (Figs. 2A and 2B and Figs. 3A–3C).

Similar results were illustrated by Pang et al.[23] in 2014 in a series of case studies with 12 children using large check size, high-contrast, black-and-white, checkerboard pattern that reversed at 2 Hz. Using a single ECD model, the sources of VEFs were displayed on the patient's brain MRI. The VEF did not demonstrate significant differences in regard to the P100m latency or dipole moment. However, in the affected/lesional occipital lobe, there was a lateral shift in the dipole localization. The authors concluded that this was most likely due to mass effect from the lesion and also noted, "… function can be preserved when functional cortex is shifted, but not when it's damaged." In addition, they concluded, "This demonstrates the added value of MEG recordings as a tool in the neurologic examination."[23]

In this regard, Pang et al.[23] expanded the potential utilization of VEFs. Specifically, VEFs could be completed as a screening test to evaluate mass effect of lesions within functional cortex. At times, acquiring brain MRI in children can be challenging, while MEG is often a child-friendly technology. By quickly identifying VEFs that are abnormal, a patient's brain MRI could then be expedited if needed.

In another study, MEG and magnetic resonance axonography were used to reduce the risk of neurologic deficits in patients undergoing stereotactic irradiation. Overall, approximately 70% of the treatment plans were modified using these techniques. The authors concluded that the integration of evoked fields, including VEFs, and magnetic resonance axonography could limit functional complications from radiation therapy.[24]

Similarly, the use of three-dimensional anisotropy MRI and VEF were described in a case report from 2004.[25] These

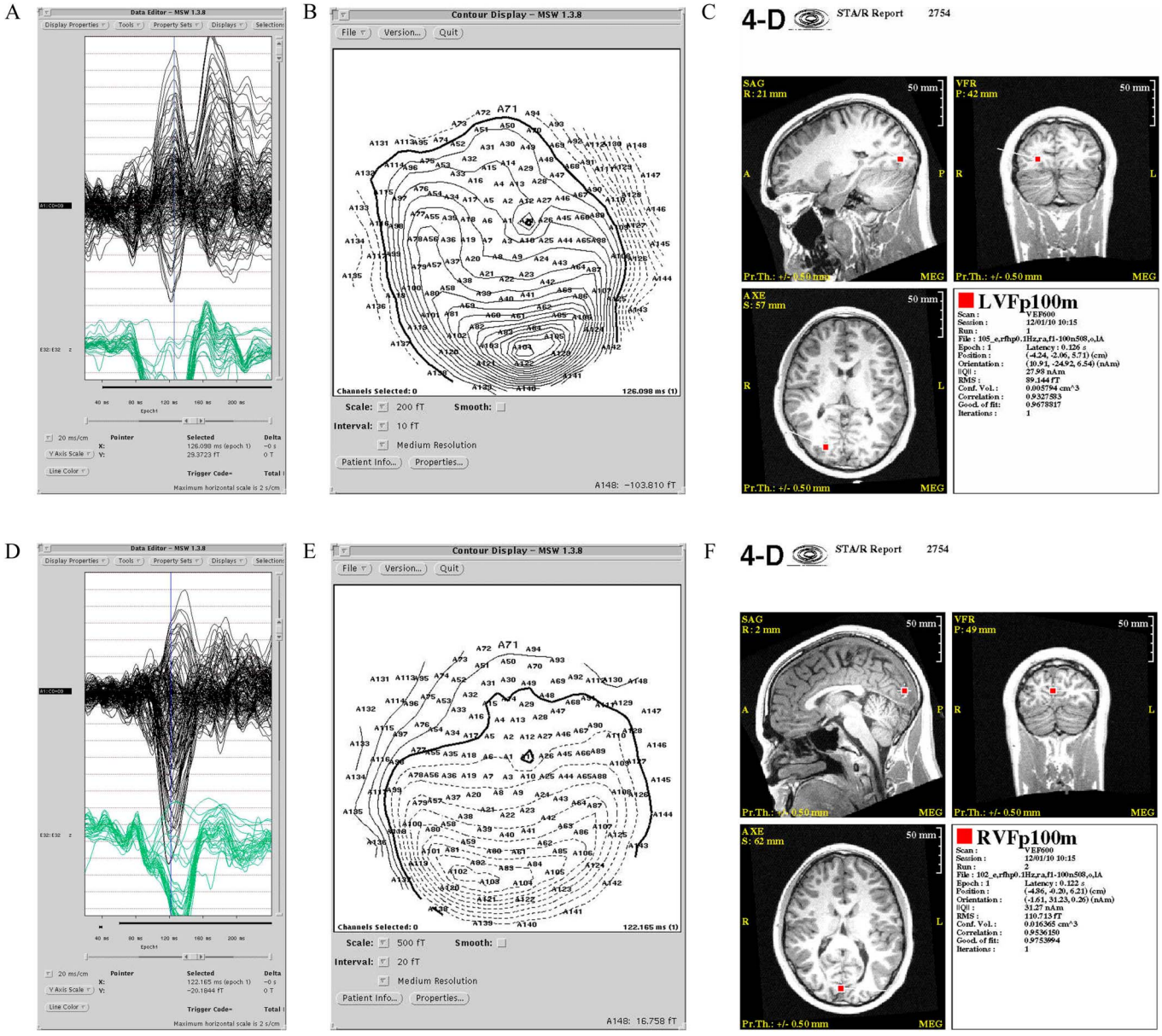

FIG. 1. **A**–**F**, Normal VEFs. The patient is a 19 year-old right-handed young man with drug-resistant focal epilepsy. His seizures would often consist of a visual disturbance without a loss of awareness. Video-EEG monitoring revealed seizures arising from the bilateral occipital lobes, and MEG demonstrated a source at the junction of the right superior parietal lobule and occipital cortex. **A**–**C**, The VEF for left hemifield stimulation, including the P100m peak (**A**), contour plot (**B**), and single ECD localization (**C**). **D**–**F**, Results of right hemifield stimulation with the P100m peak (**D**), contour plot (**E**), and single ECD (**F**). AXE, axial; ECD, equivalent current dipole; LVF, left visual field; MEG, magnetoencephalography; RVF, right visual field; SAG, sagittal; VEF, visual evoked fields; VFR, coronal plane.

techniques were used preoperatively to accurately localize optic radiations and primary visual cortex in a patient with an occipital lobe tumor. There was complete resection of the tumor with no visual filed deficits before or after the surgery.[25] Therefore, the combination of VEFs with tractography can be valuable not only in limiting injury to functional cortex but also in potentially reducing damage to white matter pathways.

The utility of VEFs in identifying visual cortex has been well established, and CPGs have detailed the minimum requirements for acquiring, analyzing, and reporting VEFs.[3,6] In addition, several studies have documented the utility of VEFs in differentiating normal and abnormal visual cortex, tailoring surgical resections, and as a possible screening tool for other diagnostic testing.[16,22–25] However, in clinical practice, the use of VEFs is relatively uncommon.[26] In a survey of clinical MEG centers in the United

TABLE 1. ACMEGS Clinical Practice Guidelines for VEF[3]

Indications
Localization of primary visual cortex before neurosurgical resections.
Assessment of abnormal visual function.
Stimulation
Typically generated using specialized presentation computer with image shown on a back-projection screen
To eliminate partial visual field effects, projectors must be chosen that can reduce the projected image.
To eliminate time errors or jitter, a timing synch pulse that is accurate to within 1 ms can be recorded by the MEG system to determine if the stimulus trigger pulse was accurately recorded.
To assess the visual system, full-field, hemifield, and/or quadrant steady-state stimuli may be used; contrast, luminance, screen placement, check size, and field size to produce appropriate subtended visual angle should follow the parameters used for conventional scalp visual evoked potential guidelines.
Half-field checkerboard reversal pattern with 1-s ISI is the most common procedure.
A fixation point should be provided. If the patient cannot fixate well, full-field stimulation should be used.
Adequate sleep of the patient before VEF testing is essential.
Data acquisition
Band pass of 0.03–300 Hz with a digitization rate of at least 1,000 Hz is preferred to facilitate postprocessing of the raw data.
Recording the raw data is mandatory to permit discarding undesirable trials or channels post hoc.
Real-time averaging is optional and may help to determine the number of necessary trials; 200–500 trials may be required to yield an adequate number of acceptable trials. Averaging off-line after data collection permits noise reduction processing and manual or automatic artifact rejection.
Epoch duration of −100 to 300 ms.
Stimulus channel indicators should be present and clearly labeled in the raw data to indicate stimulation triggers.
Jitter should be less than 50 microseconds.
Head position measurement should be carried out before each ensemble or data block. Use of continuous head position tracking is preferred if available.
The testing paradigm should be repeated to assess reproducibility and ensure consistent results.
Optional real-time averaging can be helpful to obtain an estimate of the SNR.
Data analysis
Recording of raw data should be mandatory and analysis system must permit post hoc averaging.
The analysis system must permit inspection of raw data.
Off-line averaging after data acquisition permits:
Noise reduction processing;
Elimination of artifact-containing traces;
Judicious selection of band-pass filtering (typical high pass cutoff from 1 to 9 Hz and low pass cutoff from 50 to 100 Hz).
Include sufficient trials to obtain a robust response, typically 100–200 artifact free epochs.
Source localization
During source analysis computations, the location of the P100m should be identified.
Ensemble replications should differ from each other by less than 5 mm for the localization of the P100m.

ACMEGS, American Clinical Magnetoencephalography Society; ISI, inter-stimulus interval; MEG, magnetoencephalography; SNR, signal-to-noise ratio; ms, milliseconds; VEF, visual evoked fields.

States, only 62 VEF studies were completed across 15 centers from 2006 to 2007.[26] The reasons behind the low use of VEFs in clinical practice are not well understood, but it could be related to a relatively low prevalence of epilepsy and tumors in the occipital cortex.

NEW CLINICAL VEF APPLICATIONS

Clinically pertinent VEF studies that would affect clinical decision making are limited. However, presently, several VEF studies are exploring the utility of VEF in various disease states. This is in line with the ACMEGS second position statement that advocated for "further systemic clinical research that seeks to establish other clinical indications for MEG."[6] Although the impact of these studies on clinical decision making has not been completely elucidated, these studies have shown promise in identifying various brain functions and classifying and characterizing different disease states.

For example, a recent study evaluated the peak latency of the first four components of VEFs in people with idiopathic Parkinson's disease (IPD) compared with healthy controls. The N75m and P100m components were significantly greater with the N75m-component latency markedly increased in people with IPD compared with healthy controls. Additionally, the N75m latency positively correlated with the Unified Parkinson's Disease Rating Scale score, indicating a greater disease burden. The authors also suggested that these results were induced by retinal damage and noted that the underlying pathophysiology of IPD may develop in conjunction with visual dysfunction in the early stages of IPD.[27] Therefore, the VEF abnormalities could be an independent marker of disease state and/or disease progression.

In another study, a single ECD was used to analyze VEFs in subjects with unilateral spatial neglect (USN) from a stroke. The presence or absence of the P100m and N145m after hemifield stimulation was determined. All three patients exhibited left USN, and the study demonstrated that early VEFs are disrupted. It also supported the hypothesis that visual processing deficits are different based on the clinical subtype of USN and the location of the lesion. For example, one patient in this study (patient 1) had an absent N145m response and a parietal lobe lesion, while

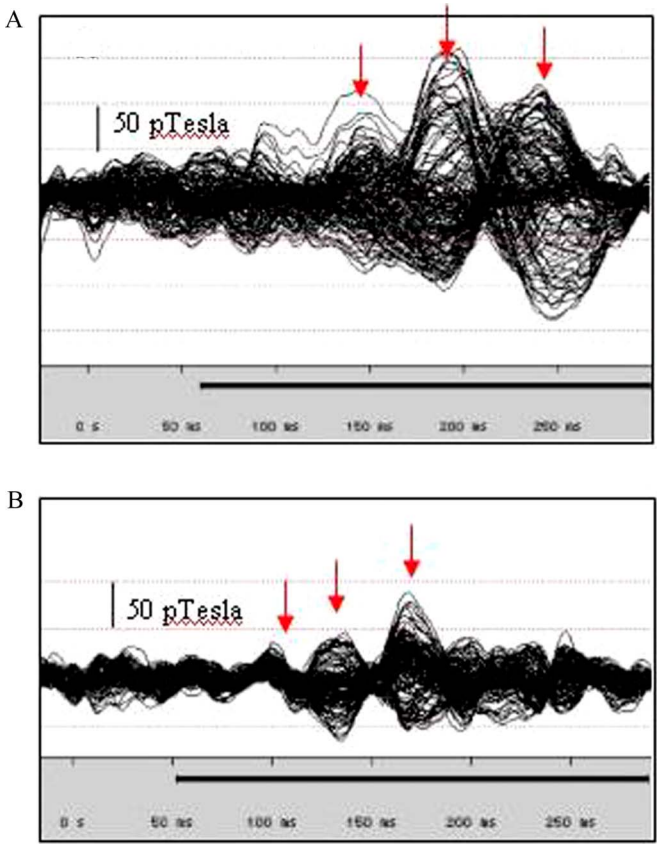

FIG. 2. **A** and **B**, VEFs in a patient with a right occipital mass. The patient is a 51-year-old man with a right occipital cystic mass and enhancing mural nodule. On examination and Goldmann perimetry, there was a left homonymous hemianopsia. **A**, VEF waveforms from left hemifield stimulation (affected hemisphere), while (**B**) demonstrates normal waveforms (N75m, P100m and N145m) following right hemifield stimulation. Please note the scale bar should correspond to 50 fT, not 50 pT as labeled. VEF, visual evoked fields.

another patient (patient 2) had USN but a lesion extending to the temporoparietal junction with an absent P100m response. The authors suggested the possibility of using VEFs to study subtypes of neglect.[28]

Visual evoked fields were also studied in human immunodeficiency virus (HIV)–associated neurocognitive disorders and multiple sclerosis (MS).[29,30] In 2013, Wilson et al.[29] evaluated visual processing in individuals with HIV. In this study, subjects viewed a small checkerboard pattern in the top right visual quadrant. In place of a single ECD, beamformer technique was used and results coregistered to the patient's brain MRI. Control subjects without HIV exhibited increased neuronal synchronization in the theta and alpha frequency bands within the right dorsolateral prefrontal cortex, right frontal eye fields, and posterior cingulate. In contrast, HIV-infected participants displayed reduced synchrony in these regions, and furthermore, the magnitude of these decreases in many cortical association regions was correlated to the neuropsychologic performance. The study concluded, "MEG-based imaging holds potential as a noninvasive biomarker for HIV-related neuronal dysfunction …."

Barratt et al.[30] used beamformer to analyze visuomotor responses in patients with MS. Beamformer is a spatial filtering technique that differs from the single ECD. This technique uses the MEG sensors and combines the signals recorded at each region in the brain to increase the signal-to-noise ratio (e.g., resolution). This technique then scans the entire brain region to find the active neural regions. In this study, time-to-peak postmovement beta rebound (a phenomenon associated with long-range connectivity of sensorimotor systems) during cognitive tasks (symbolic digit modalities test) was significantly increased in people with MS when compared with healthy controls. This result has clinical significance in that reduction in information processing speed is the most commonly affected cognitive domain in MS.[30] Although the methodology in this study differs from that in IPD (detailed above), the results suggest using visual tasks as a biomarker for disease progression in both IPD and MS. Specifically, in regard to MS, measuring the postmovement beta rebound may serve as a biomarker for cognition in people with MS.

Steady-state visually evoked fields were examined in processing positive and negative impression images. This study used the International Affective Picture System, which is used to examine emotional processes. A total of 200 images were categorized as "negative," "positive," and "neutral" according to the categorization in each subject. The location of the sources was within the same area in the occipital lobe. However, the amplitude of steady-state visually evoked field source was larger for "negative" impression images compared with "positive" impression images. The authors concluded that the emotional object modulated the steady-state visually evoked field amplitude. Furthermore, steady-state visually evoked field could be a measure of emotion.[31]

Visual images have frequently been used in MEG to evaluate cognitive function in healthy subjects, and repeated visual presentations may be used to collect data regarding underlying functional brain networks. For example, in a recent study of visuospatial attention, the investigators identified frequencies and anatomic networks in phase synchronization using source localized MEG data. Their results demonstrated that visuospatial attention was associated with long-range synchronization of high-alpha activity (10–14 Hz) within the frontal, parietal, and occipital regions. Additionally, stronger high-alpha phase synchronization was associated with decreased reaction times to attended stimuli.[32] Although this study did not use VEFs in the strictest sense, it may provide an opportunity to use VEFs in research and eventually clinical practice as a tool for measuring attention and other cognitive functions.

The implementation of these results into current clinical practice remains to be determined. However, they have provided insight in regard to normal brain functions (e.g., emotions) and the pathophysiology of various diseases from IPD to USN following stroke to HIV-associated neurocognitive disorders and MS.[27–32] The expansion of evoked fields, specifically VEFs, into other disease states may provide new clinical indications for VEFs outside of surgical planning.

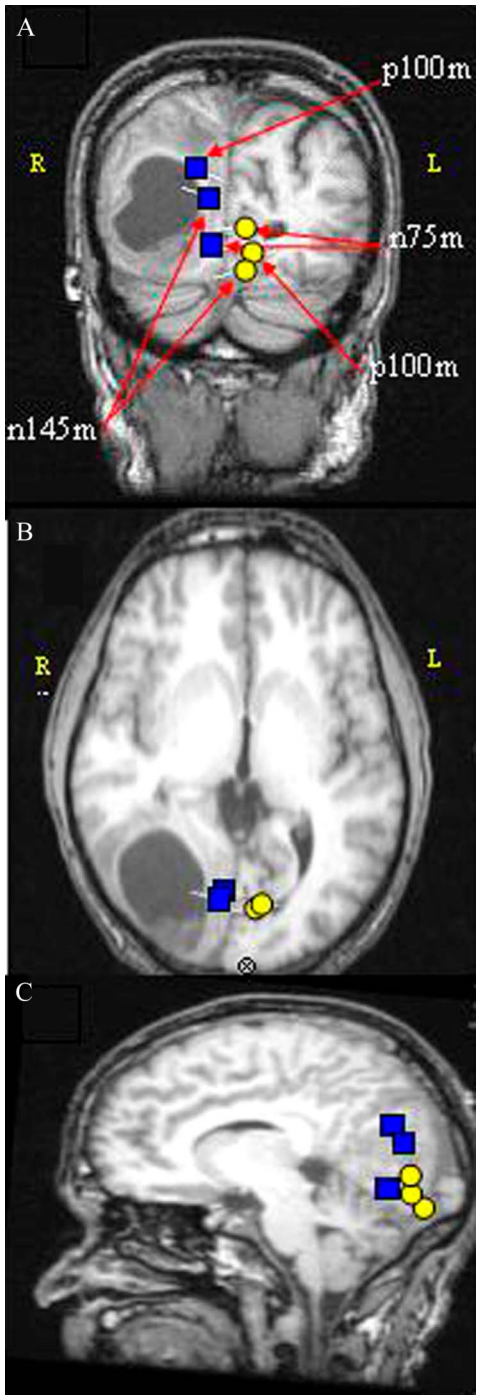

FIG. 3. **A**–**C**, VEFs in a patient with a right occipital mass. **A**–**C**, Patient from Fig. 2 (51-year-old man with a right occipital mass) with VEFs displayed on their structural brain MRI. Left hemifield stimulation is represented by blue squares and right hemifield stimulation is denoted with yellow circles. Coronal slice (**A**): 1.3 cm; axial slice (**B**): 4.6 cm; sagittal slice (**C**): 1.5 cm. These results changed surgical planning from complete resection of tumor, cyst, and margins to tailored resection of the tumor only. Following surgery, his left homonymous hemianopsia improved immediately. VEF, visual evoked fields.

RAMIFICATIONS AND RECOMMENDATIONS FOR CLINICAL PRACTICE

With the creation of the ACMEGS CPGs in 2011, the acquisition and analysis of spontaneous cerebral activity and evoked fields was standardized. Although not regularly used in clinical practice, the utility of VEFs in identifying visual cortex has been well recognized, and several studies have documented the ability of VEFs to differentiate normal and abnormal visual cortex and tailor surgical resections.[15–25] As described in previous paragraphs, more recent studies have suggested that VEFs could be used as a screening tool in assessing the need for more expedited structural brain imaging (brain MRI).[23] Other VEF studies have explored their utility in various disease states.[27–32] These studies have suggested that VEFs could be used to study disease pathophysiology (e.g., IPD) or as a biomarker in conditions such as HIV-associated neurocognitive disorders.[27,29] These clinical research studies provide support for future clinical applications of MEG and specifically VEFs.

CONCLUSIONS

Therefore, at this time, there is evidence that supports the current CPGs outlined by the ACMEGS in 2011. Continued research using VEFs outside of presurgical mapping of visual cortex may lead to new VEF clinical indications. If these techniques can be validated and standardized for specific diseases (e.g., HIV-associated neurocognitive disorders and MS), their inclusion in new clinical practice guidelines would be warranted. However, presently, the current CPGs for VEFs are sufficient, and VEFs should be used clinically to identify visual cortex and potentially tailor surgical resections.

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