

Institute for Biomagnetism and Biosignalanalysis

EEG AND MEG SOURCE ANALYSIS IN FOCAL EPILEPSY

May 20, 2025 Carsten H. Wolters



- Complementarity of EEG and MEG
- How to exploit this complementarity in combined EEG/MEG source analysis
- Focal epilepsy patient case studies
- Summary

Introduction

- 0.5%-1% of world population suffers from epilepsy and 70-80% of patients successfully treated with drugs
- For those who are still pharma-resistent after 2-3 drugs
 - Probability of success of a further different drug: 6% (Wiebe et al 2001)
 - Probability of success of a surgical treatment: 50% (Wiebe et al 2001)
- Indispensable prerequisite for surgery: Focal epilepsy->Localization
 - o Gold standard: Video-monitoring and visual inspection of the EEG (Wilson 1996)
 - MRI: Identification of an underlying lesion
 - PET and Neuropsychology: Localization of a functional deficit
 - Source analysis of
 - EEG seizure (ictal) activity (Plummer et al., 2008; Rullmann et al., 2009)
 - EEG/MEG interictal activity: "irritative zone" (Stefan et. al., 2003; Aydin et al., 2015,2017)

Zone-concept in epilepsy diagnosis



EEG(/MEG) registration during a seizure (ictal) Interictal spikes in EEG/MEG



0.2sec

0.5pT

5mV

2pT/

5mV



[Courtesy of Stefan Rampp]

MEG EEG ECG 0.2 680 2 pT/ 2 mV

Clear signal in MEG, poor signal in EEG

[Courtesy of Stefan Rampp]

Clear signal in MEG, poor signal in EEG =>tangentially oriented source



[Courtesy of Stefan Rampp]

[Piastra, Nüßing, Vorwerk, Clerc, Engwer & Wolters, Human Brain Mapping, 2021]

Introduction: Sensitivity of EEG and MEG

- Blue: Sensitivity EEG > MEG
 for radial and deep sources
- Red: Sensitivity MEG > EEG in sulcal wall areas



Introduction: Complementarity of EEG and MEG

- Iwasaki et al 2005:
 EEG/MEG: 72% (31/43 pat)
 Only EEG: 2% (1/43 pat)
 Only MEG: 19% (8/43 pat)
 None: 7% (3/43 pat)
- Knake et al 2006:

EEG/MEG: 75% (50/67 pat)
Only EEG: 3% (2/67 pat)
Only MEG: 13% (9/67 pat)
None: 25% (17/67 pat)

What should we use? MEG instead of EEG? Only EEG?



*EEG spikes, MEG spikes > 70%

Fig. 3. Populations of spikes that were detected only in magnetoencephalography (MEG) (unique MEG spikes in *black*), only in EEG (unique EEG spikes in *white*), and commonly in both EEG and MEG [same spike detected in both modalities (EMEG) spikes in *gray*] are shown on a percentage scale for 39 patients who had at least one spike. Common EMEG spikes account for a relatively small proportion of the total spikes (median, 25.7%). The patients are roughly divided into those with a large number of EEG spikes (n = 13), those with a large number of MEG spikes (n = 15), and those with no dominancy (n = 2).

Introduction: Combined measurement of EEG and MEG



275 channel axial gradiometer whole-cortex MEG 128 channel EEG

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[Aydin, Vorwerk, Küpper, Heers, Kugel, Galka, Hamid, Wellmer, Kellinghaus, Rampp & Wolters, Plos One, 2014]

SEP/SEF skull conductivity calibration







SEP/SEF skull conductivity calibration



SEP/SEF skull conductivity calibration



Figure 3. Skull conductivity calibration graph. RV (in %) obtained from Algorithm 2 in step 2.d. for different skull conductivity parameters for 6C (red) and 3C (blue) head models. The differences to the calibrated head models $6C_Cal$ and $3C_Cal$ (indicated by the black bar, see also Table 1) in source reconstruction are indicated by boxes with dashed frames: Difference in source location x (top row, in mm), orientation o₂ (middle row, in degree) and strength m₂ (bottom row, in %).

Skull-conductivity calibration: Individual calibration curves in a group study (20 subjects)



Figure 4. Skull conductivity calibration graph. Residual variance (RV in %) curves as they were estimated by the skull conductivity calibration procedure. The RV curves are presented as a function of the skull compacta conductivity for all the subjects. The horizontal axis is in mS/m and the vertical axis is in %. Each curve is color-coded by the age of the subject.

[Aydin, Vorwerk, Küpper, Heers, Kugel, Galka, Hamid, Wellmer, Kellinghaus, Rampp & Wolters, PLOS ONE, 2014] [Antonakakis, Schrader, Aydin, Khan, Gross, Zervakis, Rampp & Wolters, Neurolmage, 2020] [Schrader, Antonakakis, Rampp, Engwer & Wolters, Phys Med Biol, 2020]

Combined EEG/MEG source analysis in calibrated head model



MEG nearly not influenced

Structure

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Patient

- □ In 2009: 11 year old boy
- □ In 2001: In the age of 3
 - diagnosis of refractory (pharmaco-resistent) focal epilepsy and dysembryoplastic neuroepithelial tumor (DNET)
 - DNET- and focus-resection
- In 2009
 - □ again epileptic seizures
 - DNET-relapse anterior to the motor-cortex close to resection-area from first surgery

MRI segmentation



Modeling of brain conductivity anisotropy



Original DTI data

FA-map after registration

FA-map on T1-MRI

Effective medium approach model (DTI <-> CTI):

Model DTI<->Conductivity Tensor Image (CTI) [Tuch et al., Ann. NYAS, 1999]

Linear model DTI<->CTI [Tuch et al., PNAS, 2001]

Validation of DTI<->CTI model in silk yarn phantom [Oh et al., ISMRM, 2006]

Improved DTI artifact correction and registration [Ruthotto et al., Phys Med Biol, 2012]

Finite element method (FEM) mesh generation



EEG preprocessing





Presurgical EEG source analysis



Goal function scan (Mosher, 1992; Knösche, 1997)

MNE (Hämäläinen & Ilmoniemi, 1984)

sLORETA

(Pascual-Marqui, 2002)

Dipole fit (Scherg and von Cramon, 1985)

Result: Posterior to the lesion in lateral premotor cortex

Validation using intracranial EEG



ECoG peaking electrodes

EEG dipole fit result

Comparison with more homogenized head models

Table 4

Differences of dipole fit results in the volume conductor models of FE conductivity labeling section and the result using model 6CompAnisoBrain

Model	Loc. diff.	Orient. diff.	Rel. Mag. diff.	GOF
	(in mm)	(in degree)	(in percent)	(in %)
6IsoComp	0.21	4	2.2	97.05
3IsoComp	8.97	18	19.7	96.59

Summary

- First study in highly-resolved (1mm) 6-compartment anisotropic head model plus tumor modeling using accurate and fast FEM-methods
- Significant localization and orientation differences to standard 3-compartment head model
- Recommendation to use different inverse approaches ("converging evidence") for a more reliable detection of the epileptogenic focus
- Presurgical source localization was evaluated with post-surgical intracranial EEG: Only small differences, most probably due to craniotomy and resulting post-surgical brain shift
- Source orientation in posterior direction, i.e., in direction of the epileptogenic tissue, in agreement with (Salayev et al., 2006), who postulated this for central and interhemispheric epileptic activity

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Patient history



- 17 year old female suffering from pharmaco-resistant focal epilepsy,
- MRI Negative,
- **FDG-PET:** a diffuse and extended left fronto-temporal hypometabolism.
- Stereo-EEG: 14 intracerebral depth electrodes, 167 contacts

[Aydin, Vorwerk, Dümpelmann, Küpper, Kugel, Heers, Wellmer, Kellinghaus, Haueisen, Rampp, Stefan & Wolters, *PLOS ONE*, 2015] [Aydin, Vorwerk, Küpper, Heers, Kugel, Galka, Hamid, Wellmer, Kellinghaus, Rampp & Wolters, *PLOS ONE*, 2014]

Spike detection



- Select 10 clear spikes and average
- Template matching
- Visual control
- 200 spikes

"Knowing where a spike or seizure originates from is more important than where it goes. The importance of MEG localization increases if it precedes or is at least synchronous with the correlate EEG spike." (Ebersole & Ebersole 2010) [Aydin, Vorwerk, Dümpelmann, Küpper, Kugel, Heers, Wellmer, Kellinghaus, Haueisen, Rampp, Stefan & Wolters, *PLOS ONE*, 2015] [Aydin, Vorwerk, Küpper, Heers, Kugel, Galka, Hamid, Wellmer, Kellinghaus, Rampp & Wolters, *PLOS ONE*, 2014]

Sub-averaging procedure



Same spike is not allowed to appear in the same sub-average twice.

- Random sub-averages of 200 single spikes:
 - 200 → Av1
 - $200 \rightarrow Av5$
 - 200 → Av10
 - 200 → Av15
 - $200 \rightarrow Av20$
 - $200 \rightarrow Av25$
 - 200 → Av30
 - 200 → Av35
 - $200 \rightarrow Av40$
 - 200 → Av45
 - 200 → Av50

For EEG, MEG, EMEG and 11 time instants \rightarrow 72600 localization

Example sEEG and EEG spikes



The union of green and red spheres shows the sEEG leads measuring interictal activity, and red spheres alone show the leads measuring seizure onset.

[Aydin, Vorwerk, Dümpelmann, Küpper, Kugel, Heers, Wellmer, Kellinghaus, Haueisen, Rampp, Stefan & Wolters, PLOS ONE, 2015]

Source reconstructions of Av10 at different instants of time



EEG, MEG and EMEG dipole scan peaks of Av10 for different time points. Blue dipoles illustrate the noninvasive reconstructions, both green and red spheres show the sEEG leads where frequent interictal activity can be measured, and only red spheres show seizure onset leads.

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Patient

- 49 years old woman, suffering since 47 years under pharmaco-resistent focal epilepsy
- 8 different drugs and still 100-200 seizures per month
- Seizure-semiology: Tingling in right anterior chest-area, rising nausea, loss of conscience, tonic and hypermotoric movements of right arm and leg

Skull-conductivity calibrated realistic head model and cortical source space



10 averaged spikes at maximum global field power: Time-point 0 ms



EMEG source analysis at -7 ms (radiological convention)

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3D-FLAIR 3T-MRI and morphometric analysis



Retrospectively visible in 3D-FLAIR a subtle right-frontal "bottom of sulcus" focal cortical dysplasia (FCD)...

...that was confirmed in morphometric analysis (MAP07: Huppertz et al., 2005)...

ZOOMit MRI in pre-localized ROI at -7 ms

ZOOMit MRI



...as well as when using a 3T MRI T2 ZOOMit "parallel transmit" sequence with 0.5 mm isotropic resolution (Siemens, Erlangen; Riffel et al., 2015).

MEG and EEG topographies and EMEG source analysis at -23 ms





3T MRI (3D-FLAIR) and morphometric analysis



Even retrospectively in 3D-FLAIR hardly visible "left supra-insular " FCD...

...that could also only weakly be confirmed by morphometric analysis (MAP07: Huppertz et al., 2005)...

ZOOMit MRI in pre-localized ROI at -23 ms (radiological convention)

ZOOMit MRI



..., but a little bit better visible in the T2 ZOOMit.

DTI tractography between both localized FCDs



Overview: EMEG source analysis



Information in single modality EEG or MEG too noisy



Radio-frequency thermo-coagulation (RFTC)



Patient got RFTC in left supra-insular FCD and positive outcome supported our diagnosis

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PerEpi non-invasive diagnosis: EEG and MEG of averaged 1050 interictal epileptiform discharges (IEDs)



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EEG and MEG source analysis of the subaveraged IEDs







Retrospective MRI analysis showed an FCD type IIb

- Source reconstruction led to detection of focal cortical dysplasia (FCD) of type IIb, which was not described earlier by the neuroradiologist
- Lesion close to Broca's area

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Patientin

- 28 Jahre alte Frau, pharmako-resistente Epilepsie seit dem 8.Lebensjahr (2-3 x /Nacht, selten tagsüber)
- <u>Anfallstyp 1 (häufig)</u>: Rumpfvorbeugung, Hin- und Herwerfen des Oberkörpers, Vokalisationen für 30 60 Sek.
- Anfallstyp 2 (seltener): Bewegungsarrest, Starren, Schmatzen
- Nicht-invasive prächirurgische Diagnostik 2000 an einem großen/bekannten Epilepsiezentrum (14. LJ):
 - MRT: leichtgradige Hippokampussklerose rechts
 - Interiktuale Epilepsie-typische Potentiale rechts temporal
 - EEG-Anfallsbeginn rechts temporal

Neurochirurgie 2000 (nicht am UKM)

- Anteriore Temporallappenresektion rechts inkl. Amygdala-Hippokampektomie (14. LJ / 2000)
- Post-operativ anfallsfrei bzgl.
 - Anfallstyp 2
- Anfallstyp 1 unverändert







- Im Alter von 28.Jahren: Verheiratet und Kinderwunsch, aber bei der hohen Dosierung von Valproat ca. 10% Risiko für kindliche Fehlbildungen
- 2x Versuch, Valproat auszuschleichen scheiterte

Nicht-invasive prächirurgische Diagnostik 2014



MEG-Quellenanalyse aus 9 gemittelten MEG-Spikes am Spike-Onset rechts-fronto-lateral organisiert

- Dipol-Fit (roter Pfeil)
- Stromdichte-Rekonstruktion (gelb-rotes Patch)

Nicht-invasive prächirurgische Diagnostik 2014



MRT (3T, 3D FLAIR): mögliche FCD rechts fronto-lateral

Neurochirurgie 2015

- Invasive Diagnostik mit 2 Tiefenelektroden:
 Anfallsbeginn in der FCD
- Wada-Test (Injektion eines Narkose-Mittels in die Hirnschlagader): Sprachbereiche nicht betroffen
- Empfehlung zur erweiterten Läsionektomie
- Navigationsgestützte Resektion 07/2015
- Histologie: FCD Typ II B



B

A



Postoperatives Ergebnis

- Kein klinisch-neurologisches Defizit
- Post-operativ komplett anfallsfrei
- Da Valproat bereits vor OP abgesetzt wurde, stand einer möglichen
 Schwangerschaft nichts mehr im Wege





Operation statt Medikamente bei Epilepsie und Schwangerschaft

Das Baby kann kommen

Epilepsie-Therapie bei Schwangeren

fen können, das wird für die werdende Mutter Sonja Plonka nichts Neues sein. Doch bisher war es kein Babygeschrei, das die 29-Jährige um den Schlaf brachte. Drei bis acht epileptische Anfälle plagten sie seit ihrem sechsten Lebensjahr pro Nacht - je nach Medikamentenzusammenstellung. Eine Zeit lang gelang es, dass sie anfallsfrei war. "Mit dem Medikaentsprechenden ment war mein Wunsch. schwanger zu werden, völlig ausgeschlossen, da die Gefahr für Fehlbildungen zu groß war", erzählt die verhei- die Anfälle gefunden zu haratete Dortmunderin.

ihrem Wunsch das erste Mal nik für Neurochirurgie mitim UKM (Universitätsklinikum Münster) vor, durch Patientin für zwei Wochen einen Aufruf zu einer Studie eingesetzt wurden. "Bereits urteilung hilft, dass bei einer frei bleibt."

MÜNSTER. Nicht durchschla- wurde Plonka auf das Klinikum aufmerksam, heißt es in einer Pressemitteilung.

"Nach einer Messung der magnetischen Aktivität des Gehirns durch das Team von Privat-Dozent Dr. Carsten Wolters vom Institut für Biomagnetismus und einem Forschungs-MRT haben wir eine Anlagestörung im rechten Stirnlappen entdeckt", erklart Oberarzt Dr. Gabriel Möddel, Leiter des Bereichs Epileptologie in der Klinik metergenau die betroffene tionsbereiche Neuromuskuläre Erkrankungen am UKM. Die Vermutung, den Auslöser für ben, bestätigte sich bei wei-2013 stellte sie sich mit terer Diagnostik in der Klitels Tiefenelektroden, die der



Die elektrische Übererregung von Sonja Plonkas Gehirn ist deutlich auf dem Bildschirm zu sehen. Doch das gehört der Vergangenheit an. Jetzt ist die 29-Jährige anfallsfrei und schwanger - zur Freude von Dr. Gabriel Möddel.

zehn Sekunden vor dem An- Hirnoperation keine für die chungsergebnisse zusammen, heißt es weiter.

Vor der OP versicherten nen", erklärt Möddel. sich die Mediziner noch mit Test, der durch Injektion

fall konnte man damit milli- Sprache wichtigen Funkgeschädigt für Schlafmedizin und Stelle im Gehirn definieren", werden. "Danach wussten fasst Möddel die Untersu- wir, dass wir die zwei betroffenen Zentimeter ohne größeres Risiko entfernen kön-

"Dieser Eingriff ist die derdem sogenannten Wada- zeit wirksamste Therapie bei Epilepsie und Sonja Plonka eines Narkosemittels in die hat damit eine Chance von Hirnschlagader bei der Be- 80 Prozent, dass sie anfalls-

Zusammenfassung

- MEG-Quellenanalyse kann einen wichtigen Beitrag zur prächirurgischen Epilepsie-Diagnostik leisten
- Könnte zukünftig Patienten u.U. invasive Diagnostik ersparen!?
- MEG weniger durch Knochenlücken beeinflusst als EEG: MEG also insbesondere von Nutzen bei vor-operierten Patienten
- Individuelles FEM-Kopfmodell kann Modellierung des "breach-rhythm" und damit auch EEG und kombinierte EEG/MEG Quellenanalyse ermöglichen

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- EEG and MEG are modalities with complementary sensitivities
- Combined EEG/MEG source analysis can significantly stabilize the accuracy and confidence of reconstructions (Antonakakis et al., 2019,2020), especially at early (noisy) time points (Aydin et al., 2015,2017)
- The use of earlier activity than spike-peak and spike sub-averaging strategies can avoid mis-localizations due to propagation (Aydin et al., 2015,2017)
- EEG/MEG source analysis for determination of region of interest (ROI) and then morphometric analysis and ZOOMit-MRI in ROI seems a very promising new method (use of "converging evidence") (Aydin et al., 2017)
- A combined EEG/MEG source analysis should be based on realistic multi-compartment anisotropic head models with individually-calibrated skull conductivity (Aydin et al., 2014, 2015, 2017; Vorwerk et al., 2019; Antonakakis et al., 2019,2020)

Thanks for your attention!



2010-2016







since 2016



IBB's SIM-NEURO work-group