CHAPTER 1

General Introduction

1.1 Epilepsy Surgery

In the Netherlands about 120,000 persons have epilepsy and each year 12,000 new diagnoses are made\(^1\). Epilepsy is a collective term for a family of disorders having a tendency for recurrent epileptic seizures, defined as follows (Fisher et al. 2005):

An epileptic seizure is a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain.

The primary strategy for treatment of epilepsy is anti-epileptic drugs (AEDs). However, about 20 to 30\% of the patients with epilepsy does not respond to AEDs (Lardizabal 2008). In that case, the epilepsy is called medically intractable (Passaro 2006; Panayiotopoulos 2007). Other commonly used terms are refractory or pharmaco-resistant epilepsy.

If the seizures start in a limited cortical area (i.e. partial seizures), patients are potential candidates for epilepsy surgery. The goal of resective epilepsy surgery is to remove or disconnect those brain areas that are crucial for the generation of epileptic seizures (i.e. epileptogenic zone) without affecting functional brain areas (Rosenow et al. 2001). For a successful operation, it is of utmost importance to accurately determine which brain region should be the target of surgery. The epileptogenic zone is a theoretical concept, since there is currently no technique that can guarantee whether the removal of a certain area will result in seizure freedom. When the patient is seizure-free after surgery, it is concluded that the epileptogenic zone must have been located within the resected area (Rosenow et al. 2001).

\(^{1}\)www.epilepsievereniging.nl
The location and extent of the epileptogenic zone can be estimated by combining several (non)invasive diagnostic techniques ranging from electroencephalography (EEG) to magnetic resonance imaging (MRI) and neuroimaging techniques to neuropsychological tests (Rosenow et al. 2001; Mathern et al. 2008). Ideally, the results of different techniques have a high degree of overlap, but in practice it appears to be more complex (Carreno et al. 2008). Therefore, there is still a need for the development of improved methodologies that contribute to the estimation of the epileptogenic zone.

In this context, this thesis focuses on the added value of a new neuroimaging technique in the presurgical evaluation: the combination of EEG and functional magnetic resonance imaging (fMRI). EEG is currently the most important diagnostic technique, measuring electrical activity through electrodes placed at the scalp. EEG can determine the occurrence of epileptic activity with a high temporal precision, but gives only a rough estimate of the location of the activity. MRI, on the other hand, provides a good spatial estimate of all brain regions related to neuronal activity. However, it is not possible to determine which changes in hemodynamics are related to epileptic activity based on MRI alone. Therefore, the combination of these two modalities may provide a unique opportunity to reveal an epileptic network with a good spatial resolution. The next sections will give an introduction of EEG and MRI as separate techniques, their advantages and disadvantages will be discussed in more detail, as well as the reasons why their combination may contribute to the presurgical evaluation.

1.2 EEG

1.2.1 Scalp EEG

The most important reason to record the EEG is to determine lateralization and onset of the seizures (i.e. seizure onset zone). Epileptic seizures are characterized by paroxysmal changes of electrical activity (Sperling et al. 2008). The typical seizure patterns recorded by EEG depend on the seizure type and the region that generates the seizures. Therefore, ictal EEG is useful to classify seizure types and to determine their onset. For presurgical evaluation, EEG is usually combined with video during long-term monitoring in an epilepsy monitoring unit (Bromfield et al. 2006). Video provides an objective measure to examine the clinical manifestations of a seizure (i.e. symptomatogenic zone) (Bromfield et al. 2006). Medication withdrawal is often necessary for seizures to occur more frequently.

A second type of events that is typical for the EEG of patients with epilepsy are interictal epileptiform discharges (IEDs). These are abnormal discharges that occur between seizures. Unlike seizures, IEDs are not associated with apparent clinical symptoms. The most common IEDs are spikes, sharp waves, and spike-wave
complexes (Figure 1.1) (Binnie et al. 1999; Noachtar et al. 2009b). Spikes and sharp waves are both transients that can clearly be distinguished from background activity, usually with a negative component relative to other areas (Chatrin et al. 1974). The difference between spikes and sharp waves is their duration, which is shorter than 70 ms for spikes and between 70 and 200 ms for sharp waves, but there is no difference in their diagnostic information (Noachtar et al. 2009b). The regions from which IEDs are recorded are often closely related to the region where seizures are generated (Rosenow et al. 2001), but IEDs are often seen over a larger area of cortex (Hamer 2008). IEDs are present in 90% of the patients with epilepsy (Binnie et al. 1999) and are rarely seen in normal subjects (Walczak et al. 2008). Therefore, the presence of IEDs in the EEG is an indicator for the diagnosis of epilepsy.

EEG can be recorded with a high temporal resolution, in the order of hundreds of ms. However, the spatial resolution is relatively low. It has been suggested that at least 6 to 20 mm² of cortex must be synchronously active to be detected with scalp EEG (Eccher et al. 2008; Buzsaki et al. 2008). Furthermore, the magnitude of the signal is reduced due to the resistive properties of the layers surrounding the brain, such as the cerebrospinal fluid, the skull, and the scalp, that have different conductivities. (Lopes da Silva et al. 2005; Hamer 2008; Walczak et al. 2008). For these reasons, epileptic activity that only involves a small area of cortex may not be detected with scalp electrodes (Walczak et al. 2008) and if activity originates in deeply situated cortex, scalp EEG will only reflect propagation of activity (Walczak et al. 2008). Since the conductivity of the different tissues is not homogeneous, but varies with thickness and bone structure (Lopes da Silva et al. 2005), the quantitative relationship between dendritic currents and scalp potentials is rather complicated.

### 1.2.2 Invasive EEG recordings

A solution for the limitations of scalp EEG are invasive EEG recordings. Invasive EEG can be recorded with depth electrodes inserted in the brain tissue (e.g. stereo-electroencephalography (SEEG)) or with subdural grids and strips implanted on the surface of the brain (electrocorticography (ECoG)) (Figure 1.2) (Nguyen et al. 2004).
The advantage of invasive EEG with respect to scalp EEG is that it directly records activity from the cortex. Therefore, there is no disturbance by the layers of the skull, which results in an increased signal-to-noise ratio. Furthermore, the signals are less affected by electromyographic or ballistocardiographic artifacts (Noachtar et al. 2009b). The main disadvantage of these techniques is the limited spatial sampling. If, for example, the electrodes do not cover the seizure onset area, they will only reflect propagation of seizures. Therefore, accurate hypotheses from noninvasive techniques are necessary prior to electrode placement. Due to the additional risks involved with the implantation, invasive EEG recordings are only used in complex cases in whom noninvasive techniques are not congruent, or when the epileptogenic zone is anatomically too close to eloquent cortex (Noachtar et al. 2009a; Carreno et al. 2008).

The decision which type of electrodes to use depends mainly on the brain region that needs to be investigated (Noachtar et al. 2009b). Deeply situated regions are typically better investigated with depth electrodes (Palmini 2008; Noachtar et al. 2009b; Spencer et al. 2008). Furthermore, depth electrodes provide insight in the spatiotemporal dynamics of seizures, because electrodes can be implanted in the brain regions that are assumed to play a role in the onset and early propagation of the seizures (Palmini 2008). A disadvantage of depth electrodes with respect to subdural grids is that the sampled cortical volume is relatively small (Palmini 2008). With subdural grids large connected areas can be investigated, which make exact cortical mapping possible (Palmini 2008; Noachtar et al. 2009b). In addition, the experience of the different epilepsy centers plays a role in the decision for the type of invasive electrodes (Noachtar et al. 2009b).

1.3 Functional MRI

In contrast to structural MRI that is used to reveal anatomical pictures of the brain, fMRI can be used to reveal information about brain function. fMRI provides indirect information about neuronal activity by measuring the changes in metabolic requirements related to neuronal activity. The most commonly used fMRI contrast is blood oxygenation level-dependent (BOLD) fMRI, which is based on the level of deoxyhemoglobin in the vascular system of the brain (Huettel et al. 2009c). The next sections will briefly explain the physiological basis and measurement of BOLD fMRI.

1.3.1 Physiological basis of BOLD contrast

The measurement of fMRI is based on the concentration of deoxyhemoglobin in the vascular bed of the brain (Huettel et al. 2009a; Kim et al. 2006). Deoxyhemoglobin has paramagnetic properties and can, therefore, act as an endogenous contrast agent. Paramagnetic substances cause local magnetic field inhomogeneities, which have an
effect on the transverse relaxation. More specifically, an increase in deoxyhemoglobin decreases the MR signal when using $T_2^*$-weighted imaging. This effect can be measured at higher field strengths (i.e. 1.5 T or higher).

During rest the concentration of oxyhemoglobin in the venous part of the vascular bed is relatively low (Figure 1.3a), but changes when neuronal activity occurs (Huettel et al. 2009c; Shmuel 2010; Binder et al. 2005). These changes in MRI signal are not directly related to neuronal activity, but reflect the energy requirements involved with processing of neuronal activity (Huettel et al. 2009c). In fact, more oxygen will be supplied than is actually consumed during neuronal activation (Huettel et al. 2009a). Therefore, the local concentration of oxyhemoglobin will be increased in the capillaries supporting the activated brain tissue and in the downstream veins, thus resulting in a decreased concentration of deoxyhemoglobin (Figure 1.3b). As a result, the local signal intensity of the $T_2^*$-weighted images will be increased.

The change in the MR signal is delayed with respect to the fast occurring neuronal activity. Different effects are assumed to play a role, such as cerebral metabolic rate for oxygen (CMRO$_2$), changes in cerebral blood flow (CBF), and cerebral blood volume (CBV) (Kim et al. 2006; Shmuel 2010; Huettel et al. 2009a). The relation between these effects can be modeled with the so-called hemodynamic response function (HRF) (Figure 1.4) (Huettel et al. 2009a; Deichmann et al. 2010; Buxton...
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Figure 1.3: Summary of the generation of the BOLD signal. (a) shows the ratio oxy- and deoxyhemoglobin during rest. When neurons in the surrounding tissue are activated (b), more oxyhemoglobin is provided by the vascular system resulting in a decreased concentration of deoxyhemoglobin. Adapted from Huettel et al. (2009a).

et al. 2004). This model shows that the signal decreases directly after neuronal activation, the initial dip. This is caused by an increased CMRO₂ and, thus, an increase of deoxyhemoglobin concentration. To correct for the oxygen consumption, CBF is increased after 1 or 2 s. An increase in oxygen due to an increased CBF causes a decreased deoxyhemoglobin concentration. This results in a total increase of the MR signal with a maximal response about 5 s after neuronal activation. Also CBV is increased, because the inflow of blood is initially larger than the outflow. CBV appears to be elevated for a longer period than CBF causing an increase in the total amount of deoxyhemoglobin. This reduces the fMRI signal, poststimulus undershoot (Buxton et al. 1998).

It should be noted that this model is a theoretical description of the expected mechanism of the BOLD response. In practice the shape of the HRF depends on stimulus conditions and varies between subjects, and even between brain regions (e.g. Handwerker et al. 2004; Aguirre et al. 1998; Conner et al. 2011; Siero et al. 2011; Rosa et al. 2010). Also negative responses have frequently been observed (Schridde et al. 2008; Smith et al. 2004; Shmuel et al. 2006; Jacobs et al. 2008), but the explanation of these negative responses is still a matter of debate.

### 1.3.2 Measurement of BOLD contrast

Most fMRI data are collected with an echo planar imaging (EPI) technique (Deichmann et al. 2010; Huettel et al. 2009d), which is an efficient way of $T₂$-weighted scanning in which images are typically acquired with a repetition time (TR) of 0.5 to 3 s. The spatial and temporal resolution of the fMRI data depend on several factors (Huettel et al. 2009a). The maximal possible spatial resolution is affected by the spatial relation between neuronal activity and the vascular system (Huettel et al. 2009a). In an optimal situation, signal changes are only related to the changes
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Figure 1.4: The theoretical HRF is the result of a combination of effects: increase in oxygen demand (CMRO$_2$), cerebral blood flow, and cerebral blood volume. Each have a different effect on the ratio of oxy- and deoxyhemoglobin, resulting in a response that is maximal about five seconds after the neuronal activation. Adapted from Deichmann et al. (2010)

in deoxyhemoglobin in the capillaries closest to the site of neuronal activation. However, also larger and more distant vessels can contribute to the MR signal. Generally, the spatial resolution is determined by the voxel size. The optimal voxel size is balanced between a good signal-to-noise ratio, which requires large voxels, and spatial resolution implying small voxels. A large spatial resolution is necessary to eliminate partial volume effects, which means that multiple tissue types may contribute to the MR signal of a given voxel. Although the voxel size cannot be infinitesimally small, the spatial resolution of fMRI is much better than that of EEG. Therefore, it is possible with fMRI to visualize activity from multiple sources and deeply situated cortex, such as mesial temporal structures.

The temporal resolution is mainly determined by the chosen TR (Huettel et al. 2009a; Kim et al. 2006): a shorter TR will in principle increase the temporal resolution. But choosing a shorter TR will decrease the number of slices that can be acquired within TR, thus decreasing the spatial resolution. After all, it is not possible to obtain a very high temporal resolution, because the hemodynamic response is much slower than neuronal activity ($\approx 5$ s, see Figure 1.4). Therefore, the temporal resolution of fMRI is always much lower than that of EEG.

To investigate a specific brain function, usually a task or a stimulus is presented
to the subject that triggers the phenomena one wants to investigate (Aguirre 2006; Huettel et al. 2009b). These studies are called paradigm-driven fMRI experiments. The most popular design is a blocked design, in which stimuli are presented in repeated blocks, typically in the order of tens of seconds. A second approach is an event-related design, in which stimuli are presented as very short individual events (in the order of milliseconds) (Josephs et al. 1997). The difference between these two approaches is that the first one has a higher detection power, whereas the second experimental design is better to estimate the shape of the HRF (Aguirre 2006; Liu et al. 2001; Liu et al. 2004; Dale 1999). Furthermore, a pseudo-random order of stimuli is often applied in event-related designs in order to reduce habituation effects in the subject (Liu et al. 2001).

The analysis of paradigm-driven fMRI experiments is based on the difference in BOLD signal between activation and baseline conditions. This contrast is typically formulated within a general linear model (GLM) framework, which is a model-driven approach to detect the brain regions that are significantly associated with the presented task or stimulus (Figure 1.5). In the presurgical evaluation, paradigm-driven fMRI is used to determine the location of the eloquent cortex (Duncan 2010). For that purpose, tasks and stimuli have been designed related to visual, sensorimotor, language, and memory functions (e.g. Richardson 2003; Chakraborty et al. 2008; Krakow et al. 2007; Binder et al. 2005). In theory, fMRI should also be able to detect the brain regions that are involved with the onset and propagation of epileptic activity, but epileptic activity occurs spontaneously and cannot be manipulated with a specific stimulus or task. However, in combination with EEG it appears to be a very suitable technique to delineate epileptic networks.

In contrast to paradigm-driven fMRI approaches are resting-state fMRI experiments during which the subject does not have to perform a specific task, such that spontaneous brain activity can be investigated. The subject is asked to relax and lie still with eyes closed, without thinking of something in particular (Cole et al. 2010). Resting-state data are analyzed with data-driven approaches (Cole et al. 2010) such as correlation analysis between fMRI signals of regions of interest or spatial independent component analysis (ICA) (Beckmann et al. 2004; Damoiseaux et al. 2006; Valente et al. 2010). So far, there are a few studies suggesting that these techniques are able to identify epileptic networks (LeVan et al. 2010a; Rodionov et al. 2007; Thornton et al. 2010b).

1.4 Simultaneous recording of EEG and functional MRI

1.4.1 Rationale of simultaneous EEG and fMRI

As explained in the previous sections, the main motivation for simultaneous recording of EEG and fMRI is to combine the best properties of these modalities: the high
Simultaneous recording of EEG and functional MRI

Visual stimulus paradigm

fMRI signals

Correlation Pattern

Figure 1.5: Example of a paradigm-driven fMRI experiment using a visual stimulus. A flickering checker board was presented to a subject for blocks of 20 s. The stimulus caused an increase in the fMRI signal of a voxel in the visual cortex. The result of the GLM analysis is a correlation pattern projected onto an anatomical MRI indicating which voxels were significantly associated with the stimulus.

temporal resolution of EEG and the high spatial resolution of fMRI (Salek-Haddadi et al. 2003; Herrmann et al. 2008; Laufs et al. 2008; Rosenkranz et al. 2010). This may sound as an ideal situation, but one has to realize that EEG and fMRI both measure different aspects of neuronal activity.

The most often used integration of EEG and fMRI is EEG-correlated fMRI, in which phenomena in the EEG are used to inform the fMRI analysis (Figure 1.6). With this approach the question can be answered which brain regions are associated with spontaneous brain activity visible in the EEG (Salek-Haddadi et al. 2003). As application in the presurgical evaluation, EEG-correlated fMRI could reveal the brain regions that are associated with the onset and propagation of epileptiform activity (Salek-Haddadi et al. 2003; Gotman et al. 2004), with a much better spatial resolution than when EEG is used alone and without the need for (complicated) source reconstruction models. Most studies to date focus on the correlation between the occurrence of IEDs and fMRI data, because seizures occur less frequently and large movements are usually involved. In that sense, the analysis of the data is similar to that of an event-related approach (section 1.3.2). Apart from this clinical application, EEG-correlated fMRI has been used to increase our understanding of the brain’s resting state (Salek-Haddadi et al. 2003; Laufs 2008), for instance to investigate the generators of the alpha rhythm (e.g. de Munck et al. 2007; Goldman
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Neuronal Activity

\[ \text{EEG signals} \quad \text{fMRI signals} \]

\[ \text{fMRI-informed EEG} \quad \text{EEG-correlated fMRI} \]

Figure 1.6: Neural activity can be indirectly measured with EEG and fMRI. Simultaneous recording of EEG and fMRI can be used in two approaches. First, fMRI is used to constrain the EEG data, fMRI-informed EEG. Second, the EEG information is used to analyze the fMRI data, EEG-correlated fMRI. Adapted from Kilner et al. (2005).

et al. 2002; Laufs et al. 2003a; Moosmann et al. 2003) and sleep phenomena (Schabus et al. 2007).

EEG-correlated fMRI is only one of the possible ways to integrate the information from simultaneous EEG and fMRI measurements. Another approach is using the fMRI data to inform the EEG data (fMRI-informed EEG, Figure 1.6). For example, active areas yielded by fMRI can be used as a constraint for dipole estimation (Bénar et al. 2010). This approach could also be an important application in the presurgical evaluation of epilepsy, but is beyond the scope of this thesis. In the remaining part of this thesis, the abbreviation EEG-fMRI will be used to indicate the EEG-correlated fMRI approach.

1.4.2 Technical aspects

EEG-fMRI cannot be performed with standard clinical EEG equipment, because this would compromise the patient’s safety, the quality of the EEG data, and the quality of the fMRI data (Allen 2010; Gutberlet 2010; Krakow et al. 2000). Therefore, the experimental set-up should meet certain requirements including special MR-compatible equipment developed from non-ferromagnetic materials (Ives et al. 1993). Figure 1.7 shows the set-up used for most EEG-fMRI recordings described in this thesis. The set-up is comparable to the set-up described by other institutions (e.g. Lemieux et al. 1997; Gotman et al. 2004; Laufs et al. 2008). The recordings are performed with a 3 T MR scanner of Philips (Medical Systems, Best, Netherlands) or a 1.5 T MR scanner of Siemens (Magnetom Sonata, Siemens, Erlangen, Germany), using EEG equipment of MicroMed (Treviso, Italy). The electrode wires are connected to an MR-compatible amplifier (SD MRI 64, MicroMed) placed as far as possible from the bore (Figure 1.7, 1). The amplifier is connected to a computer in the control room through a fiber optic cable (Figure 1.7, 2).
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The most important factors affecting both patient’s safety and the EEG quality are induced electromotive forces. These electromotive forces occur when current conducting loops are present during switching of the gradients and radiofrequency (RF) pulses and due to loop movements in the static field caused by small head movements or scanner vibrations (Lemieux et al. 1997). Although the presence of loops is inevitable when measuring EEG inside the MR scanner, the area of the loops and their movement should be kept to a minimum. For that purpose, the patient’s head is immobilized with foam pads (Figure 1.7, 3), electrode leads are bundled from the vertex of the head to the amplifier and are twisted for cancellation of induced currents (Figure 1.7, 4), and the leads are immobilized with sandbags (Figure 1.7, 5). To prevent tissue heating due to induced currents, current limiting resistors are placed directly after each electrode (Figure 1.7, 6) (Lemieux et al. 1997).

Although this set-up reduces the movement of electrode leads and the existence of loops substantially, the EEG is still obscured by artifacts related to the induced electromotive forces (Figure 1.8a). These artifacts can be divided into two types: artifacts related to fMRI acquisition and artifacts related to cardiac pulsation. The first type of artifacts is induced by the RF excitation pulse and switching of the gradients. Fortunately, the frequency of the RF pulses (> 1 MHz) exceeds the range of the normal EEG and can be filtered with adequate low-pass filtering (Stern 2006;
Eichele et al. 2010). However, the frequency of the artifacts related to the switching gradients (i.e. gradient artifacts) overlaps with the frequencies of the normal EEG and has an amplitude that is 10 to 20 times larger. Therefore, the first EEG-fMRI recordings were performed with a spike-triggered design (Lazeyras et al. 2000; Al-Asmi et al. 2003). In these recordings, fMRI acquisition started when an IED was observed in the EEG by an experienced EEG specialist. This method is obviously practically difficult, because someone has to review the EEG continuously on-line. Furthermore, no information is available about the EEG during the scanning period.

Since the gradient artifacts are directly related to the acquisition paradigm, the artifacts are to a large extent reproducible from scan to scan (Figure 1.8a). This led to the development of artifact removal techniques that can be applied off-line. Most algorithms are based on the so-called average subtraction algorithm (Allen et al. 2000), which computes a template of the artifact for each channel and removes that from the data. To make this possible, an accurate coupling is necessary between EEG and fMRI. In our case, this coupling is provided by a triggered pulse sent to the EEG acquisition computer. Furthermore, the sampling rate of the EEG needs to be sufficiently high to create a template which is reproducible from epoch to epoch (> 1 kHz). Figure 1.8b shows an example of an epoch that is corrected for the gradient artifacts.

The second artifact, the pulse artifact, or also called the ballistocardiographic artifact, is related to the pulsation of the heart (Debener et al. 2010a; Eichele et al. 2010). The artifact maximum has a delay of about 200 ms with respect to the R-peak in the electrocardiogram (ECG) (Figure 1.8b) (Laufs et al. 2008). The amplitude of the artifact is in the range of the physiological EEG (∼10 - 200 µV) and is larger in stronger magnetic fields (Debener et al. 2008). The underlying mechanism of the pulse artifact is not precisely known, but it is believed to be a combination of different effects (Eichele et al. 2010; Debener et al. 2010a). Some studies have demonstrated that the main contributor to the artifact is a short nodding head rotation related to the pulsatile flow (e.g. Nakamura et al. 2006; Yan et al. 2010). A second effect are slight movements of electrodes close to pulsatile blood vessels. Furthermore, changes in blood flow may induce currents that are present in the EEG (i.e. Hall effect). The pulse artifact may have different waveforms for different subjects, and is usually also different for each electrode lead due to their orientation in the magnetic field (Figure 1.8b). Furthermore, during the EEG-fMRI recording the shape of the artifact varies between heart beats due to differences in cardiac output, heart rate, or small movements of the patient.

Many algorithms exist that attempt to remove the pulse artifact. In general, the algorithms can be divided into two approaches (Debener et al. 2010a). The first approach is based on the subtraction of an artifact template (Allen et al. 1998), similar to the average subtraction algorithm used for gradient artifacts. More specifically, a template is created from the artifacts of successive heart beats (Figure 1.8b). The
Aim of the thesis

1.5. Aim of the thesis

From the moment that simultaneous acquisition of EEG and fMRI was technically feasible (Ives et al. 1993), EEG-fMRI has been applied to patients with epilepsy. The number of studies is still increasing. In general, EEG-fMRI studies demonstrate the promising value of EEG-fMRI in the presurgical evaluation: a significant BOLD area is often found in close proximity to the presumed epileptic focus (e.g. Bénar et al. 2002; Bagshaw et al. 2006; Salek-Haddadi et al. 2006; Zijlmans et al. 2007; Liu et al. 2008; Kobayashi et al. 2006b; Thornton et al. 2010a). However, the reported yield of EEG-fMRI varies between 50 and 100%, in which yield generally means the percentage of EEG-fMRI data sets that revealed meaningful results compared to other (non)invasive investigations of the patient. The variations in yield may have several explanations. For example, the yield of EEG-fMRI will be influenced partly by the type of patients that are included: a homogeneous patient group with a high spike rate in routine EEG or a heterogeneous group of complex patients with varying aetiology. Other explanations are differences in the analysis of the EEG and fMRI data and the precise definition used for the term "yield". EEG-fMRI methodology is still being improved and the clinical validation of the results has just started.

The general aim of the research proposed in this thesis is twofold: (1) to improve and (2) to evaluate the potential of EEG-fMRI as a new noninvasive tool in the presurgical evaluation of patients who are candidates for epilepsy surgery. Regarding the first aim, we addressed the following data analysis questions:

- What is the influence of the applied HRF model on the yield of EEG-fMRI?
- To what extent is the detection of epileptic networks with EEG-fMRI hampered by effects of non-interest, such as respiration and cardiac activity?
Figure 1.8: EEG recorded during fMRI scanning is obscured with artifacts (a). The largest artifacts are related to gradient switching. The insert shows the shape of the artifact of two EEG channels for one slice. These gradient artifacts can be removed by applying an average subtraction algorithm (b). Note that, the shape of the artifact is dependent on the protocol used and the type of MR scanner. The second type of artifacts are pulse artifacts (the maximum of the artifact is indicated with the blue marker) that are related to the pulsation of the heart. These artifacts are more variable in nature than the gradient artifacts. (c) shows the same epoch but now corrected for the pulse artifacts. An iED was annotated in this epoch by an EEG technician (black arrow).
With regard to the analysis of the EEG data, we observed that the correction of the current artifact removal approach (Gonçalves et al. 2007) was not sufficient for all EEG data sets. Therefore, also improvements of the EEG artifact correction algorithms were investigated.

The second aim of this thesis focuses on the evaluation of the EEG-fMRI results. It appears that the EEG-fMRI correlation pattern usually yields more activated brain regions than just one “epileptic focal area”. Therefore, we addressed the question how to interpret these activated brain regions. For instance, they could be related to onset and/or propagation of epileptic activity, and might thus represent an interictal epileptiform network. Finally, considering the importance of spatial ICA in resting-state fMRI analysis, we explored whether spatial ICA could contribute to the analysis of the fMRI data of patients with epilepsy, even when no IEDs are visible in scalp EEG.

1.6 Outline

The next three chapters of this thesis describe methodological improvements. In chapter 2, different analytical fMRI strategies are compared to detect the brain regions correlated with IEDs. The model with the highest level of concordance is used as EEG-fMRI analysis method in the remaining chapters of this thesis. In chapter 3, the effect of physiological noise (i.e. cardiac output and respiration) on the fMRI data was investigated. Since fMRI is based on the ratio of oxy- and deoxyhemoglobin, changes in fMRI signals may not only be related to neuronal activity, but also to physiological variations. We developed a method based on the pulse oximeter signal to correct for these effects. The topic of chapter 4 is the introduction of novel EEG artifact removal techniques. Starting from the average subtraction method, several improvements are made allowing, for example, to account for temporal overlap of subsequent pulse artifacts.

Chapter 5 and 6 focus on the systematic evaluation of EEG-fMRI in the presurgical evaluation. For this purpose, the EEG-fMRI findings are compared to invasive EEG recordings. The comparison between these modalities is complicated by their differences in temporal and spatial resolution. Chapter 5 presents a framework for a systematic comparison of the EEG-fMRI and invasive EEG findings tested in five patients implanted with depth electrodes. In chapter 6, this framework was applied to a group of 16 patients who underwent subdural grid and strip recording. In this group of patients, the EEG-fMRI findings were related to their interictal findings in the ECoG data, but also to the seizure onset zone and resection area.

Finally, chapter 7 presents preliminary results on the possible existence of an epileptic resting-state network identified from fMRI analysis with spatial ICA. For validation, the results of this data-driven technique are compared to the state-of-the-art EEG-fMRI analysis. The thesis ends with a general discussion and conclusions about the methodological and clinical implications of the results presented in this thesis.