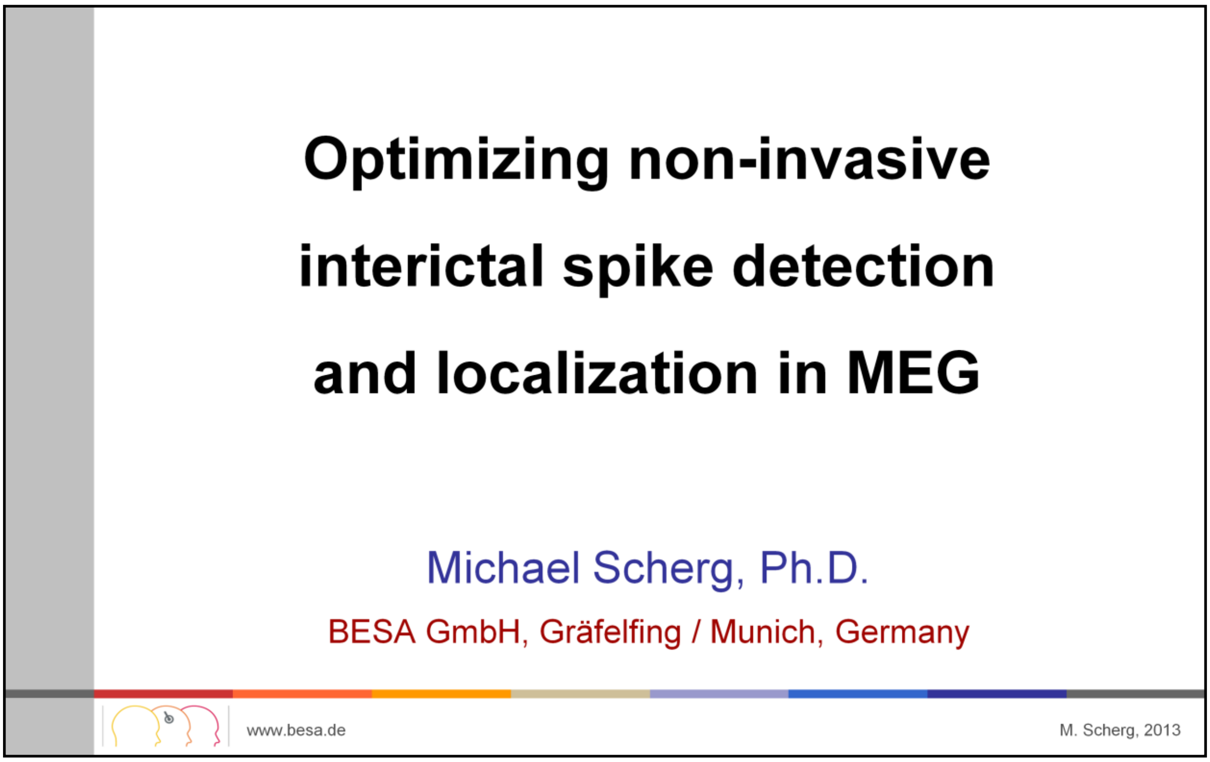
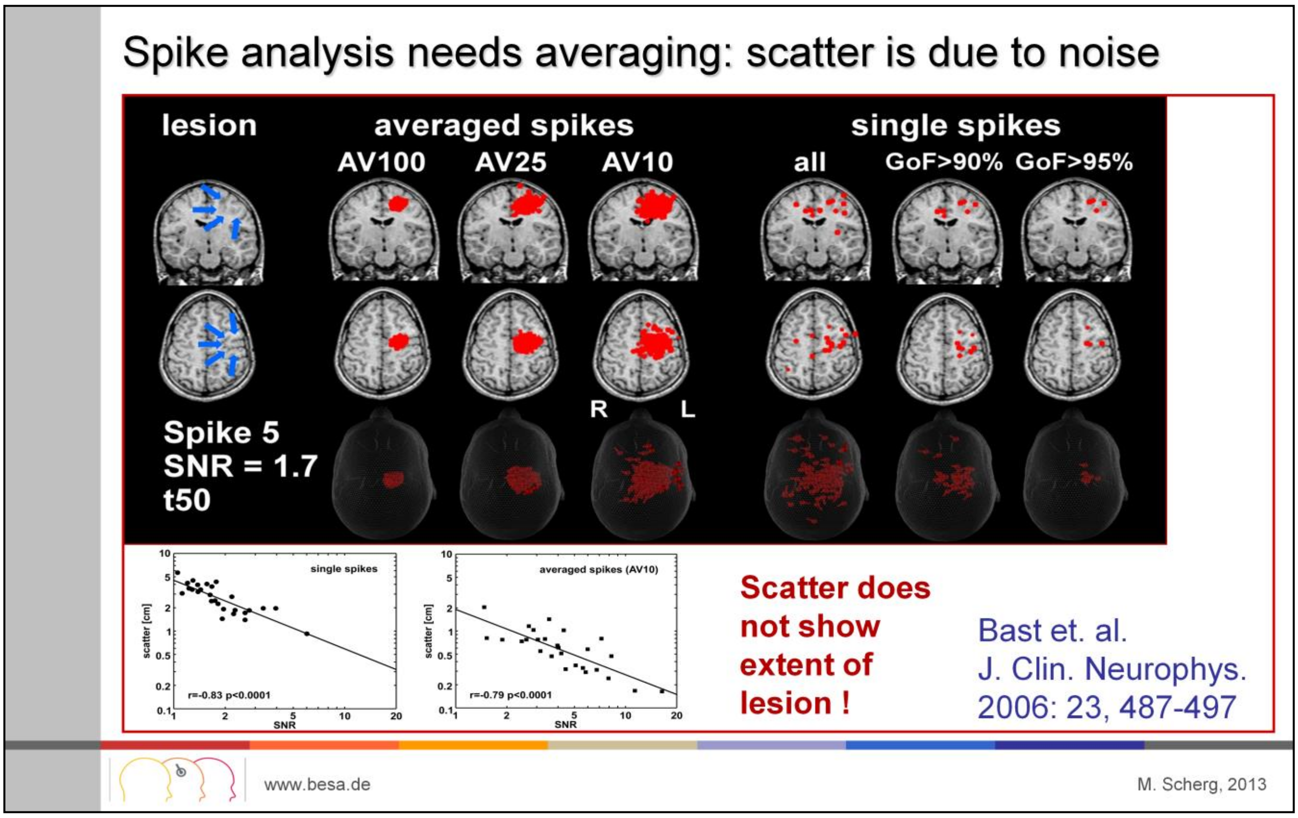


This presentation was held at the meeting of the International Society for the Advancement of Clinical Magnetoencephalography, Sapporo, August 2013.

Disclosure:

Michael Scherg is a shareholder and employee of BESA GmbH.

He has been heading the development of the software packages BESA Research and BESA Epilepsy.



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%. Similar problems were found in the same cases with the simultaneously recorded MEG data (unpublished).

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 EEG montage with wide coverage (AV33).

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 EEG background noise. Thus, scatter plots of dipoles or averaged dipoles do not reveal the extent of an irritative spiking zone. Rather, they reflect the uncertainty in estimating the center location. To estimate the center of the onset region reliably, at least 25 spikes should to be averaged.

Problems

Preprocessing

- Slow processing due to high digitization rates and many channels
- Large amount of data, not in one file.
- Spikes are hard to detect in the original MEG signals
- Long review times to scan all MEG channels
- Artifacts, e.g. MKG, interfere with detection

Localization

- Single spike localization is biased and scattered due to noise
- Onset cannot be localized without averaging
- At least two supplementary methods required

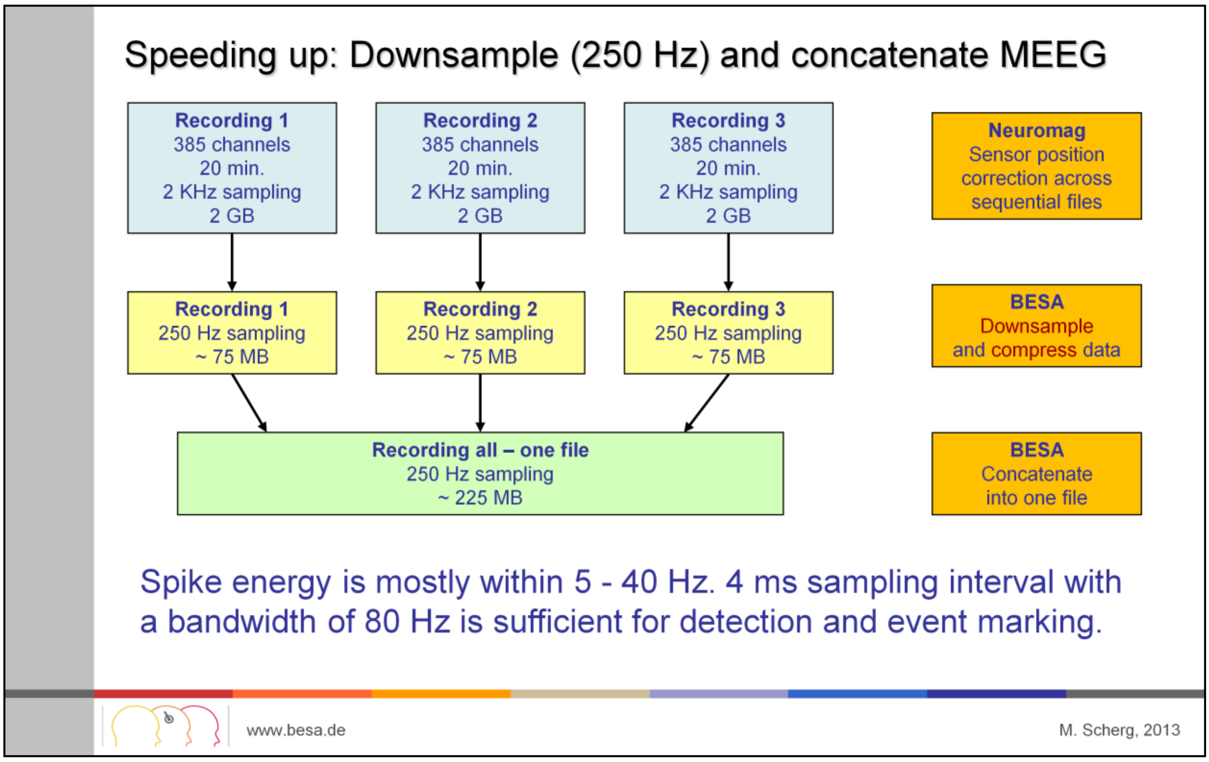
Solution: new workflow (assisted by batches in BESA 6.0)

Preprocessing

- Downsample and concatenate to one MEG file for fast processing
- Average MKG for correction and identifiy bad channels
- Create standard MEG source montage with 58 channels and MKG artifacts removed for spike scanning.
- Optimized visual marking and alignment of spikes by pattern search using special filters.

Localization

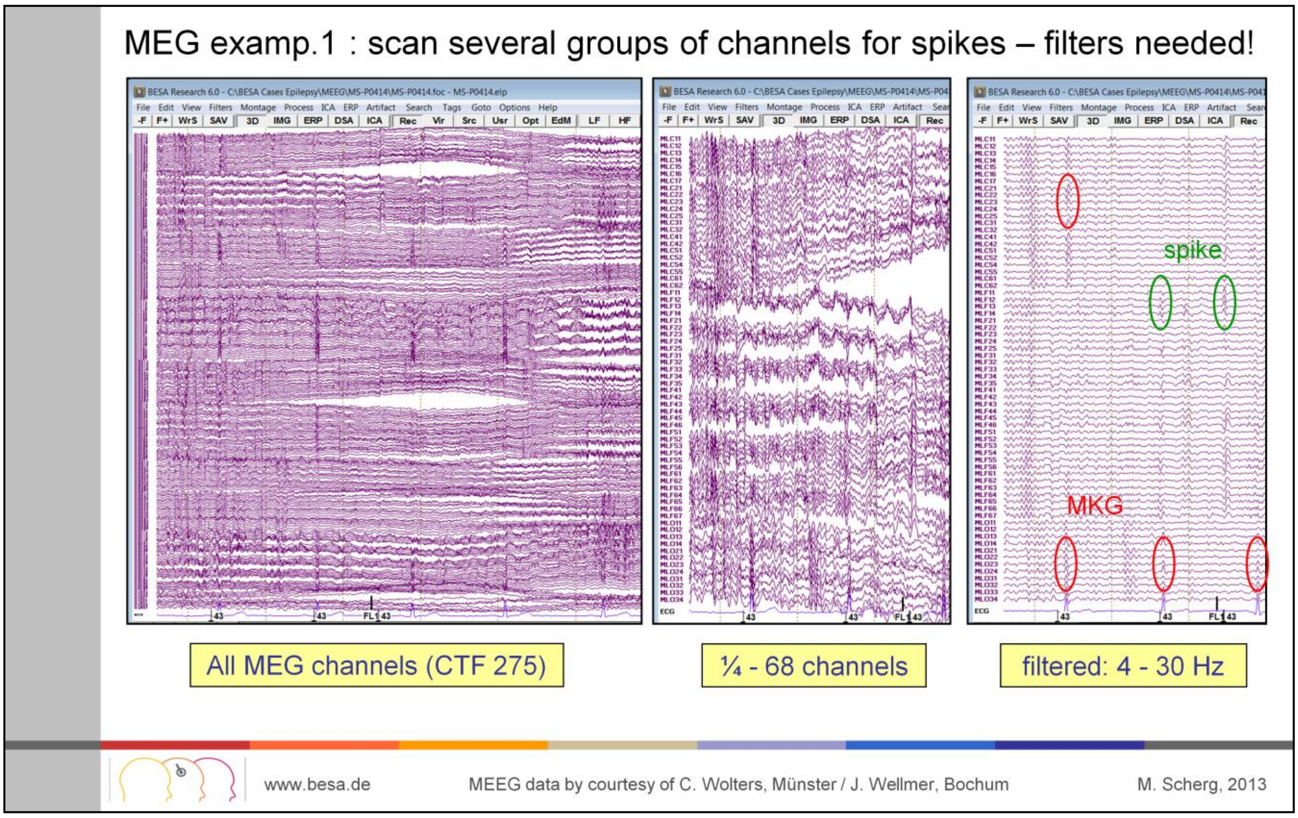
- Automated averaging of the different observed spike patterns
- Localization of sources for onset and peak by multiple source model
- Comparison of discrete sources with distributed CLARA images



Since MEG data is enormous, typically several large files are recorded per patient. Spikes need to be averaged across these recordings. Fortunately, the bandwidth of spikes is limited and allows for downsampling to e.g. 250 Hz to speed up processing. Thus, data can be reduced with compression and concatenated into one file for faster processing and for averaging of similar spikes over trials.

Concatenation requires to check the similarity of the head position in the dewar over trials or to correct the sensor positions in the different files (as done by the TSSS correction of Neuromag). This correction should be performed on all files in combination prior to downsampling and concatenation in BESA.

The goal of the fast processing in BESA is to create trigger events for spike averaging. Events files can later be used for exported data with higher bandwidth, if required for the analysis of HFOs, for example.



MEG example 1: data from a 25-year female patient with non-lesional focal epilepsy. One spike type was observed by an expert rater both in MEG and EEG.

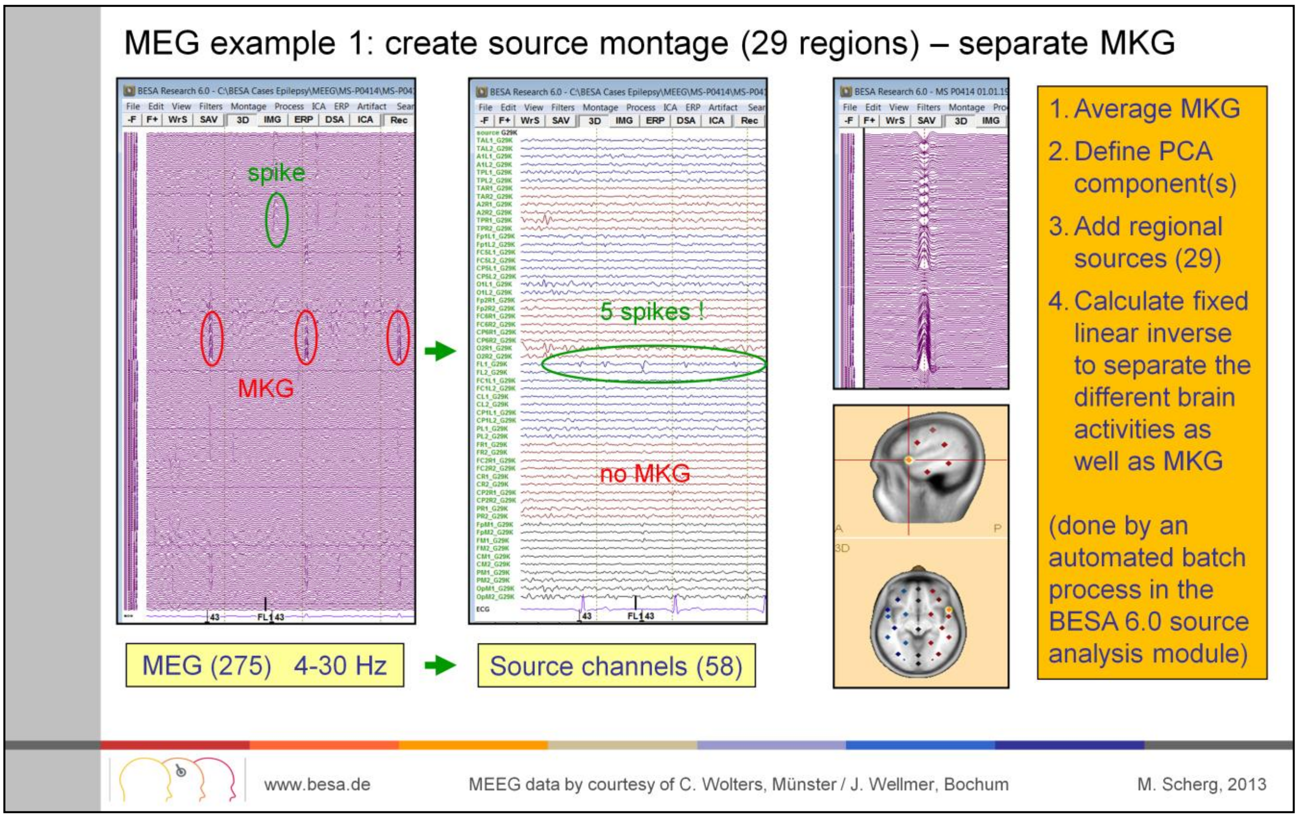
The large number of channels and the wide bandwidth of MEEG data makes visual scaning for interictal spikes difficult. Typically, several groups of channels need to be reviewed.

Filtering is required and helpful to see focal spikes emerge from the noisy MEEG background signals.

In our experience, a bandwidth of 4-30 Hz is useful for MEG. For very sharp spikes, 4-60 Hz or 8-60 Hz proved helpful (often requiring a 50 Hz notch filter). The same filters are useful to find similar spikes by pattern seach. For EEG, a bandwidth of 2-35 Hz is used in BESA as standard for spikes and slow waves, but 4-30 Hz may be useful as well for sharper spikes in EEGs with EMG artifacts.

During the automated averaging process, spikes are averaged over an epoch of 500 ms before and after the spike peak without filtering to keep the full bandwidth for further processing of the averaged files.

Thus, the narrow-band filtering simply helps to improve visual recognition as well as detection and alignment of similar spikes by pattern search.

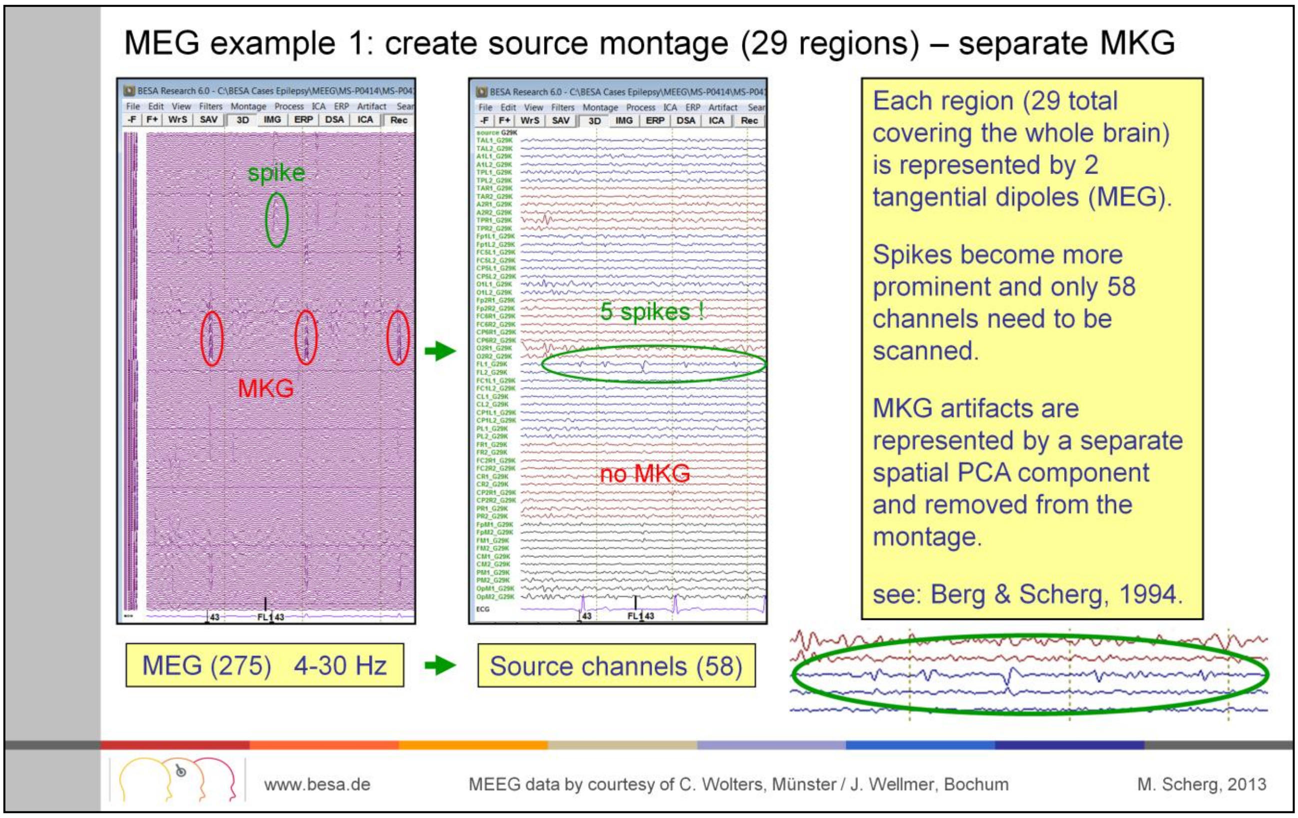


MEG example 1: data of a 25-year old female. In several 3T-MRI scans a lesion could not be documented. Seizure semiology was compatible with a left temporal, EEG and PET with a left frontal origin.

In the original MEG channels, spikes are widely distributed and recognition is blurred to some extent by MKG and other artifacts.

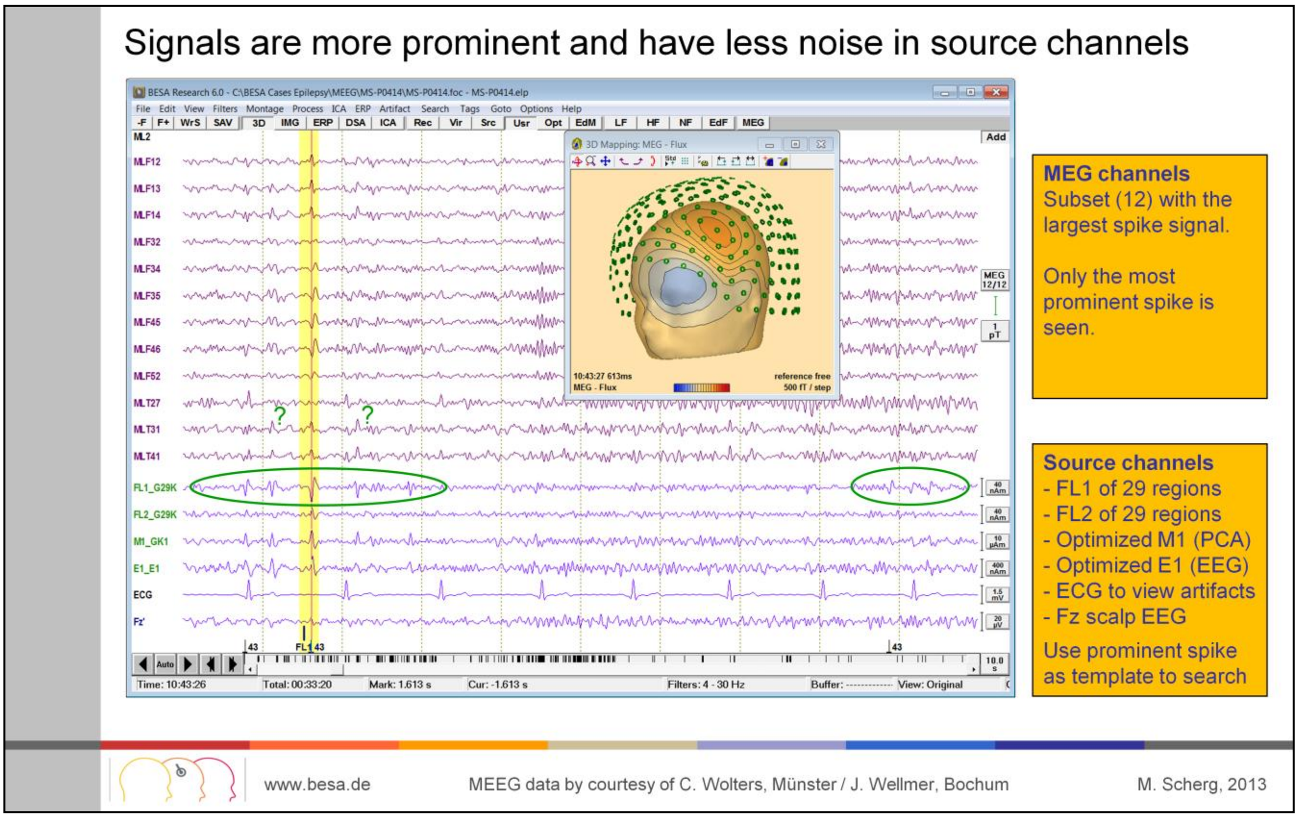
By transforming the signals into the brain using a set of 29 evenly distributed regional sources, the number of channels to be scanned can be reduced to 58 source channels (2 tangential dipoles per region). At the same time, the MKG artifact can be represented by 1-2 spatial components (topographies estimated by a PCA analysis of the averaged MKG artifact) and combined with the 58 dipole topographies to calculate a fixed linear inverse operator that separates brain and MKG activities (cf. Scherg et. al. 2002; Ille et al. 2002; Berg and Scherg 1993).

In the automated batch, the user marks the R-wave in the EKG/MKG average and selects the number of PCA components, before the batch adds the 29 regional sources to compute a fixed linear inverse stored as source montage. Reviewing the data with this transformation is very convenient and allows for fast paging while scanning for spikes.



The linear source transformation explains the MEG data with a very high accuracy (> 99%) while the (focal) spike activity is projected into one or just a few nearby sources.

Typically, this linear transformation enhances visual perception of spikes, as shown above and in the next slides, and removes the MKG artifacts.



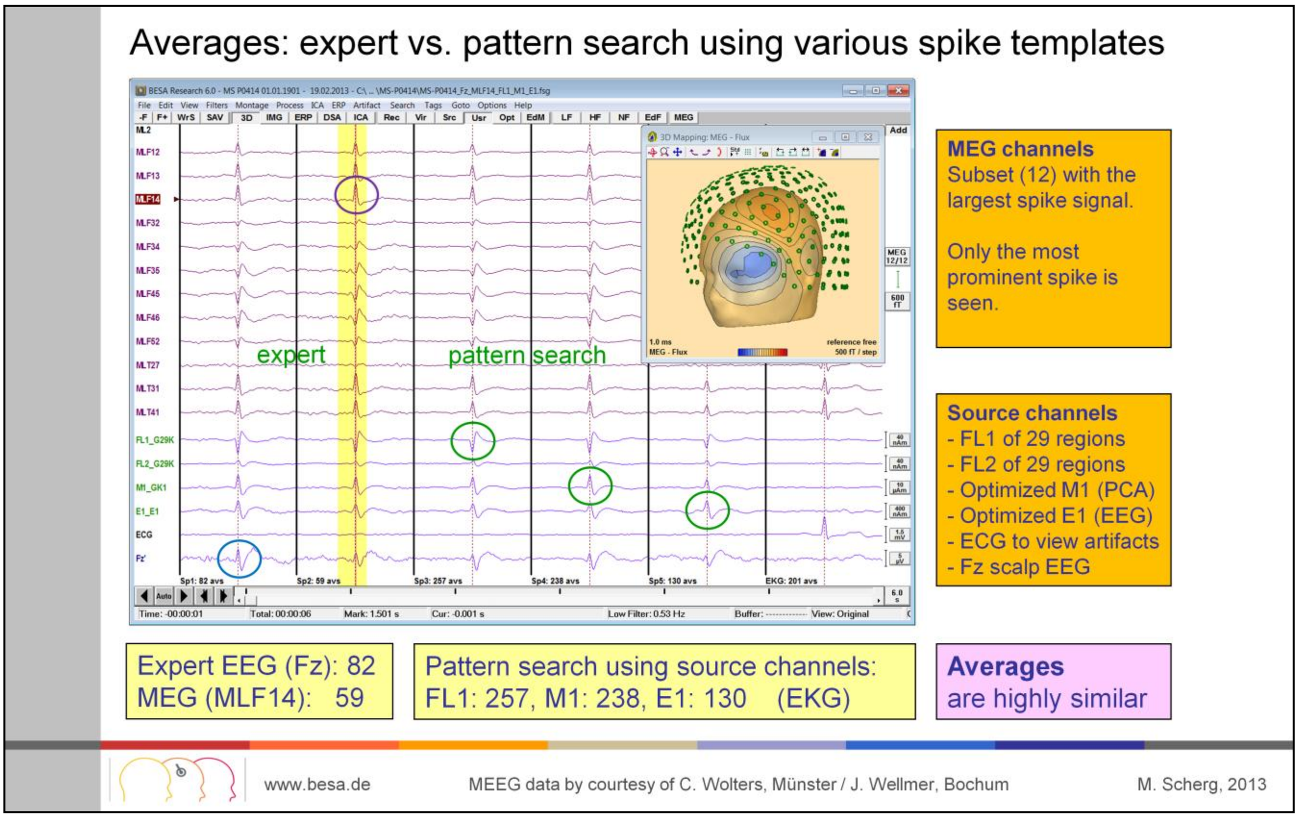
Above, a subset of 12 MEG axial gradiometer channels (CTF) is shown containing the channels that exhibit the largest spike signals (purple).

Below, the source channel FL1 (green, derived from the 2 left frontal tangential dipoles) exhibit a clear train of 5 focal spikes and a later train of 3 spikes (green markers). Both spike trains are much less conspicuous and more overlapped with other activities in the original MEG signals. In fact, only 1 of the eight spikes is easily identified in the (best !) group of channels.

Further below, a single optimized MEG source channel (M1) and an optimized single EEG source channel (E1) are displayed. Both show the first spike train but with more noise than the standard 58-channel source montage G29K.

At the bottom, the EKG and Fz channels are displayed.

Fz and the MEG channel MLF14 (3rd from top) were the most prominent channels where an expert rater marked EEG and MEG spikes.

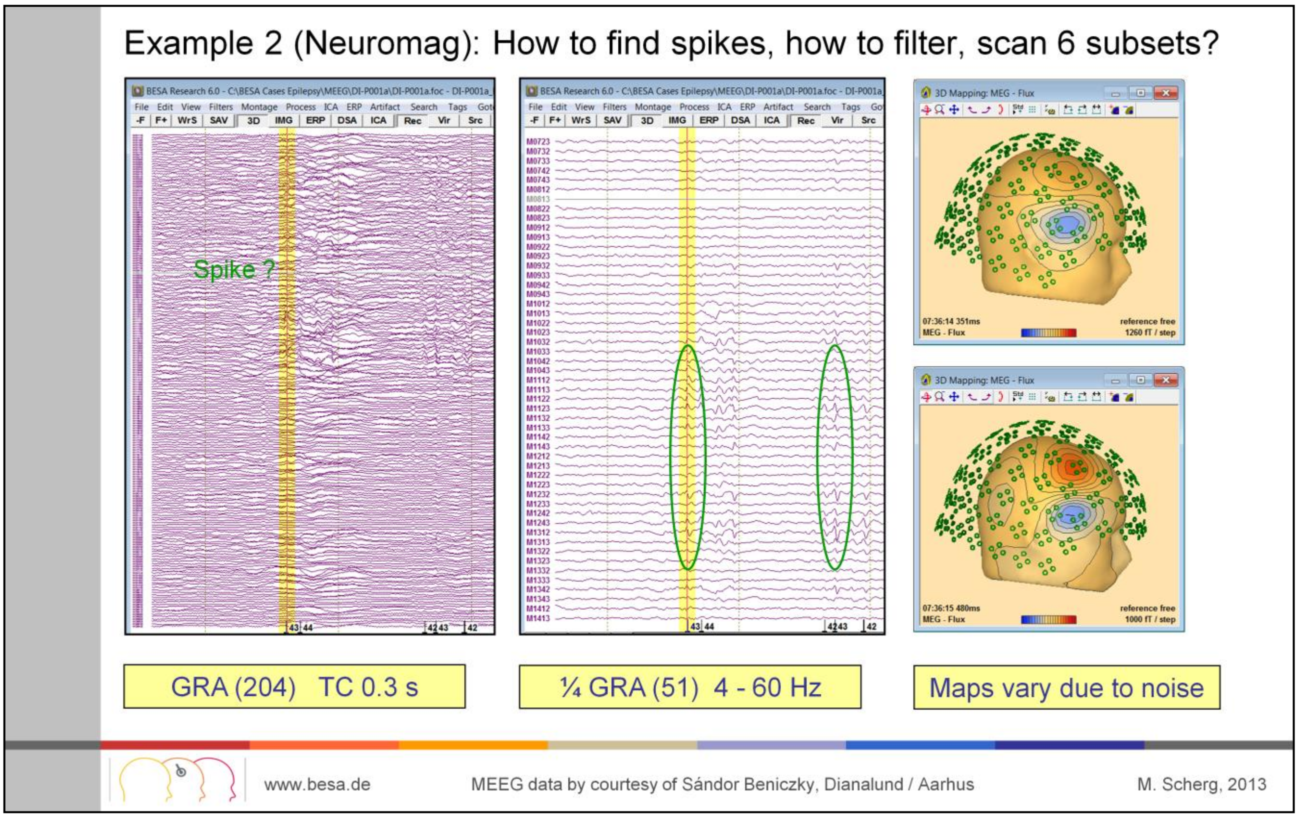


Averages obtained by expert visual inspection of the EEG (1st segment, 82 spikes marked at Fz) and the MEG (2nd segment, 59 spikes marked at MLF14) are compared with 3 pattern searches using source channels (MEG: FL1, M1; EEG: E1). The number of detections was considerably higher (4 times in MEG!) using the pattern search on the source channels as compared to visual scanning of the original MEG and surface EEG channels.

The averaged signals are highly similar over the subset of 12 MEG channels and over the source channels.

The source channel averages also document the perfect alignment of EEG with MEG. When using MEG (FL1 or M1) as templates, the amplitude of the averaged EEG source E1 is only slightly reduced as compared to using E1 as template and vice versa.

Note: this effect, although small, is likely due to the jitter of the spike pattern induced by the overlap of different background activities in MEG and EEG rather than to a jitter in the timing of the EEG vs. the MEG spike. This background jitter is bound to influence the timing in pattern detection (calculated at a fine subscale of the sampling interval in BESA), thus reducing the averaged signal in the other modality that does not have the same peak-shifting overlap.

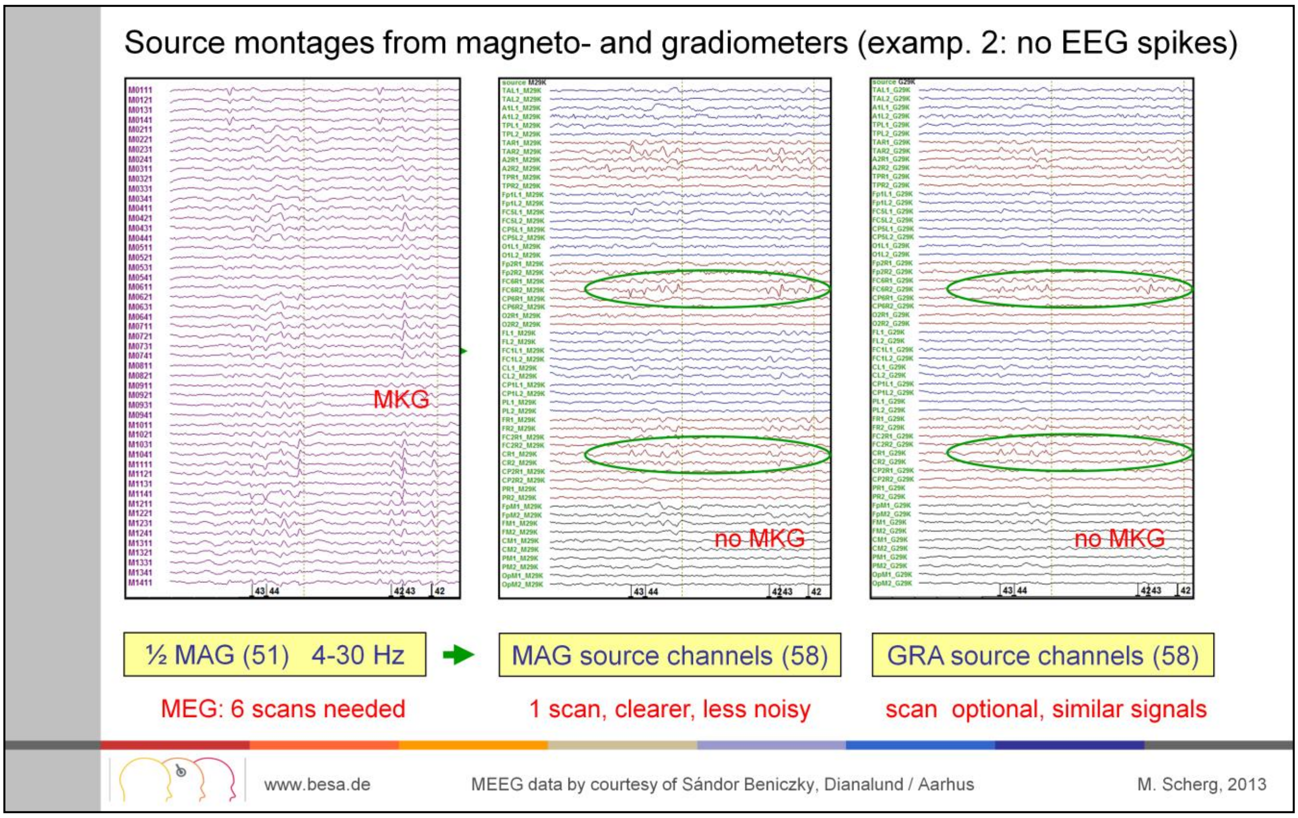


MEG example 2: data of a 22-year old male with an epileptic focus deep in the right frontal operculum that was confirmed by subdural and depth recordings.

In the Neuromag-306 recording, we ought to scan 6 subsets to observe spikes in any region possible plus the additional 64 EEG channels. Again, filtering is necessary for improved spike recognition over MEG background.

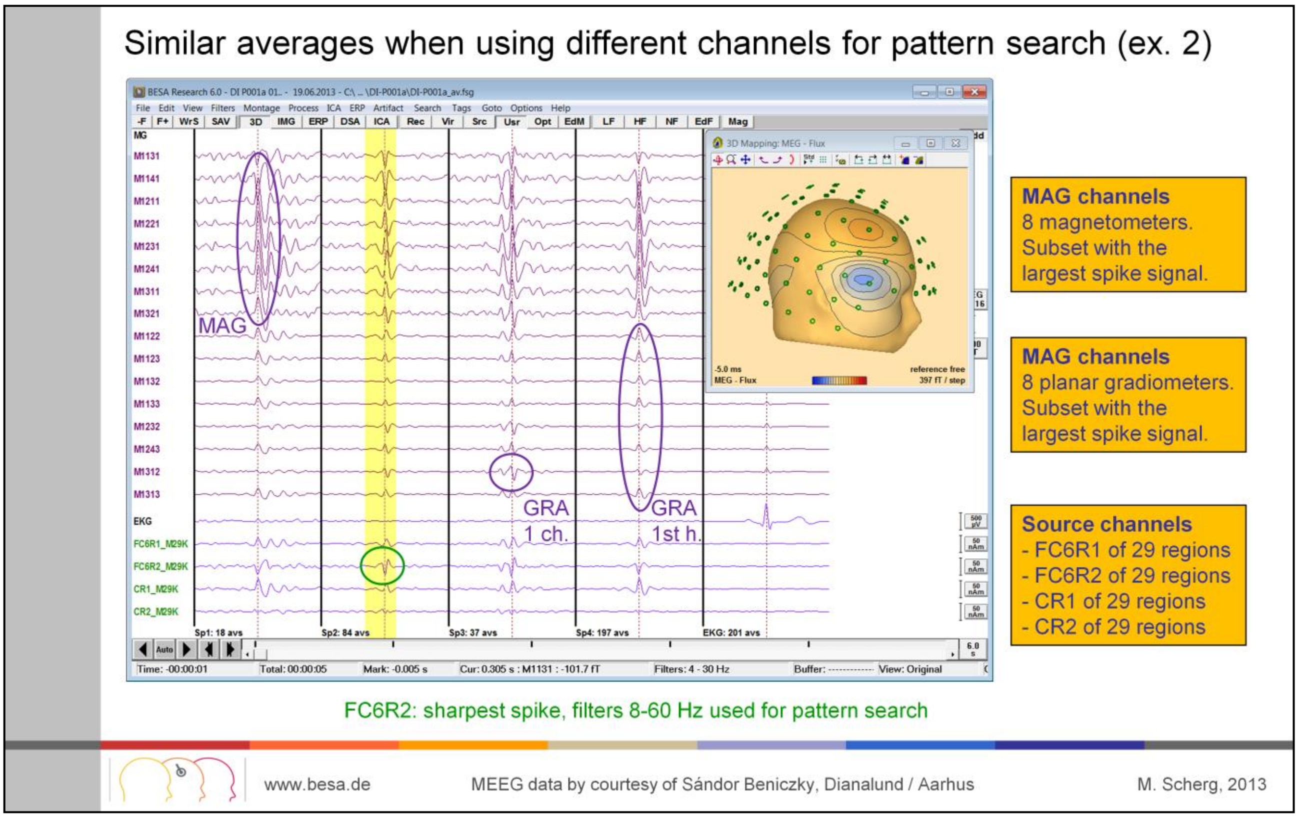
Similarly, mapping of the spikes requires narrow filtering to avoid bias due to the (large!) slow background activity. However, in the original data, mapping can only be done at the peak and the variability of the topographies is mainly due to overlapping other activities that normally blur the onset to such an extent that it cannot be mapped.

Furthermore, even after filtering, it can be difficult to assess from the MEG traces whether different events are related to the same spike type, e.g. the 2 marked spikes above that were detected by source pattern search.



Spikes become clearer with a more narrow filter band of 4-30 Hz (left), but the overlapping MKG makes comparison of different spikes (as the ones marked by triggers 43 from source pattern search) difficult.

In a Neuromag-306 system, we can use either the magnetometers (middle) or the gradiometers (right) to create the 58 MEG source channels. Often the magnetometer-based source signals are clearer (MKG removed from both). Repetitive spiking can best be seen in the source channels FC6R2 and CR1 (indicating a focal origin between these channels that are labeled according to electrode conventions). Spikes appear sharper at FC6R2 as compared to CR1 and the surface channels.



MEG example 2:

Averages obtained by different pattern searches are highly similar in their distribution across channels. However, their temporal patterns differ depending on the channels used for pattern search:

Left: Using a set of magnetometers with a large spike pattern (18)

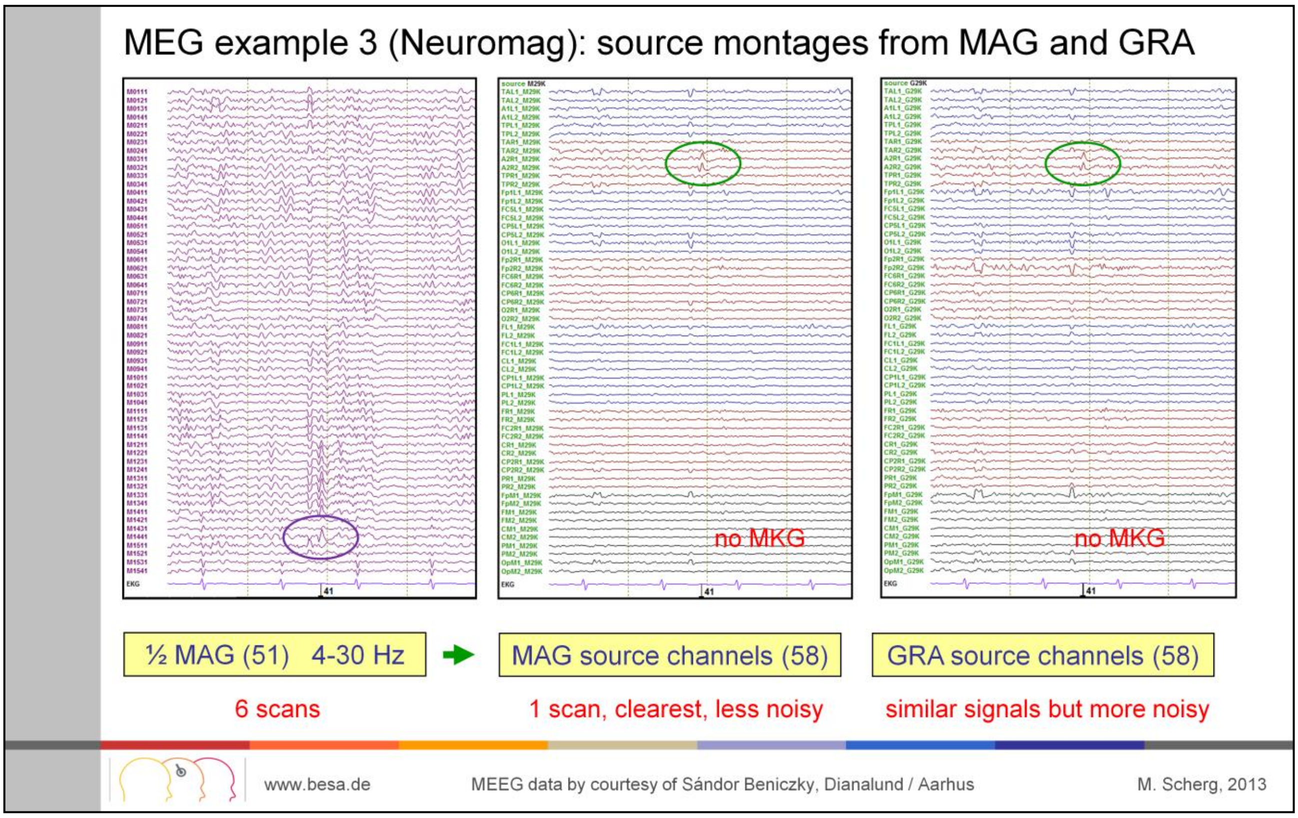
2nd: Using the sharp spike at FC6R2 (84)

3rd: Using a repetive pattern in one gradiometer channel (37)

4th: Using all 201 gradiometer channels with a low similarity threshold (197).

Right: EKG

The sharpest spike pattern with the least amount of preceding repetitive discharges was found using the FC6R2 source channel. Later on, this average will be used for localization.

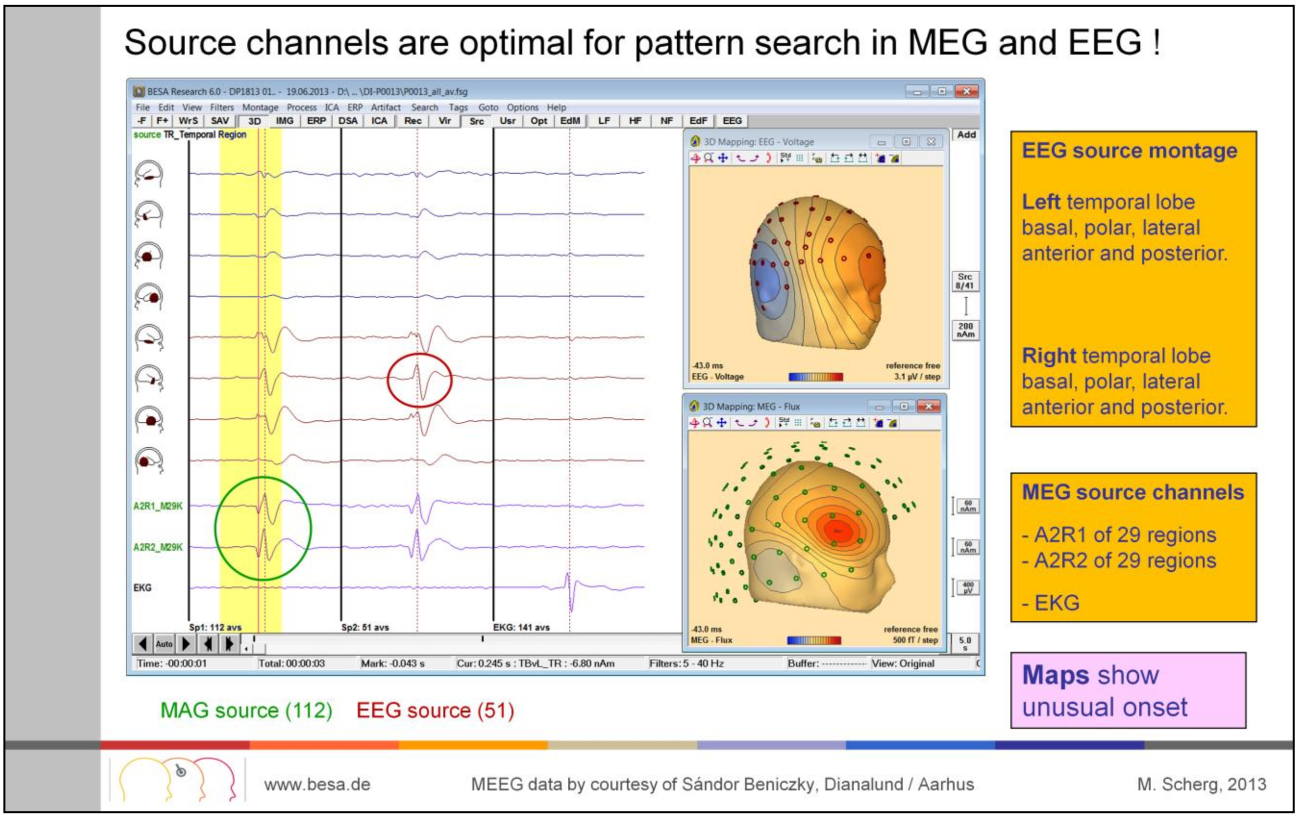


MEG example 3: data of a current case, a 14-year old boy with an unclear right temporal or frontal epilepsy. No lesion was observed in MRI. Seizure semiology was without certain localization or lateralization. Seizures were short, 15-30 s with motor arrest. Ictal SPECT suggested right temporal lobe and insula; a seizure during the PET scanning suggested right frontal lobe while the EEG recorded during this episode showed right frontal ictal activity. Patient is still under study.

In the Neuromag-306 recording, we ought to scan 6 subsets to observe spikes in any region possible plus the additional 64 EEG channels. Again, a band pass of 4-30 Hz delineates the focal spike clearly over the MEG background.

Artifacts make the observation of spikes in the original magnetometer channels more difficult (left). Amongst several channels, channel M1441 shows the spike (trigger 41) best, but exhibits a noisier baseline as compared to the source channels carrying the spike.

The source montages show the spike most clearly with different patterns in the source channels A2R1 and A2R2. Emergence from the background noise appears superior in the source montage derived from the magnetometers (middle) as compared to the gradiometers (right).



MEG example 3:

Averages were obtained using the A2R1 & A2R2 MAG source channels in combination (left) and the right temporal-polar EEG source channel as templates (middle). The obtained averages are similar, but more spikes were detected using MEG (112) as compared to EEG (51).

Despite using the clear polar EEG pattern for search, the average revealed a sharp spike consistenly preceding the related temporal-polar EEG activity, most prominent in the MEG source channels, but also visible in the basal and lateral EEG source channels. This early onset spike has a 3D topography that is not consistent with any of the typical spikes occuring at the basal, lateral, polar and Sylvian surfaces of the right temporal lobe as, e.g. in mesial temporal lobe epilepsy.

Summary: Optimized detection and averaging of spikes

Preprocessing

- Downsample and concatenate to one file for fast processing
- Average MKG artifact for correction and identification of bad channels
- Standard MEG source montage with 58 channels for improved spike perception with MKG artifacts removed.
- Only one visual scan is needed when using optimized filters (4-30/60 Hz).
- Optimized alignment of spikes for averaging by pattern search
- Alternative: detect more spikes using an optimized spike source channel

-> Localization of spike onset - averaged spikes have better signal !

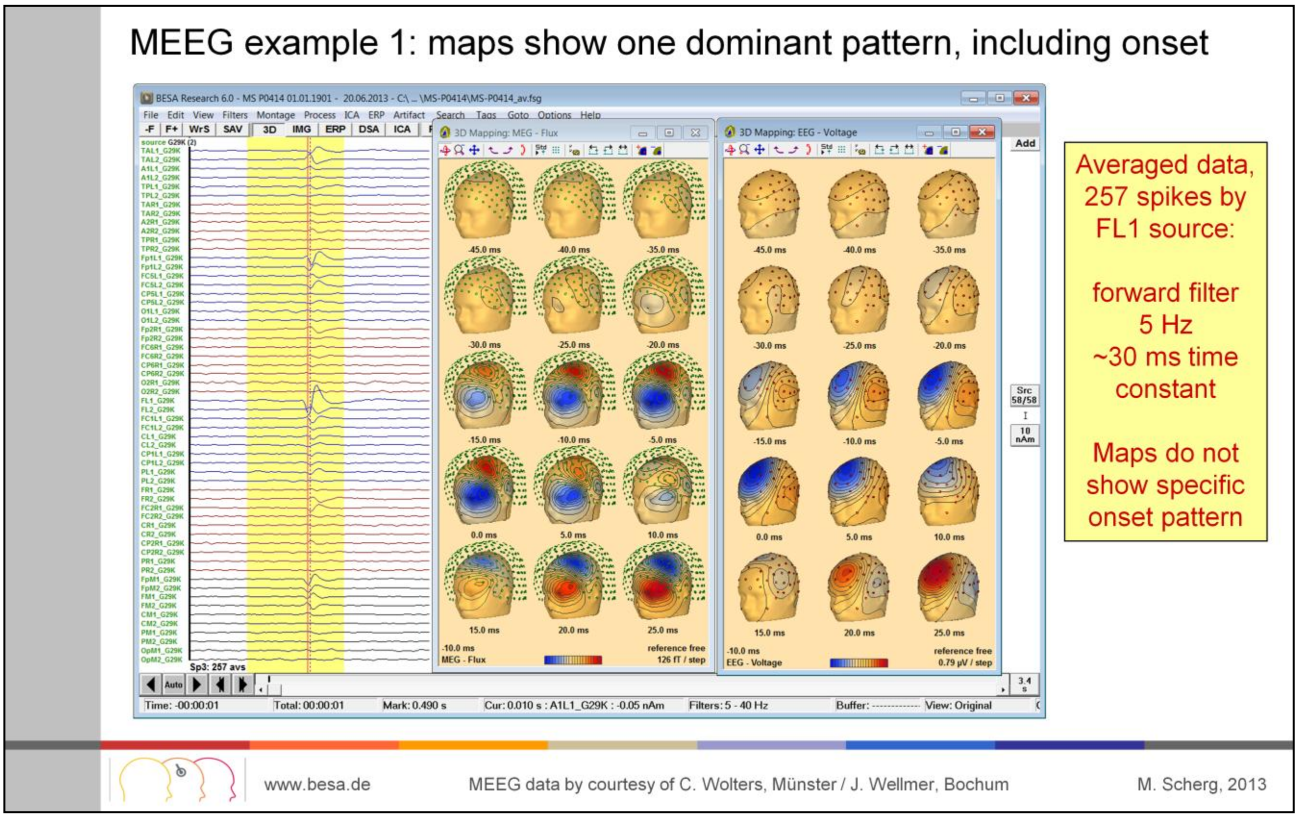
Localization: find spike onset using different methods

Localization

- Automated averaging of the different observed spike patterns (wideband)
- Check onset by
  1. Use forward filter to set baseline and reduce slow overlap
  2. Use serial maps to observe if pattern changes from onset to peak
  3. Use principal components analysis and butterfly plot to set onset interval
- Multiple source model and CLARA images done by automated batches

For EEG examples and more details see talks and tutorials on www.besa.de

Localization results will be shown here for MEG examples 1-3.



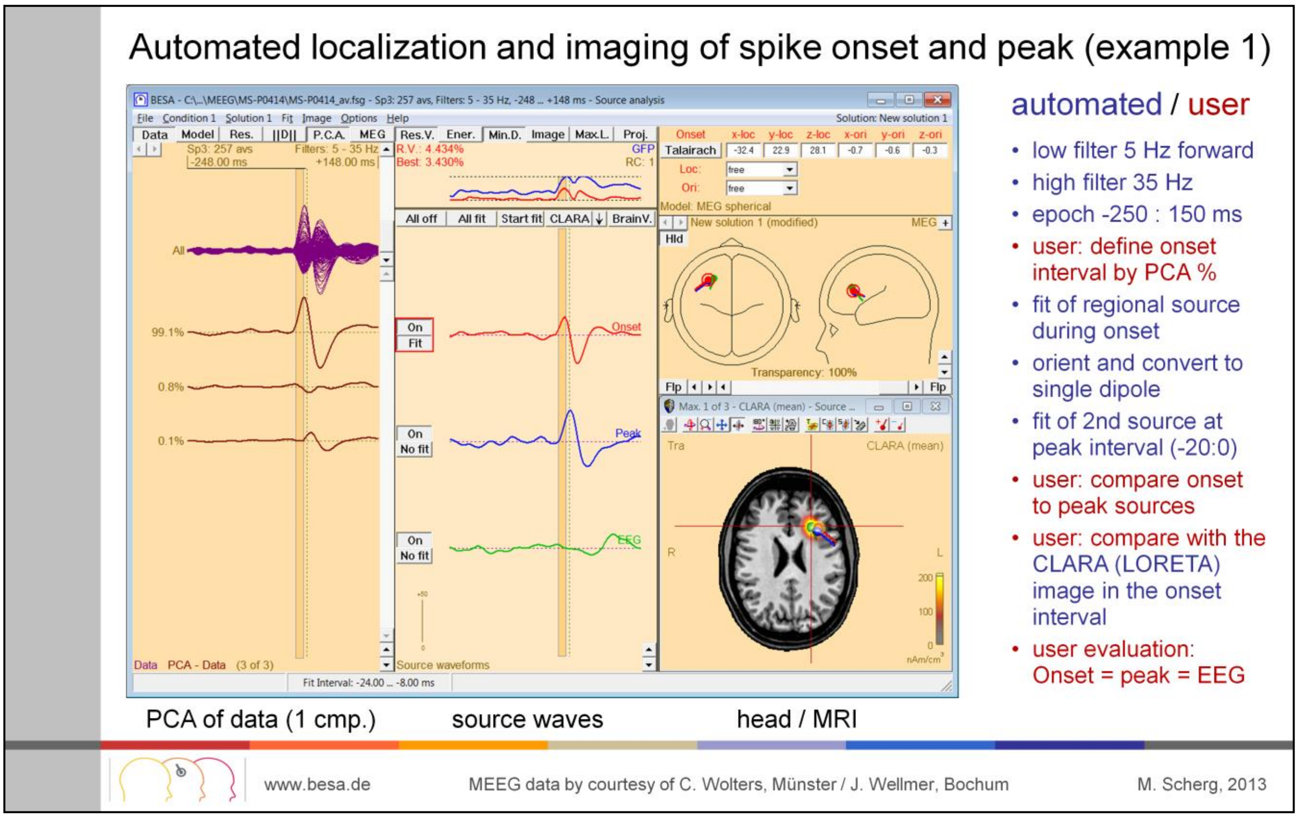
MEG example 1:

Averages are computed from the original MEEG with wide-band filter settings over an epoch of +-500 ms around the spike events defined by visual marking or pattern search. In this case, the largest number of left frontal spikes was detected and optimally aligned using the MEG source channel FL1.

For further processing, i.e. onset mapping and localization, the averaged signals are filtered using a low forward filter of 5 Hz, corresponding to a time constant of 30 ms, and a high cutoff of 40 Hz.

In example 1, neither the EEG nor the MEG topography show a pattern that differs from the peak pattern (0 ms) during the rising time (20 ms) of the spike. Thus, there is no indication of spike propagation prior to the peak.

Note: Intrinsically, the forward filter of 5 Hz (or 10 for very sharp spikes) sets an optimal baseline to observe and map the spike onset deflection. Unfortunately, in most MEG system only zero-phase shift filters are available that spread energy of the peak symmetrically to both sides, i.e. peak activity with inverted polarity may overlap and bias the onset signal. Therefore, filters are often kept relatively open and a visually guided baseline is set prior to spike onset. This also presents a local high-pass filter with the danger of zeroing-out the onset activity, if the baseline is set too close to the spike peak. In any case, trends in preceding slow activities are not removed and may still overlap and bias spike topography and localization. The use of zero-phase shift low filters (at 2, 4, or 8 Hz; 12 dB/oct.) was useful for visual scanning and pattern search since they suppress slow activities better. But, for onset localization forward filtering is needed.



Localization of onset and peak is done by an automated batch process to secure the adequate setting of filters, epoch etc. At some steps, the batch function requests user input (indicated in red). When the source analysis window is displayed, the user is asked to mark the onset interval graphically. This step is helped by a visual comparison of the automatically calculated principal components analysis (**PCA** – displayed on the left) with the butterfly overplot of the MEG or EEG signals.

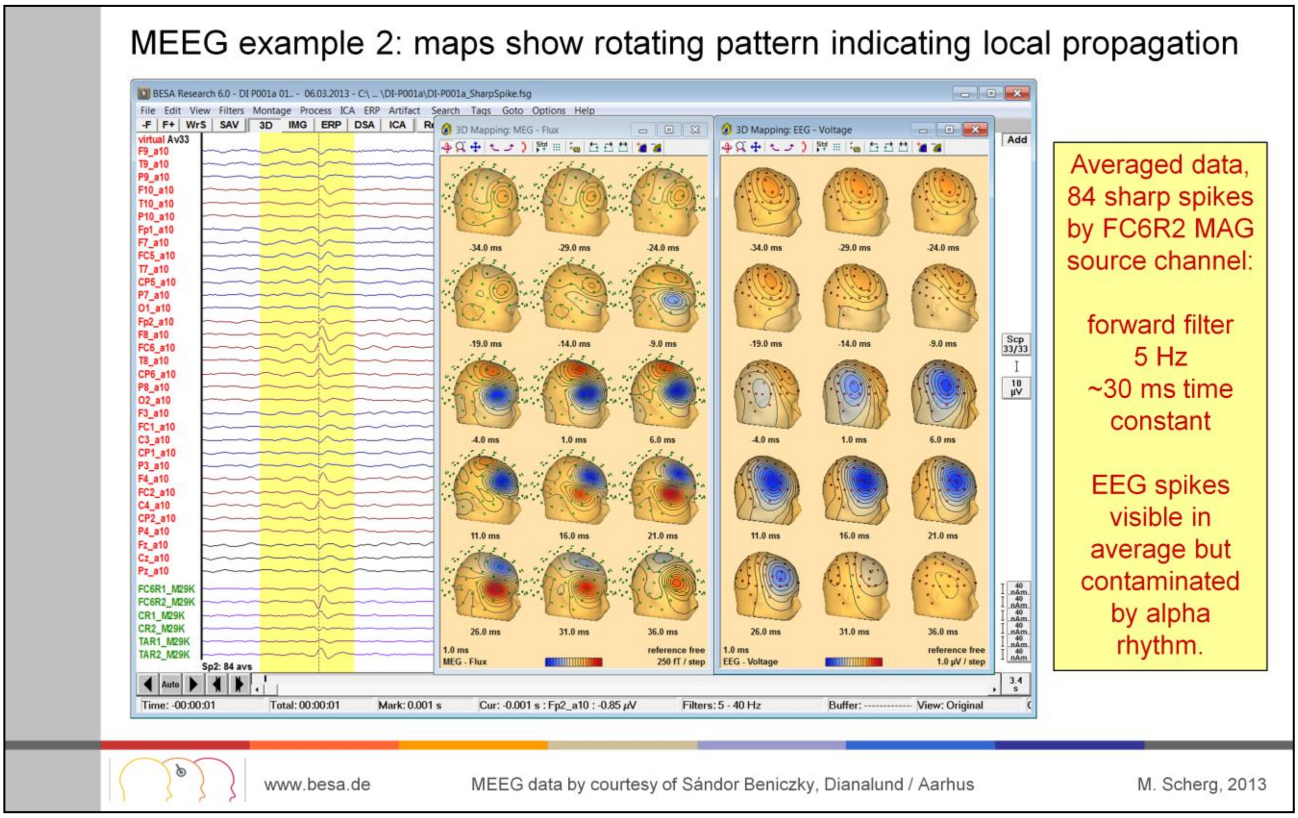
The onset interval is defined by finding the initial interval that exhibits **one dominant principal component** (accounting for a data variance of more than 90-95%). Its prominent waveform (here: 99.1%) is compared to the wings in the butterfly plot to assess, whether it comprises the peak or an earlier activity.

In our example 1, only one component appears in the MEG onset interval.

Next, the batch fits a **regional source** into the user-defined onset epoch and rotates the 2 underlying orthogonal, tangential dipoles such that the first **dipole** is oriented to explain all the activity at the maximum of the onset interval. Only the first dipole of the regional source is retained (red). It shows the center location and orientation of the initial activity implicitly assumed to be uni-focal.

Then, the batch fits a **regional source** into the peak epoch (-20:0 ms) while the onset dipole is present in the 2-source model to avoid contamination of the peak activity by on-going activity in the onset area. The batch process then tests further hypotheses. Here, one of the alternative hypotheses is shown with independent MEG dipole sources fitted into the onset (red) and peak (blue) epochs, showing no propagation. This slide also shows the dipole fitted to the EEG peak for comparison (green).

The localizations of MEG onset, MEG peak and EEG peak are almost identical. Orientation is slightly different with an earlier spike waveform of the onset dipole, indicating a minor local rotation of the spiking patch along the cortical surface.

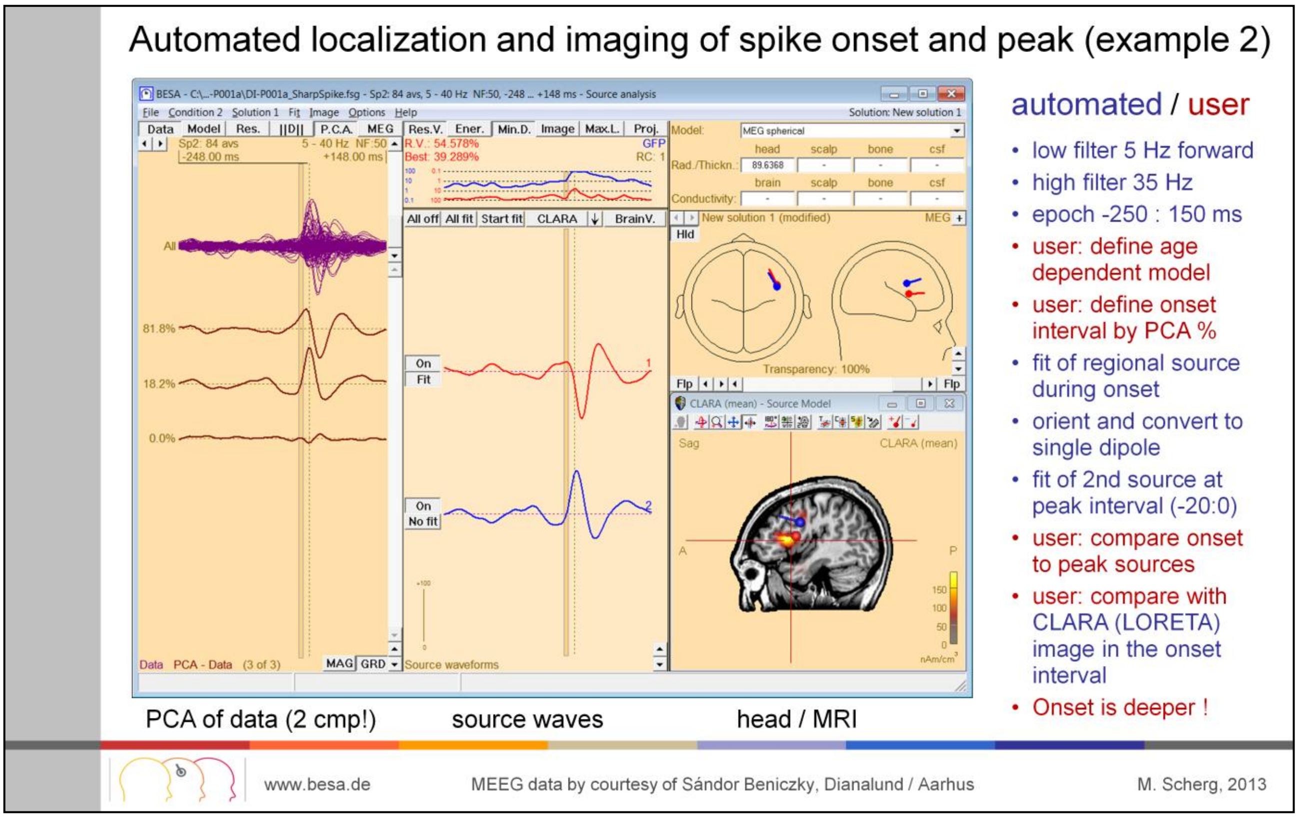


MEG example 2:

Averages are computed from the original MEEG with wide-band filter settings over an epoch of +-500 ms around the spike events defined by visual marking or pattern search.

In this case, the largest number of sharp right frontal spikes was detected and optimally aligned using the MEG source channel FC6R2. This average is used for onset mapping and localization after filtering with a low forward filter of 5 Hz, i.e. a time constant of ~30 ms, and a high cutoff frequency of 40 Hz.

In example 2, some rotation is seen both in the EEG and MEG topographies prior to the peak (-9 ms : +1 ms). The rotation in the maps suggests spike propagation prior to the peak.

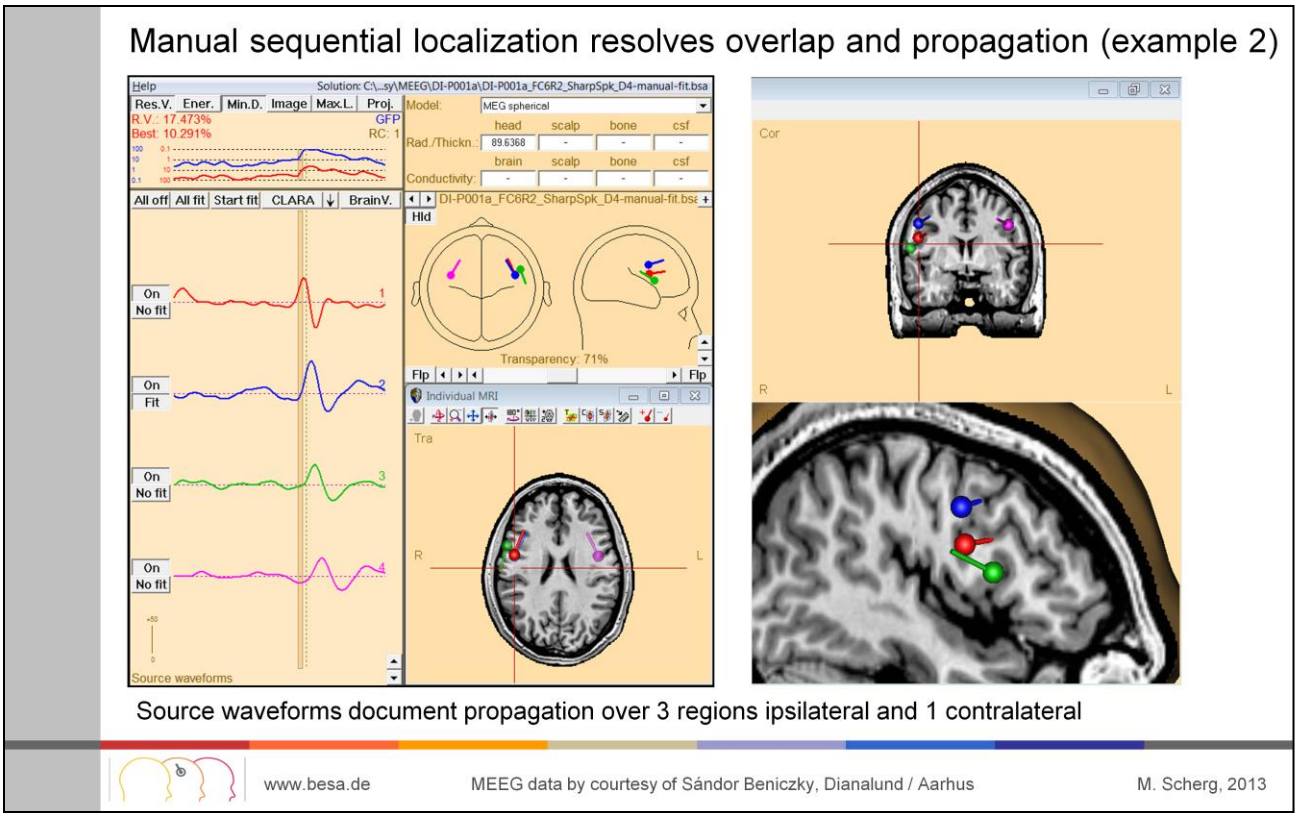


In this case, careful shifting of the onset epoch backward from the peak yielded a separation of 2 components with the 1st being dominant in the marked interval (81.8%) while the 2nd undergoes zero-crossing (its maximum is at the spike peak) – this potentially helping localization by a single source. Similarly, the butterfly plot show different patterns in the overlaid MEG gradiometer signals.

After defining this interval, the batch fitted 2 sources into the onset and peak epochs and converted them to dipoles.

The onset localization appears lower in the right frontal lobe by ~2 cm and is confirmed by the CLARA image.

However, the source waveform pattern of the onset dipole looks more complex than a simple spike pattern. Also, the maps, CLARA and the bilateral hypothesis testing by the batch showed propagation to contralateral frontal cortex. Therefore, we analyzed this sharp averaged spike further by fitting multiple dipoles manually.



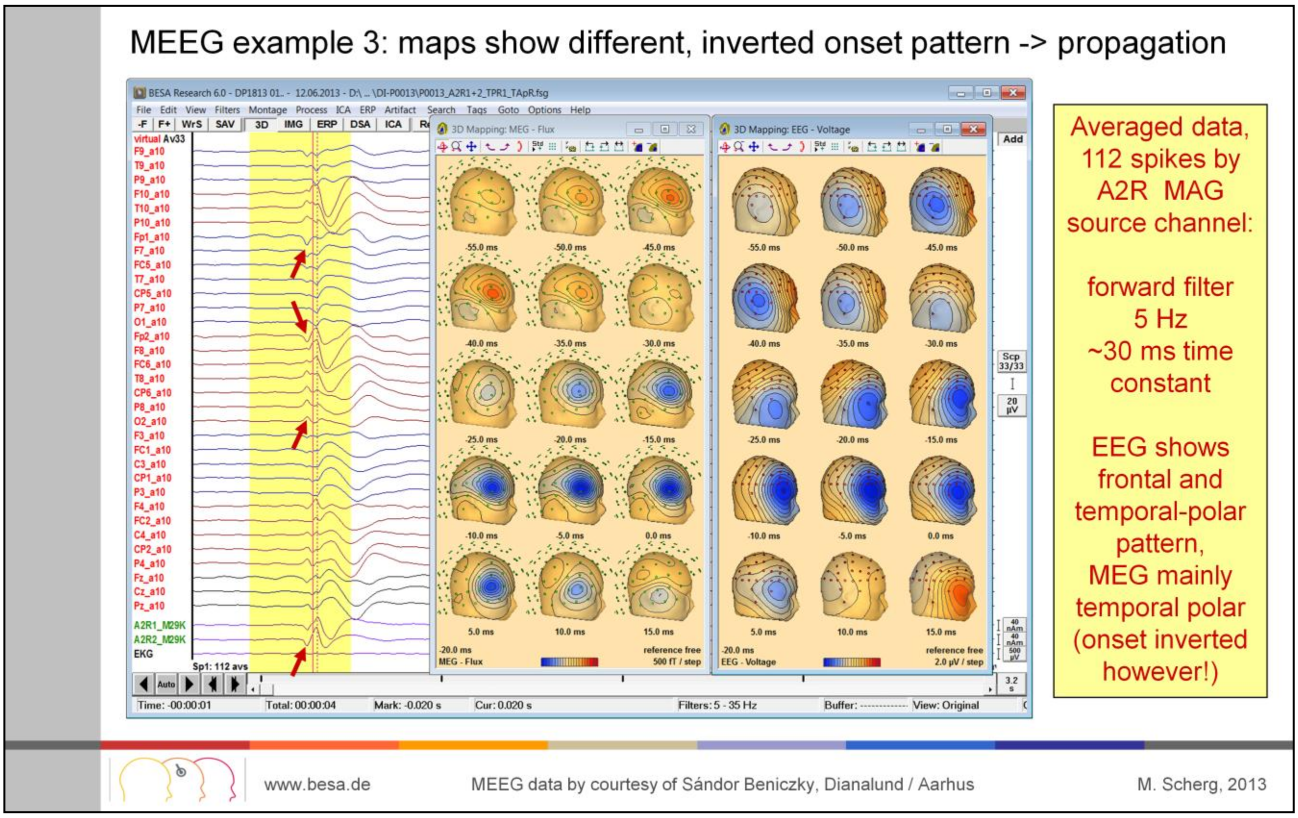
The MEG activity could be explained much more accurately by a multiple dipole model with 4 equivalent dipoles, 3 in the right frontal, 1 in the left frontal lobe.

The source waveforms are clearly separated in time, have typical focal spike patterns, and the activity appears to propagate from the onset zone (red) to the cortical surface above (blue, peak delay 12 ms) and to its homologous area in the other hemisphere (purple, 32 ms). Propagation is also seen from the one side of the onset gyrus (red) to the other (green, 20 ms).

The orientation of the dipoles is perpendicular to the nearby cortical surfaces and, thus, confirms this interpretation as does the clear separation of simple spike waveforms by the linear inverse operator. The onset spike appears to be sharpest while dispersion during propagation widens the following compound spikes.

Such a fine resolution by a linear inverse is only possible because the information contained in the large number of MEG sensors is sufficiently redundant to be reduced to 4 discrete source waveforms - as has been shown also with sensory evoked potentials.

In this case 2, the onset localization (red dipole) was confirmed by depth electrode recordings in the right frontal operculum. This region was also confirmed by EEG spike onset localization.



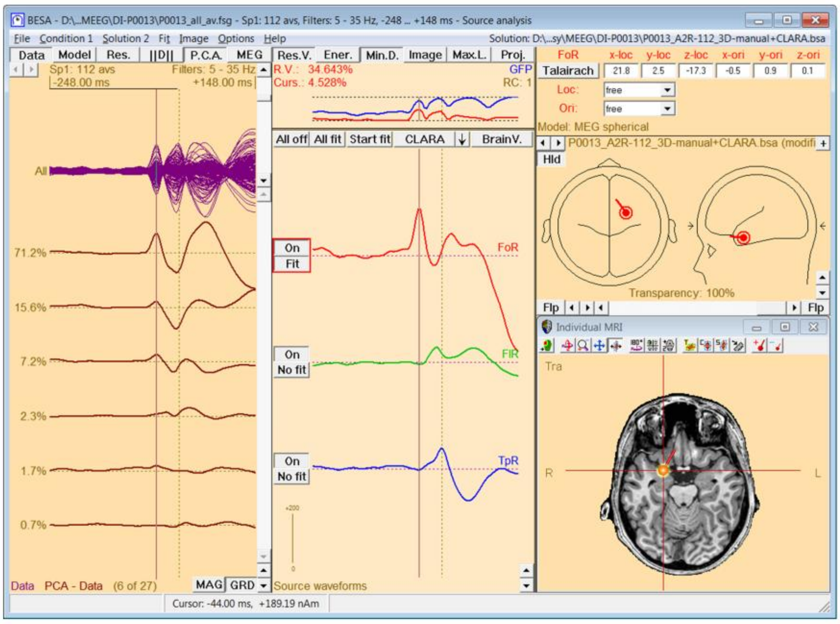
MEG example 3:

Averages are computed from the original MEEG with wide-band filter settings over an epoch of +-500 ms around the spike events defined by visual marking or pattern search. In this case, the largest number of right temporal spikes was detected and optimally aligned using the 2 tangential MEG source channels A2R.

The maps at and prior to the peak (-20:0 ms) appear temporal-polar, but 45 ms prior to the peak a strong activity is seen in the EEG with a lateral-temporal negativity and a mid frontal positivity (maximum at Fp1 & Fp2 – cf. red arrows).

This earlier peak is also seen in the MEG source channel A2R2 (lowest arrow).

Localization of MEG spike onset activity and propagation (example 3)



PCA of data (3 cmp.!) source waves head / MRI

automated / user

- low filter 5 Hz forward
- high filter 35 Hz
- epoch -250 : 150 ms
- user: define onset interval by PCA %
- fit of regional source during onset
- orient and convert to single dipole
- fit of 2nd source at peak interval (-20:0)
- user: compare onset to peak sources
- User: add third source at frontal peak of CLARA and orient.

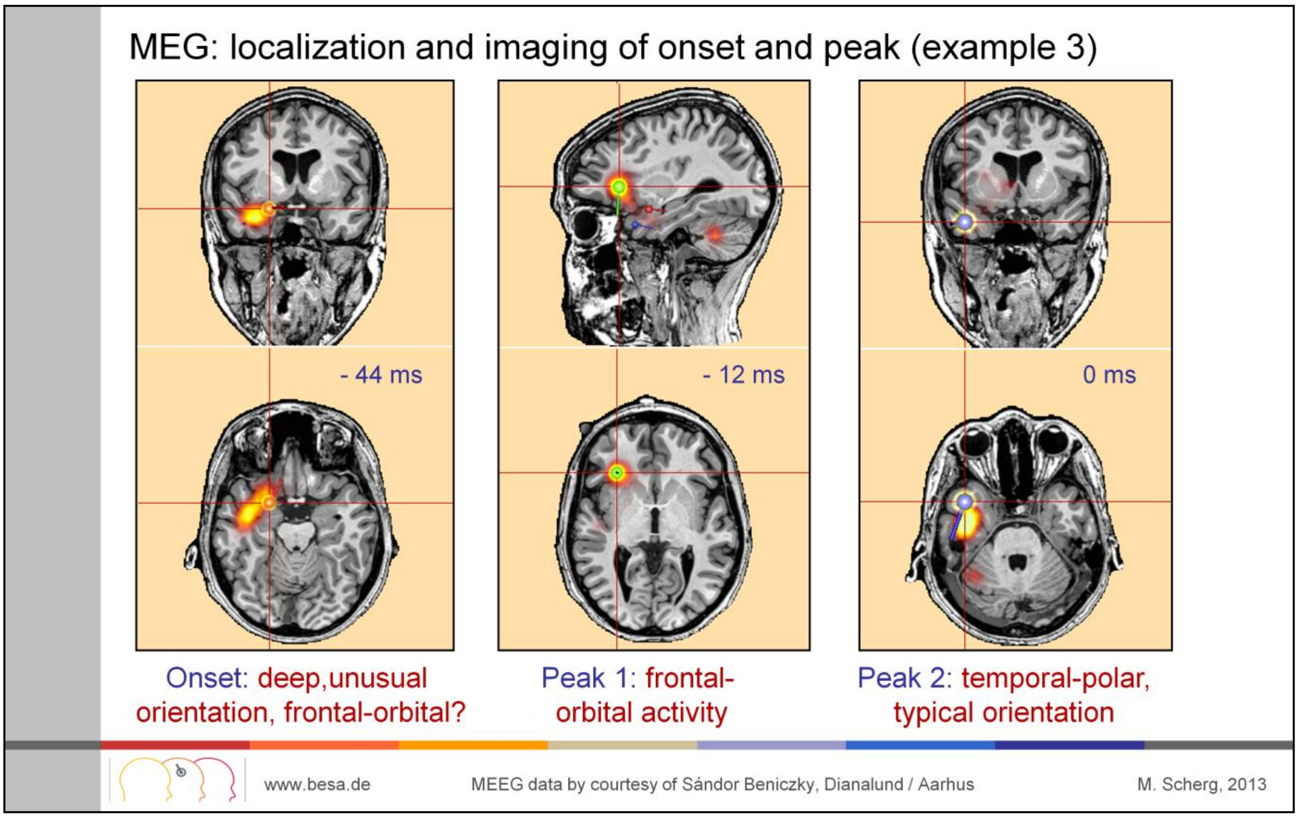
Onset and 2 peak activities separated

www.besa.de MEEG data by courtesy of Sándor Beniczky, Dianalund / Aarhus M. Scherg, 2013

The PCA over the whole epoch shows 3 major components (left).

The MEG onset activity (-44 ms) can be well explained by a single dipole (red). Its orientation, however, is more consistent with frontal-opercular cortex (surface negative!) than with the temporal pole. The blue dipole, fitted to the peak independently, represents the temporal-polar activity. The green dipole, seeded in the second center of activity imaged by CLARA, reflects a vertical activity of the right frontal lobe peaking at -12 ms, i.e. after the onset and prior to the temporal-polar peak.

Note: Dipole source activities are separated because their orientation is different. They exhibit clearly different onsets. Equivalent locations are relatively close to each other and cannot resolve the origin without taking orientations into consideration (cf. next slide).

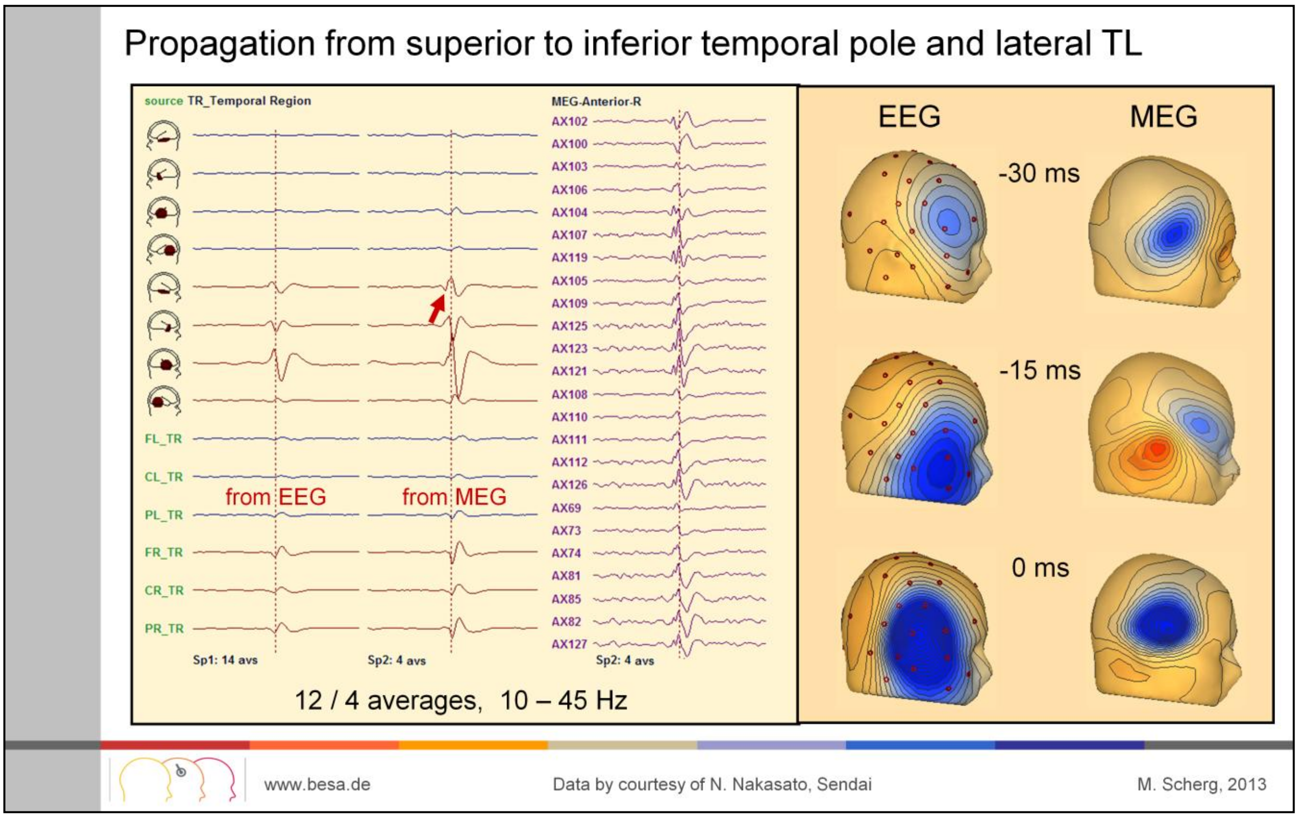


Left: the focus of the distributed model at the peak of the onset activity (-44 ms) cannot dissociate between a temporal-polar and fronto-opercular origin. Dipole orientation is more consistent with frontal-opercular cortex.

Middle: at a latency of -12 ms, the CLARA image shows an additional peak in the right frontal-opercular cortex.

Right: the peak activity localizes more superfically and more inferiorly in the right temporal pole (blue dipole).

Thus, the multiple source analysis suggests a careful inspection of clinical and other imaging data to decide if the onset is in deep frontal, or temporal / insular cortex.



MEG example 4:

This right temporal spike in a 61-year old male patient shows the activation of a particular surface in the temporal-polar region and a considerable propagation. Here, we analyzed 4 spikes averaged from a sharp transient in the MEG.

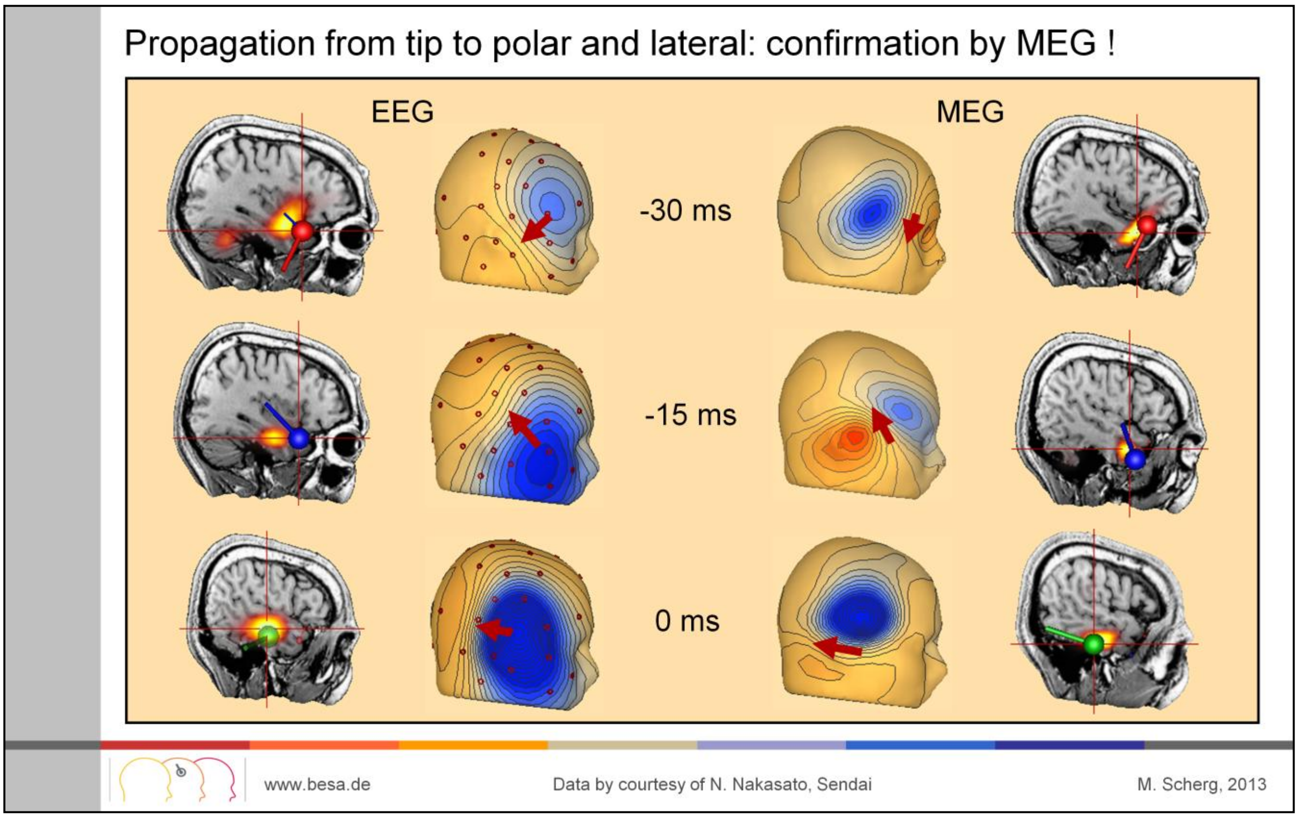
Note that the initial EEG dipole map at -30 ms shows a frontal negativity. When considering the accompanying inferior positivity and the gradients of the equipotential lines, it becomes evident that the underlying center is more inferior and corresponds to an oblique equivalent dipole pointing down and inwards.

The initial downward component is confirmed by the MEG map at -30 ms.

15 ms before the peak we observe the typical right temporal polar pattern, while superficial lateral activity with partly posterior orientation dominates at the peak (0 ms). Again, the polar current 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 (red arrow). This source signal is constructed using a vertical dipole in the right basal temporal region within a multiple source model covering also the polar and lateral 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, since it is the only source in this region with this orientation.

After this short initial superior spike, the typical propagation to the polar and lateral regions was seen in the right temporal polar and lateral source waveforms.



In contrast to the EEG, the MEG is dominated by the polar and basal activity and blind to the radial part. At the peak, the MEG map is more complicated and not clearly dipolar. The strong radial dipole of the lateral anterior temporal surface is only seen in the EEG. 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 of the temporal lobe.

MEG localization appeared a little more confined, but far from being able to identify precisely which part of the anterior temporal lobe was spiking. Here as well, the orientation was needed to dissociate the superior surface of the temporal tip from the basal polar surface.

Summary: MEEG localization and imaging of averaged spikes

- Averaging improves the spike signal to allow for the analysis of onset.
- Thus, activity occurring systematically before the peak is revealed.
- If this has a different topopgraphy, it can be identified by maps and PCA.
- Localization of onset and peak sources and comparison with CLARA images at different latencies provides more security in onset localization.
- Simple localization of single spikes at the peak can be misleading and is easily biased by other overlapping brain activities.
- Optimized forward filtering is needed for onset analysis.
- EEG mapping and localization supplements MEG findings.
- The systematic workflow in BESA with MEG source montages and the comparison of 2 imaging methods proved extremely helpful to find, average and localize spike onset consistent with other clinical findings.

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

www.besa.de