INVITED REVIEW

Normal Variants in Magnetoencephalography

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Summary: Normal variants, although not occurring frequently, may appear similar to epileptic activity. Misinterpretation may lead to false diagnoses. In the context of presurgical evaluation, normal variants may lead to mislocalizations with severe impact on the viability and success of surgical therapy. While the different variants are well known in EEG, little has been published in regard to their appearance in magnetoencephalography. Furthermore, there are some magnetoencephalography normal variants that have no counterparts in EEG. This article reviews benign epileptiform variants and provides examples in EEG and magnetoencephalography. In addition, the potential of oscillatory configurations in different frequency bands to appear as epileptic activity is discussed.

Key Words: Magnetoencephalography, Normal variants, Epilepsy.

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BACKGROUND

The history of magnetoencephalography (MEG) is short compared with EEG, and therefore, the time needed—many decades in EEG—to confidently identify waveforms that "stand out" but are normal physiologic variants has not yet accrued.

These variant patterns have no pathologic significance. So-called benign epileptiform variants (Table 1) represent a subgroup, which show characteristics reminiscent of epileptic activity but are not related to any form of epilepsy. Sharp slopes and increased rhythmicity may be mistaken for interictal spikes and ictal seizure activity. In consequence, epilepsy may be wrongly diagnosed or true epilepsy may be mislocalized and misclassified as, for example, being multifocal.

In EEG, this is a well-known caveat in the context of epilepsy diagnosis and presurgical evaluation.[1] In MEG, however, little has been published either on the specific appearance of normal variants in MEG or on variants seen with MEG but less frequent or not at all in EEG. Knowledge and experience with a variety of waveforms from EEG however supports interpretation of MEG studies, especially when simultaneous EEG is recorded.[2]

This article aims to review MEG correlates of the most common normal variants, frequently encountered in recordings of epilepsy patients. Furthermore, MEG-specific variants are presented, which do not appear in a similar manner in EEG. We constrain the review to benign epileptiform–appearing variants, as these pose the greatest risk for misinterpretation, especially because epileptic focus localization for presurgical evaluation is one of the main clinical applications of MEG.

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General Considerations

Most EEG variants are radial in orientation or are generated by extended areas. The different sensitivity of MEG in comparison to EEG is therefore a significant factor causing different appearances of normal variants. Also, MEG is not sensitive to the radial component of a neuronal source.[3] In addition, large synchronously activated areas result in an increasingly radial sum dipole.[4] Furthermore, deeper sources show lower amplitudes in MEG, whereas sources on cortical surfaces closer to the skullcap present with higher signal-to-noise ratios in comparison to EEG.

Fields of vertex waves, for example (Fig. 1), have a predominantly radial component. While they are easy to identify in the EEG, MEG only shows signals from spurious tangential sources at the border of the field (e.g., over frontal and temporal regions). Without EEG, these waveforms can be difficult to distinguish from epileptic spikes or sharp waves. However, supramarginal sharp transients can be observed in the EEG of young children, but they disappear with further maturation and are usually not found in adults. In contrast, MEG is highly sensitive to the underlying mostly tangential sources and frequently detects these normal variants also in adults.

Simultaneous recording of even only low-density EEG is therefore not only highly recommended to recognize normal variants[5] but also helpful to detect and differentiate artifacts, such as eye blinks, muscle artifacts, and ECG and pulse artifacts. Finally, simultaneous EEG may yield additional spike types, which may not be visible in the MEG.[2,6]

The currently available MEG systems use different types of sensor designs. These differences of course impact the morphologic features and topography of the recorded fields. Planar gradiometers measure the magnetic field gradient on a plane parallel to the head surface. They strongly suppress noise and are highly sensitive for sources close to the skullcap. Interpretation is straightforward, as the amplitude distribution shows a maximum roughly over the generating sources. However, planar gradiometers reduce amplitudes of deeper sources even further in addition to the limited sensitivity of MEG for such regions. Magnetometers in contrast retain the sensitivity for deep source up to this

TABLE 1. EEG variants in MEG

Variant	Occurrence	Age Group, year	EEG					MEG
			Morphology	Single/Series	Slow Wave	Region	Uni-/Bilateral	
Transients								
Wickets	Drowsiness, sleep, sometimes during wakefulness	Adults, >30–40	Sharp, arciform, negative sharp, positive rounded	Single and series (6–11 Hz)	No	Temporal, parietal	Unilateral, independent bilateral	More irregular appearance because of different sensitivity
Small sharp spikes (SSS, BSSS, BETS)	Light sleep	Adults	Short (50 milliseconds), sharp, small spikes	Single	Subtle	Temporal	Unilateral, independent bilateral	Similar, may have larger amplitudes, unilateral occurrence may be more typical because of limited recording type
POSTS	Sleep	Age 6–12 and older	Sharp, monophasic, "reverse check-mark," medium to low amplitudes	Series (4–5 Hz), sometimes single	No	Occipital	Midline	May show multiple phases, deep localization because of diffuse distribution
Bursts/trains								
6-Hz spike waves	Wakefulness, drowsiness, not during sleep	Adolescents, young adults	Short, low-amplitude spike, prominent wave	Series (5–7 Hz) of <1 s	Yes	Occipital (FOLD-type), anterior (WHAM-type)	Bilateral synchronous	Similar but spike may be subtle with a more dominant wave
14- and 6-Hz positive spikes	Drowsiness, light sleep	Adolescents, young adults, children age > 3–4	Positive sharp, negative, rounded spikes, medium amplitude	Series (6–7 Hz or 13–14 Hz) of ∼1 s	No	Temporal posterior	Unilateral or bilateral independent	Low-amplitude oscillatory appearance or no correlate
RTTD	Relaxed wakefulness, drowsiness	Adolescents, young adults	Negative sharp, positive rounded or sharp patterns	Long series (5–7 Hz), no evolution	No	Temporal	Bilateral synchronous or independent	Similar, sharp/rounded appearance may be positive or negative, basal, midtemporal lobe localizations, tight clusters with uniform orientation
SREDA	Wakefulness	Middle aged, elderly	Mono- or biphasic waves with rhythmic theta/delta, abrupt onset, slow offset, 20 s to minutes	Series, up to minutes	Delta/theta components	Parietal	Unilateral or bilateral synchronous	Similar, topography corresponding to EEG, more pronounced morphology

BETS, benign epileptiform transients of sleep; BSSS, benign sporadic sleep spikes; FOLD, female, occipital, low amplitude, drowsy; POSTS, positive occipital sharp transients of sleep; RTTD, Rhythmic temporal theta of drowsiness; SREDA, subclinical rhythmic electrographic discharge of adults; SSS, small sharp spikes; WHAM, waking, high amplitude, anterior, male.

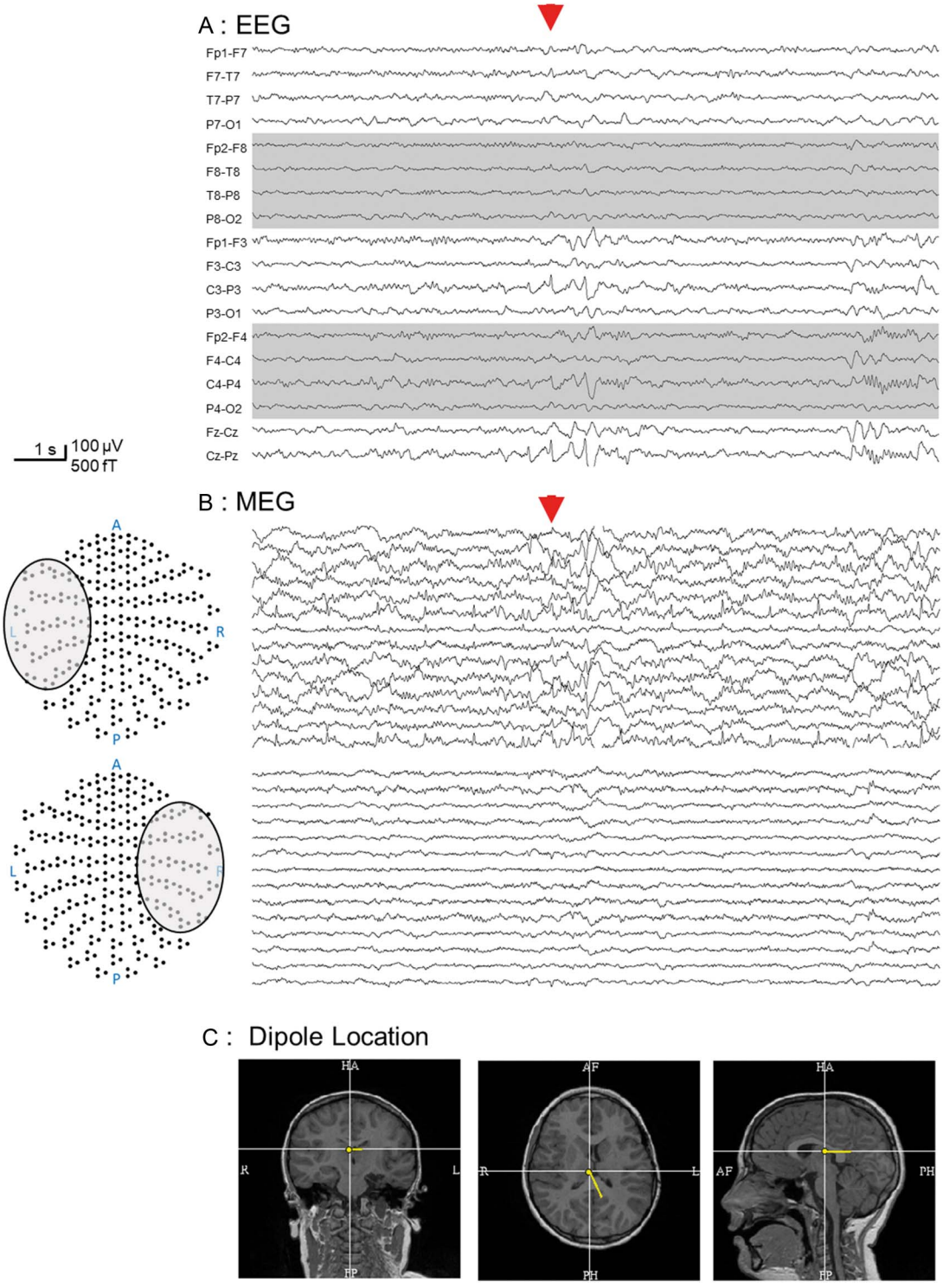

FIG. 1. Vertex wave mimicking a left frontocentral sharp wave. This 8-year-old patient underwent a left temporal lobe resection prior to the MEG, producing the asymmetrically increased signal background and abnormal slowing in the left hemisphere on the EEG seen in (**A**). This young child's head was displaced to the left inside the MEG recording array, also giving an appearance of a higher left-sided signal on MEG (**B**, planar gradiometers, 1.5–55 Hz band-pass filter). The distinct vertex waves on EEG correspond to MEG signals detected over both opercular regions but lack typical vertex wave morphology. Localization shows deep midline dipoles (C). MEG, magnetoencephalography.

technical limit. However, they are more susceptible for noise and are more difficult to interpret. Amplitudes show a gradient over the generating source, whereas the positive and negative poles are offset potentially even to other regions. Interpretation of the waveforms not only can thus rely on the position of these poles but also has to consider the complete field distribution. Axial gradiometers show a similar amplitude distribution. However, because they measure the difference in field strength along a radial axis, they are less sensitive to noise and to deeper sources. In these aspects, they take a position between planar gradiometers and magnetometers.

Next to technical aspects, the investigated patient population further influences interpretation of the data. The examples shown in this review have been recorded from children, adolescents, and adults. We have not included data from young children and newborns. While there is considerable overlap, the spectrum of patterns generated by the early developing brain is very broad and exceeds the scope of this review. In addition, there is relatively less MEG data available for this age-group. Based on the experience with EEG, it would be expected that young children also show a broad range of normal variants in much higher frequencies than older patients.

NORMAL VARIANTS

Benign epileptiform variants both in MEG and EEG can be divided into several subgroups, sharing common characteristics: sharp transients, MEG-specific transients, burst/trains, and oscillations.

Sharp Transients

Sleep Transients

Localization using single equivalent current dipole analysis models the source as a single point. Therefore, when discharges with a relatively wide field are localized using a single equivalent current dipole, the location may be artificially pushed deeper to account for the more widespread cortical activation. This phenomenon is seen very commonly with diffuse sleep transients, as exemplified by the excessively deep midline location of the vertex wave in Fig. 1. Parenthetically, this figure also illustrates that MEG localization is not affected by a skull breach (note the increased EEG amplitude of the frontocentral discharge on the left) nor by asymmetrical placement within the MEG recording dewar (because the head was deviated to the left, the MEG signals from that hemisphere were much higher than from the right).

As is well known in electroencephalography, normal sleep activity is not always absolutely midline. Figure 2 illustrates two asymmetrically situated K-complexes, both of which have a worrisome spike and slow wave morphologic feature on MEG. Because of MEG's often earlier detection of a discharge, events can appear more "spikey" on MEG. The neighboring spindles, however, reassure us that this is benign. Locations of MEG activity during sleep can be found in an article by Lu et al.[7]

Wickets

Wickets (Fig. 3) are sharp, arciform patterns, which may occur in series or as single patterns. Especially, the single patterns pose problems for differentiation from epileptic spikes. Series of wickets show frequencies between about 6 and 11 Hz. The typical morphologic feature shows a negative sharp and a positive rounded component in EEG. Wickets never show subsequent slow waves. They occur over temporal and parietal regions either unilaterally or (independent) bilaterally. Wickets are more frequent in drowsiness or sleep and are typically observed in adults older than 30 and 40 years.

In MEG, wickets mostly exhibit very similar characteristics. Individual patterns also show rounded and sharp components; however, because of the different configuration of magnetic fields, the strict association with the positive and negative half-waves is not necessarily preserved. While wicket series show a regular morphology with limited variability over subsequent wickets, MEG wicket trains can be irregular with considerable variance. The reason for this different appearance even in simultaneous recordings is probably the different sensitivity to radial components. While the EEG signal may remain almost unchanged when the underlying source rotates from a tangential to a more radial orientation, the MEG amplitude will decrease. Thus, a regular and stable wicket series in the EEG may correspond to variable amplitudes with shifting topography in the MEG.

Benign Sporadic Sleep Spikes/Small Sharp Spikes/Benign Epileptiform Transients of Sleep

Benign sporadic sleep spikes (Fig. 4) are sometimes referred to as small sharp spikes (SSS) or benign epileptiform transients of sleep. As the name suggests, they appear as sharp transients with small amplitudes and short durations, typically shorter than approximately 50 milliseconds. Similar to wickets, SSS do not show a prominent subsequent slow wave, although more subtle slow deflections may be observed. Small sharp spikes only occur as single events and never as series. They are seen independent bilaterally over temporal areas. However, shorter recordings, which are typical for MEG, may show them only unilaterally. They appear most frequently during sleep stages 1 or 2 and disappear with deeper stages of sleep, which differentiates them from epileptic spikes, which may become more frequent.

Again, the appearance in MEG is in many cases very comparable. However, even quite subtle SSS can have an MEG correlate with surprisingly large amplitude. A subsequent wave component may be visible or appear considerably more prominent. This leads to an appearance that resembles epileptic spike waves more closely and thus deviates from the EEG appearance significantly. A potential explanation may be that SSS generators, especially of the following wave, are in confined superficial cortex areas. The generated activity would be less obvious in EEG but can be prominent in MEG. Consequently, MEG SSS may be easily mistaken for epileptic spikes if no simultaneous EEG is recorded. In such cases, the distribution over temporal areas may hint at the true nature of the event, although the characteristic independent bilateral distribution may be observed only with longer recordings, exceeding the duration of a standard MEG recording.

Positive Occipital Sharp Transients of Sleep

Other sharp transients with epileptiform appearance are the so-called positive occipital sharp transients of sleep. As the name

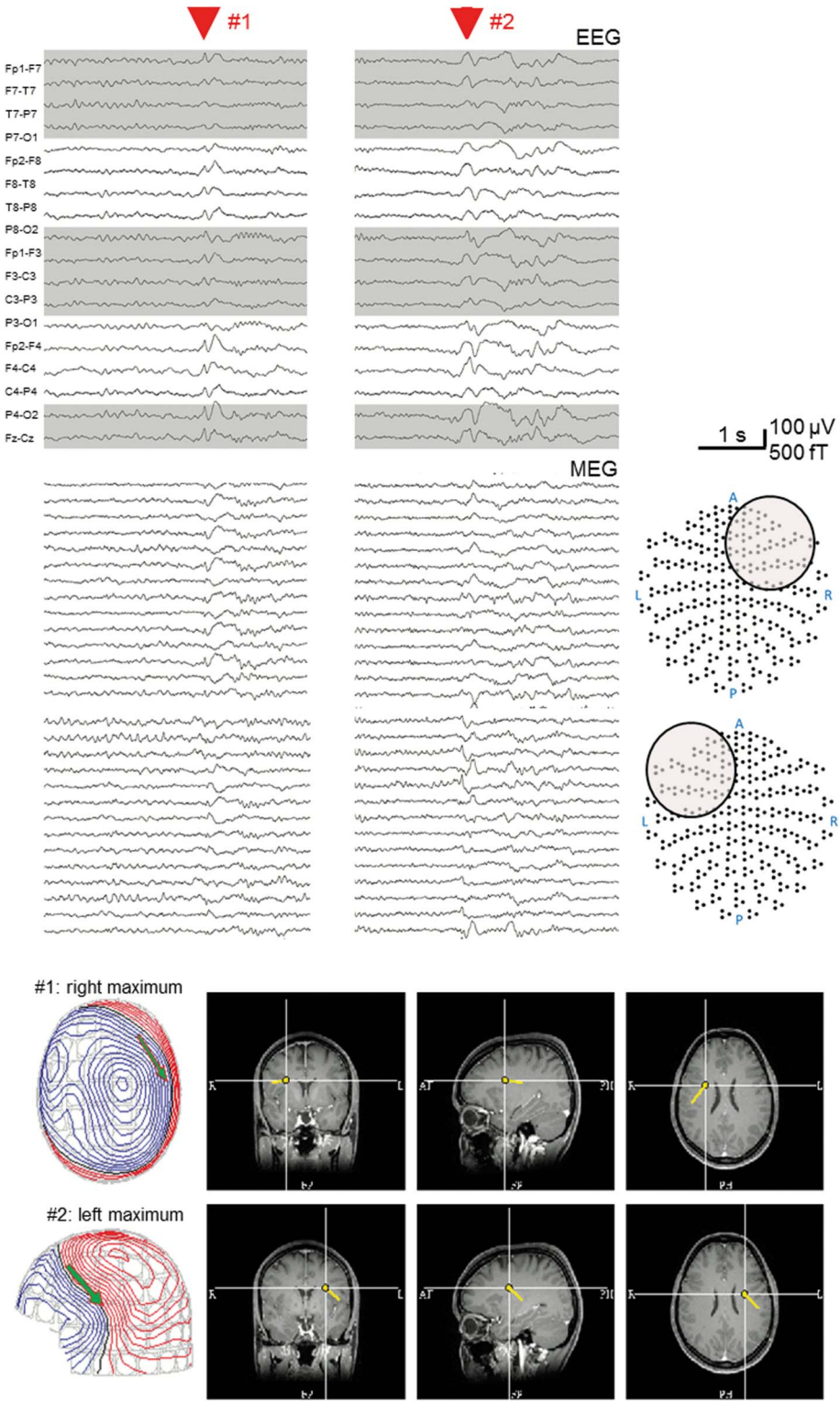

FIG. 2. K-Complexes from a normal MEG study, which included copious sleep. In the MEG traces (planar gradiometers, 1.5–55 Hz bandpass filter) on the right hand side of (**A** and **B**), the discharges (#1 and #2) have a spike and slow wave morphology. Notice, however, the spindle that immediately follows, seen most easily on the EEG channels, confirming that these K-complexes, normal sleep transients. Because of MEG's higher spatial resolution, discharges that seem only slightly asymmetrical on EEG are shown to be considerably off the midline on MEG. MEG, magnetoencephalography.

implies, they occur over occipital areas mainly during sleep stages 1 and 2. It has been suggested that their frequency is somewhat higher during daytime naps and thus may potentially occur during MEG recordings. Their morphologic feature is sharp and usually monophasic, resembling a reverse check mark, without a subsequent slow wave. Their amplitude is medium to low, around 50 to 100 µV. Individual patterns may occur; however, usually, several positive occipital sharp transients of sleep occur in series of 4 to 5 Hz.

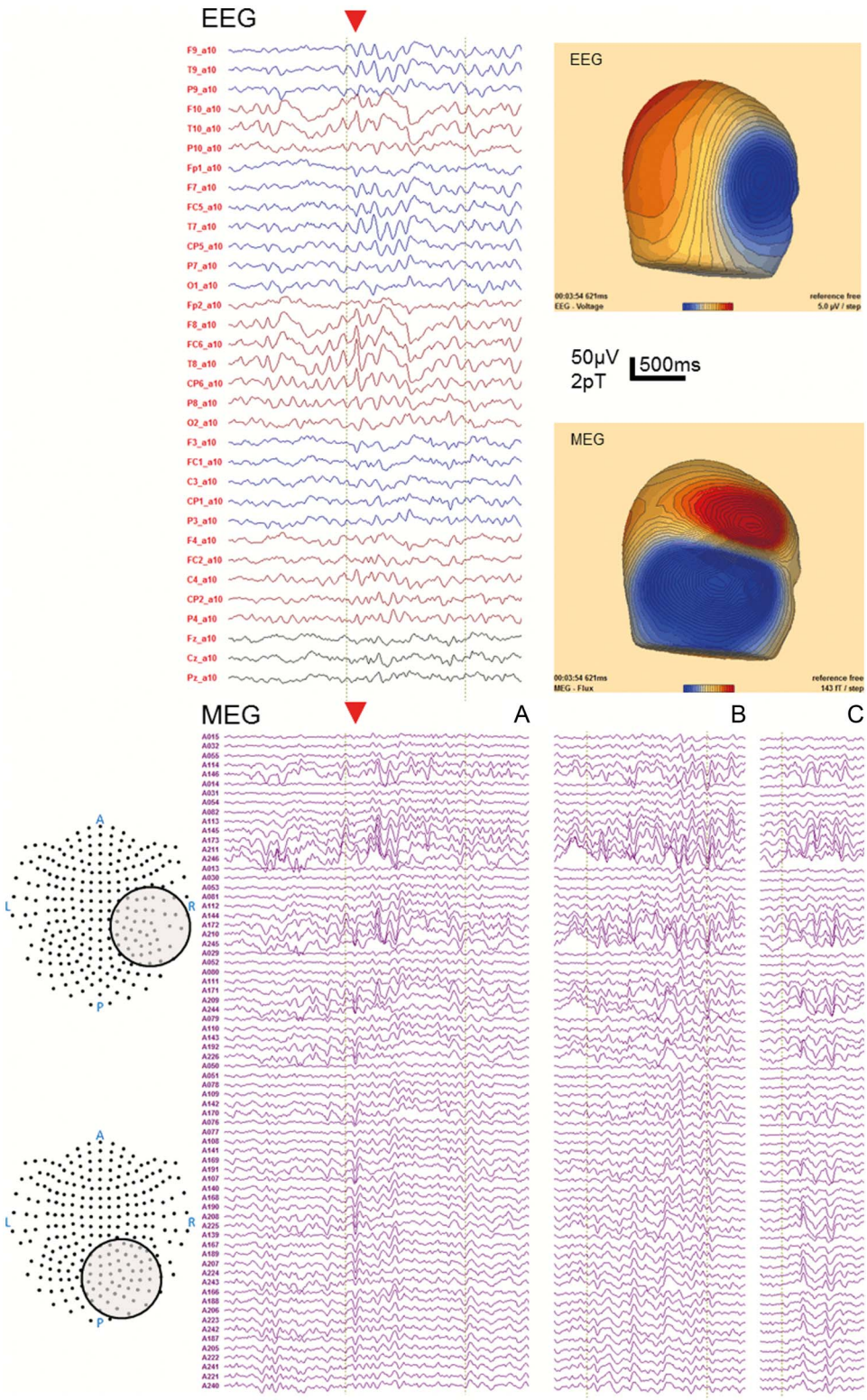

FIG. 3. Wickets in EEG and MEG (magnetometers, 1–40 Hz band-pass filter) (**A**), as well as further examples in MEG only (**B** and **C**). Amplitude maps are shown for example **A** at the time point marked by the triangle marker. Channels of MEG show magnetometer data from different areas. Examples (**A** and **C**) represent examples of wickets occurring in trains/bursts, whereas **B** is an example of a singular sharp MEG wicket waveform, which is nevertheless part of a more subtle oscillation. MEG, magnetoencephalography.

In MEG, positive occipital sharp transients of sleep may show multiple phases and a more variable appearance, more closely resembling an epileptic spike.[8] However, the typical monophasic time course may also be observed. The sources localize to the occipital midline and show both vertical and horizontal orientations (Fig. 5). Positive occipital sharp transients

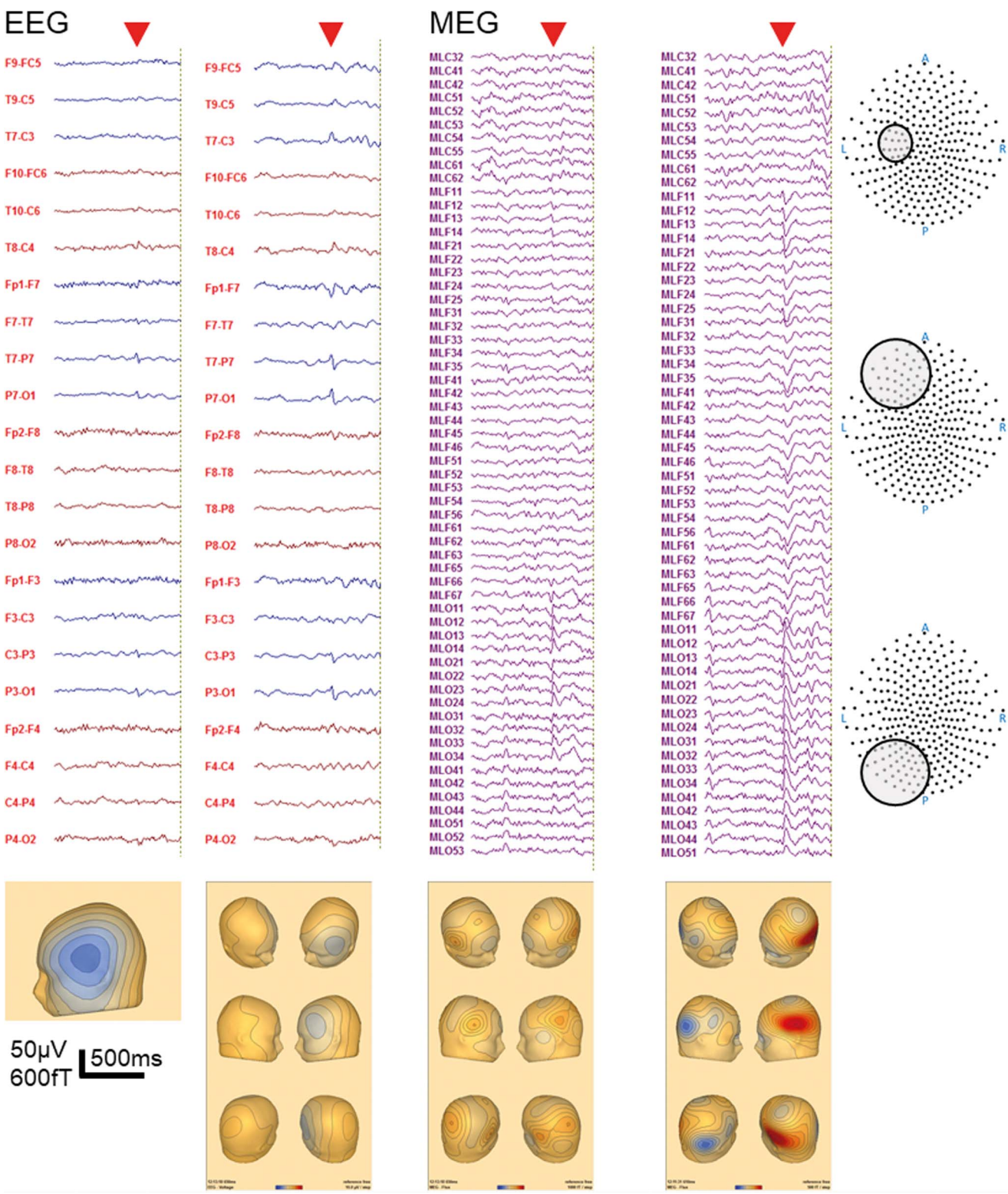

FIG. 4. BSSS in simultaneous EEG (left) and MEG (right, magnetometers, 1–40 Hz band-pass filter). Amplitudes maps are shown for the time points marked with triangles. While EEG shows only small waveforms, the MEG correlates vary in amplitude and appearance, probably because of differences in orientation of their generators and the sensitivities of EEG and MEG. BSSS, benign sporadic sleep spikes; MEG, magnetoencephalography.

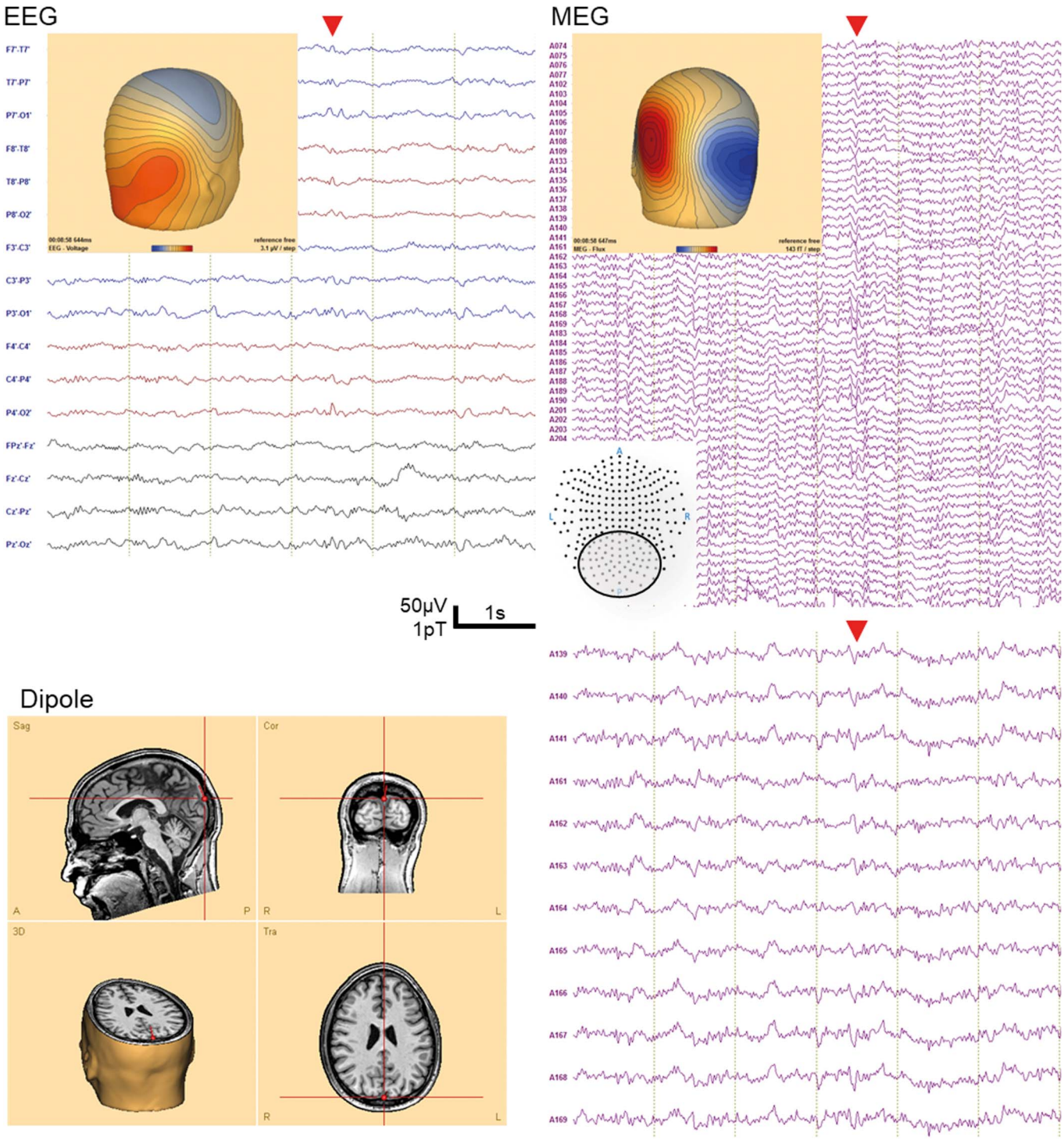

FIG. 5. POSTS in EEG (left) and MEG (right, subselection of posterior channels, magnetometers, 1–40 Hz band-pass filter) showing an occipital pattern with respective occipital dipole localization near the midline. In some cases, topography and dipole localization may be shifted to either side. The MEG waveform shows a spike-like pattern followed by a subtle wave in some channels (A161, A162, A163), which is not always present. MEG, magnetoencephalography; POSTS, positive occipital sharp transients of sleep.

of sleep may also exhibit an artifactually deep single equivalent current dipole location because of a diffuse occipital distribution.[8]

Magnetoencephalography-Specific Transients

There are normal variants that are ordinarily seen only in the MEG channels and will be unfamiliar to the novice magnetoencephalographer. The morphologic features of many of these MEG-unique transients mimic epileptic discharges. Analogous to the tragedy of misidentifying normal transients in EEG as epileptic,[1] mistaking a normal MEG variant for an epileptic discharge, can lead to inappropriate therapeutic decisions or—in the worst case—a misplaced intracranial investigation. Like normal but epileptiform-appearing EEG transients, normal MEG variants can stand out prominently from the background and be very sharply contoured, making proper identification on purely morphologic grounds very difficult. In addition, MEG variants may occur with any phase, depending on the orientation of the sources. That is, the magnetic flux patterns may be reversed, leading to dipole models, which differ by 180° in orientation but have similar localizations (Fig. 11 for an example).

Magnetoencephalography variants with sharp morphologic features are frequently encountered in perisylvian, supramarginal, and perirolandic localizations. They occur during wakefulness and drowsiness, but the influence of different sleep stages is unclear. These spike-like waveforms are also known in EEG, where they are considered a developmental phenomenon that usually resolves by puberty. Because of the high sensitivity of MEG to sulcal sources, these may still be seen in MEG beyond that age.

Because the clinical application of MEG plays its most critical role in the evaluation of epilepsy patients in whom accurate localization of the epileptogenic zone is paramount for the determination of their candidacy for resective surgery, distinguishing truly epileptic discharges from epileptiform-appearing variants is one of the most important tasks of the magnetoencephalographers. The following normal variants can be especially vexing.

Sharp Perisylvian Magnetoencephalography Transients

In continuous MEG recordings of epilepsy patients, sometimes, sharp transients over the temporoparietal cortex are identified. Their morphologic feature is sharp, although not prototypical for epileptic spikes. The duration is in the range of an epileptic spike or sharp wave (i.e., 50 to 200 milliseconds). The field distribution is focal but may occur independently bilateral. Source localization yields perisylvian dipoles. Typically, there is no relation to the side or region of the epileptogenic zone. Clinical significance and specificity for patients in epilepsy is unclear.

Supramarginal Transients

The inferior parietal lobule hosts one of the most common MEG-unique normal variants. In the typical patient, as shown in Fig. 6, their morphologic feature is sharp, although not prototypical for epileptic spikes. The duration is in the range of an epileptic spike or sharp wave (i.e., 50 to 200 milliseconds). The

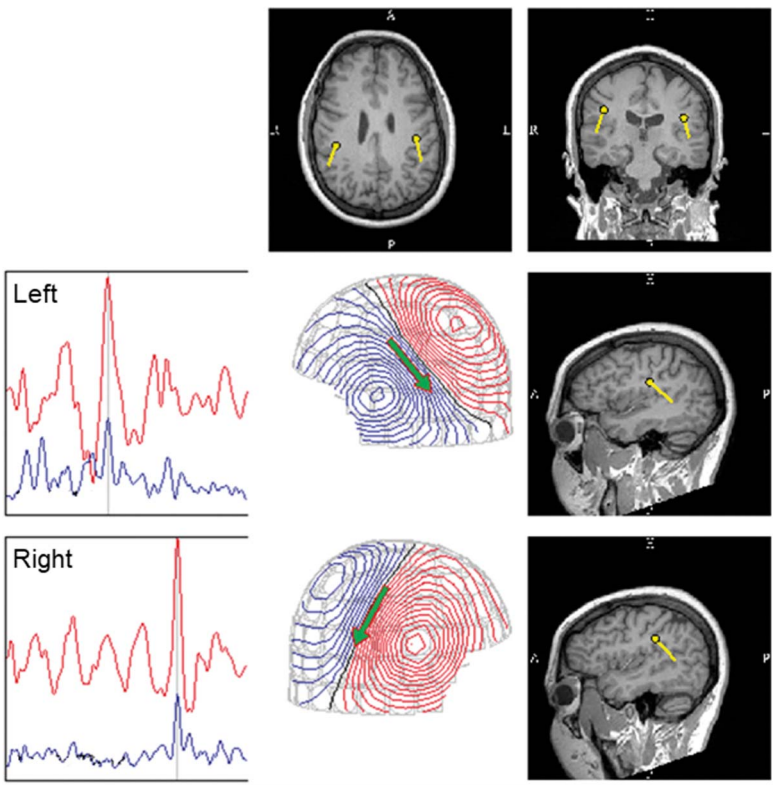

FIG. 6. Supramarginal transients: The field patterns, with the red/darker isocontour lines representing magnetic efflux (planar gradiometers) and the blue/lighter ones influx, demonstrate a dipolar pattern, and the dipole fits were statistically excellent. These two examples are from a 33-year-old patient, with left temporal lobe epilepsy, and show the classical location of the benign supra-marginal transients.

field distribution is focal but may occur independently or simultaneously bilateral.

While they usually have no EEG correlates, reinspection of the simultaneous EEG—after identifying the transient on MEG—will occasionally reveal a very small EEG transient, which would have been missed without the MEG fiducial. The second discharge in Fig. 7 illustrates this phenomenon, in the C4-P4 derivation, where a tiny transient can be appreciated on EEG, and somewhat less so on C3-P3 in the previous discharge. However, the simultaneous MEG shows very clear sharp transients. Note that the MEG morphology, while prominent, has a "benign" shape on both left and right, with an upslope that is more gradual than the downslope. These supramarginal transients often occur in runs (as shown in Fig. 8), and the case shown in Fig. 7 also illustrates that these transients are not limited to sleep (note the eye movements and electromyographic artifact on EEG).

Of course, not all MEG-unique discharges that localize to the posterior perisylvian region are benign. The example in Fig. 9 is from a patient with a normal MRI, whose discharges in the inferior parietal lobule were unilateral. The tip-offs that these are genuine epileptic spikes are that a small minority of discharges from the same region did exhibit tiny EEG spike correlates and many of the discharges on MEG included prominent after-going slow waves—a feature well known to electroencephalographers that increases the likelihood that a given transient is an epileptic spike.

Perirolandic Transients

Because the sensory and motor functions are located adjacent to the central sulcus, it is critically important not to misidentify transients from this region as epileptic discharges. Sharp transients that localize close to the hand motor area are often seen on MEG.

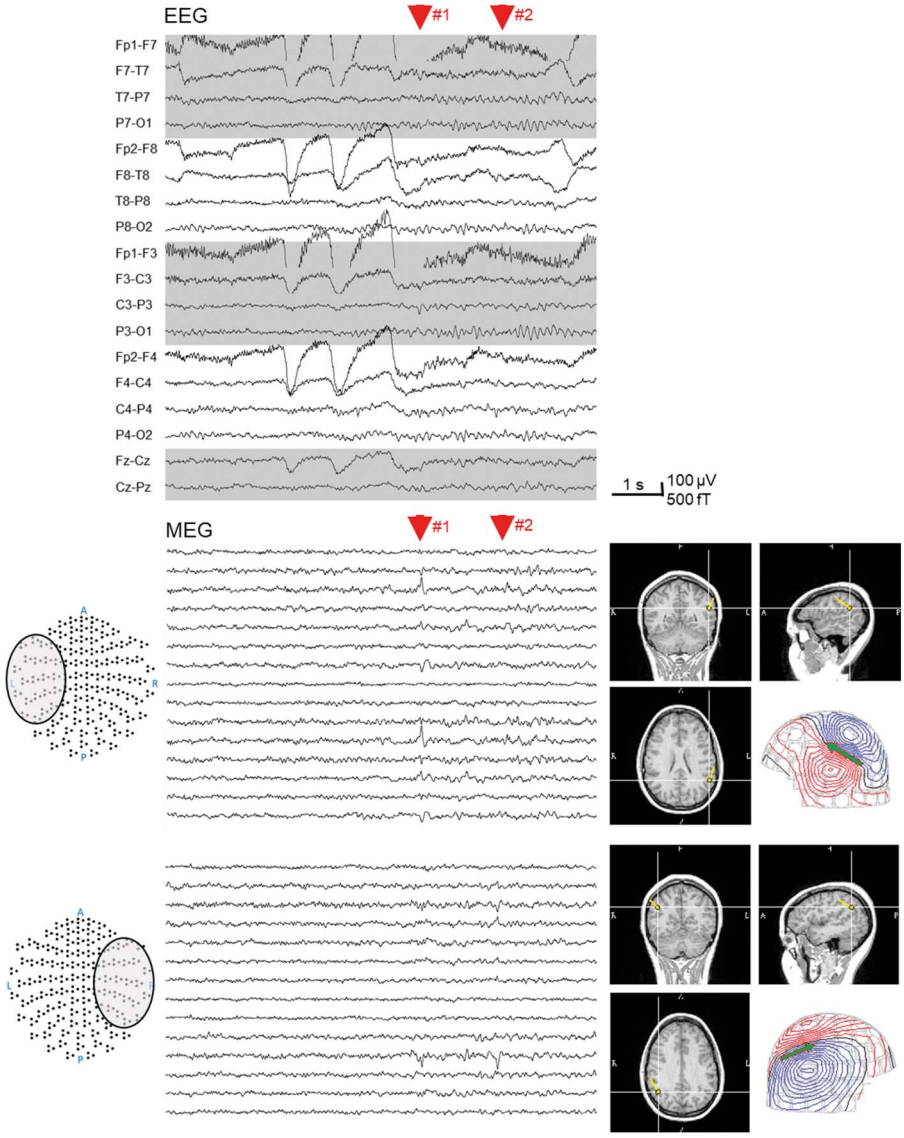

FIG. 7. Supramarginal transients: This common variant occurs during both wakefulness and sleep. The figure includes one discharge from each hemisphere less than 2 seconds apart. The awake state is confirmed by the eye movements and frontal electromyographic activity seen on the EEG, which also includes barely perceptible deviations in the left (#1) and right (#2) centroparietal derivations. On the MEG channels, these transients stand out markedly from the background (planar gradiometers 1.5–55 Hz band-pass filter). The results of single equivalent current dipole source localization is illustrated on the lower right place; these discharges in the typical left and right supramarginal gyral locations. The MEG examination on this 16-year-old patient was entirely normal. MEG, magnetoencephalography.

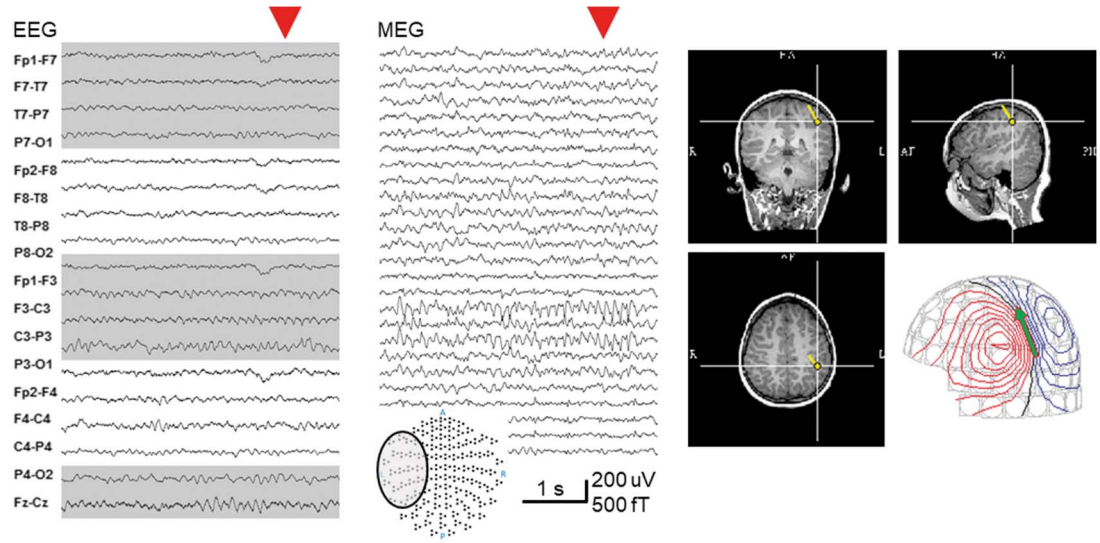

FIG. 8. Sometimes benign supramarginal transients occur in runs. On the MEG (planar gradiometers), the highly rhythmical and notched discharges can be seen to be sustained for 3 to 4 seconds. The supramarginal location and the benign morphology confirm that this is physiologic. The supramarginal or SII/parietal operculum is known to produce its own approximately 10 Hz "sigma" rhythm[16] (1.5–55 Hz band-pass filter). MEG, magnetoencephalography.

In Fig. 10, the benign-appearing morphology, absent EEG correlate, and characteristic localization in the right central sulcus are shown. These transients will most often be seen in the same region as the hand somatosensory responses, as demonstrated by the symmetric locations in the patient in Fig. 11.

In a patient with intractable epilepsy, MEG is an excellent tool for confirming that a patient has more than one epileptogenic zone, an especially important finding if epilepsy surgery is being contemplated. Be especially cautious, however, if the MEG points to a location remote from the lesion or inconsistent with the patient's semiology. In these circumstances, the possibility that the localized discharges are physiologic transients must be considered. Figure 12 illustrates a patient with clear abnormalities in the right hemisphere, but a benign perirolandic discharge on the left.

These relatively common normal MEG variants were first described by Ebersole and Ebersole.[9] They can be distinguished from truly epileptic discharges not only by their location but also by their often bilaterally occurring, homotopic locations, the absence of an EEG correlate, a "benign-appearing morphology" (e.g., without a slow wave, failure to interrupt the background), lack of concordance with the patient's seizure localization from semiology, or other studies.

The fact that these transients are MEG unique (i.e., possessing no correlate in the simultaneously recorded EEG) comes from the same anatomic circumstance that makes MEG so much more sensitive to truly epileptic discharges[2,6,10]—namely, they arise from cortical locations that are best configured for generating tangential fields.

Bursts/Trains

Six-Hz Spike Waves

Six-Hz spike waves or "phantom spike and wave" (Fig. 13) consist of a series of individual pattern with similar morphologic features. The repetition frequency may vary from 5 to 7 Hz. Individual patterns show a short (<30 milliseconds), low amplitude spike (<30 μV) and a prominent wave (50–100 μV) in EEG. The duration of a series is typically short, below 1 second. Six-Hz spike wave occur synchronously bilaterally during wakefulness and drowsiness but disappears during deeper sleep stages. They have been described in adolescents and young adults and less frequently or not at all thereafter.

Two subtypes are distinguished based on their topography, time of appearance, and gender of the patient.[11] The female, occipital, low amplitude, drowsy-type is seen in female patients with predominantly occipital topography, low amplitude, and during drowsiness. In contrast, the waking, high amplitude, anterior, male-type occurs during wakefulness, has high amplitudes over anterior areas, and is associated with male gender. While female, occipital, low amplitude, drowsy is considered a benign normal variant, waking, high amplitude, anterior, male is potentially associated with epileptic abnormalities.[11] This association is, however, disputed,[12] and stronger evidence for any clinical significance is lacking.

In MEG, the morphologic feature is similar to EEG and also shows a subtle spike with a subsequent dominant wave. In some cases, the spike may only be seen in a few channels, potentially superimposed by background noise and activity in others. The field shows a synchronous bilateral distribution with gradients in magnetometers or axial gradiometers over areas corresponding to female, occipital, low amplitude, drowsy or waking, high amplitude, anterior, male subtypes.

Fourteen- and 6-Hz Positive Spikes

Another form of train-like epileptiform normal variants is 14- and 6-Hz positive spikes or "ctenoids" of medium amplitude (20–60 μV; Fig. 14).[13,14] As the name suggests, this pattern consists of transients with a positive sharp and negative rounded morphology. Individual trains have durations of around 1 second

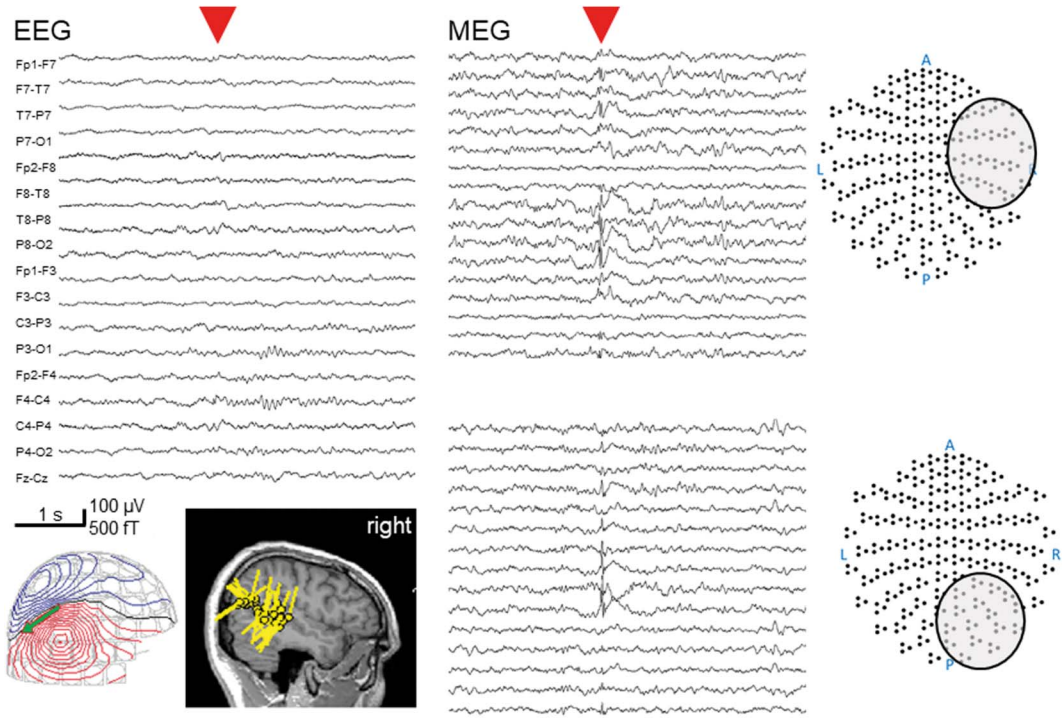

FIG. 9. Pathologic transient: Patient with normal MRI. Dipole sources are located in the typical region of the supramarginal transients but were only seen in the right hemisphere. The EEG shows a very tiny spike in the right temporal leads (other similar discharges had no visible deflection on EEG). In favor of this being a physiologic transient is the mostly MEG-unique appearance, the posterior perisylvian location, and the normal MRI. Suggesting that this is not benign is the unilaterality, the somewhat more inferior and posterior location of some discharges, and the very prominent after-going slow wave seen only in the MEG channels (planar gradiometers, 1.5–55 Hz). MEG, magnetoencephalography.

and frequencies of either 6 to 7 Hz or 13 to 14 Hz. They show mostly a temporal posterior topography and occur during drowsiness and light sleep. Fourteen- and 6-Hz positive spikes are a phenomenon, which is observed in adolescents and young adults. In MEG, this pattern sometimes appears as a low-amplitude 14 or 6 Hz oscillation with moderately sharp cycles.

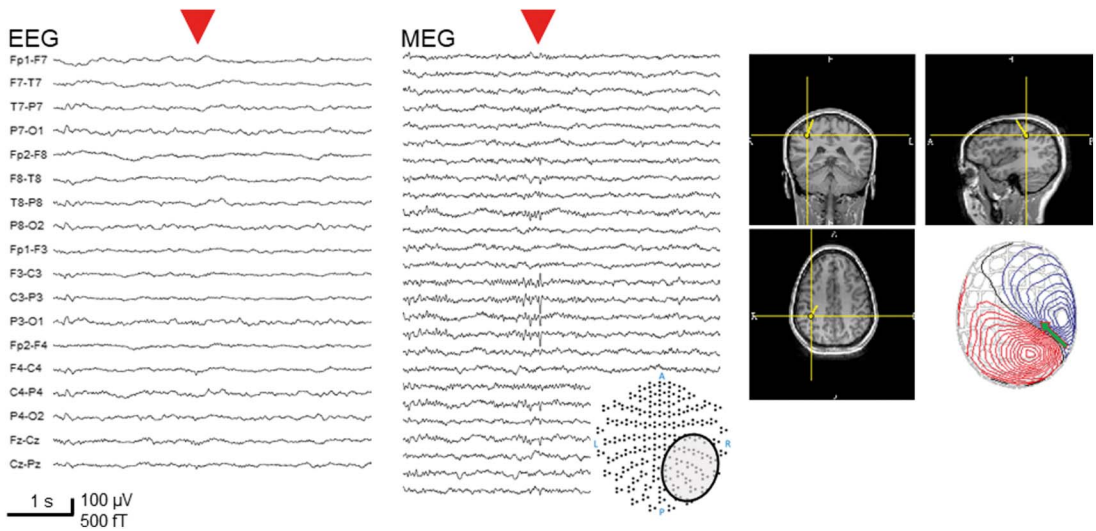

FIG. 10. Typical central sulcus benign variant. The MEG (planar gradiometers) shows a large transient, while there is no correlate on the simultaneous EEG. Single equivalent current dipole localization of this transient places it in the central sulcus. Based on the benign-appearing morphology, lack of EEG correlate, and location, this is certainly a perirolandic normal variant (1.5–55 Hz). MEG, magnetoencephalography.

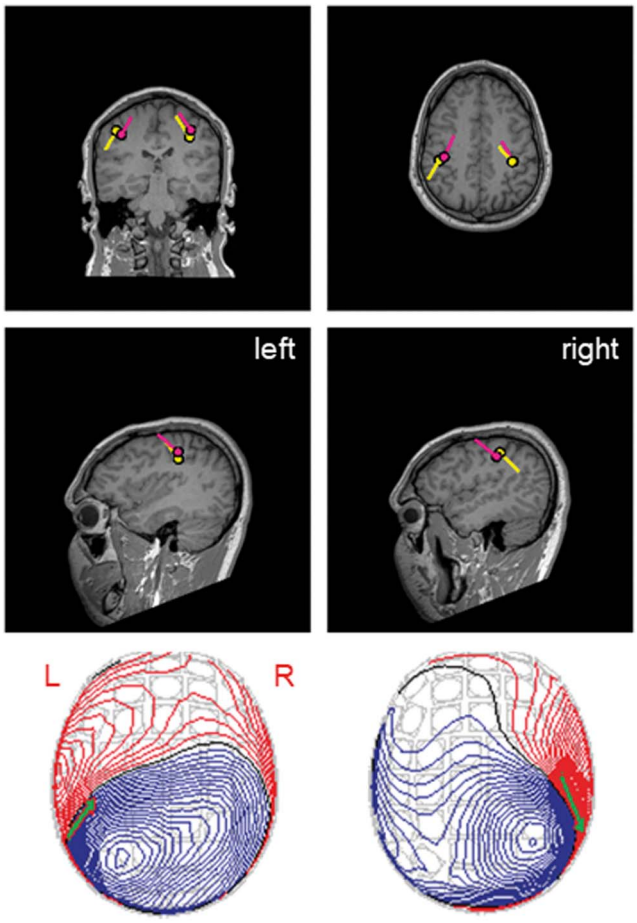

FIG. 11. Bilateral perirolandic transients planar gradiometers (1.5–55 Hz localizations shown in yellow) are from a normal MEG study. The pink (dark) markers indicate the localization of the somatosensory evoked fields (SEFs) in response to median nerve stimulation. Colocalization of the spontaneous perirolandic transients and the median nerve SEFs is the norm. MEG, magnetoencephalography.

However, a MEG correlate may also be missing completely, because of predominantly radial orientation of the generating sources. Figure 14 shows examples for both types in the same patient.

Rhythmic Temporal Theta of Drowsiness/ Psychomotor Variant

Rhythmic temporal theta of drowsiness (RTTD or rhythmic midtemporal discharges) or the so-called psychomotor variant consists of bursts and long runs of negative sharp and positive rounded or sharp patterns in EEG. The ongoing activity has a frequency between 5 and 7 Hz and shows no evolution. The topography in EEG is midtemporal either synchronous bilateral or independent with shifting emphasis of either side. Like 14- and 6-Hz positive spikes, RTTD also mostly occurs in adolescents and young adults but in relaxed wakefulness and drowsiness, not typically during sleep. Because of its morphology and especially because of the long durations, RTTD may be mistaken for ictal activity. However, seizure activity shows an evolution over time, which is not the case for RTTD.

In MEG, the morphology of RTTD resembles the EEG correlate; however because of the different recording characteristics, the sharp and rounded aspects of individual transients are not tied to a general polarity. Sources can be localized to the basal and midtemporal lobe, as well as to the transition to the occipital cortex. Because of the monomorphic signals, dipoles are tightly clustered and show a rather uniform orientation.[15]

Subclinical Rhythmic Electrographic Discharge of Adults

A final form or train-like epileptiform normal variant is the subclinical rhythmic electrographic discharge of adults (SREDA). This activity consists of mono- and biphasic waves with interspersed rhythmic delta and theta oscillations. It shows an abrupt onset and a slow, gradual offset over the course of around 20 seconds to minutes. The topographical appearance is bilateral synchronous or unilateral. Subclinical rhythmic electrographic discharge of adults can be observed during wakefulness and almost never during sleep. Patients with SREDA are typically middle aged to elderly.

The appearance of SREDA fulfills all characteristics for an electrographic seizure, unlike RTTD. However, SREDA never has a behavioral correlate. Patients thus have to be observed and asked for any symptoms to distinguish SREDA from seizures. By principle, differentiation of SREDA from subclinical seizures is difficult and requires a more comprehensive evaluation of EEG/MEG and comparison to clinically apparent seizures of the patient.

Oscillations

Physiologic oscillations are not strictly considered benign epileptiform normal variants, as their typical appearance has no definite similarity with either interictal or ictal epileptic patterns. However, certain configurations may mimic epileptic activity. In addition, oscillatory MEG activity has been described, which was observed in patients with epilepsy and successfully used for focus localizations. Distinguishing between normal and pathologic oscillations is thus sometimes necessary in clinical practice.

Alpha

Alpha oscillations (Fig. 15) may be mistaken for interictal spikes, when single or a few consecutive waves have a sharp appearance and show increased amplitude in comparison to the ongoing alpha. Unlike spikes, such configurations appear symmetric. They are not followed by a slow wave; however, overlap with background theta or delta may mimic such. Parieto-occipital topography, identical to that of clear physiologic alpha activity, and changing laterality hints at such exaggerated alpha waves in contrast to epileptic activity. In addition, other areas show region-specific alpha or alpha-like oscillations (e.g.,"sigma" over the SII-cortex[16] and "tau" over the auditory cortex).[17] Mu activity may also be subsumed under this category. All of these are physiologic and may give rise to transients or short amplified signal trains, which may be mistaken for epileptic activity.

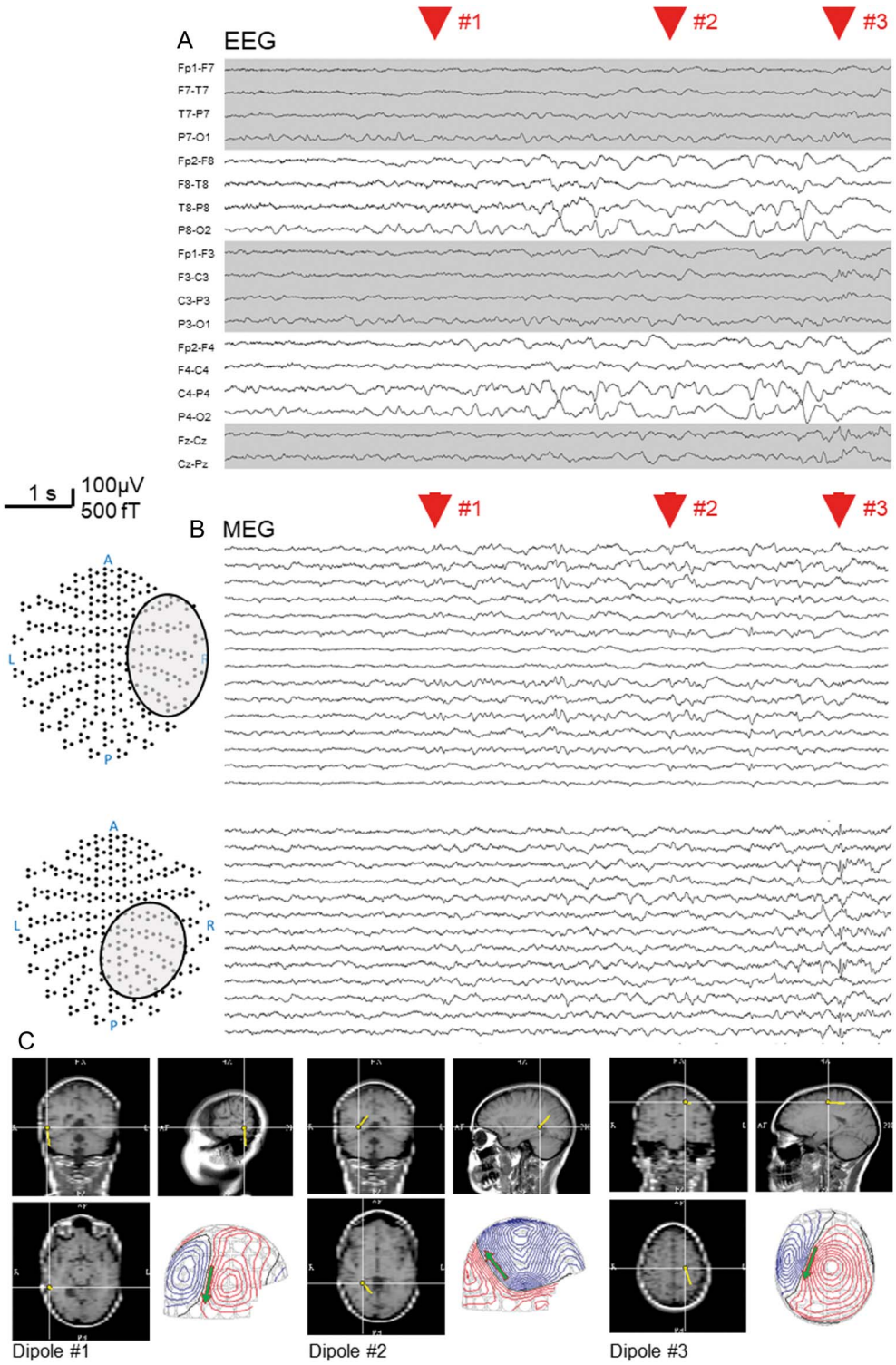

FIG. 12. Perirolandic transient: This patient had a remarkably abnormal recording, with obvious slowing, some sharply contoured, in the right hemisphere, seen clearly on the EEG in (**A**). The smaller discharge #3 can be seen as an irregular sharp transient at Cz. In the MEG tracings in (**B**) (planar gradiometers), discharge #1 and #2 are seen as sharp waves, which localize in (**C**) to two locations in the right temporal-occipital region. Discharge #3, however, has a considerably different sensor morphology and distribution (note the topographical map at the bottom of **C**); it represents a typical central sulcus (perirolandic) benign transient in the opposite hemisphere (1.5–55 Hz). MEG, magnetoencephalography.

Beta

Beta oscillation may only rarely be confused with e.g., polyspikes. However, the higher sensitivity of MEG in comparison to EEG for neocortical sources[18,19] may cause increased amplitudes. In such cases, beta may be more visible and easier to confuse with epileptic activity, especially if the simultaneous EEG shows only subtle or no correlates at all.

It is noteworthy, however, that beta activity has been successfully used to localize focal cortical dysplasias, even in the absence of epileptic spikes.[20] Therefore, while beta oscillations

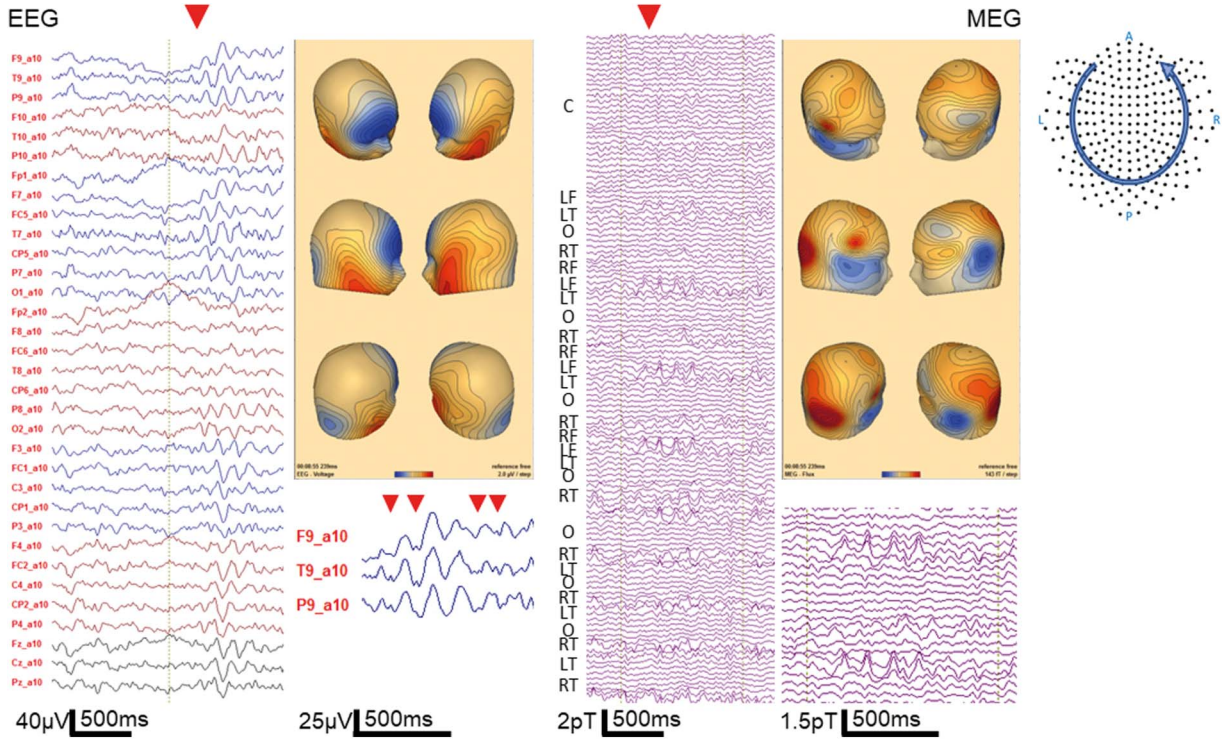

FIG. 13. Subtle 6-Hz spike waves with subtle spike components in temporal leads (e.g., F9, T9, see zoomed inset). The magnetometer MEG data do not show these spike patterns in this case. However, the correlate of the EEG wave is enhanced and has a sharper appearance, which may thus be mistaken for a series of rhythmic sharp wave. MEG, magnetoencephalography.

should not be confused with typical epileptic activity, there may be circumstances that lead to epilepsy- and focus-associated beta.

Mu Activity

Mu activity (Fig. 16) is regarded as the resting state alpha correlate of the motor cortex and occurs in runs over the central region with different lateralization. It is observed during wakefulness and is suppressed by motor action of the contralateral body or in some cases visualization or observation of motor action. It is not suppressed by eye opening, differentiating it from visual alpha. Its morphology is arciform with sharp negative and rounded positive phase. It resembles the greek letter mu, lending the activity its name. While it is easy to identify in EEG, the higher sensitivity of MEG for neocortical sources may again exaggerate amplitudes. Sometimes MEG displays single or a few mu waves, which are then especially prone to be taken as epileptic activity and may overlap with variants of perirolandic transients. The typical morphology, combined with bilateral independent appearance, helps to distinguish mu.

Delta/Theta

While delta and theta oscillations are not easily confused with epileptic spikes, normal runs of slow oscillations may be misinterpreted as intermittent rhythmic delta activity. While most forms of regional intermittent rhythmic delta activity is considered nonpathologic, temporal intermittent rhythmic delta activity is associated with epileptic spikes and sharp waves and represents a marker of mainly temporal lobe epilepsy, to smaller degree extratemporal lobe epilepsy.[21–25]

Furthermore, research has demonstrated that slow activity in the delta and theta range may originate in the epileptic network, even if no classical temporal intermittent rhythmic delta activity morphology is visible.[26–28] Such epileptic slow waves may be subtle and accessible mainly to computerized procedures.[26,29]

Rhythmic Midline Theta or Ciganek Rhythm

Rhytmic midline theta or Ciganek rhythm is a subtype of theta oscillations and occurs over the central area near the midline and consists of smooth, spikey, or mu-like 5 to 7 Hz theta waves.[30,31] Amplitudes increase and decrease continually. Rhythmic midline theta can be observed during wakefulness and drowsiness and is suppressed by eye opening or motor action. Similar to mu activity, the sometimes sharp, arciform appearance and potentially exaggerated amplitudes may lead to misinterpretation as epileptic activity.

CONCLUSIONS

In summary, the setting of MEG recordings, especially of continuous resting state for epileptic focus localization, is prone to the occurrence of a variety of normal variants resembling epileptic activity, as many variants occur during drowsiness or sleep. While prevalence is not exceedingly high, they

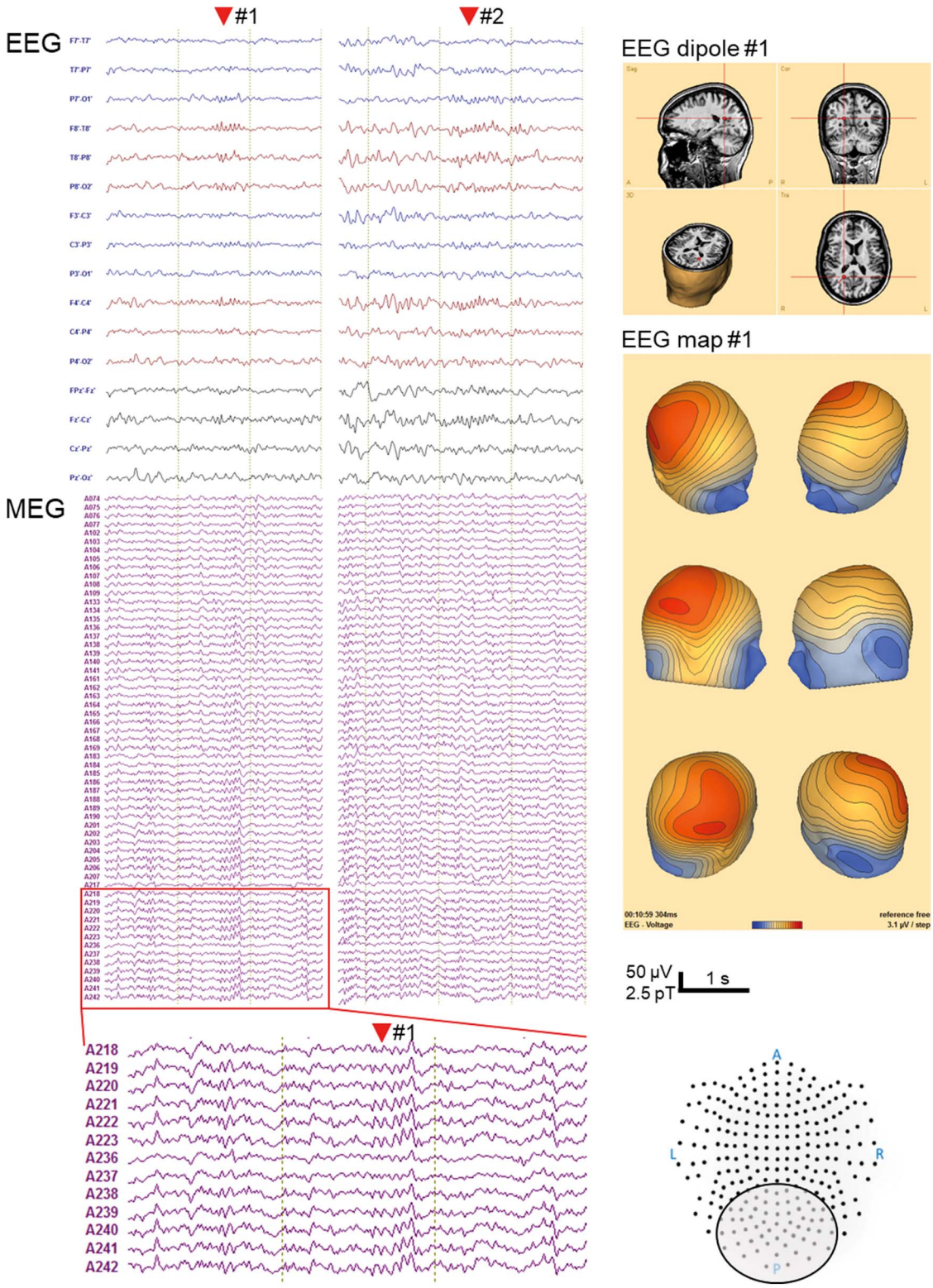

FIG. 14. Two examples of 14- and 6-Hz positive spikes or "ctenoids" from the same patient. Example #1 has a subtle MEG (magnetometers) correlate that consists of an oscillatory appearance with some sharpness of the individual cycles. The dipole localization from the EEG data shows a generator with a predominantly (but not completely) radial orientation, which explains the low MEG amplitude. Example #2 has no obvious MEG correlate; the EEG amplitude map again shows a radial topography. All data were filtered using a 1 to 40 Hz band-pass filter.

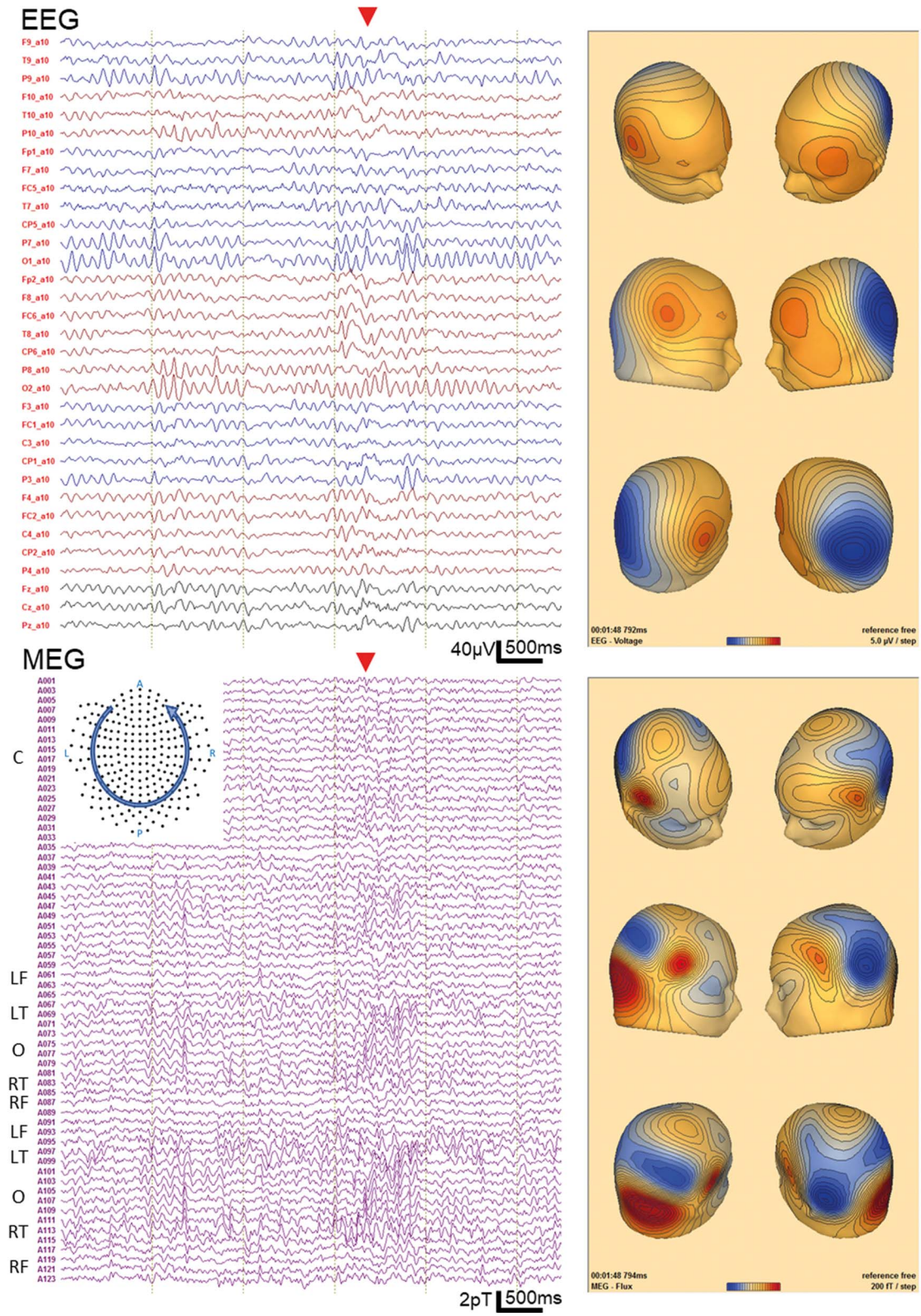

FIG. 15. Alpha oscillations in EEG and MEG with the characteristic posterior topography in both modalities. The waveforms in the magnetometer MEG data, however, have an irregular shape and somewhat variable topography because of the insensitivity of the MEG for radial components of the alpha generators. All data were filtered using a 1 to 40 Hz band-pass filter. MEG, magnetoencephalography.

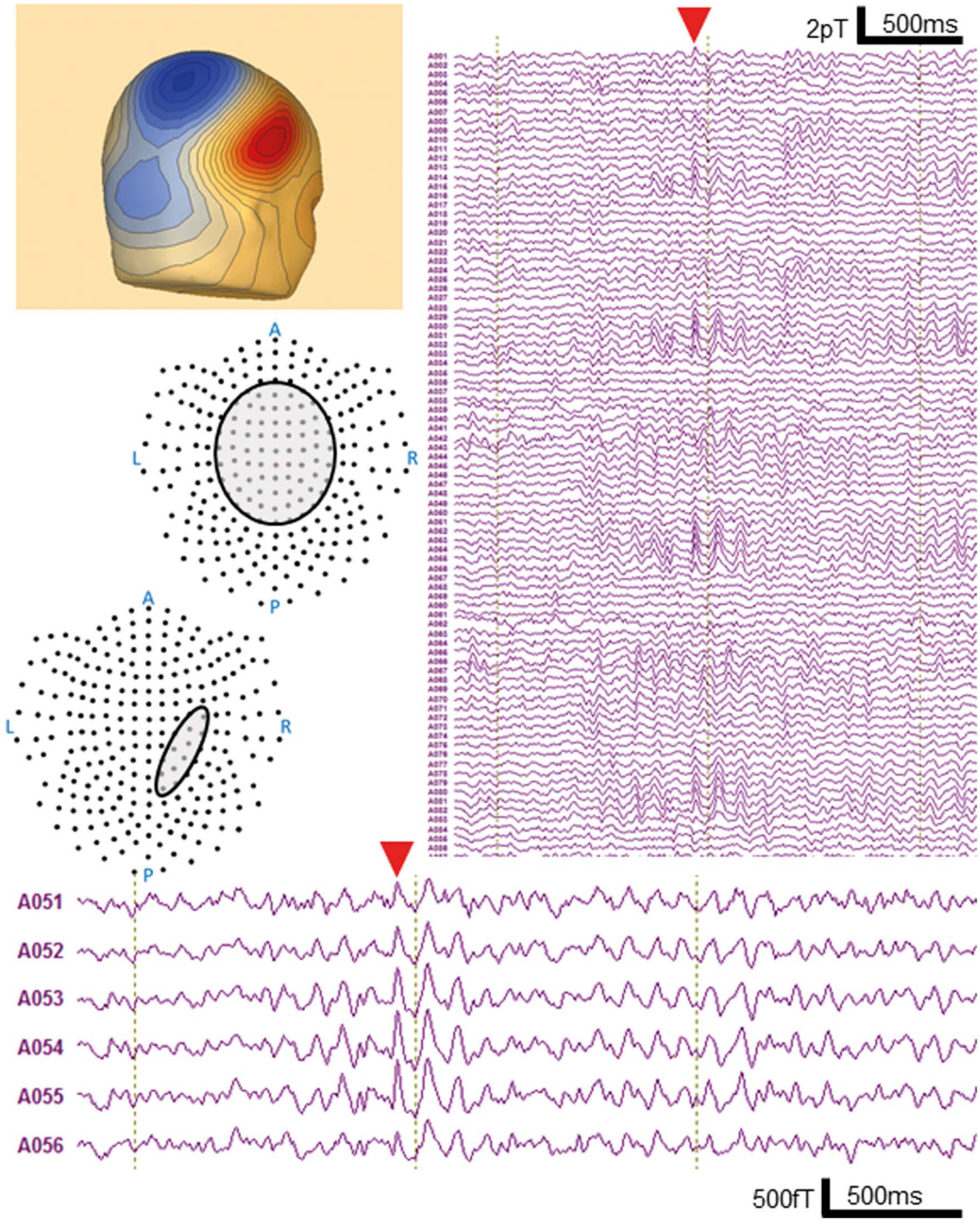

FIG. 16. Mu activity in magnetometer MEG data with the characteristic central topography. The individual waveforms, which frequently occur in trains but may also appear as singular events, are sharp usually without a following wave component. All data were filtered using a 1 to 40 Hz band-pass filter. MEG, magnetoencephalography.

nevertheless present a significant source of error potentially leading to false diagnosis and mislocalization.

For identification of such normal variants, recording of simultaneous EEG is recommended, even if EEG is then not used for source analysis.[5] In this case, a 10–20 montage with a low number of electrodes is sufficient. In addition, or if this is not possible, specific characteristics should be considered warning signs and require closer examination: bilateral occurrence,

especially if independent and varying over time, appearance in a series of rhythmic events and temporal topography. If possible, a comparison of wakefulness with drowsiness or sleep can be helpful, in addition to interaction with the patient when there is the suspicion of high-amplitude mu activity.

REFERENCES

1. Benbadis SR. "Just like EKGs!" Should EEGs undergo a confirmatory interpretation by a clinical neurophysiologist? Neurology 2013;80(suppl 1):S47–S51.
2. Iwasaki M, Pestana E, Burgess RC, Lüders HO, Shamoto H, Nakasato N. Detection of epileptiform activity by human interpreters: blinded comparison between electroencephalography and magnetoencephalography. Epilepsia 2005;46:59–68.
3. Barkley GL, Baumgartner C. MEG and EEG in epilepsy. J Clin Neurophysiol 2003;20:163–178.
4. Ahlfors SP, Han J, Lin FH, et al. Cancellation of EEG and MEG signals generated by extended and distributed sources. Hum Brain Mapp 2010;31:140–149.
5. Bagić AI, Knowlton RC, Rose DF, Ebersole JS. American clinical magnetoencephalographysociety clinical practice guideline 1: recording and analysis of spontaneous cerebral activity. J Clin Neurophysiol 2011;28:348–354.
6. Knake S, Halgren E, Shiraishi H, et al. The value of multichannel MEG and EEG in the presurgical evaluation of 70 epilepsy patients. Epilepsy Res 2006;69:80–86.
7. Lu ST, Kajola M, Joutsiniemi SL, Knuutila J, Hari R. Generator sites of spontaneous MEG activity during sleep. Electroencephalogr Clin Neurophysiol 1992;82:182–196.
8. Kakisaka Y, Wang ZI, Enatsu R, et al. Magnetoencephalography correlate of EEG POSTS (positive occipital sharp transients of sleep). J Clin Neurophysiol 2013;30:235–237.
9. Ebersole JS, Ebersole SM. Combining MEG and EEG source modeling in epilepsy evaluations. J Clin Neurophysiol 2010;27:360–371.
10. Stefan H, Hummel C, Scheler G, et al. Magnetic brain source imaging of focal epileptic activity: a synopsis of 455 cases. Brain 2003;126:2396–2405.
11. Hughes JR. Two forms of the 6/sec spike and wave complex. Electroencephalogr Clin Neurophysiol 1980;48:535–550.
12. Klass DW, Westmoreland BF. Nonepileptogenicepileptiform electroencephalographic activity. Ann Neurol 1985;18:627–635.
13. Niedermeyer E, Knott JR. On the significance of 14 and 6 per second positive spikes in the EEG. Arch Psychiatr Nervenkr Z Gesamte Neurol Psychiatr 1961;202:266–280.
14. Gibbs EL, Gibbs FA. Atlas of electroencephalography. Cambridge: Addison-Wesley, 1952.
15. Lin YY, Wu ZA, Hsieh JC, et al. Magnetoencephalographic study of rhythmic mid-temporal discharges in non-epileptic and epileptic patients. Seizure 2003;12:220–225.
16. Narici L, Forss N, Jousmäki V, Peresson M, Hari R. Evidence for a 7- to 9-Hz "sigma" rhythm in the human SII cortex. Neuroimage 2001;13:662–668.
17. Lehtelä L, Salmelin R, Hari R. Evidence for reactive magnetic 10-Hz rhythm in the human auditory cortex. Neurosci Lett 1997;222:111–114.
18. Goldenholz DM, Ahlfors SP, Hämäläinen MS, et al. Mapping the signal-to-noise-ratios of cortical sources in magnetoencephalography and electroencephalography. Hum Brain Mapp 2009;30:1077–1086.
19. Ossenblok P, de Munck JC, Colon A, Drolsbach W, Boon P. Magnetoencephalography is more successful for screening and localizing frontal lobe epilepsy than electroencephalography. Epilepsia 2007;48:2139–2149.
20. Heers M, Hirschmann J, Jacobs J, et al. Frequency domain beamforming of magnetoencephalographic beta band activity in epilepsy patients with focal cortical dysplasia. Epilepsy Res 2014;108:1195–1203.
21. Reiher J, Beaudry M, Leduc CP. Temporal intermittent rhythmic delta activity (TIRDA) in the diagnosis of complex partial epilepsy: sensitivity, specificity and predictive value. Can J NeurolSci 1989;16:398–401.
22. Brigo F. Intermittent rhythmic delta activity patterns. Epilepsy Behav 2011;20:254–256.
23. Geyer JD, Bilir E, Faught RE, Kuzniecky R, Gilliam F. Significance of interictal temporal lobe delta activity for localization of the primary epileptogenic region. Neurology 1999;52:202–205.
24. Normand MM, Wszolek ZK, Klass DW. Temporal intermittent rhythmic delta activity in electroencephalograms. J Clin Neurophysiol 1995;12:280–284.
25. Tao JX, Chen XJ, Baldwin M, et al. Interictal regional delta slowing is an EEG marker of epileptic network in temporal lobe epilepsy. Epilepsia 2011;52:467–476.
26. Kaltenhäuser M, Scheler G, Rampp S, Paulini A, Stefan H. Spatial intralobar correlation of spike and slow wave activity localisations in focal epilepsies: a MEG analysis. Neuroimage 2007;34:1466–1472.
27. Ishibashi H, Simos PG, Castillo EM, et al. Detection and significance of focal, interictal, slow-wave activity visualized by magnetoencephalography for localization of a primary epileptogenic region. J Neurosurg 2002;96:724–730.
28. Baayen JC, de Jongh A, Stam CJ, et al. Localization of slow wave activity in patients with tumor-associated epilepsy. Brain Topogr 2003;16:85–93.
29. Schönherr M, Stefan H, Hamer HM, Rössler K, Buchfelder M, Rampp S. The delta between postoperative seizure freedom and persistence: automatically detected focal slow waves after epilepsy surgery. Neuroimage Clin 2016;13:256–263.
30. Cigánek L. Theta-discharges in the middle-line—EEG symptom of temporal lobe epilepsy. Electroencephalogr Clin Neurophysiol 1961;13:669–673.
31. Westmoreland BF, Klass DW. Midline theta rhythm. Arch Neurol 1986;43:139–141.