Simultaneous EEG and functional MRI

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List of Abbreviations

AAL	anatomic automatic labeling
AEDs	anti-epileptic drugs
BOLD	blood oxygenation level-dependent
CBF	cerebral blood flow
CBV	cerebral blood volume
$CMRO_2$	cerebral metabolic rate for oxygen
CT	computed tomography
ECG	electrocardiogram
ECoG	electrocorticography
EEG	electroencephalography
EPI	echo planar imaging
fMRI	functional magnetic resonance imaging
FDR	false discovery rate
FIR	finite impulse response model
FOV	field of view
GLM	general linear model
HFO	high frequency oscillations
HRF	hemodynamic response function
IC	independent component
ICA	independent component analysis
IED	interictal epileptiform discharge
IRF	impulse response function
MEG	magnetoencephalography
MRI	magnetic resonance imaging

PAA	period amplitude analysis
PET	positron emission tomography
PPG	photoplethysmogram
RF	radiofrequency
RVT	respiratory volume per time
SEEG	stereoelectroencephalography
SPECT	single-photon emission computed tomography
TR	repetition time
VIPH	variation in pulse height

Summary

Epilepsy is a neurological disease characterized by epileptic seizures. In the Netherlands about 120.000 persons have epilepsy. Most of them can be treated successfully with anti-epileptic drugs. However, 20 - 30 % of the patients does not respond to medication. These patients are potential candidates for epilepsy surgery, which aims to remove those brain regions that are responsible for the generation of seizures (i.e. epileptogenic zone). To create hypotheses about the location and extent of the epileptogenic zone several (non)invasive techniques are combined, ranging from electroencephalography (EEG) and magnetic resonance imaging (MRI) to neuropsychological tests.

In this context, we investigated the added value of a relatively new technique: simultaneous EEG and functional MRI (EEG-fMRI). EEG and fMRI are both techniques to measure neuronal activity. EEG measures electrical activity through electrodes at the scalp and is able to indicate the occurrence of epileptic activity [seizures or interictal epileptiform discharges (IEDs)] with good temporal resolution. However, the spatial resolution is relatively low, because the EEG signals represent a mixture of activity from different sources. fMRI, on the other hand, has a good spatial resolution. This technique provides an indirect measure for neuronal activity, which is based on changes in the ratio of oxy- and deoxyhemoglobin in the blood related to the occurrence op neuronal activity. Co-registration of EEG is necessary to determine whether changes in fMRI are related to epileptic activity. The epileptic events that are visible in the EEG during scanning are correlated with the fMRI time series yielding a correlation pattern indicating which brain regions were significantly more active during IEDs than in periods without visible IEDs in the EEG. The combination of EEG and fMRI provides a unique way to investigate epileptic networks with a high spatial precision.

The technical problems involved with the recording of EEG in the MRI environment are largely solved; under certain conditions and with special equipment it is safe to record EEG inside the MRI. However, the analysis and interpretation of the data are not straightforward. Therefore, the general aim of this thesis was to improve and to evaluate the potential of EEG-fMRI as a noninvasive technique in the presurgical evaluation of patients with medically intractable epilepsy.

Chapter 2 and 3 focus on the analysis of the fMRI data. In chapter 2 different analytical strategies for the correlation of EEG and fMRI were compared. The results suggest that the yield of EEG-fMRI is increased when a flexible approach is used, in which no assumptions are made about the precise underlying relation between EEG and fMRI, the hemodynamic response function (HRF). Since the HRF can vary over subjects and brain regions, the use of a more flexible approach, where the HRF is estimated from the data, increases the yield of fMRI.

Chapter 3 demonstrates that it is also important to correct the fMRI signals for variations in physiological functioning. These variations can be measured by a pulse oximeter at one of the subject's fingers. The variations in pulse height (VIPH) are related to respiration and cardiac output. VIPH appears to explain a large part of the fMRI signals, both in healthy volunteers and patients with epilepsy. Therefore, it is important to correct for these effects, especially when the subject has an abnormal breathing pattern during the experiment, as one of the patients with epilepsy in our study. When this physiological effect is taken into account the correlation pattern reduces from a very widespread correlation pattern to a pattern with a maximal BOLD response in the right temporal lobe. This region coincided with the resection area. The inclusion of VIPH regressors in the correlation model is not only important for the analysis of EEG-fMRI data of patients with epilepsy, but is relevant in general for resting-state fMRI studies, during which spontaneous brain activity is measured.

The yield of the EEG-fMRI analysis is dependent on the IEDs that are visible in the EEG. The detection of epileptic events is hampered by the presence of gradient and pulse artifacts in the EEG. Gradient artifacts result from switching of the gradients for slice selection, whereas pulse artifacts are related to the pulsation of the heart. Both types of artifacts can be removed off-line from the EEG with dedicated algorithms. Most of these algorithms are based on the average artifact subtraction principle, in which a template is created by averaging the artifact that is subsequently subtracted from the raw EEG data. In chapter 4 extensions of this approach are presented to further improve the correction of the EEG data. First, it appears that the gradient artifacts may differ slightly between scans. By clustering the artifacts and creating a template for each cluster, the correction was improved. Second, the pulsation artifacts appear to overlap from heartbeat to heartbeat. Therefore, the correction of the EEG data is improved when this overlap is taken into account.

Chapter 5 and 6 focus on the evaluation of the EEG-fMRI results. Most EEG-fMRI analyses yield a correlation pattern consisting of multiple activated brain regions. Our hypothesis was that these regions form an epileptic network including the onset and propagation of epilepsy related activity. For validation, the EEG-fMRI findings were compared to the results of invasive EEG data. These data are acquired either by depth electrodes implanted inside the brain tissue or by electrode grids placed on the subdural surface of the brain. In chapter 5 a semi-automatic procedure for the analysis of the invasive data is presented such that the EEG-fMRI findings can be compared systematically with the invasive EEG data. This method was tested for five patients who were implanted with depth electrodes. In chapter 6 the application of the same method was described for the EEG data of sixteen patients recorded from subdural grids. In all data sets there was at least one region that was concordant with active invasive electrodes during IEDs. Furthermore, the EEG-fMRI results were compared to the location of the seizure onset zone and resection area: the EEG-fMRI correlation pattern included the seizure onset zone in 83 % of the data sets and the resection area in 93 % of the data sets. For some patients, we were able to validate an epileptic network of onset and propagation regions.

Although in most patients relevant results are obtained with EEG-fMRI, in some patients no IEDs are detected in the EEG during scanning. This may have several explanations, for instance the limited scanning period (about 45 minutes) or an origin located in deep lying structures. When no IEDs are present, the data cannot be analyzed with the current EEG-fMRI approach. Chapter 7 is an explorative study to the use of independent component analysis (ICA), a data-driven approach independent of the EEG. The preliminary results suggest that it is possible to find epileptic networks with ICA, even in the absence of visible IEDs in the EEG. This finding provides further perspective for the use of resting-state fMRI in clinical practice.

In conclusion, the yield of EEG-fMRI increases with the methodological improvements presented in this thesis. Furthermore, the results of EEG-fMRI are clinically relevant, because EEG-fMRI is usually concordant with IEDs in the invasive EEG data and includes the seizure onset zone and resection area. For this reason, there is an important role for EEG-fMRI in the surgical planning, especially with regard to the determination of the implantation strategy. In comparison to other noninvasive techniques in the presurgical evaluation, EEG-fMRI will have an added value in patients in whom a focus from deeply lying structures or multifocal epilepsy is expected. In addition, EEG-fMRI is able to reveal the whole network from onset to propagation, which is more difficult to achieve with EEG alone.

Nederlandse Samenvatting

Co-registratie van EEG en functionele MRI
een niet-invasieve techniek in de prechirurgische evaluatie van focale epilepsie

Epilepsie is een neurologische aandoening die wordt gekenmerkt door epileptische aanvallen, die het dagelijkse functioneren van de patiënt substantieel kunnen beïnvloeden. In Nederland hebben ongeveer 120.000 mensen epilepsie. Twintig tot dertig procent van de patiënten reageert onvoldoende op medicatie. Zij kunnen in aanmerking komen voor een operatie waarbij het hersengebied verwijderd wordt dat cruciaal is voor het veroorzaken van aanvallen, het epileptogene gebied. Om de precieze locatie van het epileptogene gebied te bepalen, ondergaat de patiënt voorafgaand aan deze operatie een breed scala aan onderzoeken, van electroencefalografie (EEG) en magnetic resonance imaging (MRI) tot aan invasieve EEG onderzoeken.

In dit proefschrift wordt de toegevoegde waarde onderzocht van een relatief nieuwe techniek, namelijk de co-registratie van EEG en functionele MRI (EEG-fMRI). EEG en fMRI zijn beiden technieken om hersenactiviteit te meten. Met EEG wordt elektrische neuronale activiteit met behulp van elektroden geplaatst op de schedel. Op dit moment is EEG de belangrijkste techniek voor de diagnose van epilepsie. EEG is in staat om epileptische activiteit (aanvallen of interictale epileptische ontladingen) met een goede temporele precisie te meten. De spatiële resolutie is echter relatief laag, omdat het EEG een weergave is van verschillende bronnen. fMRI heeft juist een zeer goede spatiële resolutie. Deze techniek meet hersenactiviteit gebaseerd op veranderingen in zuurstofconcentratie in het bloed, die het gevolg zijn van zuurstofopname na neuronale activatie. Co-registratie van EEG is nodig om te controleren of de waargenomen veranderingen in het fMRI signaal het gevolg zijn van epileptische ontladingen. Het EEG wordt dus alleen gebruikt om te bepalen op welke momenten er epileptische ontladingen plaats vindt tijdens het scannen. Deze momenten worden vervolgens gecorreleerd met de fMRI signalen. Het resultaat is een correlatiepatroon dat aangeeft welke gebieden significant actief zijn tijdens epileptische ontladingen.

De technische problemen rondom het simultaan meten van EEG en fMRI zijn grotendeels opgelost; het is onder bepaalde condities en met speciale apparatuur veilig om EEG in een MRI scanner te meten. De analyse en interpretatie van de gegevens is echter niet eenvoudig. Het doel van dit proefschrift was dan ook om de analyse van EEG-fMRI data te optimaliseren en de resultaten te evalueren, zodat EEG-fMRI gebruikt kan worden als een niet-invasieve techniek in de prechirurgische evaluatie van patiënten die kandidaat zijn voor een operatie.

Hoofdstuk 2 en 3 van dit proefschrift richten zich op de analyse van de fMRI data. In hoofdstuk 2 zijn verschillende analytische strategiën met elkaar vergeleken. De resultaten laten zien dat de opbrengst van EEG-fMRI verhoogd wordt wanneer er in het model vooraf geen aannames gemaakt worden over de precieze onderliggende relatie tussen EEG en fMRI, de hemodynamische respons functie (HRF). Omdat de HRF verschillend kan zijn tussen patiënten en tussen hersengebieden, is een flexibel model beter dan een model waarin een vaste vorm voor de HRF wordt aangenomen.

In hoofdstuk 3 wordt aangetoond dat het belangrijk is om de fMRI signalen te corrigeren voor variaties in fysiologische functies. De veranderingen in fysiologische functies zijn te meten met een puls oximeter op een vinger van de proefpersoon. De verschillen in amplitude van dit signaal geven de veranderingen in de ratio van oxy- en deoxyhemoglobine weer als gevolg van ademhaling en hartslag. Deze veranderingen blijken een groot gedeelte van het fMRI signaal te verklaren, zowel bij gezonde proefpersonen als bij patiënten met epilepsie. Daarom is het belangrijk om te corrigeren voor de artefacten die gerelateerd zijn aan fysiologische functies. Deze bevinding is niet alleen van belang voor fMRI-onderzoek bij patiënten met epilepsie, maar ook voor fMRI-onderzoeken tijdens rusttoestand waarbij spontane hersenactiviteit gemeten wordt.

De sensitiviteit van de fMRI analyse is afhankelijk van de epileptische pieken die in het EEG gemarkeerd worden. De detectie van epileptische pieken wordt echter bemoeilijkt door de artefacten die in het EEG ontstaan door de schakelingen van de gradiënten en pulsaties van het hart. Beide typen artefacten kunnen met behulp van algoritmes achteraf gecorrigeerd worden. De meeste algoritmes maken een sjabloon van het artefact door middeling van diverse artefacten; vervolgens wordt dit sjabloon van de ruwe EEG-signalen afgetrokken. Hoofdstuk 4 bevat een voorstel voor uitbreiding van dit algoritme, zodat de correctie van het EEG verbeterd kan worden. De gradiënt-artefacten blijken niet zo stabiel te zijn tijdens lange registraties. Door de artefacten te clusteren en per cluster een sjabloon te maken, wordt de correctie beter. Verder werd aangetoond dat de pulsatie-artefacten van hartslag tot hartslag kunnen overlappen. Door hier rekening mee te houden wordt de correctie van het EEG beter.

In hoofdstuk 5 en 6 ligt de nadruk op de evaluatie van de EEG-fMRI resultaten.

Het correlatiepatroon bestaat bij de meeste patiënten uit meerdere geactiveerde gebieden. De hypothese is dat deze gebieden een interictaal netwerk vormen van gebieden die het begin van de epileptische ontladingen weergeven en gebieden die gerelateerd zijn aan spreiding van deze activiteit over de cortex. Om dit te valideren, zijn de uitkomsten van EEG-fMRI vergeleken met intracraniële registraties. Bij deze registraties worden diepte-elektroden in de hersenen of matjes met elektroden op de hersenschors geplaatst. Deze invasieve registraties worden gezien als de gouden standaard om het begin van de aanvallen te lokaliseren. In hoofdstuk 5 beschrijven we een methode om de invasieve data te analyseren, zodat een systematische vergelijking met EEG-fMRI mogelijk is. Deze methode is geëvalueerd voor vijf patienten die in het kader van hun operatie geregistreerd zijn met diepte-elektroden. Vervolgens is deze methode in hoofdstuk 6 toegepast op data van zestien patiënten waarbij elektrodenmatjes geplaatst zijn. De sensitiviteit van EEG-fMRI bleek hoog: voor bijna iedere patiënt kwam tenminste één gebied overeen met het gebied waar volgens de invasieve EEG data de interictale epileptische ontladingen beginnen. Daarnaast zijn de EEG-fMRI resultaten ook vergeleken met de klinische meer relevante informatie, zoals de plek waar de aanvallen beginnen en het gebied dat succesvol verwijderd is tijdens de operatie. Het EEG-fMRI correlatiepatroon liet tenminste één geactiveerd gebied zien dat overeenstemming vertoont met de locatie van het begin van de aanvallen in 83 % van de data sets en het geopereerde gebied in 93 % van de data sets. In sommige patiënten was het mogelijk om een epileptisch netwerk te valideren dat zowel het begin als de spreiding van epileptische ontladingen weergeeft.

Een nadeel van EEG-fMRI is dat de analyse sterk afhankelijk is van het aantal epileptische pieken die in het EEG gedetecteerd worden. Het komt regelmatig voor dat er geen pieken optreden tijdens het scannen door de relatief korte tijdspanne van het onderzoek (ongeveer 45 minuten). Ook kan het voorkomen dat de pieken niet door het EEG gezien worden, omdat ze in diep gelegen hersengebieden gegenereerd worden. Wanneer er geen pieken in het EEG te zien zijn, kan de data niet geanalyseerd worden met de hiervoor beschreven modelmatige aanpak. Hoofdstuk 7 beschrijft een exploratieve studie naar het gebruik van een data-gestuurde aanpak die onafhankelijk is van het EEG, namelijk independent component analyse (ICA). Het lijkt erop dat het mogelijk is om met ICA het epileptische netwerk te vinden, óók als er geen pieken in het EEG gevonden worden. Dit biedt perspectief voor het gebruik van fMRI in de prechirurgische evaluatie zonder noodzakelijke co-registratie van het EEG.

Tot slot, met dit onderzoek hebben we laten zien dat de opbrengst van EEG-fMRI onderzoeken hoger wordt met de door ons voorgestelde methodologische verbeteringen. Verder hebben we ook aangetoond dat de resultaten van EEG-fMRI relevant zijn voor de prechirurgische evaluatie. Omdat EEG-fMRI niet veel informatie mist (in bijna alle gevallen vond EEG-fMRI het gebied waar de aanvallen beginnen), lijkt de methode zeer geschikt om te bepalen waar invasieve elektroden geplaatst moeten worden. Ten opzichte van andere onderzoeken heeft EEG-fMRI vooral een toegevoegde waarde voor de prechirurgische evaluatie van patiënten bij wie diep in de hersenen gelegen bronnen of multifocale epilepsie verwacht wordt. Verder kan met EEG-fMRI het hele netwerk dat betrokken is bij interictale epileptiforme ontladingen in kaart gebracht worden, iets wat veel moeilijker is met EEG alleen.

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Na ruim vier jaar is mijn proefschrift dan bijna af! Dit had ik niet kunnen bereiken zonder de begeleiding, ondersteuning en medewerking van anderen. Ik wil dan ook graag van deze gelegenheid gebruik maken om iedereen te bedanken.

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Liefs,
Petra
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List of Publications

Papers

van Houdt PJ, de Munck JC, Zijlmans M, Huiskamp G, Leijten FS, Boon PA, and Ossenblok PP (2010a). Comparison of analytical strategies for EEG-correlated fMRI data in patients with epilepsy. *Magn Reson Imaging* 28.8, pp. 1078–86

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van Houdt PJ, de Munck JC, Leijten FSS, Huiskamp GJM, Colon AJ, Boon PAJM, and Ossenblok PPW (submitted). Understanding EEG-fMRI correlation patterns in presurgical evaluation of focal epilepsy

van Houdt PJ, Ossenblok PPW, Colon AJ, Leijten FSS, Verdaasdonk R, Boon PAJM, and de Munck JC (in prep). An explorative study to the existence of an epileptic resting-state fMRI network

de Munck JC, van Houdt PJ, Verdaasdonk RM, and Ossenblok PP (2012). A semi-automatic method to determine electrode positions and labels from gel artifacts in EEG/fMRI-studies. *Neuroimage* 59.1, pp. 399–403

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Curriculum Vitae

Petra van Houdt was born in Hulst on April 11, 1983. After finishing her secondary education at the Reynaertcollege (previously known as St. Jansenius) in 2001, she studied biomedical engineering at the Eindhoven University of Technology. During her studies, she carried out an internship at the department of physiology of the Semmelweis University (Budapest) investigating the adaptation of the intact rat heart to changes in workload. She performed her graduation project at the department of clinical physics of Kempenhaeghe, working on an algorithm for automatic detection of obstructive sleep disordered breathing. After her graduation in 2007, she worked as a junior researcher in Kempenhaeghe to evaluate and complete this algorithm and to publish the results. At the end of 2007, she started her PhD project at Kempenhaeghe and VU University Medical Center with a focus on epilepsy. The results of the research are described in this thesis, entitled "Simultaneous EEG and functional MRI: a noninvasive tool in the presurgical evaluation of focal epilepsy". In this period, she visited the laboratory of Prof.dr. Jean Gotman of the Montreal Neurological Institute. Currently she is working as a researcher on a follow-up study that focuses on the development of more data-driven analytical approaches.