# Source Analysis of Interictal Spikes in EEG and MEG

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# Overview

- Methods
  - Interpreting 3D scalp maps of EEG and MEG
  - Averaging of similar spikes using pattern search
  - 3D mapping of averaged spikes at onset and peak
  - Multiple source analysis of onset and peak
  - Comparison with imaging (e.g. iterated LORETA)
- Case reports: illustrating a systematic workflow
  - simultaneous EEG (41ch) - MEG (160ch) – Sendai
  - simultaneous EEG (33ch) - MEG (122ch) – Heidelberg
  - Goal: identify region of spike onset zone and compare to spike peak



Overviews of advanced methods of digital EEG review and source analysis can be found in:

Scherg M, Ille N, Bornfleth H, Berg P (2002). Advanced tools for digital EEG review: virtual source montages, whole-head mapping, correlation and phase analysis. J. Clin. Neurophysiol. 19: 91-112.

Scherg M, Bast T, and Berg P (1999). Multiple source analysis of interictal spikes: Goals, requirements and clinical value. J. Clin. Neurophysiol. 16: 214-222.

Further papers on source analysis of interictal epileptic activity:

Bast T, Boppel, T, Rupp A, Harting I, Hoechstetter K, Fauser S, Schulze-Bonhage A, Rating D, Scherg M (2006). Noninvasive source localization of interictal EEG spikes: effects of signal-to-noise-ratio and averaging. J. Clin. Neurophysiol. 23: 487-497.

Bast T, Ramantani G, Boppel T, Metzke T, Ozkan O, Stippich C, Seitz A, Rupp A, Rating D, Scherg M (2005). Source analysis of interictal spikes in polymicrogyria: Loss of relevant cortical fissures requires simultaneous EEG to avoid MEG misinterpretation. Neuroimage 25: 1232-1241.

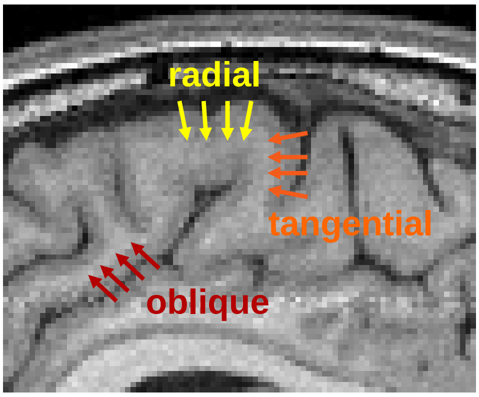
Bast T, Oezkan O, Rona S, Stippich C, Seitz A, Rupp A, Fauser S, Zentner J, Rating D, Scherg M. (2004). EEG and MEG source analysis of single and averaged interictal spikes reveals intrinisc epileptogenicity in focal cortical dysplasia. Epilepsia 45: 1-11.

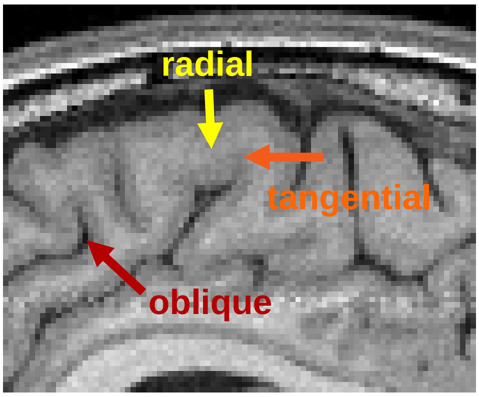
Scherg, M., Bast, T., Hoechstetter, K., Ille, N., Weckesser, D., Bornfleth, H., Berg, P. (2004). Brain source montages improve the non-invasive diagnosis in epilepsy. International Congress Series, 1270C: 15-19

Papers can be obtained as PDF file from the author (mscherg@besa.de).

## Neuronal currents flow perpendicular to the cortex and create multiple dipole fields

net current density * area = equivalent dipole moment



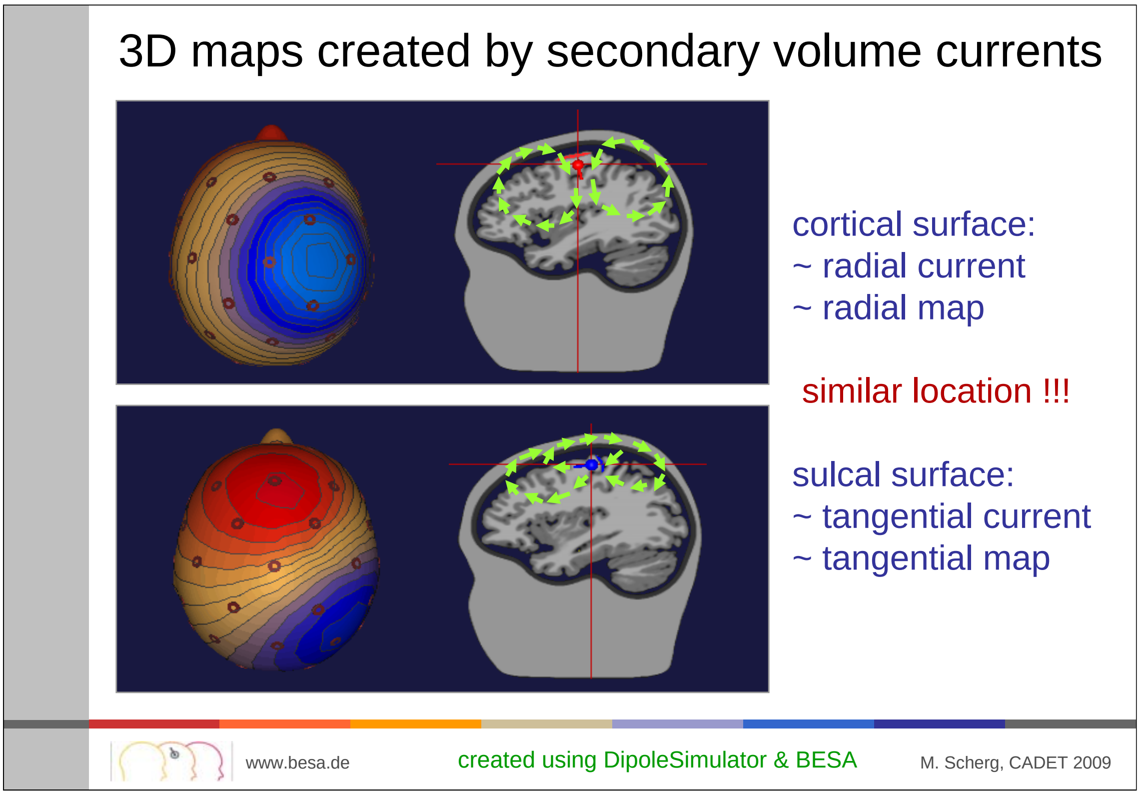






Neuronal current in the cortex flows predominantly perpendicular to the cortical surface for two reasons: First, the pyramidal cells in the cortical columns are aligned perpendicular to the cortical surface. Second, the dendritic trees that are parallel to the cortical surface have near-rotational symmetry and the electric fields of the related intracellular currents cancel to a large degree.

The intracellular current vectors of nearby cortical columns sum linearly and can be represented very accurately by an equivalent, compound dipole current vector. The magnitude, or strength, of the equivalent dipole is proportional to the number of activated neurons and therefore correlates with the area of activation and the mean dipole current density per square cm. Areas with up to 4 cm in diameter (!) can be very accurately (>99%) modeled by a single equivalent dipole.

Currents at the cortical convexity have a predominantly radial orientation, currents in cortical fissures have predominantly tangential orientation. Generally, a patch of activated cortex in a sensory, motor or spiking area will have an oblique orientation depending on the net orientation of the activated cortex.

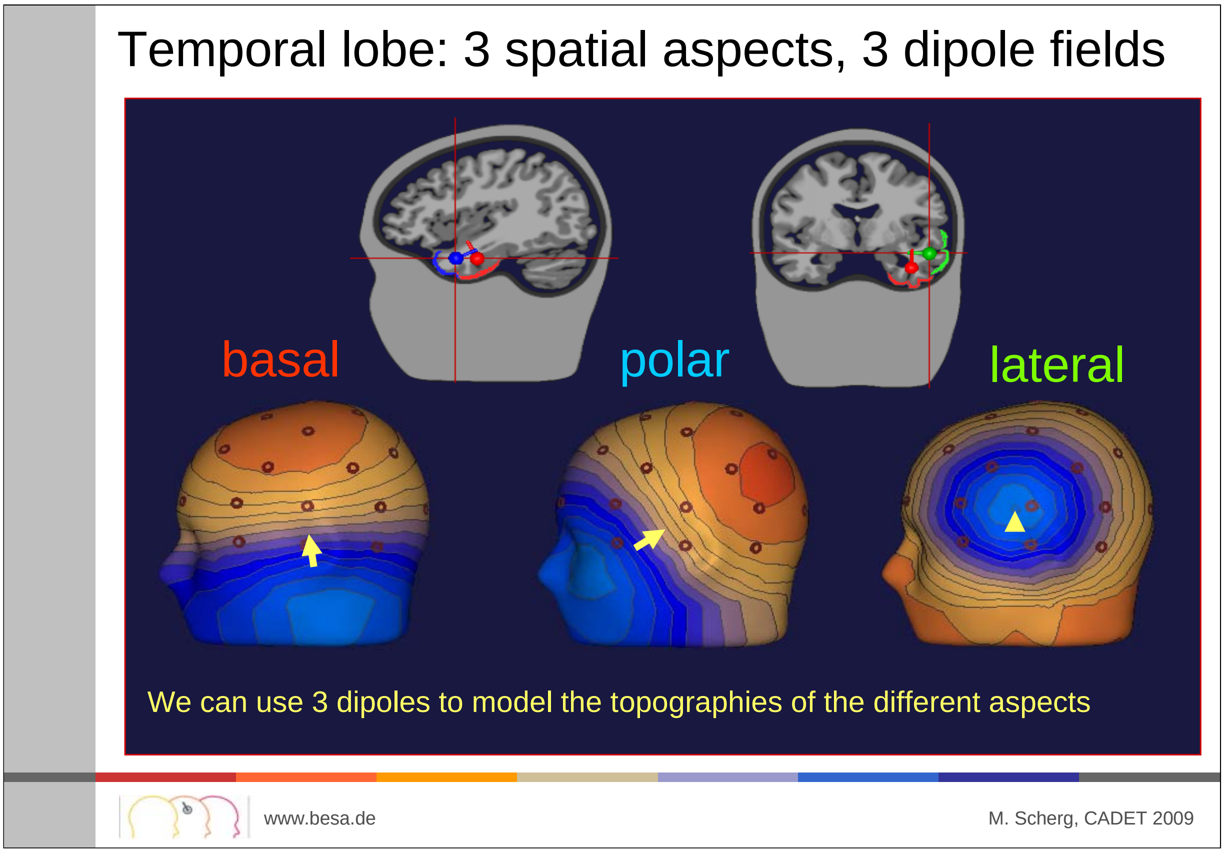



Current loops in a conductive medium like the head are closed. Therefore, the intracellular currents resulting from action and post-synaptic potentials are accompanied by secondary return currents in the head volume. Since the brain and scalp have a higher electrical conductivity as compared to the cranium, most currents return within the extracellular brain space. Only a very small fraction flows out through the poorly conducting cranium and along the scalp before returning to the brain.

An ideal patch of superficial cortex creates a net radial current flow that can be very accurately modeled by an equivalent dipole near its center. The volume conduction results in a widespread, smeared voltage topography over the whole scalp with a negative maximum over the activated superficial cortical sheet. A corresponding more widespread positivity appears on the other side of the head. By physics, any negativity has a corresponding positivity somewhere else over the head.

A cortical patch in a fissure generates tangential currents. The small return currents through the scalp create a dipole map with symmetric positive and negative poles aligned in the direction of the dipole current. The voltage directly over the source is zero, but the voltage gradients are maximal. The source is below the site of the densest equipotential lines. These lines and the whole shape of the topography carry more information on the location of the underlying generators than the colorful peaks.

Reference-free voltage maps can be calculated approximately by spherical spline interpolation around the whole head using the physical fact that the voltage integral over a conducting sphere is zero in the range of EEG frequencies, i.e. in a quasi-static case.




Let us consider what kind of maps we might expect if different aspects of the temporal lobe are activated, e.g. by an epileptic spike that typically involves more than 6 $cm^2$ of cortical surface to become visible in the scalp EEG.

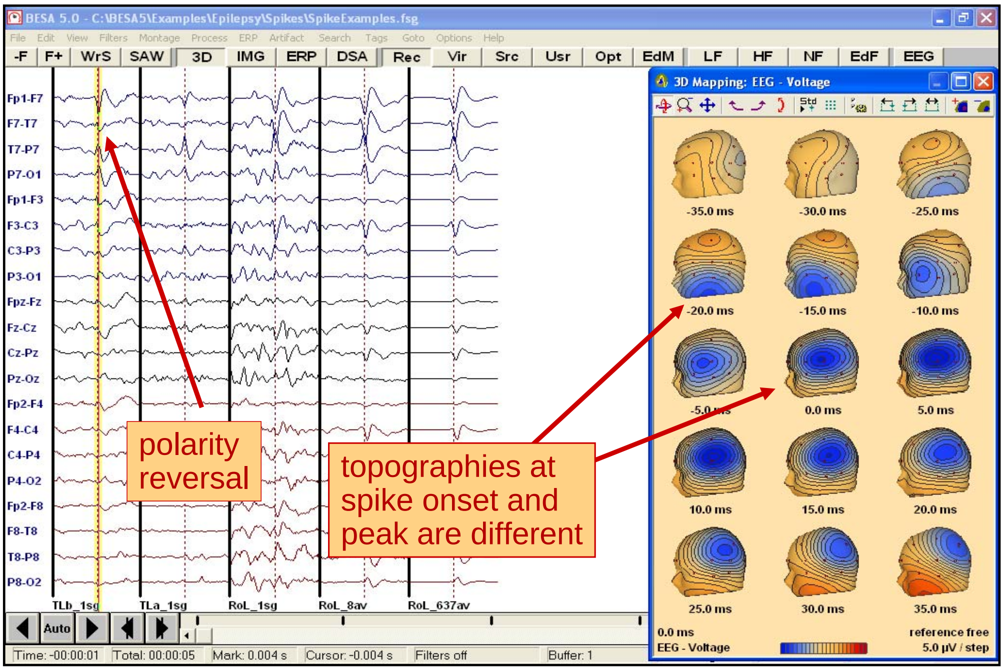
Anatomically, each temporal lobe has 3 major surfaces, or aspects: basal, polar and lateral. Larger spikes in the EEG (> 50 µV) are likely to be oriented prependicular to the gross area they originate from. Therefore, we can expect the dipole fields to match the cortical surfaces that have a net vertical (basal), anterior-posterior (pole), or radial (lateral) orientation.

Therefore, each temporal cortex can be modeled by 3 equivalent dipoles reflecting the basal, polar and lateral aspects, as illustrated above for the left temporal lobe. In addition, the large lateral region can be divided up and represented by an antero-lateral and a postero-lateral radial dipole.

The topographies that can be expected to be seen at the scalp are quite different: Predominantly tantential patterns are related to basal and polar activities and radial patterns to the lateral convexity.

To some extent, the vertical basal dipole will also pick up source currents in the supratemporal plane of the Sylvian fissure. Then, the spike polarity can help dissociate which side of the Sylvian fissure is discharging. Basal spikes have the opposite polarity to spikes that originate at the superior surface of the temporal pole.

## 3D maps show propagation temporal basal, polar, lateral

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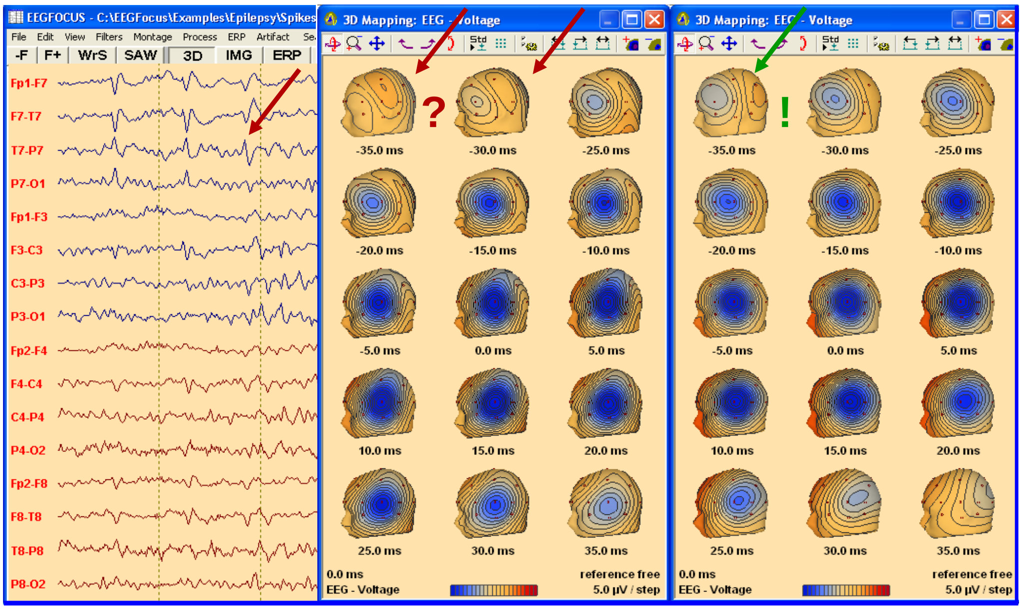
This example file shows single spikes of 3 patients and 2 averaged spike segments of the 3rd patient. The 3D-map of the first single spike shows a left temporal negative peak. The peak at time zero exhibits the typical polarity reversal in the longitudinal bipolar montage.

However, the temporal evolution of the serial maps starting 35 ms before the spike peak shows a rapidly changing topography from spike onset to peak with an initial vertical dipole field during spike onset.

The initial negativity is below the temporal lobe and is picked up mainly by the inferior temporal electrodes. Using spherical spline interpolation the negative peak below the temporal lobe can be extrapolated with sufficient accuracy.

The negativity appears to rotate forward towards the temporal pole before changing into the radial pattern at spike peak. The rotation of the map from the initial vertical topography to a radial-lateral pattern indicates propagation from basal to polar and lateral. Thus, at the spike peak there is already some overlap from the wave phase at the basal region that shifts the negative peak higher up.

## Averaging is needed to identify onset map: tangential field




**long. bipolar** **single spike** **8 averages**

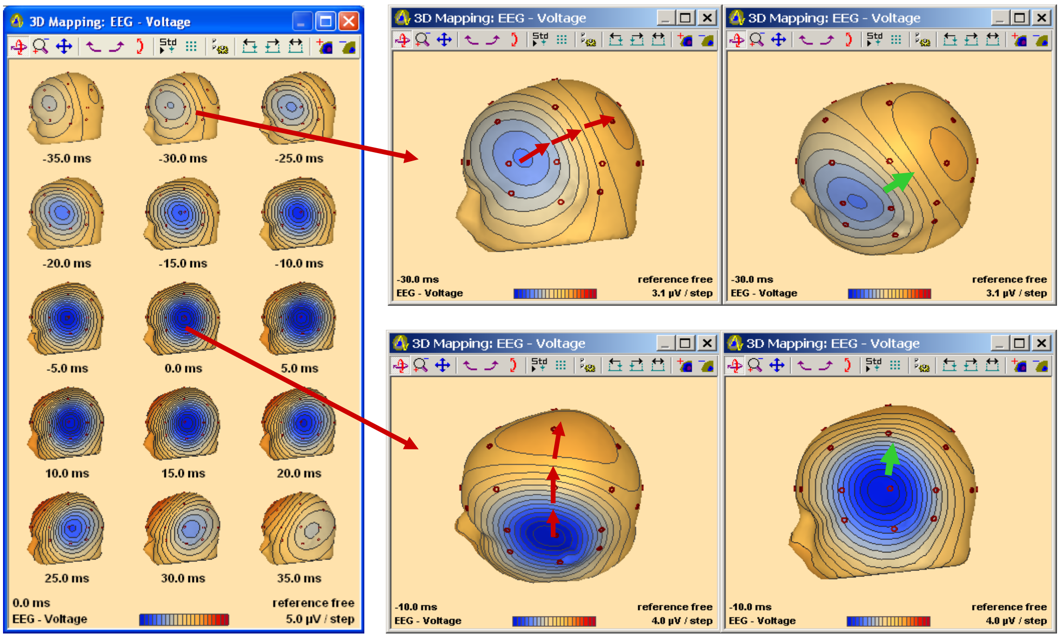


The single spikes of the 3rd patient show a polarity reversal between F7-T7 and T7-P7 similar to typical temporal lobe spikes. The corresponding radial map at the spike peak has a maximum negativity over the temporal lobe.

Spike onset is unclear and varies between the single spikes. The single spike map during onset reflects mostly EEG background activity.

After averaging, the tangential topography during spike onset becomes apparent. The onset pattern shows a negativity over the frontal cortex and a more superior horizontally oriented, oblique dipolar pattern.

## 3D whole head map interpretation: estimate the source!




inspection of 3D map | connect +/- peaks | find max. gradient



More detailed inspection of the whole head topography reveals an estimate of an 'equivalent dipole' above the Sylvian fissure (green arrow) for both the tangential onset map and the more radial peak map.

How can we estimate the 'approximate source location' from the maps?

First, consider a line connecting the negative and positive maxima on the scalp (red arrows). This line follows the shortest connection having the highest voltage gradient (~ narrowest distance between equipotential lines).

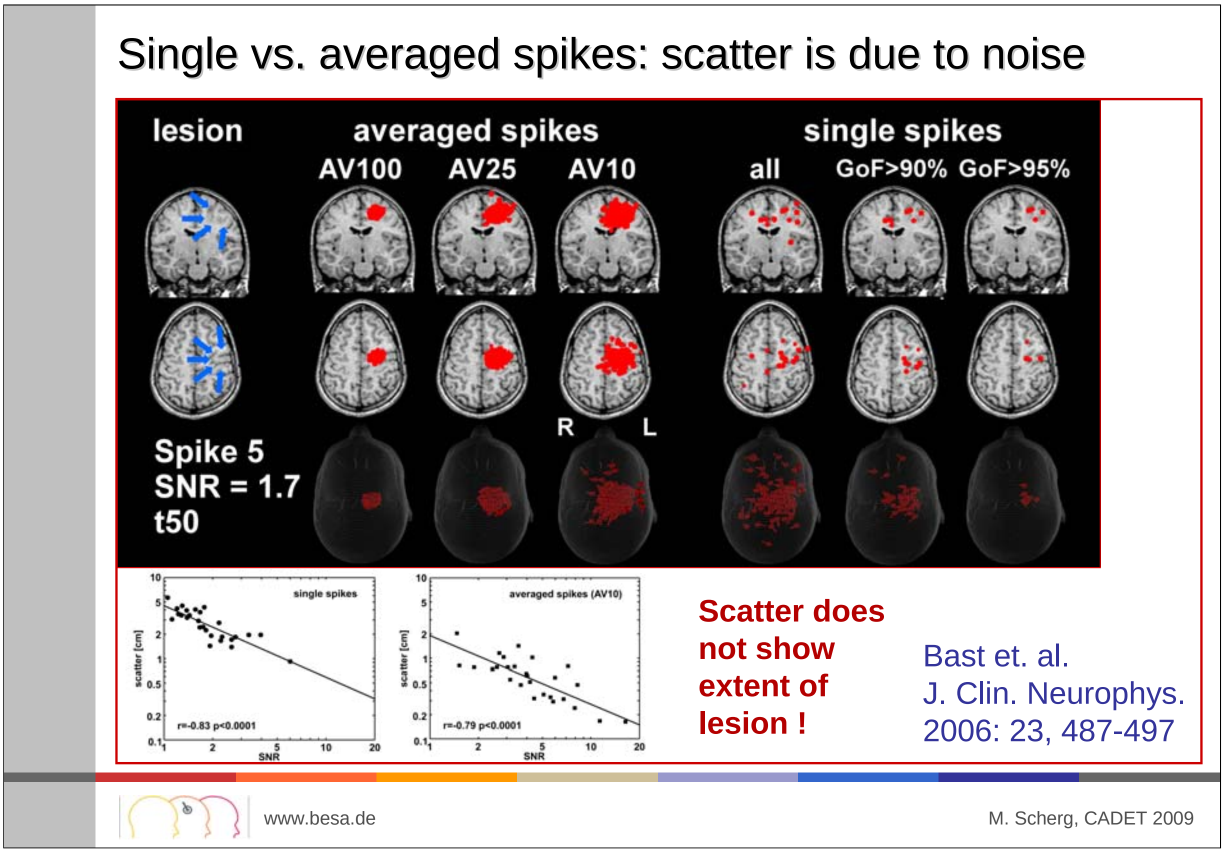
Second, find the region of highest gradients.

In a close-to-tangential map (upper row), the equivalent location is approximately below the area of maximum gradient (green arrow).

In a close-to-radial map (lower row), the center location is shifted slightly from the negative peak towards the positive pole along the region of largest gradient.

The equivalent centers of both maps are similar and point to a circumscribed region of origin in the rolandic cortex above the Sylvian fissure. Polarity indicates that the tangential rolandic spike is likely to arise from the anterior wall of the post-cental gyrus (~face area) with ensuing propagation to the surface of the gyrus (radial map), since the tangential onset current is flowing backwards (positivity is posterior).

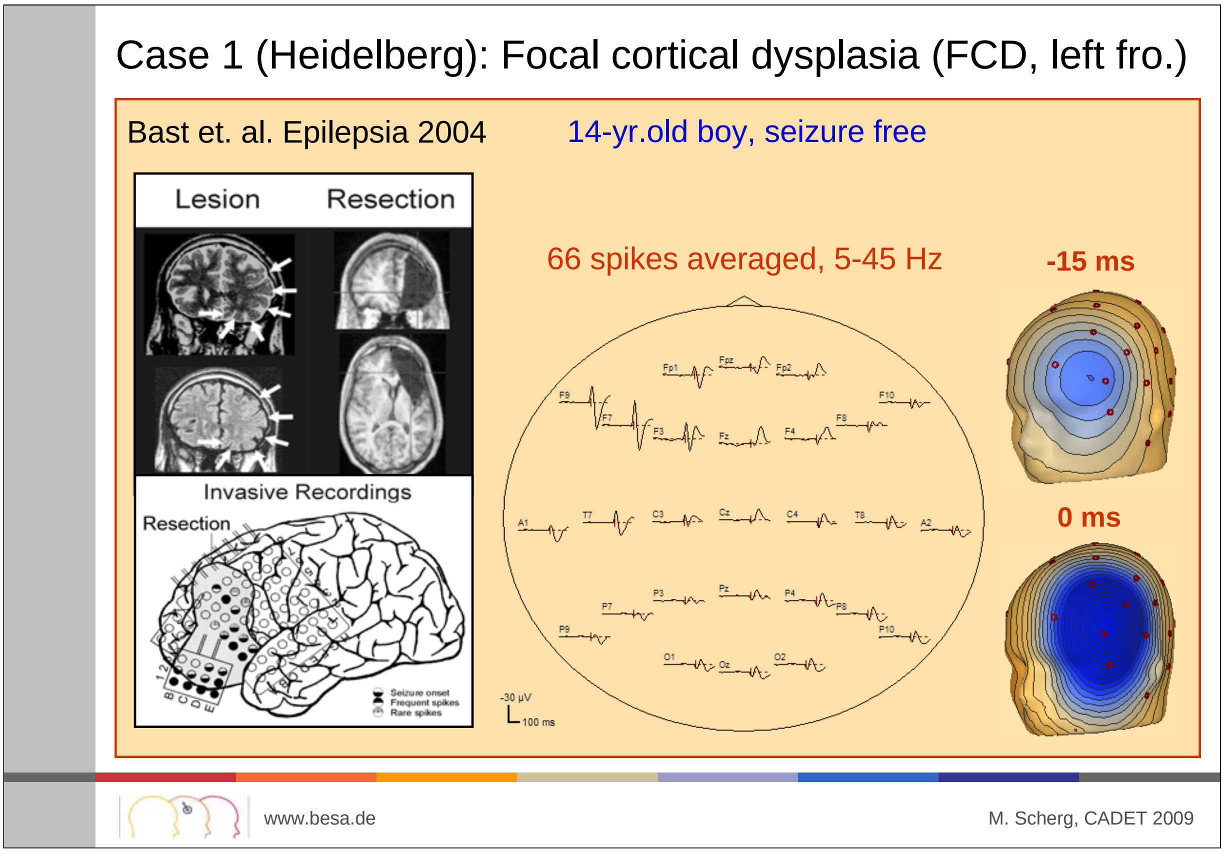
With this concept, 3D maps can be interpreted with considerable accuracy, if the pattern appears to be predominantly dipolar. Thus, the bias towards misinterpreting the location of the negative peak as the generating region can be largely avoided, e.g. in the case of the so-called paradox lateralization – for an example see further on.




In a recent paper, Bast et al. (2006) showed that it is rarely possible to identify and localize spike onset using single spikes. Even at a latency half-way between onset and peak, only a very small number of spikes exhibit sufficient signal quality over the EEG background (right) such that they can be localized using a single equivalent dipole with a goodness of fit of more than 90%.

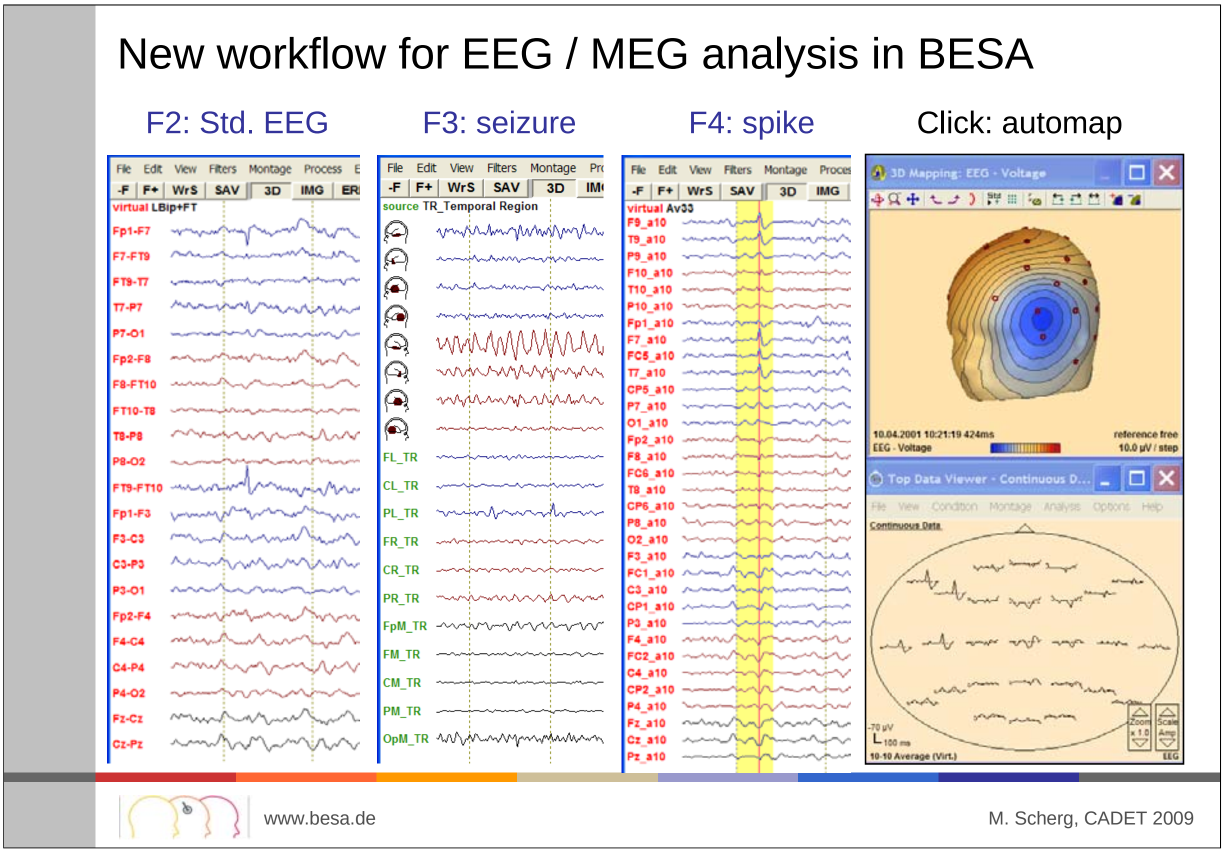
Thus, averaging of spikes with similar spatio-temporal distributions is mandatory to reveal the topography and localization of spike onset. This can be done best by doing a pattern search on the peak channel in a source montage using a good spike template or using all channels in a virtual average reference montage with wide coverage (see further on).

If one localizes single spikes or even groups of 10 or 25 spikes by equivalent dipoles, the center locations of these dipoles scatter (left). This scatter is highly correlated (>85%) with the EEG background noise. Thus, scatter plots of dipoles or averaged dipoles do not reveal the extent of an irritative spiking zone. Rather, they depict the uncertainty of the estimation of the center location. To estimate the center of the onset region reliably, at least 10-25 spikes need to be averaged.




We will now be learning the systematic processing steps that are needed to analyze spike onset and peak. This will be illustrated with a first case taken from our publication on spike analysis in cases with focal cortical dysplasia (FCD). Intracranial grid recording in this 14 year old boy showed left frontal inferior spiking and seizure onset related to the lesion that was successfully resected later on.

The 3D maps show a left frontal spike onset with a lateral-frontal negativity and a posterior-parietal positivity that rotated to a typical temporal pattern at the peak of the spike.




A new workflow has been created in the BESA program that allows for the rapid setting of convenient montages and filter settings to improve visual spike / seizure detection during EEG review. Standard and optimized settings have been associated with the function keys F2-F12.

**F2:** **Presets for standard EEG review**:

Extended bipolar montage with FT9 / FT10 (Lueders)

Time constant 0.3 s

Default block marking: +- 500 ms

**F3:** **Presets for optimized seizure viewing**:

Temporal lobe source montage

Filter band: 3 – 20 Hz (zero-phase shift filters)

Default block marking: +- 1 sec for spectral analysis and phase maps

**F4:** **Presets for optimized spike viewing and pattern search**:

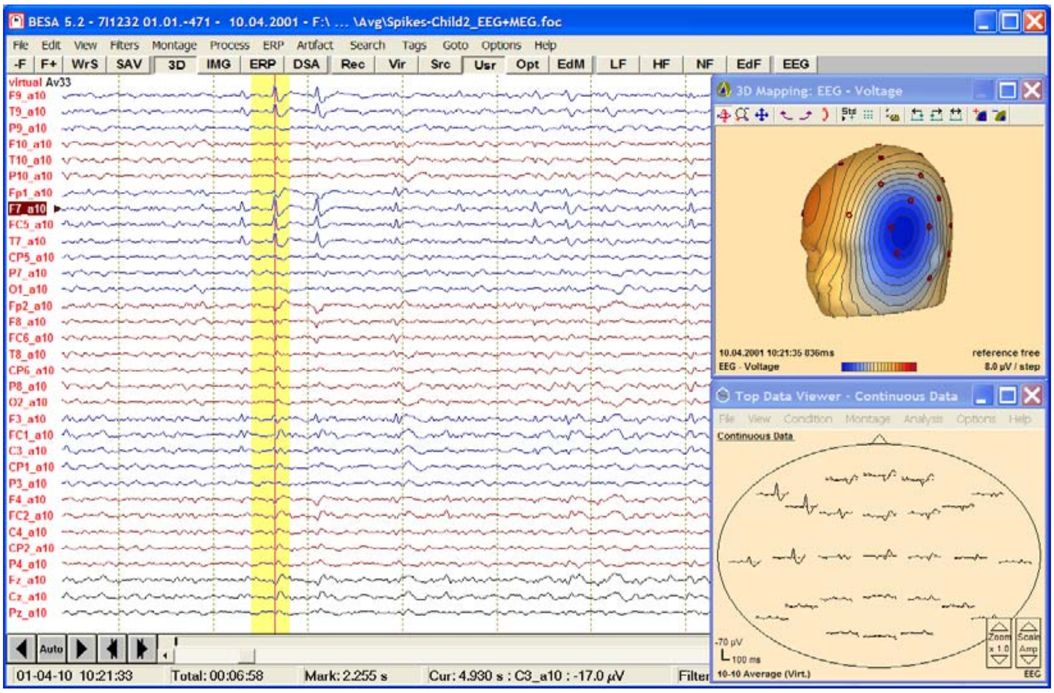
Virtual average reference montage with inferior and intermediate sites

Filter band: 2 – 35 Hz (zero-phase shift filters to reduce noise)

Default block: -250 : 150 ms for spike pattern search and analysis

**Click:** Single click onto a spike in the EEG will display a **3D maps with automatic rotation** of the viewpoint to the center of the activity (between negative and positive peaks). This allows for immediate visual analysis of the spike topography. At the same time, the maked spike segment is displayed in top view in a virtual standard average reference montage.

## Case 1: FCD-LF - inspect EEG and mark spike template

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After presetting for spike review (F4), we start reviewing in the optimized average reference montage.

Spikes, including inferior-temporal patterns, are better visible by using

**a) a virtual montage** that can extrapolate to intermediate and inferior sites even in the absence of deep electrodes,

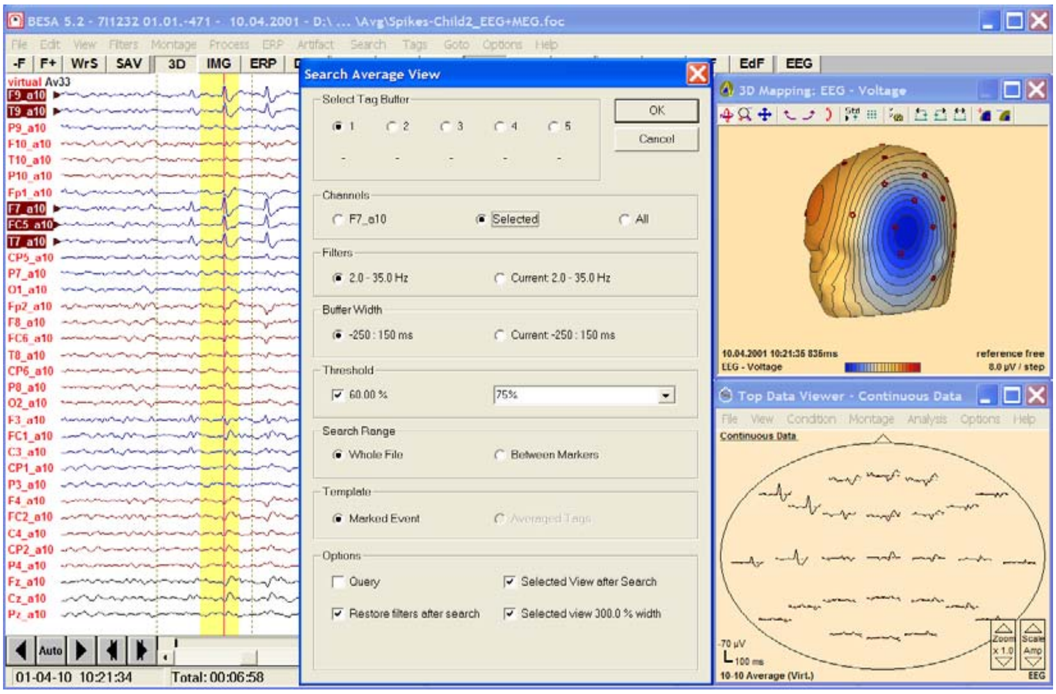
**b) the grouping of channels in three longitudinal rows** (e.g. the denser Fp1, F7, FC5, T7, CP5, P7, O1 row), and

**c) an optimized filter band** (2 – 35 Hz) that suppresses slow EEG activities and renders spikes riding on slow activity more vísible. At the same time, the high filter removes a sufficient amount of EMG activity to enhance the visibility of spikes.

We page through the EEG and look for a prominent spike that has a flat, undisturbed onset epoch (marked yellow block). This presents an ideal template for pattern search.

Click on the spike and adjust to the spike maximum in the map using the arrow keys.

## New workflow in BESA: SAV button – start preset search

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Optionally, the channels with the largest spike pattern can be marked for template search (e.g. F9, T9, F7, FC5, T7).

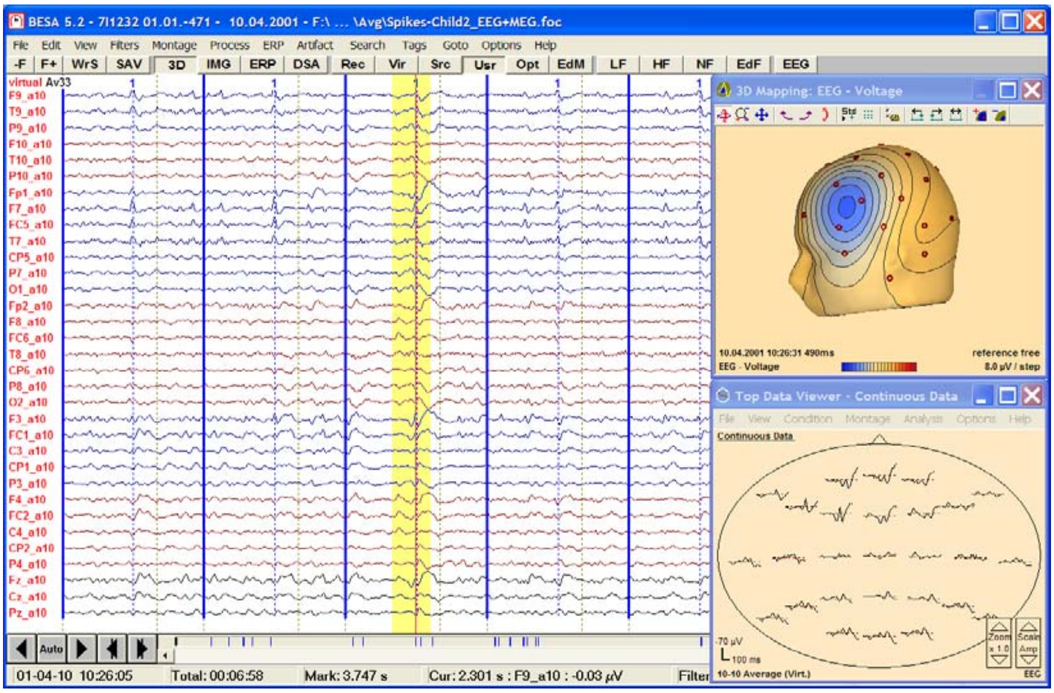
Normally, simply press button SAV to open the search-average-view dialog box. The SAV-box provides preset optimized values and the option to modify these for the pattern search that starts when pressing OK.

The largest spike channel is identified automatically, and one may choose this channel, the manually selected channel(s), or all displayed channel for template search. When using the average reference montage and a clear spike patterrn, it is recommended to use the **All** channels template. With a source montage, the **largest spike channel** can be used as proposed automatically.

If only one channel is selected, the marked pattern of this channel is shifted along the whole selected EEG epoch and correlation is assessed at peaks. If the selected threshold is exceeded, a detection marker will be created. Thus, spikes are aligned optimally in time.

If several or all channels are selected, a spatio-temporal template is calculated and aligned with all selected traces.

## Case 1: FCD-LF - inspect and delete bad detections



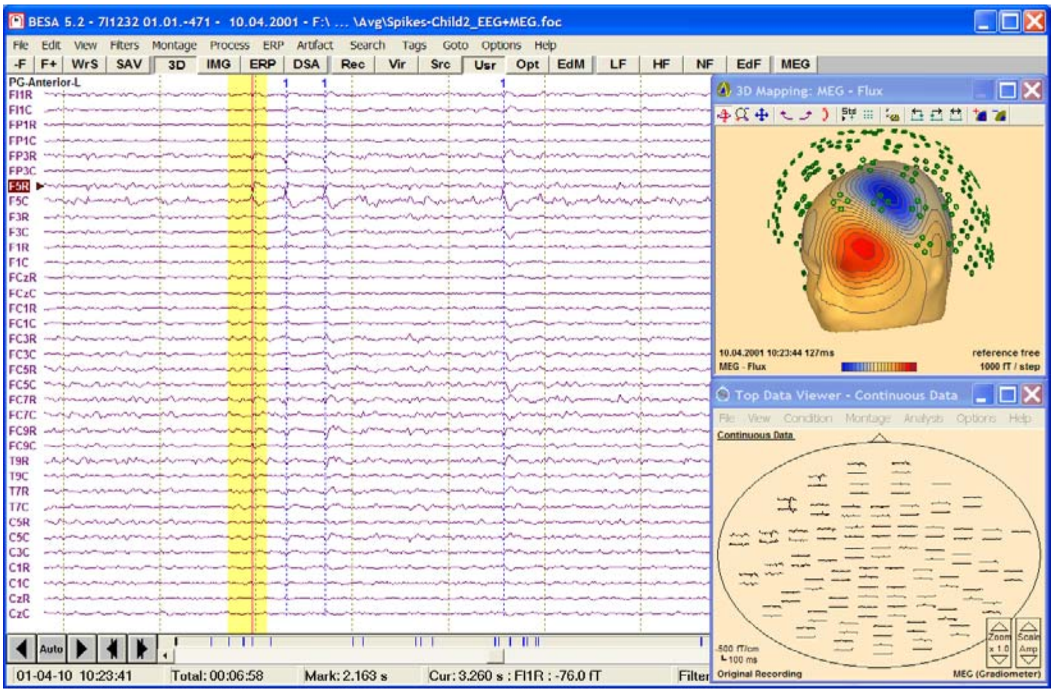



After the pattern search is completed, the detected patterns are displayed automatically. We inspect these patterns using the paging functions and delete detected events where the spike is blurred by background noise by clicking onto the noisy spike segment and pressing the delete key.

Thus, you may control the events that are included in the final average.

The preliminary average can be viewed (menu: View / Average Buffers) and used as an improved template if desired.

## Case 1: FCD-LF - inspect MEG and mark spike template



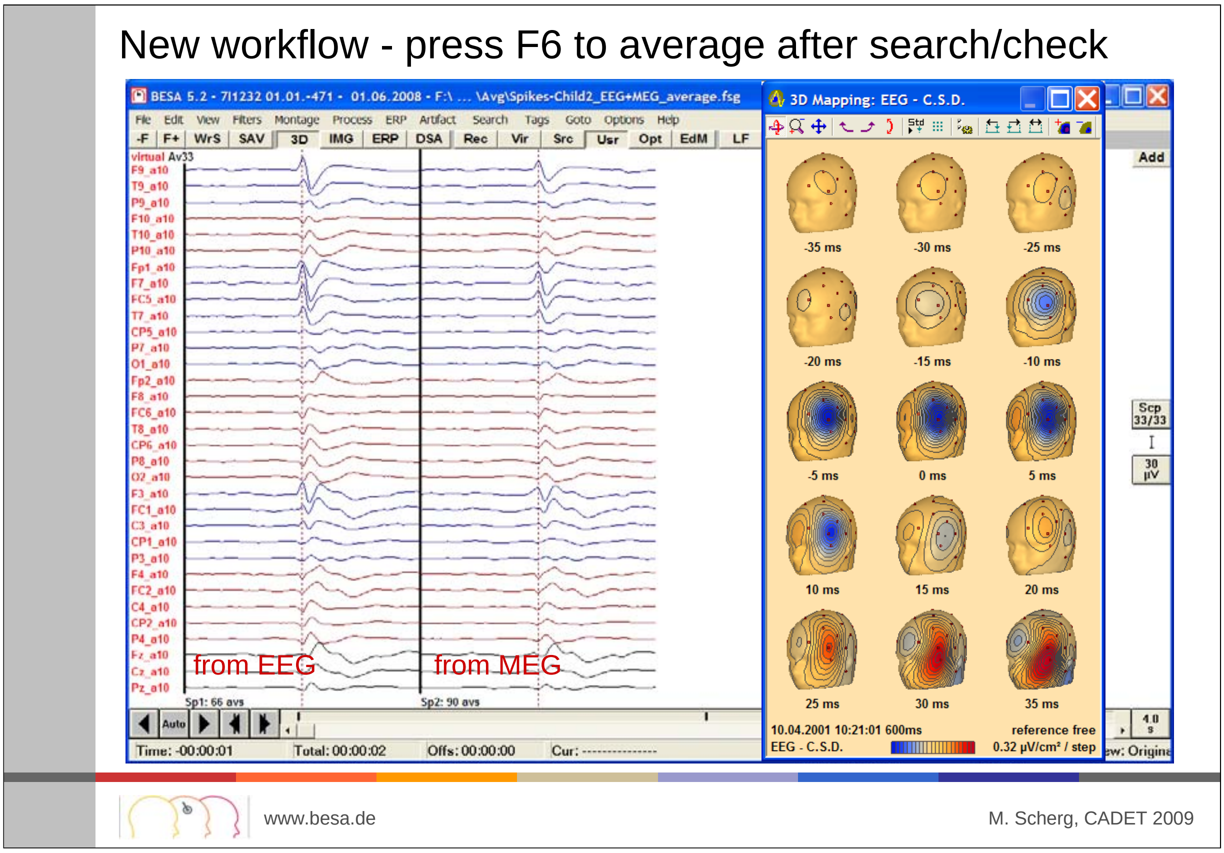



Simultaneously with the EEG, 122 MEG-channels were recorded in case 1.

The EEG spike detections were marked by the blue tags 1 (buffer 1, vertical lines).

First, we select the MEG user montage (Usr button) that shows the largest spike signals (MEG-anterior-left: quadrant montage) and can now page again to find a good MEG spike template.

We click onto the spike, align to the peak, and press SAV again to use the second template buffer. The search will now create MEG detections events (Tag 2 - red) and we may similarly inspect and delete bad detections paging though the selected view.




After completion of the spike template search using the different spike types in EEG and MEG, we press the **F6** button to obtain a file with averages of each template.

In this case, we obtain 2 averages, one with 66 spikes averaged from the EEG template search (Tag 1 is converted automatically to trigger 41) and one with 90 spikes averaged from the MEG search (Tag 2 -> trigger 42).

The spike waveforms and topographies of both template searches look highly similar in the EEG average-reference montage. Thus only one spike type was detected despite independent EEG / MEG searches.

Most MEG events coincided with the EEG events. The MEG-aligned averaged signals were only a bit smaller in the EEG, partly because the higher MEG sensitivity in this particular recording picked up a few more spikes that were smaller or noisier in the EEG and partly, because the alignment was not from the EEG pattern.

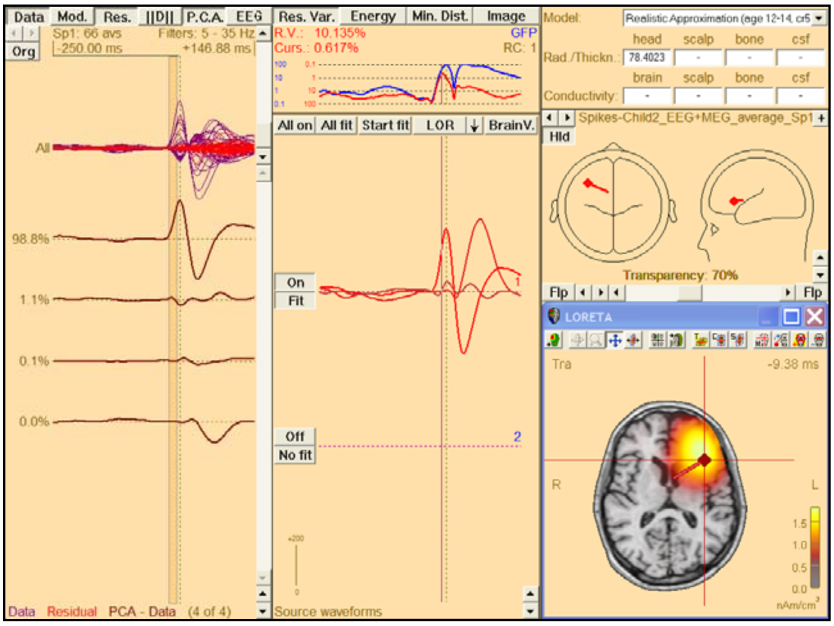
The EEG spike maps do not show a large propagation from the onset (-15 ms) to the peak (0 ms). Only a small rotation can be seen.

For the following analysis, the onset will be enhanced and flat signals will be created by using a 5 Hz low filter with forward characteristic (see next slide). Occasionally, a setting of 10 Hz or higher may be required to remove a slow background pedestal.

## New workflow - press F7 to analyze onset & peak of spike 1

EEG | PCA of data | source waves | head / MRI

- low filter 5 Hz forw.
- high filter 35 Hz
- -250 : 150 ms
- user defines age dependent model
- user defines onset interval by PCA %
- fit of regional source during onset
- orientation of regional source
- fit of 2nd source at peak interval (-20:0)
- comparsion with a LORETA image at the maximum in the onset interval
- user compares onset-peak sources






After averaging is completed, the first averaged spike segments (Sp1) can be analyzed immediately by pressing the F7 button. A list of the automated settings and analysis steps is shown above in blue.

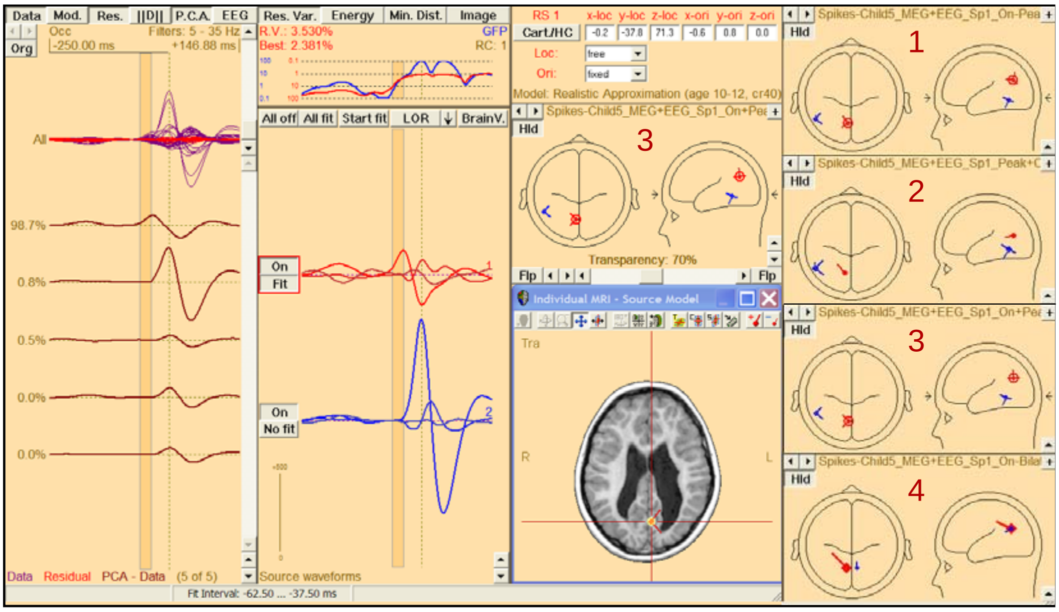
After the source analysis window opens, the user (marked in red) only needs to **select the head model** for the EEG depending on the age of the subject. Then, the batch control proposes to the user to set the onset interval by visual comparison of the automatically calculated and displayed principal components analysis (**PCA** – left) with the butterfly plot showing an overplot of the recorded channels in average reference (above).

The onset interval is defined by finding the initial interval that exhibits **one dominant principal component** (accounting for a data variance of more than 90-95%). Its prominent waveform (here: 98.8%) is compared to the wings in the butterfly plot to assess, whether it comprises the peak (here: yes) or an earlier activity. Inspection of the following PCA components shows no significant other activities in the onset interval.

Next, the batch fits a **regional source** into the onset epoch and rotates the 3 underlying orthogonal dipoles such that the first dipole is oriented to explain all the activity at the maximum of the onset interval. The individual MRI (if available) is loaded and a **LORETA image** is computed for comparison.

If the center of the image and the source localization coincide, the center of the region of onset has been defined. Note that neither method displays the extent of the activated zone – this information is not availabe from the scalp. The extent of the LORETA image shows the intrinsic smoothing of the method and the low resolution of the scalp EEG (here: 33 channels).

## Press F7 to get different solutions for a propagating spike

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In contrast to the previous case 1, the PCA of the averaged spikes in case 3 (for more details see below) and the butterfly plot showed an onset activity different from the peak. In the onset interval of -62 : -37 ms, the first PCA waveform explains 98% of the variance and is orthogonal to the peak waveform rising at the end of this interval and, hence, having only a variance of 0.8% in this interval.

Using the batch F7, several hypotheses are tested automatically to confirm the observed difference between the equivalent onset and peak sources:

**Strategy 1 (On-Peak):** Regional sources are fitted independently in the user / PCA defined onset interval (-62 : -37 ms) and in the peak interval (-20 : 0 ms).

**Strategy 2 (Peak+On):** The regional peak source is kept in the model and an additional source is fitted in the onset interval (2-source model). This source is oriented and the first dipole is kept. Thus, the additional activity of the peak source region that may already start in the onset interval is modeled, and the remaining onset activity can be taken care of by the first dipole (red). Hereby, the ipsilateral onset activitiy remote from the peak can be confirmed in location and orientation.

**Strategy 3 (On+Peak):** The independent regional onset source (red) is kept in the model and an additional source is fitted in the peak interval. This is the physiologically most plausible and prefered solution assuming focal onset and overlap of the later part of the onset activity with the rising peak activity. Strategy 3 takes account of this overlap and corrects for the resulting shift in the location of the peak source. Peak overlap is not modeled by strategy 1 (for results see below).

**Strategy 4 (On-Bilateral):** A pair of symmetric regional sources is fitted in the onset interval to test whether a near midline activity is indeed coming from the cortical areas near the interhemispheric cleft (here: yes), or whether the onset occurs synchronously in both hemispheres. This test is important, especially for source activity oriented along the interhemispheric cleft, since such activity can be modeled very accurately by one midline source (~center location in sLORETA!)

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- Case reports: illustrating a systematic workflow
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Up to here, we have introduced the methods of spike reviewing using optimized montages and filter settings. Furthermore, we have seen the principles of template search to create averages of different spike types.

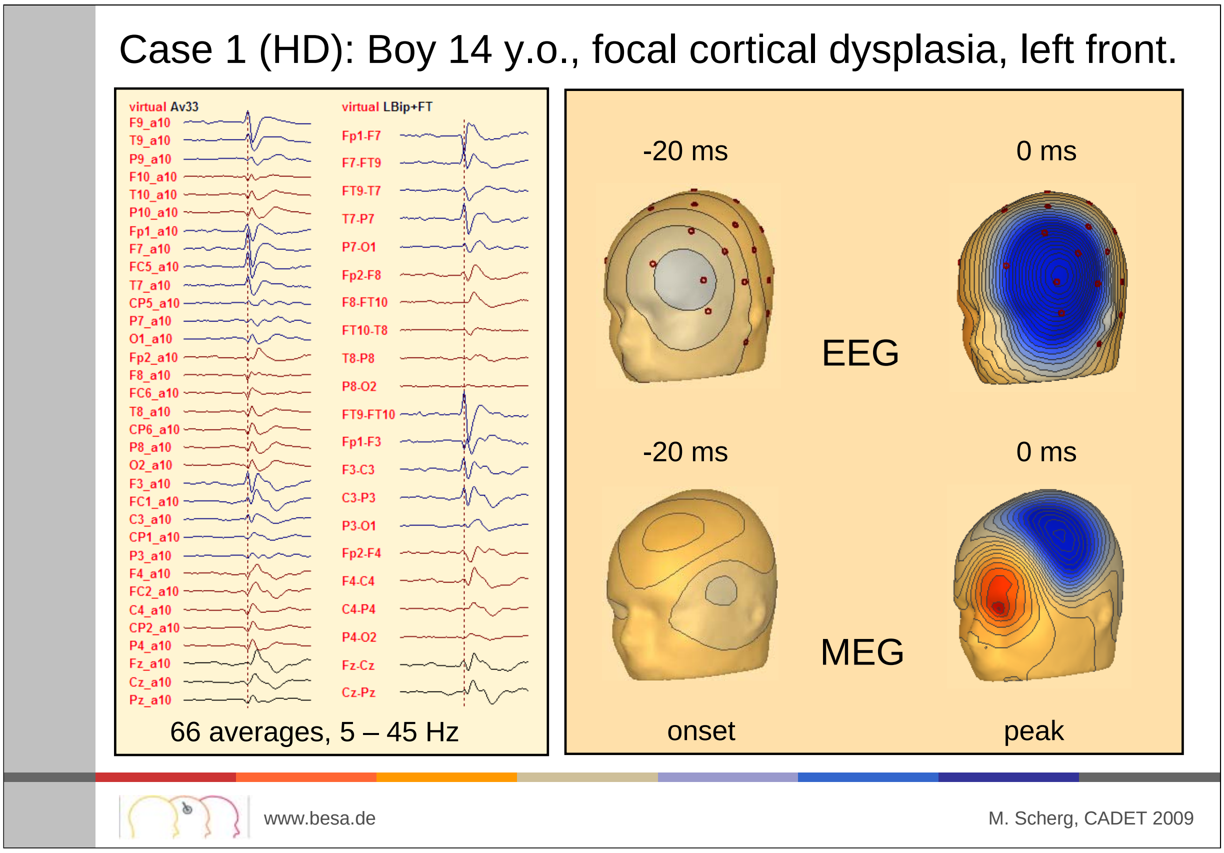
Furthermore, we have seen a brief assessment of averaged spike onset by 3D mapping and a comparison of source localization with a LORETA image.

Finally, we have also briefly addressed the importance of physiologically adequate testing of different hypotheses when working with separate sources for the onset and peak activities in a multiple source model. Evidently, single source peak localization is bound to be erroneous in EEG and MEG, if the overlap from continuing activities in remote onset zones is not accounted for.

In the following, we will now use the previous and several other, more complex, examples of simultaneous EEG / MEG recordings from the University Hospitals in Heidelberg and Sendai to demonstrate the value of

1. 3D mapping
2. Source analysis of spike onset and peak
3. Comparison with iterated LORETA images
4. Interpretation of spike orientation in addition to localization

The purpose of this approach is to assess the origin and initial propagation path of the underlying interictal activities.



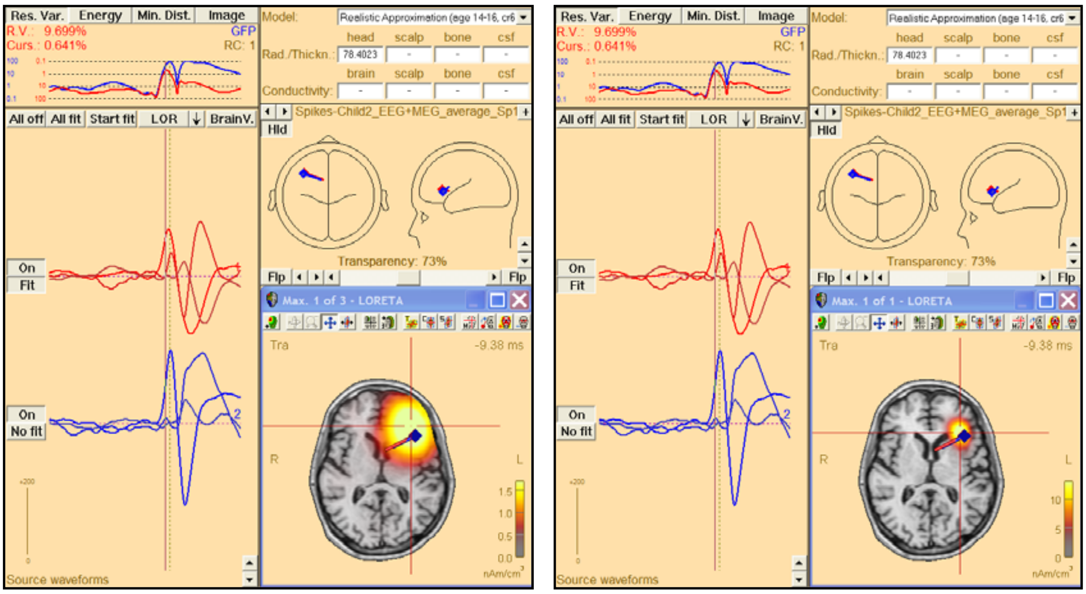

On the left, the average of 66 spikes using the spike montage with 33 virtual standard electrodes in average reference is depicted (_a10 means the whole 10-10 system is used as virtual reference). This montage (Av33) is compared with an extended longitudinal bipolar montage (LBip+FT) including vertical leads to FT9 and FT10 and one transversal lead FT9-FT10 (Lueders).

The spike peak has a maximum negativity around F7 (Av33 montage) and a corresponding polarity reversal between F7 and T7.

Using a virtual montage instead of the recording channels has the advantage of a systematic display irrespective of missing or bad electrodes. In fact, the spherical splines interpolation (cf. maps on the right) provides intrinsic smoothing that slightly reduces local artifacts / noise occuring only at one electrode (e.g. EMG).

On the right, onset and peak maps are compared for EEG and MEG. The interpretation of the 3D maps, as we learned before, points to a similar origin of onset and peak both in EEG and MEG . The map appears rotated slightly in EEG and more so in MEG, but the topography exhibits a similar center between the negative and positive extrema that resides above the Sylvian fissure in the left frontal lobe.

## Case 1: FCD-LF - interpretation of sources and LORETA




LORETA no iteration EEG LORETA 2 iterations

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The EEG source analysis presents the onset source (fit interval -25 : -9.4 ms, red) and compares it with the peak source (fit interval -20 : 0 ms, blue). Both sources almost coincide in location and exhibit only a small difference in orientation. Their source waveforms (left) share the activity and are similar.

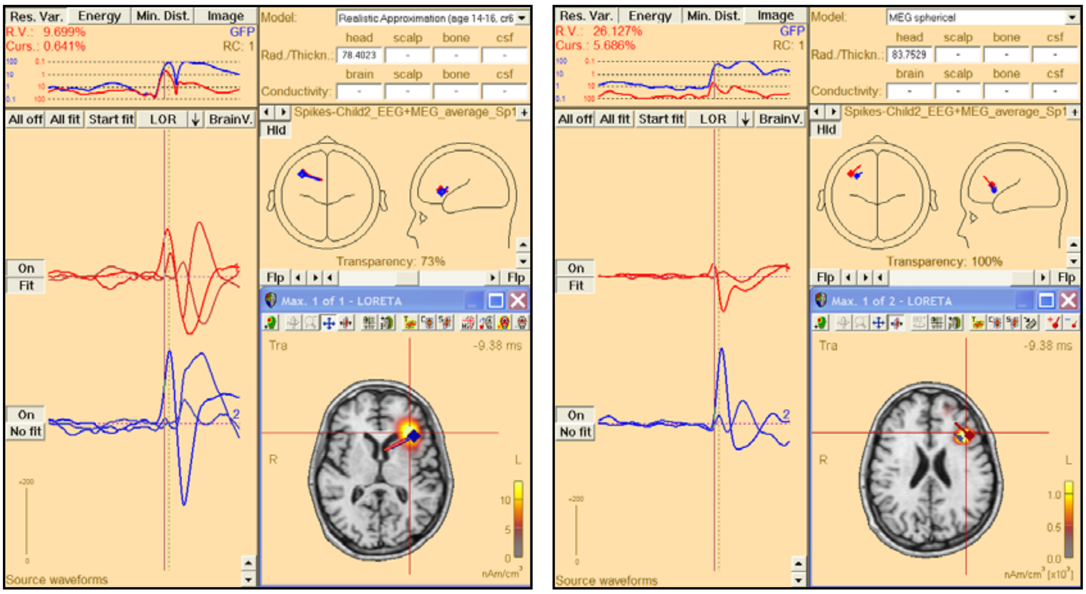
On the left a comparison with a LORETA image at the onset maximum (-9.4 ms) is depicted. The tradeoff between resolution and smoothing has been optimized such that a mirror source in the other hemisphere could be separated in the EEG (the result shows that there is no such mirror source on the right).

Separation and resolution can be enhanced by iterating LORETA twice with regularization constants appropriate for EEG and MEG, respectively, as seen on the right. The 2 iterations are especially useful for MEG to suppress the common ghost mirror foci around the source in the first LORETA image.

As shown before, the PCA over the onset interval (starting at the lowest point in the butterfly and global field power (GFP, top middle) plots exhibited one major component from a latency of -25 ms up to -9.4 ms before the spike peak. The maximum spike activity in the onset interval was at -9.4 ms.

A later peak can be seen in the 2nd dipole waveform of the red regional source that is overplotted over the 1st onset dipole waveform. The onset of this later activity with orthogonal orientation to dipole 1 indicates that the scalp topography starts rotating around -9.5 ms due to the increasing overlap of dipole 2.

## Case 1: FCD-LF - no spike propagation, EEG ~ MEG



EEG (onset = peak)    MEG (local rotation)

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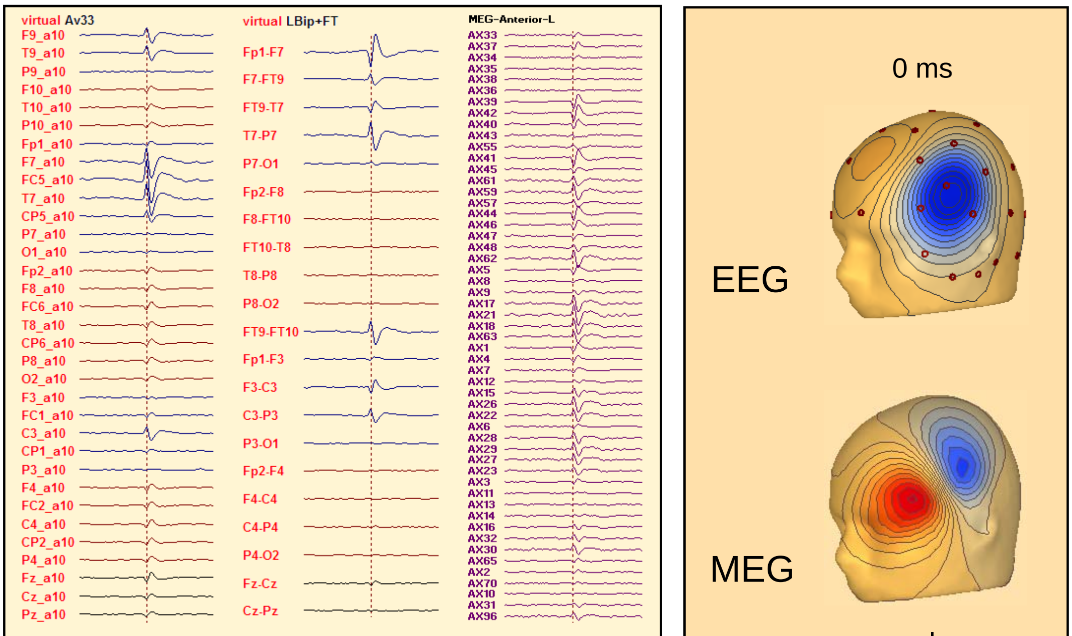
On the left, the EEG onset and peak sources are depicted again together with the iterated LORETA image. On the right the MEG onset and peak sources are overplotted over the iLORETA image (also iterated twice).

The MEG onset and peak sources (right) are slightly more separated but just a few millimeters apart and within the focus of the iLORETA image. Their orientations are more different and the onset source waveform is earlier and much smaller. This is consistent with the MEG maps shown before. Thus, propagation just involves a small local shift of the centers of activities between nearby aspects of the cortical fold that have a different orientation.

In this case, the region of activation has been defined by both methods consistently. No significant propagation has been found (this would require a distance of more than 2-3 cm between the onset and peak sources).

## Case 2 (Sendai): male, 27 y.o., left frontal lesion



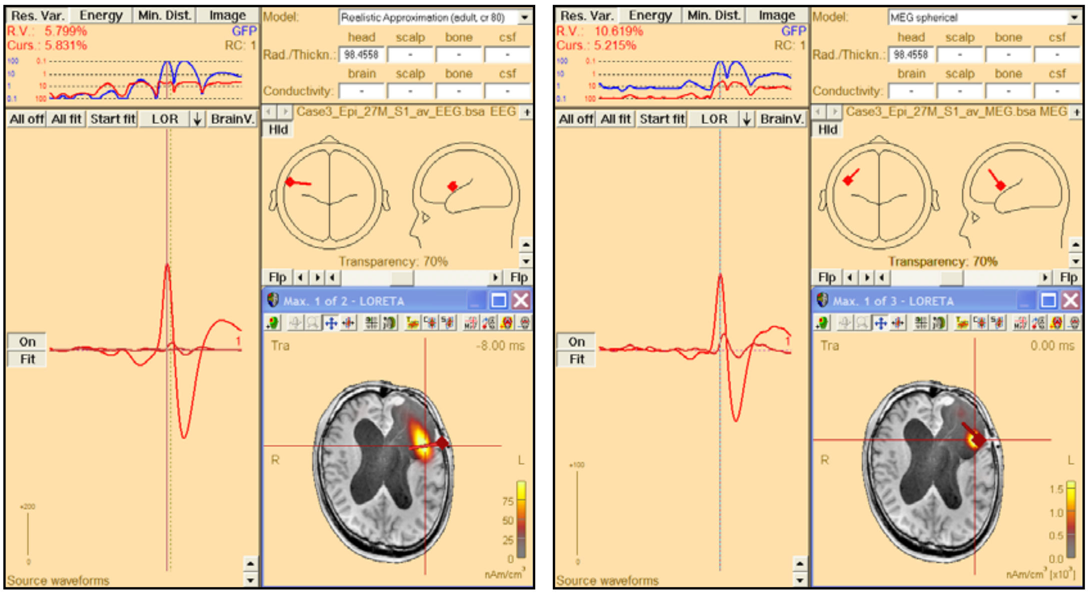

48 averages, 5 – 45 Hz



The second case also had only one major PCA component during the whole rising phase of the spike to the peak (>98%). EEG and MEG maps did not show a clear rotation. At a first glance, looking at the predominant negativity in the EEG map and the site of polarity reversal, the EEG origin might be interpreted as temporal and more inferior than the center of the beautiful MEG dipolar map.

However, follow the rules of interpreting an oblique EEG map by considering the corresponding positivity and the steepest gradients, and you can shift its center mentally towards the frontal positivity and assess the congruence of the EEG and MEG map centers.

## Case 2 (Sendai): left frontal lesion – no propagation



EEG peak: -8 ms

MEG peak: 0 ms



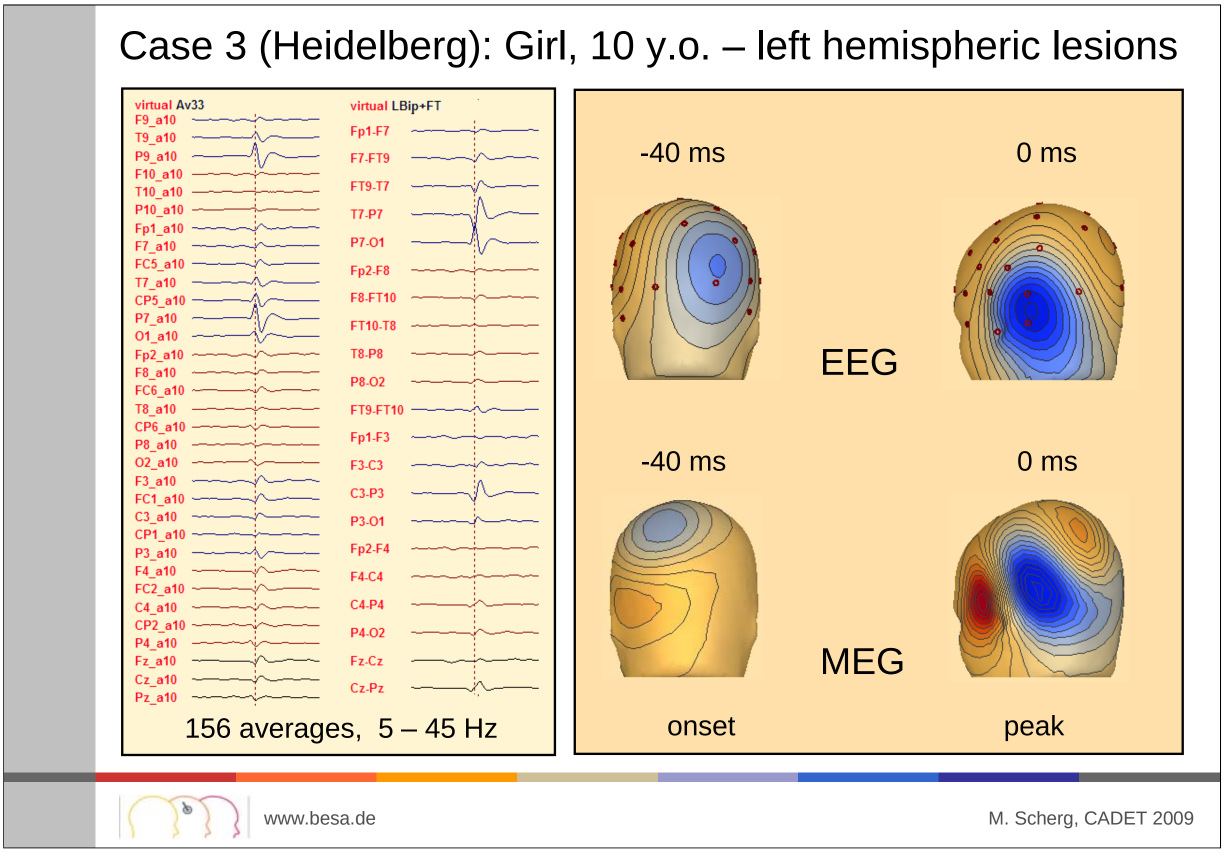
The source waveform of the 1st dipole of the regional EEG source (left) was fitted into the onset interval (-24 : - 8 ms) and peaked at – 8 ms. It was predominantly radial with a small anterior-upward component that increased a few ms later (cf. 2nd dipole source waveform). Accordingly, the 1st dipole of the MEG source exhibited a similar tangential orientation and peaked 8 ms later, i.e. at 0 ms. Note that the dipole moment of the MEG source is about 4 times smaller.

The solutions indicate that the small cortical rim next to the lesion with almost radial orientation is the site of EEG spike origin, while the MEG arises from the slightly more posterior part with partly tangential orientation.

The more superficial location of the EEG dipole is likely related to the bone defects and could be accounted for by choosing a head model with better bone conduction (~ lower age).

The deeper location of the center of the iLORETA image in the EEG shows an intrinsic property of this low resolution volume imaging method requiring a smooth current distribution. Due to the large distance between scalp electrodes the center is pushed towards the depth. The comparison of the dipole and iLORETA centers points out the limitation of estimating source depth from EEG due to a) unknown conductivities, and b) low resolution.

More consistency is seen in MEG due to its higher spatial resolution and smaller volume conduction errors. However, it appears that these and coregistration errors have pushed the source and image about 1 cm towards anterior. Thus, MEG localization must interpreted with caution as well.



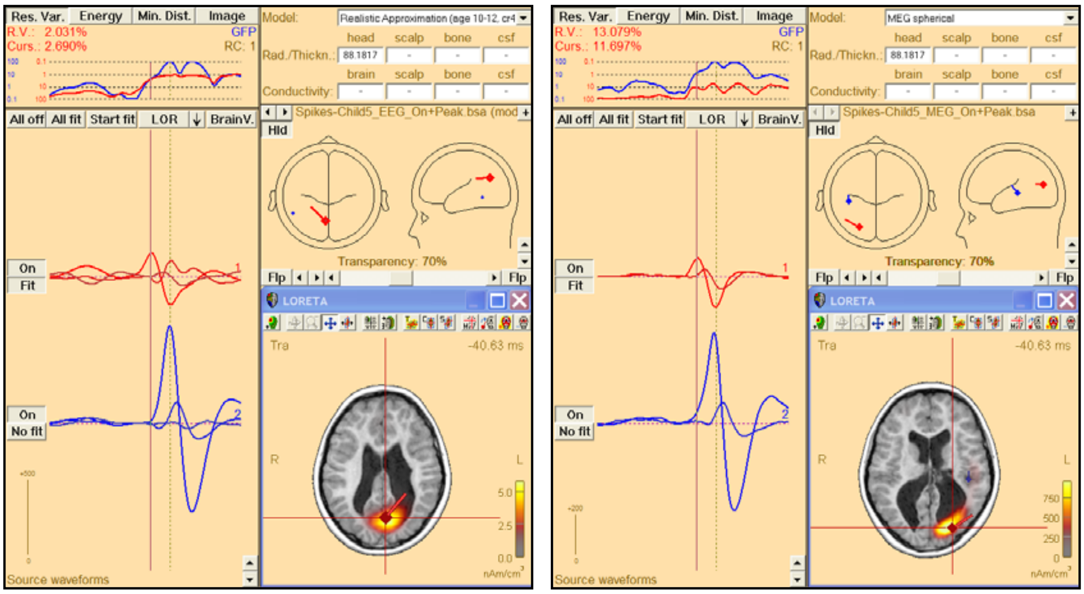

Onset and peak maps in this case are quite different. Looking at the negative peak in the EEG over O2, you might get the impression that the spike onset is in the right hemisphere. However, this is a typical case of the so-called ‚paradox lateralization‘. Again, just follow the rules of interpreting an EEG map by considering the corresponding positivity and the steepest gradients, and you can observe immediately that the map center of the EEG spike onset is in the left mesial occipital cortex, consistent with left MEG center.

At the spike peak, a clear lateralization to left posterior temporal region can be seen with a relatively similar center between T7 and P7 in both EEG and MEG while the EEG negativity appears lower and more posterior (between P7 and P9). In addition, the MEG map exhibits a 2nd, weaker dipolar pattern, that seems to reflect the polarity reversal of the onset pattern. This will be comfirmed by the dipole source waveforms in the next slide showing the opposite polarity of the onset spike waveform overlapping with the crest of the peak source.

Thus, localizing a single dipole into the peak pattern of a spike may shift its localization in a hard-to-predict manner, if the overlap of the preceding and continuing onset activity from a remote onset region is not considered.

Localizing simply by selecting the regions of maximum positivity and negativity in MEG in a map that clearly has more that one underlying dipole pattern (or high background activity) is prone to intrinsic localization errors!

## Case 3: Left hemisph. lesion: EEG / MEG onset occ. mesial




EEG onset MEG onset

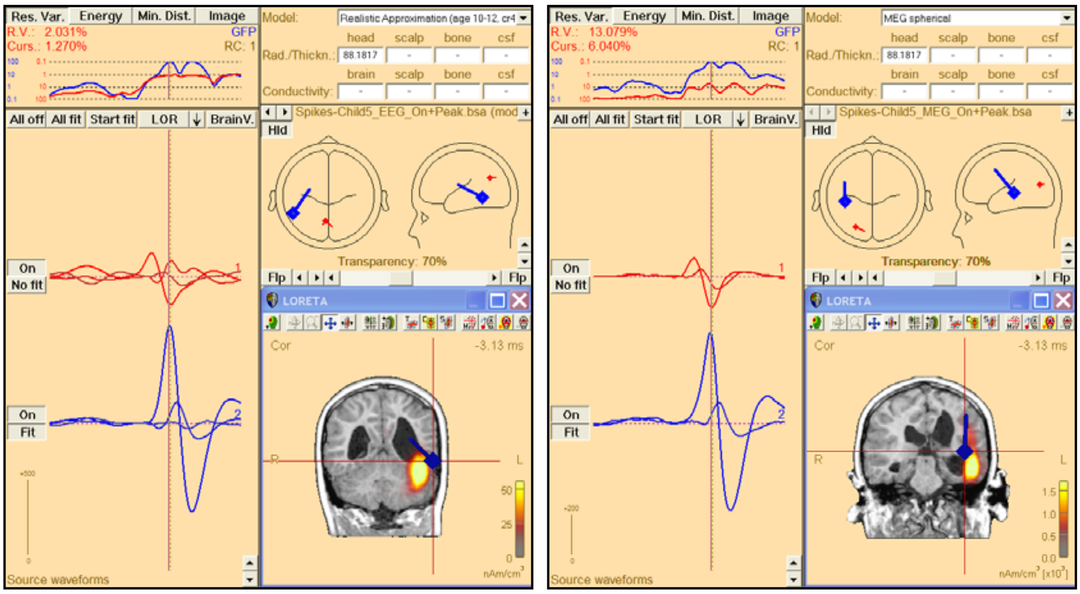


The onset activity (red, PCA: 98.7%) localizes to the mesial occipital cortex in the left hemisphere that exhibits a widespread lesion.

The interpretation of a left-sided origin is supported by the orientation of the first EEG and MEG dipoles. Both point from the interhemispheric cleft into the left occipital cortex. This is in agreement with the surface negative polarity of spikes.

The more lateral localization of the MEG could come from the beginning overlap with MEG activity already propagating to the more lateral cortex in the later part of the onset interval (cf. blue source waveform). Also the volume currents in the enlarged left ventricle might play a role here. Thus, source localization must be interpreted with care also in MEG.

## Case 3: EEG and MEG: propagation to lateral at peak




EEG peak MEG peak



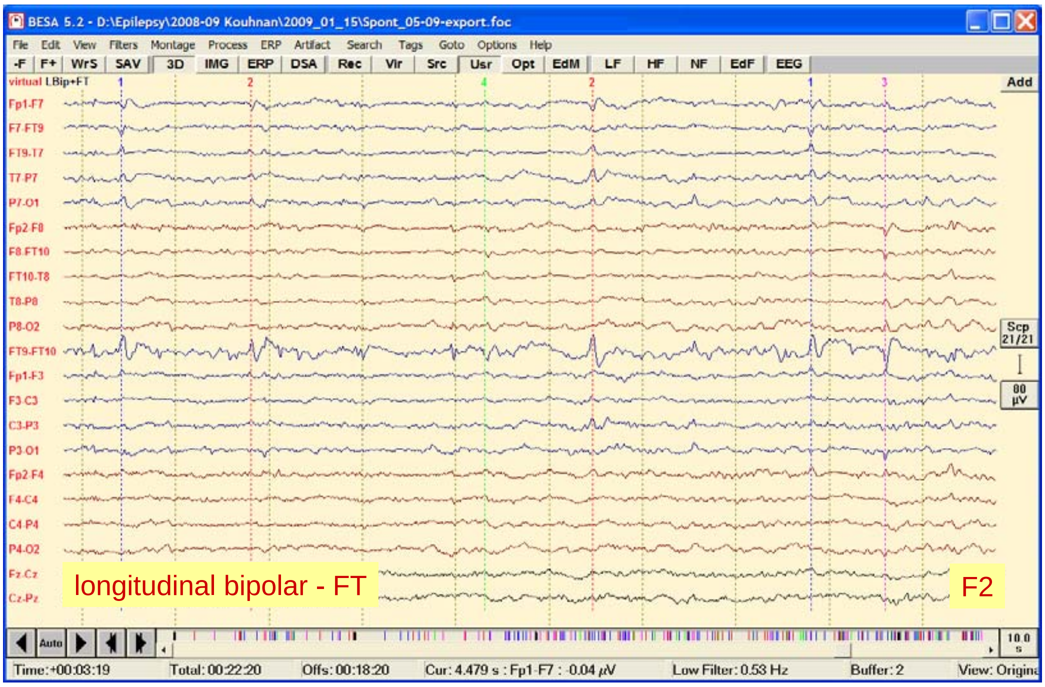
An additional regional source (blue) in the temporal posterior inferior region can explain most of the EEG and MEG activity at the peak. However, this is an equivalent source at some center of a widespread temporal-lateral inferior activation. The different orientations and localizations of the blue EEG and MEG sources indicate that their centers reflect cortical aspects of different orientations. EEG has a strong contribution from the superficial cortex that is missing in MEG. Thus, we cannot expect their centers and equivalent sources to be the same.

The iLORETA images of inferior activities have a tendency to produce more inferior spots towards the cerebellum (more so in EEG than MEG). This must be taken into account in the interpretation. However, in combination the source location and image spots indicate the dominant spiking region. EEG and MEG orientation adds the information which surfaces are involved.

At the time of the peak, the source activity in the mesial onset zone (red) shows a polarity reversal and overlaps on the strong lateral activity both in EEG and MEG. When this overlap is ignored and a single source model is applied instead of a multiple source model, the source localization of the peak source shifts (EEG: 7 mm, the onset and peak topographies are not much correlated; MEG: 28 mm towards inferior, the negative poles of both onset and peak maps overlap, see preceding MEG maps).

More detailed MEG multiple source and iLORETA analysis shows two more lateral sites of propagation between the onset and the peak. Thus, the main message of this example is the need to find and analyze the onset.

## Case 4 (Sendai): female, 67 y.o., temporal lobe epilepsy



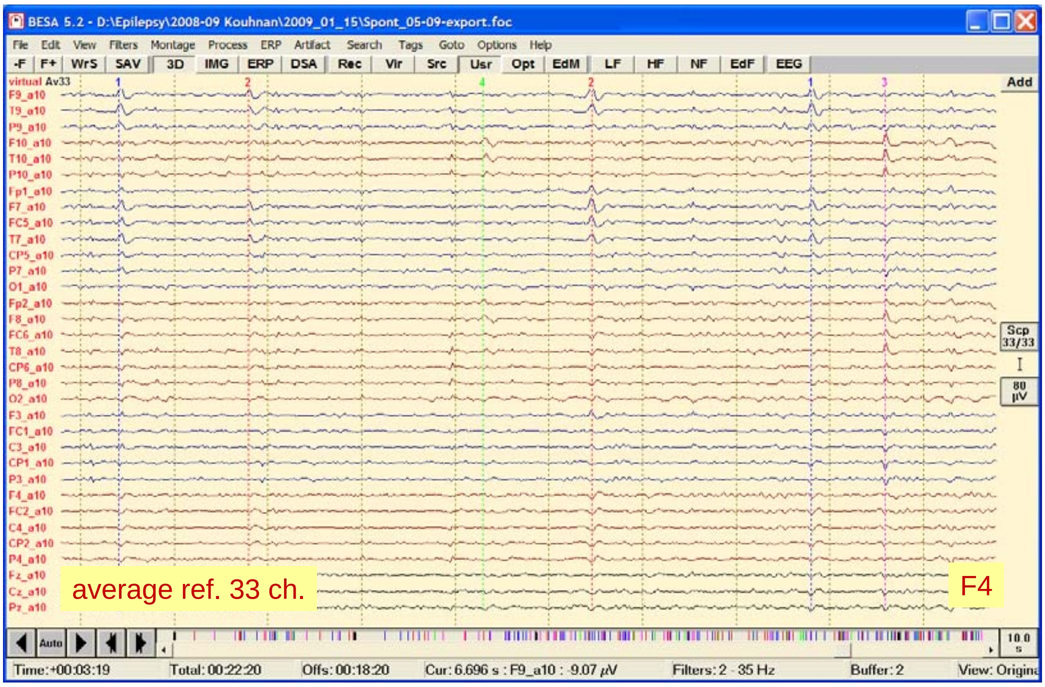



In this patient with temporal lobe epilepsy, we first inspect one 10-sec page of EEG with different standard montages and filter settings.

Pressing **F2**, we obtain a standard EEG display with the extended longitudinal bipolar montage and a transverse FT9-FT10 channel (Lueders). Standard EEG review filter are set: time constant of 0.3 sec, i.e. a low forward filter of 0.53 Hz; no high filter.

Polarity reversal can be seen between F7-T7 on the left showing 4 spikes (tags 1 & 2) and between F8-T8 showing 2 spikes (tags 3 & 4). The tags have been set by pattern search using the temporal lobe source montage described below.

## Case 4 (Sendai): EEG 33-ch. virtual montage, spike filters

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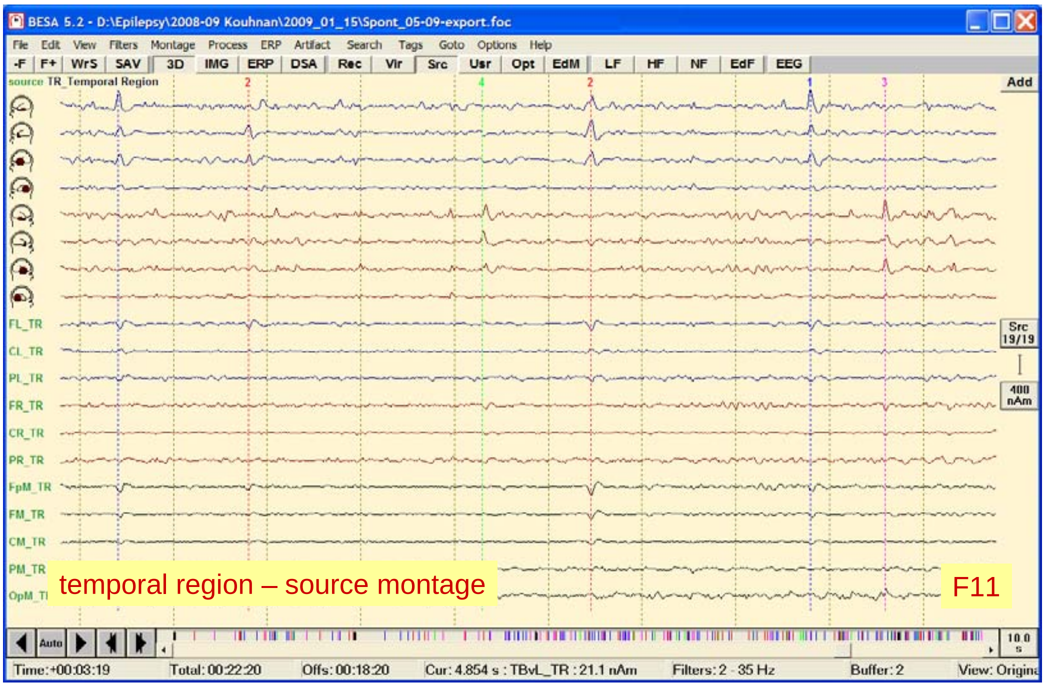
Pressing **F4**, we obtain the virtual average reference montage Av33 with inferior electrodes F9/10, T9/10, P9/10. These electrodes allow for some differentiation of spikes with tag 1/3 ( spike signal largest at T9/10, present also at P9/P10) from spikes tag  with tag 2/4 (spike signal largest at F9/10, not present at P9/P10).

Spike visibility has been enhanced by the specific spike filters set by batch F4 (2-35 Hz) that reduces low- and high-frequency background and noise. Also, the grouping of the channels increases visibility.

## Case 4 (Sendai): temp. lobe source montage, spike filters





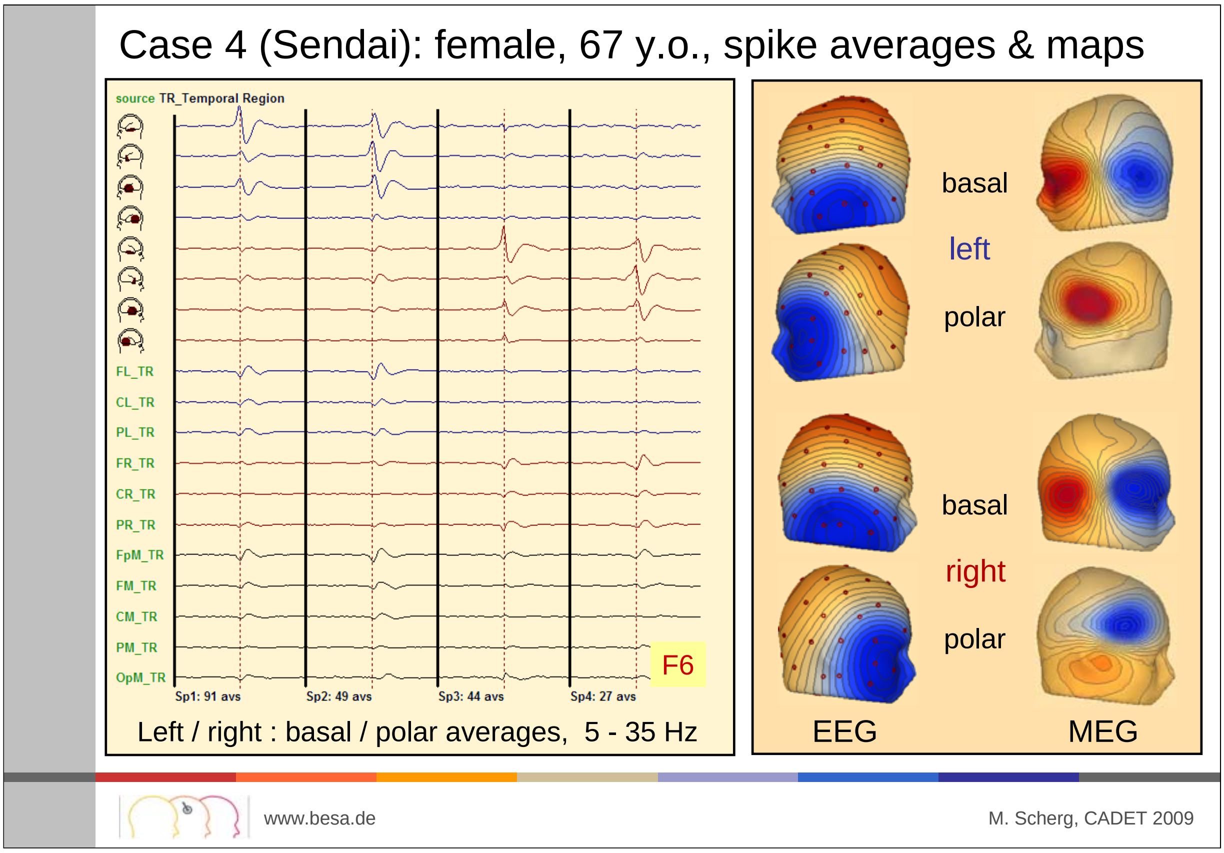

Pressing **F11**, we obtain the temporal-region source montage that estimates the activity at 4 different aspects of the temporal lobe using the potential distribution of all scalp electrodes in an inverse model. Thus, left (upper 4 traces, blue) and right (next 4 traces, red) temporal lobe activities can be separated to a large degree from each other and from the activities in other brain regions (below).

The 4 temporal lobe aspects from top to bottom in each of the left and right groups are:

- temporal-basal
- temporal-polar
- temporal-anterior lateral
- temporal-posterior lateral

Spikes with tags 1/3 show the largest and earliest activity at the temporal base, while spikes with tags 2/4 show a leading temporal-polar activity.

Based on this distinction, obvious only in this specific source montage, we were able to search for similar spikes of these basal and polar types in the left (tags 1 & 2) and in the right temporal lobe (tags 3 & 4). The displayed EEG page shows typical detections that were found using a clear template for each spike type in the appropriate source channels.



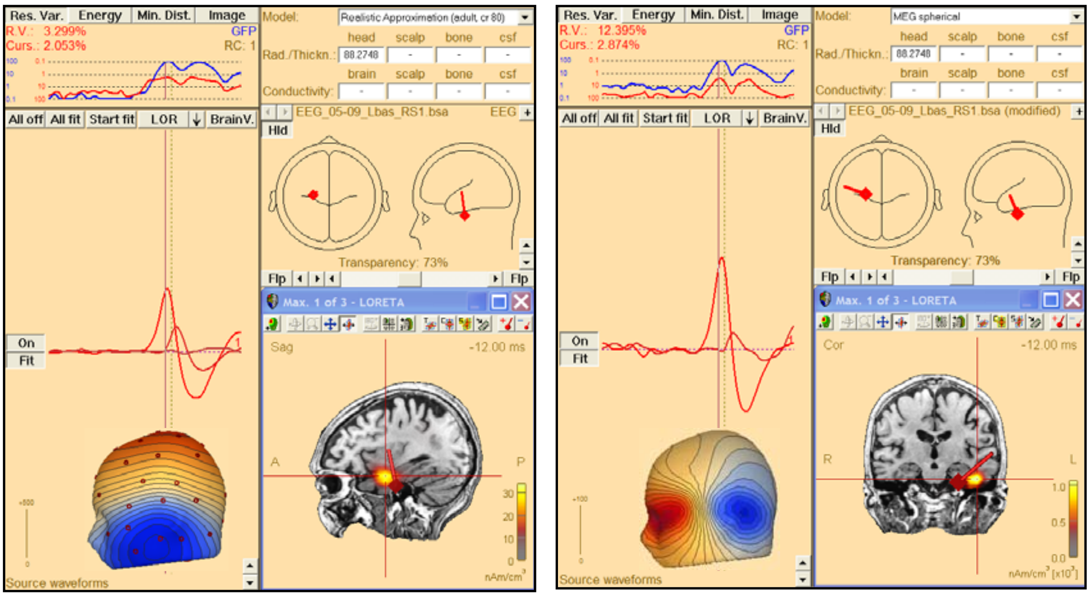

Pressing **F6**, we obtained the average as displayed above. The F6 batch has also set the filters to 5 – 35 Hz, the low filter using a forward characteristic to enhance the spike onset and remove the baseline. This allows for excellent 3D mapping of onset and peak.

Here, only the peak maps are shown to characterize the different detected spike types:

- Sp1: left basal - EEG vertical map, MEG corresponding horizontal map, same center in left temporal lobe (92 averages)
- Sp2: left polar - EEG oblique map with negative maximum over eye, MEG map with reduced inferior negativity, pointing to the same more anterior center (49 averages)
- Sp3: right basal - EEG vertical map, MEG corresponding horizontal map, same center in right temporal lobe (44 averages)
- Sp4: right polar - EEG oblique map with negative maximum over eye, corresponding orthogonal MEG map, pointing to same more anterior center (49 averages)

The leading signal at the temporal base can be seen in the basal source channels in the averages Sp1 & Sp3; the leading signal at the temporal pole can be seen in the polar channels in the average Sp2 & Sp4 that are below the basal channels.

## Case 4 (Sendai): Left temp. basal – interpret orientations !



EEG onset -12 ms MEG

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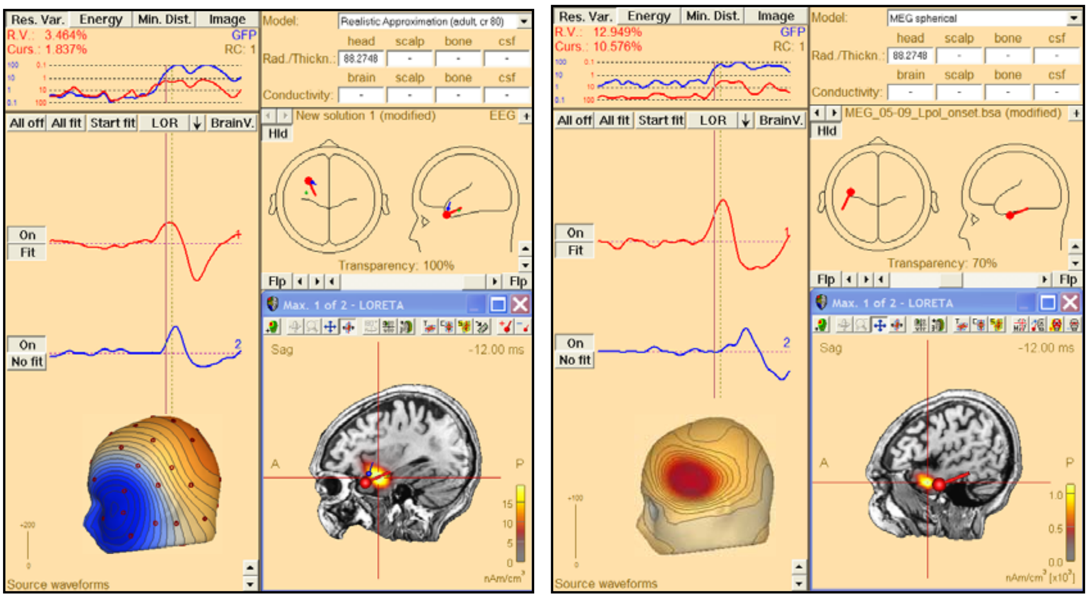
Pressing **F7**, we started the EEG source analysis and defining the onset interval of Sp1, i.e. the average of the 91 left spikes with basal onset. The red onset source and blue peak sources were then fitted automatically and overlayed with a LORETA image. The peak source was removed to show when the EEG signal starts deviating from the onset signal (onset of 2nd dipole source waveform of the red regional source). Using 2 separate batches, the MEG solution and the iLORETA solutions (2 iterations each) at the maximum of the onset interval were then computed.

Both the EEG and MEG source localizations and the iLORETA focus in the MEG point to the left basal temporal lobe as origin. In the EEG, the vertical orientation of the onset source supports this interpretation while the iLORETA image simply highlights the anterior left temporal lobe without certainty about which surface is involved. This can only be assessed by the orientation of the EEG dipole. MEG source orientation is tangential to the sphere model and, therefore, appears oblique in the coronal plane since the center is on the AC-PC line 16 mm behind AC. Thus, the MEG dipole localization should not be misinterpreted as being the true current orientation or as pointing to the hippocampal region.

In fact, at least a major portion of the anterior parahippocampal gyrus has to be active to produce the clear basal onset signals in the scalp EEG and in MEG. The extent of the basal activation cannot be estimated from EEG or MEG. Furthermore, depth should be interpreted with caution, because the equivalent vertical dipole can easily be shifted 1-2 cm deeper or laterally and still explain the data very well. Hence, orientation is the main clue to identify which surface is involved. In MEG, however, one must consider that only the tangential projection of the surface normal of the activated surface integral is seen.

## Case 4 (Sendai): Left temp. polar – interpret orientations !



EEG onset -12 ms MEG



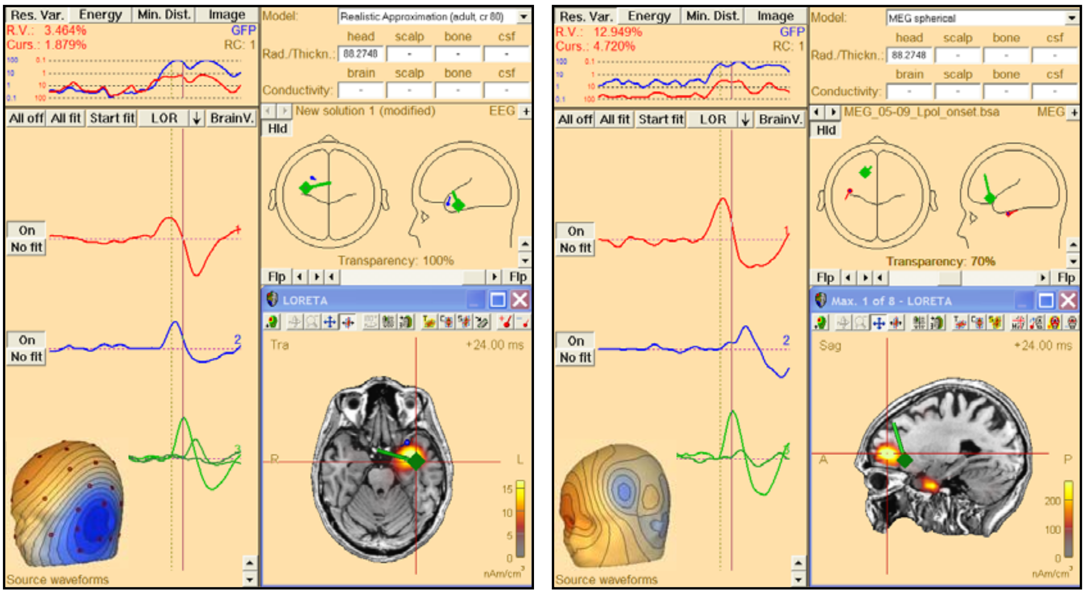
The average of the 49 spikes with left temporal polar onset in the source montage was analyzed using the corresponding batch for Sp2. To better illustrate the evolution at the onset, the onset source was separated into 2 dipoles (red = onset dipole 1, blue = onset dipole 2 of the regional source).

The red onset source is oriented backwards in EEG and MEG and points to the left polar surface as origin. This is supported by the MEG iLORETA image while the EEG – as in the basal spikes – is unspecific with respect to which aspect is involved.

However, since EEG represents the true current vector orientations as opposed to the tangential projection of the MEG dipoles, it can be seen from the orientation of the 2nd onset dipole (blue) that a rapid propagation occured to the lateral polar part that was not visible in MEG due to the radial orientation of this activity. The 2nd EEG dipole could even be localized at an equivalent location within the polar region with the location being unspecific with respect to which surfaces were involved.

The key information on the spreading involvement of the different surfaces of the anterior temporal lobe is provided by the orientations and source waveforms of both EEG dipoles. They show that the initial tangential polar spikes (red) are rapidly getting overlapped by propagation to the lateral-anterior convexity - as seen in the delayed onset of the near-to-radial 2nd EEG dipole (blue). Since the MEG cannot see this radial activity, the 2nd MEG dipole does not show a large activity during this later part of the onset interval (-12 : 0 ms).

## Case 4 (Sendai): Left temp. polar – interpret orientations !




EEG +24 ms MEG

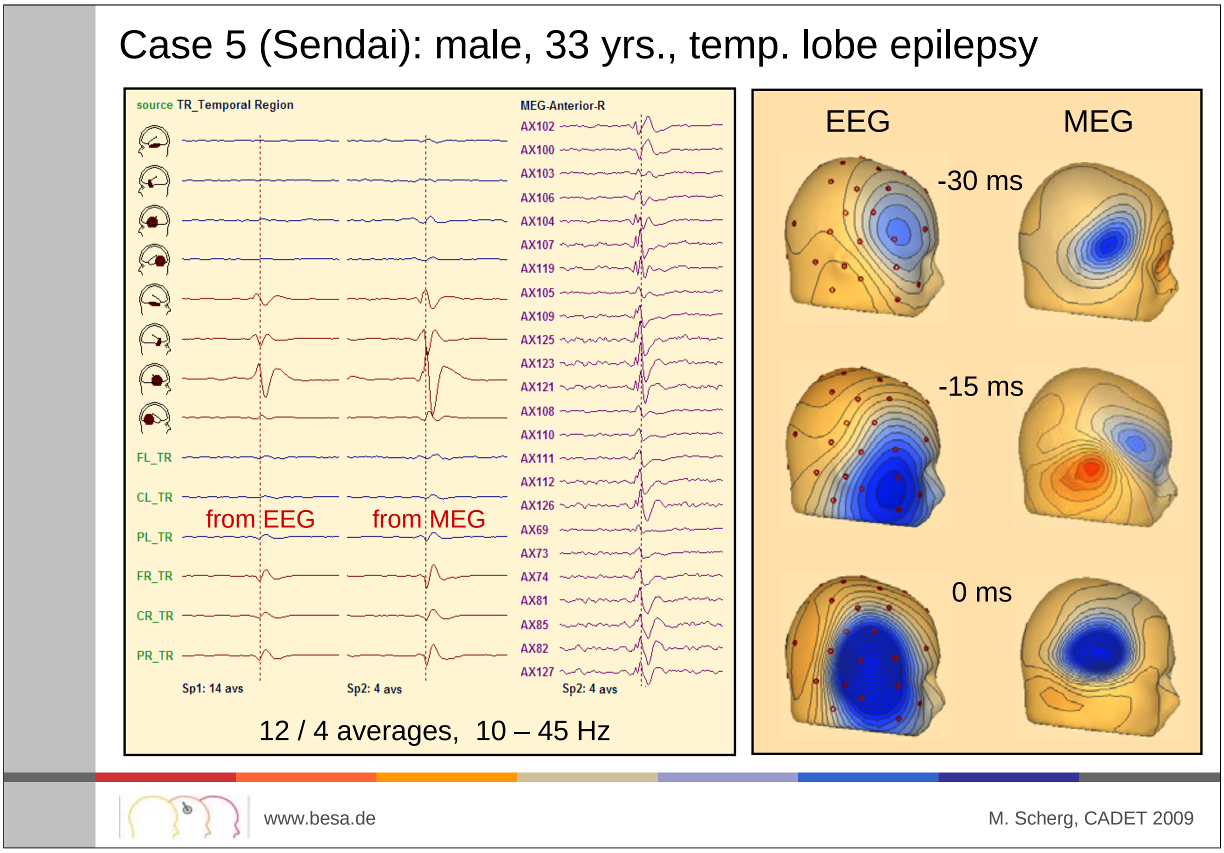


24 ms after the polar peak, the EEG map negativity has rotated to lateral inferior indicating extended involvement of the base and lateral surface. Accordingly a large near-to-radial dipole at a deeper equivalent center in the left temporal lobe can be seen in agreement with the iLORETA image.

In contrast, the MEG map is unclear and shows multiple underlying field patterns. A frontal origin of one pattern can be inferred from the MEG map. This is confirmed by the iLORETA image. It shows 2 foci, one in the left temporal lobe and another in the left fronto-polar region. The equivalent source fitted around this time assumes a compromise location in between.

This documents that the analysis of the propagated activity can be quite complex in MEG, if not only a single region contributes. The EEG on the other hand is dominated by the strong superficial activation of the left anterior temporal lobe to which MEG appears to be blind. Only the small basal activity seems to show up in the source waveform of the 2nd MEG dipole (blue) while a stronger activity seems to arise in the left fronto-polar region. This is not confirmed by EEG, however.

This illustrates that the actual propagation paths can be quite difficult to assess in detail even when the fact of propagation is evident.



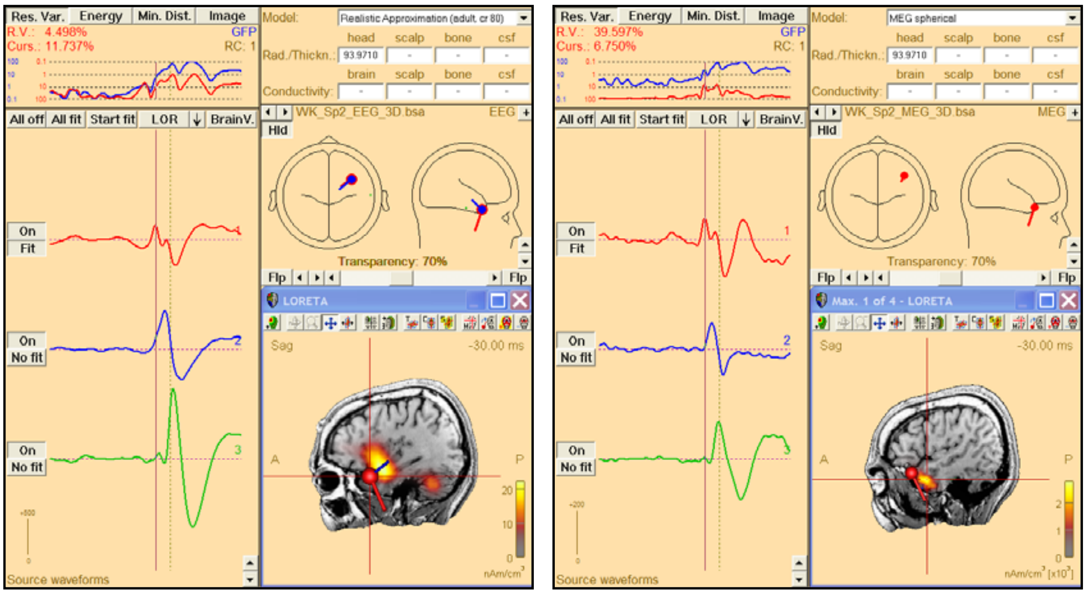

This example of a right temporal spike demonstrates the activation of yet another surface in the polar temporal region and a considerable propagation. Here, we analyze the 4 spikes averaged from a sharp transient in the MEG.

Note that the initial EEG dipole map at -30 ms shows a frontal negativity. When considering the accompanying inferior positivity and the gradients of the equipotential lines, it becomes evident that the underlying center is more inferior and corresponds to an oblique equivalent dipole pointing downwards and inwards. The initial downward component is confirmed by the MEG map at -30 ms. 15 ms before the peak we observe a typical polar pattern, while a superficial lateral activity with partly posterior orientation dominates at the peak (0 ms). Again, this is confirmed by the MEG maps.

Thus, we might conclude that the spikes are initiated at the superior and lateral surface of the right temporal pole within the Sylvian fissure. This interpretation is supported by the small downward spike in the right temporal basal source waveform. This signal is constructed using a vertical dipole in the right basal temporal region within a multiple source models covering the other aspects of the right temporal brain region, the corresponding regions on the left and all other brain regions by regional sources. Thus, the basal source waveform will pick up spikes in the supratemporal plane as well, but with inverse, downward polarity.

After this short initial superior spike, the typical propagation to the polar and further on to lateral posterior regions was seen in right temporal polar and lateral source waveforms. Averaging based on EEG led to a smoothing out of the initial sharp transients seen best in the MEG (upper left, 12 averages). Thus, based on EEG alone this spike would have been interpreted as anterior-polar onset.

## Case 5 (Sendai): right temporal lobe – ant.-superior onset



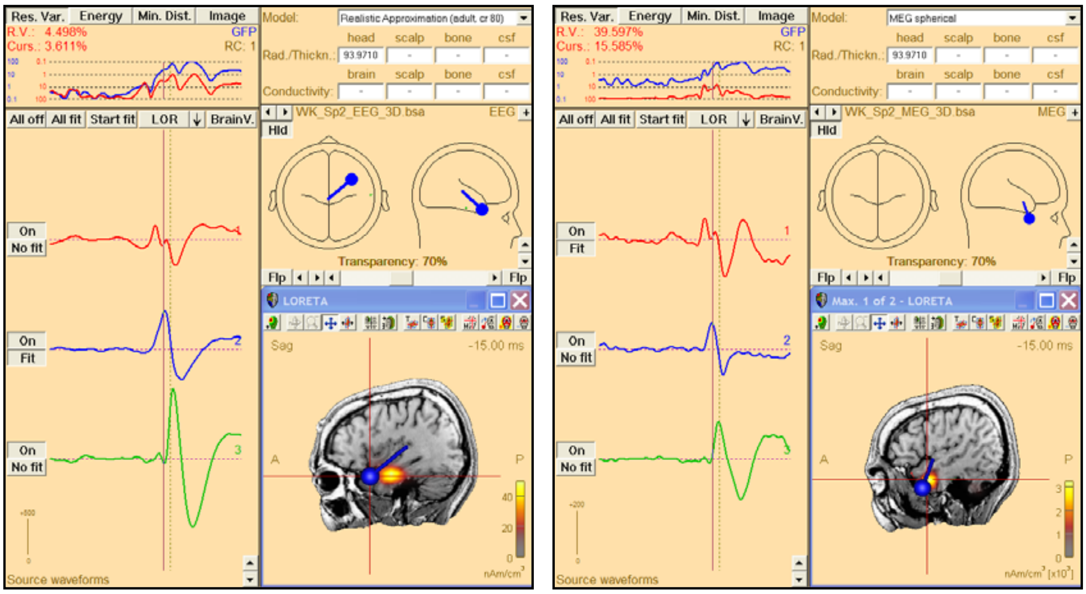

EEG onset: -30 ms MEG



Again, we have separated the regional onset source into the initial 2 dipole components (red and blue) and used only a single dipole for the peak activity (green). Both EEG and MEG are best modeled by an initial downward oriented dipole at the superior surface of the right temporal pole.

A strong polar activity follows immediately in EEG and MEG (blue) with the radial part only visible in EEG.

## Case 5 (Sendai): right temporal lobe - propagation to pole




EEG -15 ms MEG

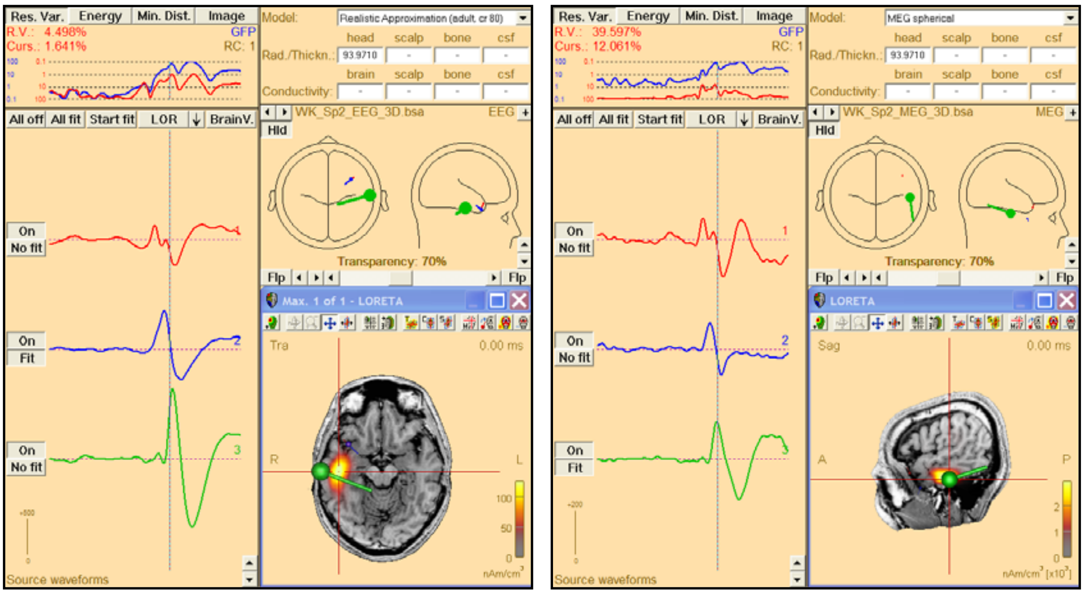


The peak of the following polar activity (blue) is at -15 ms in EEG and MEG. The EEG dipole has an upward-posterior and a strong inward orientation. This latter radial part is not seen in the MEG dipole that point only upwards and backwards.

This indicates that the MEG senses only a part of the activated cortical surface at 15 ms. Relative to the initial activity at – 30 ms when the dipole orientation was predominantly tangential (red traces), the EEG polar dipole seems to be stronger as compared to the MEG due to its additional radial part (blue traces).

Comparing the iLORETA images of EEG and MEG at the peaks of the two source activities at -30 ms and -15 ms, they appear more congruent with the source localization in MEG. Conversely, the differences in location between the equivalent sources and the centers of the iLORETA image convey the amount of uncertainty in localization in both EEG and MEG. Accuracy appears to be in the range of 1-2 cm and, orientation needs to be interpreted to identify the active surface.

# Case 5 (Sendai): right TL, propagation to basal-lateral

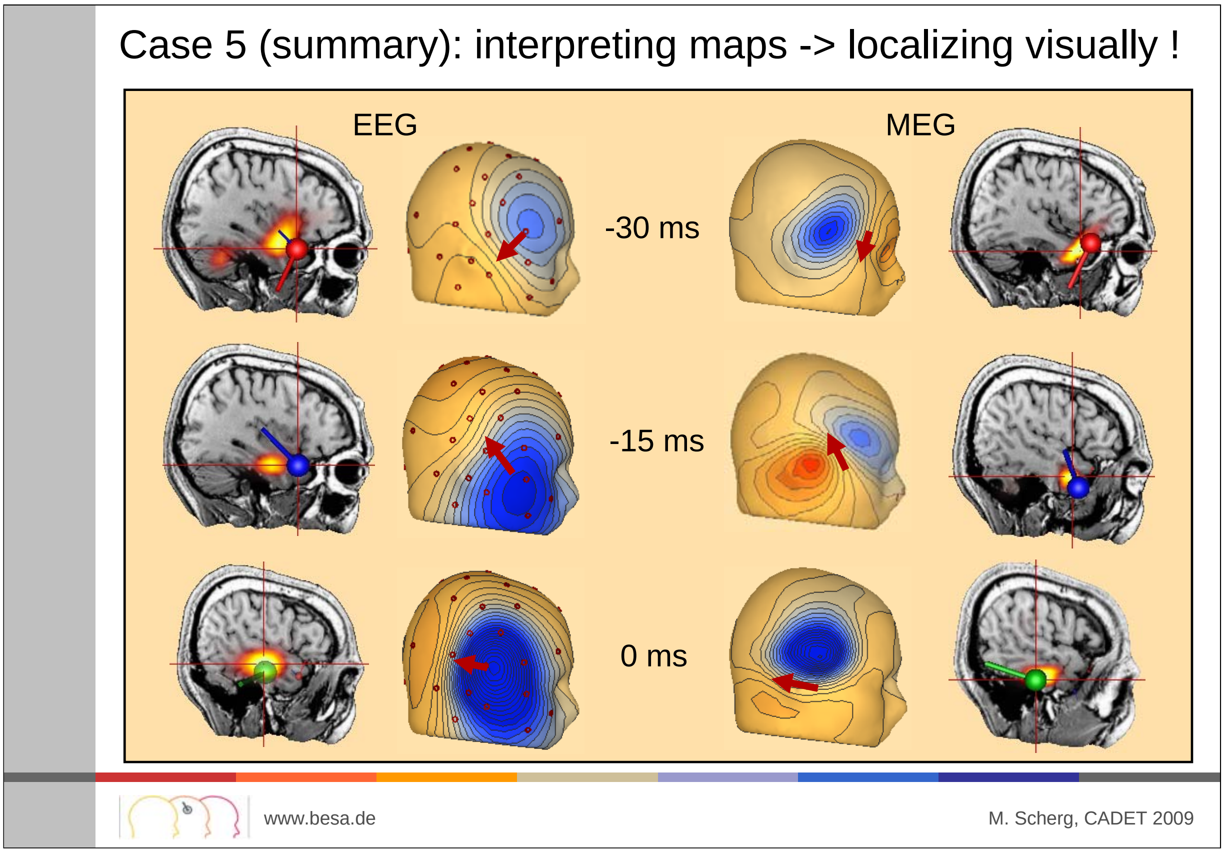



EEG peak: 0 ms MEG



At the peak, the large lateral negativity in the EEG is explained by a near-to-radial dipole that has a small backward component. This component is seen in the MEG as a tangential dipole with a relatively smaller amplitude (green traces compare to red), since the MEG is insensitive to the radial aspect.

Thus, MEG only senses a specific fissural part of the cortical activation at the time of the spike peak. The overlap from the polar region at 0 ms appears to be small in this case.




This slide illustrates that the 3D EEG and MEG maps already contained the key information for the correct interpretation of the onset and propagation:

Based on the rules of finding an equivalent center in a (predominantly) dipolar map, the downward activity at -30 ms was identifiable in both the EEG and MEG maps. Considering the fact that epileptic spikes are cortical surface negative, the only candiate for the origin of a downward-posterior current can be the upper surface of the temporal lobe within the Sylvian fissure. The anteriror location and the subsequent propagation to the inferior and lateral part of the temporal pole suggest the upper surface of the temporal pole as origin.

The polar maps at -15 ms are quite typical for temporla-polar spikes and easy to interpret. The stronger negativity and oblique, backward orientation of the EEG polar map indicates anterior, inferior and lateral involvement of the polar region. In contrast, the MEG is dominated by the inferior activity and blind to the radial part.

This is also the case at the peak where the MEG map is more complicated and not clearly dipolar. Where the MEG localizes, will strongly depend on which fissural aspects generate the predominant signals within a relatively widespread spiking zone involving the lateral and inferior cortical convexity.

## Conclusions

1. Identification of the centers of spiking regions requires the interpretation of the orientation(s) of the underlying equivalent current dipole(s)
2. In most cases, the correct interpretation of the 3D EEG topography can provide this information. MEG topographies can be more complex.
3. Localization can help and support in the interpretation. However, at least two independent methods should be compared (e.g. multiple sources, iLORETA).
4. MEG showed more consistency beween both methods, but suffers from insensitivity to spiking zones on the cortical convexity. Thus, MEG should not be recorded without EEG using an adequate electrode coverage.
5. Localization of the onset zone is required. Peak localization alone is insufficient and, sometimes, erroneous if multiple areas are involved at peak time.
6. Because propagation of more than 2.5 cm from onset to peak zones can be seen in about 30% of all cases, averaging is mandatory to achieve sufficient onset signal. Furthermore, a high forward lower filter is needed to enhance the onset signal over background (5 or 10 Hz ~ time constant 0.03 or 0.015 sec).



EEG with extended electrode coverage provided all the information required to analyze the presented cases. Only occasionally, MEG had a slight advantage in the signal-to-noise ratio for detecting deeper tangential activities, e.g. in the Sylvian fissure at the top of the temporal pole.

Long-term-monitoring of EEG will benefit enormously from an improved electrode coverage with a sufficient inferior (e.g. F11/12, A1/2, P11/12 and, possibly, FT9/10) and intermediate (FC1/2, FC5/6, CP1/2, CP5/6) electrode placement in addition to the 19 electrode of the standard 10-20 system. This standard is insufficient to estimate topography and onset reliably, especially in temporal lobe epilepsy. Given such a wide, evenly spaced coverage and adequate interpretation of the orientation and center of the voltage topography, the 3D maps of averaged spikes are usually an excellent guidance to identify the regions of spike onset and first propagations.

These improvements of the clinical EEG routine, i.e. extended electrode coverage and averaging of spikes, provide an improved guidance for further imaging and neurophysiological testing using, e.g. invasive recordings, during the presurgical monitoring of epilepsy patients.

## Thanks to all collaborators

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- Patrick Berg, University of Konstanz
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- Karsten Hoechstetter, MEGIS Software GmbH, Munich
- Dieter Weckesser, MEGIS Software GmbH, Munich
- Andrea Ostendorf, MEGIS Software GmbH, Munich
- Nicole Ille, MEGIS Software GmbH, Munich



More lectures and tutorials showing the analysis of epileptic spikes and seizures can be found along with recommended electrode settings on:

**www.besa.de**