TMS combined with fMRI

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Abstract

The work described in this thesis involves the concurrent application of Transcranial Magnetic Stimulation (TMS) and functional Magnetic Resonance Imaging (fMRI). The motivation for combining TMS and fMRI is provided by the potential for simultaneous manipulation of brain function using TMS and the detection of brain activity with a high spatial resolution using fMRI. The concurrent application of TMS and fMRI is challenging due to the strong influence of TMS on the process of magnetic resonance image formation and due to the problems related to the application of TMS inside the special environment of the MR-scanner.

In Chapters 1 and 2 some background information is given about MRI and TMS. Chapter 3 describes the experimental set-up, which was used in this project, including some tools which have been developed specifically for concurrent TMS/fMRI.

Chapters 4-6 address the technical challenges involved in the combination of TMS and fMRI. The static artefacts resulting from the presence of the TMS coil in the scanner are analysed in Chapter 4, while Chapter 5 focuses on the effects of TMS pulses on the process of image formation. The mechanisms involved in artefact production are characterised and the technical steps needed to limit the artefacts to acceptable levels are outlined. Chapter 6 provides an analysis of other technical aspects of the implementation of combined TMS/fMRI including the Lorentz forces on the TMS-coil, appropriate choice of receiver RF coils, and the ways in which MR-sequences can be made compatible with TMS pulse schemes.

Three different experimental studies involving combined TMS/fMRI are described in Chapters 7-9 of this thesis. These exploit the findings of the technical work described in the earlier experimental chapters. Chapter 7 presents an experimental study which was designed to probe the connections between left and right hemispheres. Although it proved difficult to address this question, the study usefully highlighted the difficulties associated with the practical implementation of combined TMS/fMRI studies on multiple subjects. Chapter 8 provides a demonstration of the feasibility of implementing concurrent TMS and arterial spin labelling. The results indicate that it is possible to measure event-related perfusion changes following supra-threshold TMS pulses applied at 0.1 Hz over motor cortex. Chapter 9 presents preliminary results of research in which combined TMS/fMRI is being used to monitor the effects of TMS on brain activity during execution of a simple motor task. Chapter 10 summarises the findings of the thesis work and highlights technical improvements which could benefit future experiments involving combined TMS/fMRI.
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Introduction

A chief objective in cognitive neuroscience is the identification of neural circuits underlying particular sensory, motor or cognitive processes. In the past 20 years there has been extensive progress in this field, which was in part made possible by the availability of new technologies for neuroimaging and brain stimulation.

One of the most widely used methods for neuroimaging is functional magnetic resonance imaging (fMRI) which allows detection of local changes in blood oxygenation. If these changes are correlated with periods of stimuli, there is a high likelihood that they reflect the underlying neuronal activity. Modern scanners operating at high magnetic fields allow the detection of brain activity with a spatial resolution of typically about 3 mm. A common form of presenting results of fMRI experiments are maps which show the likelihood that activity in each voxel was linked to a certain stimulus. These maps usually give a static picture and it is very difficult to isolate the contribution of each brain area and to decide at which point in a chain of causality each brain area is located.

Transcranial magnetic stimulation (TMS) is a non-invasive method for brain stimulation which can be used locally to perturb brain function or to change the excitability of the brain in a restricted region. Observable effects of TMS include for example, behavioural changes of the subject and muscle responses. Using techniques such as electroencephalography (EEG) can extend the range of the observable effects of TMS, but these techniques are still restricted because of their poor spatial resolution.

Combing TMS and fMRI is a promising approach to overcome the restrictions of each of the individual techniques. In experiments with fMRI, TMS can be used locally to perturb brain function of an active brain region. This can have an effect on the detectable pattern of brain activity where brain areas, that receive input from the perturbed region, show changes in activity. Since this approach reveals a contribution of the stimulated brain area to the ongoing brain function, it means
that TMS can extend the insight into brain activity given by fMRI data. Seen from the other side, fMRI allows the effects of TMS to be studied with a high spatial resolution. All these advantages taken together bring us to the conclusion:

*Concurrent TMS/fMRI is a very powerful tool for neuroscience.*

MRI requires a very homogeneous magnetic field over the area of the image. TMS on the other hand uses a strong and very inhomogeneous time-varying magnetic field to induce an electric field in the subject’s brain. This suggests that there is an intrinsic incompatibility between TMS and MRI.

Even if it is possible to combine TMS and fMRI, one must point out that fMRI is a technique, which produces results based on small changes in signal that are comparable in size to the noise. From this point of view we arrive at another conclusion:

*Concurrent TMS/fMRI is nearly impossible and not very promising. It’s not worth the effort.*

Both statements are exaggerated but they also have a true core. In this thesis many different aspects of concurrent TMS/fMRI are discussed with the conclusion that it is possible to combine both techniques, but there are also a range of difficulties involved in this combination.

This work presents the outcome of my PhD-project undertaken from 2006-2010 at the Sir Peter Mansfield Magnetic Resonance Centre (SPMMRC) at the University of Nottingham. The project was a collaboration with Professor Tomas Paus and Dr. Jamila Andoh from the Brain and Body Centre at the University of Nottingham.

My work covered many specific aspects of experiments with concurrent TMS/fMRI. When I started with my PhD, there was no set-up for concurrent TMS/fMRI and no one had worked on this combination before I arrived. Thus I had to start from scratch, but I could benefit from the excellent knowledge of MRI at the SPMMRC and from the experience of TMS available of the Brain and Body centre.

Part I of this thesis gives an overview of the techniques of MRI and TMS and of the set-up we have been using. My work of concurrent TMS/fMRI can be organised into three different areas which are covered by Part II and III of this thesis:

- Analysing and understanding how TMS and MRI influence each other
• Developing and improving a set-up for concurrent TMS/fMRI

• Experiments on human subjects using concurrent TMS/fMRI

The first area focuses on the imaging artefacts which occur when TMS is used inside an MR-scanner. Here a distinction is drawn between artefacts, which are constant over time and artefacts which occur only when TMS pulses are applied. Also restrictions for MR-imaging due to the presence of the TMS-coil are discussed.

The second area covers important practical problems of this combination such as how to position the TMS-coil over the target site inside the MR-scanner.

The third area is discussed in Part III. Three different experiments are presented and discussed. Besides the actual outcome of these experiments, they are also used to demonstrate the difficulties which occur when running experiments with concurrent TMS/fMRI. In the Appendix a detailed description is given of how to plan, prepare and run experiments with concurrent TMS/fMRI.
Part I

Theory and Background

Information
Chapter 1

Magnetic Resonance Imaging

Introduction

This chapter gives a short introduction to the principles of magnetic resonance imaging. Firstly Section 1.1 briefly summarises the principles of Nuclear Magnetic Resonance (NMR). In Section 1.2 it is explained how it is possible to use these concepts for imaging. Since these concepts have been described in a wide range of literature (e.g. Bernstein et al. [2004], Hashemi et al. [2004]) this chapter is kept short.

1.1 Nuclear Magnetic Resonance

NMR is a phenomenon which depends upon the alterations of the energy levels of nuclei due to the presence of an external magnetic field. The origin of these alterations is the coupling between the dipole moment $\mu$ of the spin of the nucleus and the applied magnetic field. The energy level of each spin is given by

$$E = -\mu \cdot B_0 = -\gamma \hbar m_z B_0$$  \hspace{1cm} (1.1)

In this equation $B_0$ is the applied magnetic field assumed to be in the $z$-direction, $m_z$ the quantum number describing the angular momentum in the direction of the applied field and $\gamma$ the magnetogyric ratio, which varies for different nuclei. $m_z$ can take values of $-I$ to $+I$ where $I$ is the spin quantum number of the nucleus. Only nuclei with $I > 0$ are suitable for NMR. A list of nuclei commonly used in NMR is given in Table 1.1. Since only MRI of hydrogen nuclei ($I=1/2$)
Table 1.1: Properties of nuclei used for NMR

<table>
<thead>
<tr>
<th>nucleus</th>
<th>spin, I</th>
<th>γ(MHz/T)</th>
<th>natural abundance (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^1$H</td>
<td>1/2</td>
<td>42.58</td>
<td>99.8</td>
</tr>
<tr>
<td>$^{13}$C</td>
<td>1/2</td>
<td>10.71</td>
<td>1.11</td>
</tr>
<tr>
<td>$^{14}$N</td>
<td>1</td>
<td>3.08</td>
<td>99.6</td>
</tr>
<tr>
<td>$^{23}$Na</td>
<td>3/2</td>
<td>11.26</td>
<td>100</td>
</tr>
<tr>
<td>$^{31}$P</td>
<td>1/2</td>
<td>17.24</td>
<td>100</td>
</tr>
</tbody>
</table>

is covered in this thesis, the other nuclei are not discussed any further here.

The shift in the energy level due to the magnetic field has implications which are important for understanding the principles of NMR.

1.1.1 Boltzmann distribution

The Boltzmann distribution describes the ratio of the populations of different energy states as a function of the energy difference $\Delta E = E_{\text{up}} - E_{\text{down}}$ and of the temperature $T$. Applied on populations of different spin levels $N_{\text{down}}$ and $N_{\text{up}}$ of the same type of nuclei, the equation can be expressed as

$$\frac{N_{\text{down}}}{N_{\text{up}}} = e^{-\frac{\Delta E}{k_B T}},$$

where $k_B = 1.38 \times 10^{-23} J K^{-1}$ is the Boltzmann constant. For hydrogen nuclei at 300 K and at $B_0 = 1$ T the population difference is approximately 6 ppm which means for 1,000,000 nuclei in the higher energy state there are 1,000,006 nuclei in the lower energy state. This small population difference is responsible for the NMR-signal. A higher magnetic field or a lower temperature can be used to produce a stronger signal. In clinical imaging a significant decrease in temperature is not an option and therefore a higher field strength is the best option for achieving a higher NMR-signal. The net effect of the population difference is to produce a small magnetisation of the sample.
1.1.2 Larmor Frequency and Bloch equations

In hydrogen nuclei, the allowed values of $m_z$ are 1/2 or -1/2. The energy difference between these two spin states therefore becomes (Equation 1.1)

$$\Delta E = \gamma \hbar B_0.$$  (1.3)

This energy difference is associated with a frequency difference

$$\omega_L = \Delta E / \hbar = \gamma B_0,$$  (1.4)

which is called the Larmor-frequency. $\omega_L$ describes the resonance frequency between the two energy states. If the direction of the external magnetic field is changed instantaneously, the magnetisation has a component perpendicular to the magnetic field which is called the transverse magnetisation. This transverse magnetisation starts precessing around the magnetic field at the Larmor frequency under a constant angle. This behaviour results from the torque experienced by a magnetic dipole moment in an external field and can be described by the Bloch equation omitting relaxation terms:

$$\frac{dM}{dt} = \gamma M \times B.$$  (1.5)

The equation can also be expressed in a frame which rotates at angular frequency $\gamma B$ around the z-axis. The transverse components of $M$ which oscillates with $\omega_L$ become stationary in this rotating frame.

If we now add a transverse (perpendicular to $B_0$) radiofrequency (RF) field, $B_1$, with a frequency of $\omega_L$, the magnetisation starts oscillating in the rotating frame around an axis perpendicular to $B_1$ and to the z-axis with an angular frequency of $\Omega = \gamma B_1$.

This RF-field applied over a duration of $\tau$ tips the magnetisation towards the transverse plane through an angle of $\alpha = \Omega \tau$. If it is applied over a duration of $\tau = \pi / \Omega$, it inverts the net magnetisation.

1.1.3 Relaxation

The macroscopic magnetisation has an equilibrium value of $M_0$ aligned with the direction of the applied field $B_0$ i.e. the z-axis. The application of an RF-pulse can lead to transitions of the spins resulting in a non-equilibrium number of parallel and anti-parallel spins and a net transverse magnetisation. The spin population returns to equilibrium by two different processes. Spin-lattice
relaxation returns the longitudinal magnetisation to equilibrium and the spin-spin relaxation process acts to attenuate the transverse magnetisation. Therefore, the evolution of the magnetisation can be described by the Bloch-equations including relaxation terms as

$$\frac{dM}{dt} = \gamma M \times B - \frac{e_x (M_z - M_0)}{T_1} - \frac{e_y M_x + e_z M_y}{T_2},$$

(1.6)

where $T_1$ is the spin-lattice relaxation time, which describes the recovery of the longitudinal magnetisation while $T_2$ is the spin-spin relaxation time, which describes the decay of the transverse component of the magnetisation, $M_{xy}$ ($e_x$, $e_y$ and $e_z$ are Cartesian unit vectors).

**Longitudinal spin-lattice relaxation**

Longitudinal relaxation occurs as a result of the exchange of energy between the spin system and the lattice. At equilibrium the magnetisation takes the value $M_0$, but for example RF-pulses can change this value to a value $M_z(0) \neq M_0$. The magnetisation will then return to equilibrium described by

$$M_z(t) = M_0 - (M_0 - M_z(0))e^{-t/T_1}.$$  

(1.7)

A 90° RF-pulse flips the whole magnetisation into the $xy$-plane resulting in $M_z = 0$ directly after the RF-pulse, while a 180° pulse reverses the magnetisation which results in $M_z = -M_0$. At a time of $t = \ln(2)T_1$ after the application of a 180° RF pulse the longitudinal magnetisation passes through zero, with the result that at this point in time the MR-signal produced by a 90° RF pulse is suppressed.

The value of $T_1$ varies over different tissues and with magnetic field strength. At 3T the values for white matter, gray matter and cerebrospinal fluid (CSF) were found to be 840±50 ms, 1500±200 ms and 4300±200 ms respectively (Rooney et al. [2007]).

**Transverse relaxation**

The transverse magnetisation is in phase directly after an RF-pulse. The coherent precession of the spins is the origin of the MR-signal. The amplitude of the magnetisation decays to zero from its initial value $M_{xy}(t = 0)$ as:

$$M_{xy}(t) = M_{xy}(0)e^{-t/T_2}.$$  

(1.8)

$T_2$-decay results from spin-spin interactions, which lead to a loss in coherence of the transverse magnetisation.
In practice, the NMR signal decays faster than predicted by the $T_2$ relaxation alone. The accelerated decay rate is characterised by the relaxation time $T^*_2$, which is given by

$$\frac{1}{T^*_2} = \frac{1}{T_2} + \frac{1}{T_2'},$$  

where $T_2'$ accounts for dephasing arising from inhomogeneity in the magnetic field, $B_0$. Such inhomogeneity is often caused by the different magnetic susceptibilities of different tissues. Such $T^*_2$ contrast can therefore indicate local changes in the susceptibility.

The values of $T_2$ in white and grey matter at 3T are around 110 ms and 80 ms respectively (Wansapura et al. [1999]) and for $T^*_2$ around 66 ms and 53 ms (Peters et al. [2007]).

$T^*_2$-contrast can be generated by using Gradient Echo (GE) acquisition methods with echo times which are similar to $T^*_2$.

$T_2$ contrast can be achieved by using Spin Echo (SE) acquisition methods, which apply a $180^\circ$ pulse at half of the echo time, thus reversing the precession of the spins so that they return to the starting point when they were in phase at the echo time. At this point in time the influence of $T_2'$ decay is eliminated.

### 1.1.4 NMR-signal

If a sample has a net transverse magnetisation $M_{xy}$, it produces RF-signal at the Larmor-frequency. To achieve this, an RF-pulse can be applied to a sample with a non-zero longitudinal magnetisation. A $90^\circ$ pulse for example flips the entire magnetisation into the transverse plane. Once the RF-field is switched off, the signal is in phase and it can be observed in the form of a Free Induction Decay (FID), which can be detected by a receiver coil. This FID fades away with time as described by

$$S(t) = S(0)e^{-t/T_2}e^{i(\Delta \omega t + \phi)},$$  

(1.10)

where $\Delta \omega$ is the frequency offset $\omega_0 - \omega_{ref}$ and $\phi$ is the reference phase.

In MR-spectroscopy this kind of acquisition is often used. Taking the Fourier-spectrum of the signal can reveal different compounds in the sample, which have different values of $\Delta \omega$. For imaging, this kind of acquisition is insufficient, because it does not reveal the spatial location of the signal.
1.2 Spatial encoding

To distinguish between the strength of the NMR-signal from different areas in a volume, methods for spatial encoding are applied. All these methods have in common, that they use magnetic field gradients, which penetrate freely through the sample and which allow manipulation of the NMR-signal. During the whole process the main $B_0$-field of the scanner stays stable. The three orthogonal linear field gradients coils ($G_x$, $G_y$ and $G_z$) are designed to produce a total field gradient

$$ G = e_x G_x + e_y G_y + e_z G_z. \quad (1.11) $$

The $z$-component of the magnetic field at point $r$ is then given by

$$ B_z = B_0 + G \cdot r. \quad (1.12) $$

This introduces a spatial dependence to the Larmor frequency of the precessing spins in the sample:

$$ \omega(x, y, z) = \gamma (B_0 + xG_x + yG_y + zG_z). \quad (1.13) $$

Three different methods for signal localisation using these field gradients are introduced in the following sections.

1.2.1 Slice Selection

Slice selection is a technique, which is applied during the excitation with an RF-pulse. When a gradient is applied, spins in each layer perpendicular to the gradient direction have a different Larmor frequency. An RF-pulse of only a single pure frequency would then only excite an infinitesimally thin layer of the sample. If an RF-pulse, which covers a bandwidth of $\Delta \omega$, is applied a slice with a thickness of $\Delta z$ is excited by the pulse, where $\Delta z$ is given by

$$ \Delta z = \frac{\Delta \omega}{\gamma G_z}. \quad (1.14) $$

$G_z$ is the strength of the gradient in the direction of the slice selection.

An RF-pulse with a rectangular shape in the frequency domain has the form of a sinc-function ($\text{sinc}(t) = \frac{\sin(t)}{t}$) in the time-domain. An RF-pulse which approximates a sinc-shaped waveform is often therefore used for slice selection. After the slice selection, the gradient is reversed and applied over half the time to bring the spins of the whole slice back into phase.
1.2.2 Frequency encoding

The frequency encoding process is very similar to the slice selection process, with the difference that the gradient is applied during the signal read-out. As a result spins at different positions in the frequency encoding direction have different Larmor frequencies. The acquired signal is the combination of the signals at all these different frequencies. Using a Fourier transformation, the signal can be split again into the frequency components which then can be assigned to different locations in the frequency encoding direction.

Normally the frequency encoding direction is perpendicular to the slice selection direction. The frequency encoding gradient is also called the read-out gradient, because it is applied during the signal acquisition.

The frequency

\[ \Delta \nu_R = G_x \text{Res}_x \frac{\gamma}{2\pi} \]  

is called the bandwidth per voxel where \( G_x \) is the gradient strength and \( \text{Res}_x \) is the resolution in the read-out direction.

1.2.3 Phase encoding

The phase encoding gradient is applied before the read-out in a direction which is perpendicular to the slice selection and to the frequency encoding gradients. This gradient changes the Larmor frequency over a short period of time. Because the gradient is switched off again, it does not change the frequency of the signal that is acquired in the read-out period, but it adds a phase offset which varies across different locations in the slice. By repeating the phase encoding step \( n \) times, each time followed by a frequency encoding step, it is possible to distinguish between \( n \) different locations in the phase encoding direction. Since the three encoding directions are perpendicular to one another, it is possible to create a 3D spatial map of the origin of the NMR-signal.

1.3 Image Reconstruction and k-space

The received signal is the sum of the signals arising from different locations in the sample and therefore

\[ S(t) \propto \int_V \rho(r) e^{i \int_0^t \omega_L(r,t') dt'} dV, \]  

(1.16)
where $V$ is the sample volume and $\rho(r)$ is the amplitude of the received RF-signal from the location $r$. The phase of the signal can be described by the integral of the orthogonal gradients $G_x$, $G_y$, $G_z$ over time

\[
S(t) \propto e^{i\omega_0 t} \int_V \rho(r)e^{i\gamma \int_0^t r \cdot G(t')dt'}dV,
\]

where $G(t') = e_x G_x(t') + e_y G_y(t') + e_z G_z(t')$. Since the contribution of the static magnetic field $B_0$ to the Larmor frequency can be taken out of the integral, the signal is demodulated by the central Larmor frequency, which eliminates the first term $e^{i\omega_0 t}$ of Equation 1.17. Defining

\[
k(t) = \gamma \int_0^t G(t')dt',
\]

where the space that $k(t)$ resides in is known as k-space, reduces Equation 1.17 to

\[
S(t) \propto \int_V \rho(r)e^{i\mathbf{r} \cdot k(t)}dV.
\]

This equation is now in the form of a 3D-Fourier transform. Using appropriate gradient adjustments which are synchronised with the acquisition, k-space can be filled with information. The result is a map, $S(k)$. An inverse Fourier transform applied to $S(k)$ reconstructs $\rho(r)$, which is a map of the strength of the NMR-signal. This is the basic concept of MRI.

**k-space**

These considerations show, that knowing the precise timing of the gradients defines $k(t)$. Therefore it is possible to acquire the signal during gradient switching and then to relate each sample to a different point in k-space. The frequency encoding and the phase encoding gradients are used to cycle through k-space and to fill it in a way which is appropriate for the desired image properties. The concept behind the frequency encoding and the phase encoding gradients is basically identical. The difference is their direction in space and that the frequency encoding gradient cycle traverses in one direction of k-space during the acquisition. The phase encoding gradient changes the position along a perpendicular direction before each readout. It should be noted, that phase encoding can be applied along more than one axis.

The separation of the data points in k-space $\Delta k$ defines the FOV of the image:

\[
\Delta k_{x,y,z} = \frac{1}{FOV_{x,y,z}}.
\]
Figure 1.1: Image space and k-space for an image slice which consists of $8 \times 8$ voxels.

Figure 1.2: Foldover of the image in phase encoding direction (along the x-axis). $N$ phase encoding steps are applied and the $n$th step induces a phase offset $\Delta \phi = 2\pi n/N$ at location $i$ along the x-axis. At location $i + N$ which is outside the FOV the phase offset is $\Delta \phi = 2\pi (i + N)n/N$. Since this phase offset is exactly $n2\pi$ higher compared to the phase offset at location $i$ the signal from both locations appears at the same location in the reconstructed image.
The extent of k-space spanned by the \( N_{x,y,z} \) points in each direction defines the resolution \( \text{Res}_{x,y,z} \) of the image:

\[
N_{x,y,z} \Delta k_{x,y,z} = \frac{1}{\text{Res}_{x,y,z}}.
\]  

(1.21)

A diagram of the k-space and the image space is shown in Figure 1.1. If the points of the k-space are not close enough to each other, the FOV in the phase encoding direction may not cover a large enough spatial extent. This happens because the phase information is only defined to values varying between \(-\pi\) and \(\pi\). Adding multiples of \(2\pi\) to the phase leads to an equivalent information. Tissue outside the FOV experiences with each phase encoding step exactly the same phase offset as a point inside the FOV plus a multiple of \(2\pi\). In this case the signal from the tissue outside the FOV appears in the image on the opposite side in the phase encoding direction (Figure 1.2). The image looks like an overlay of different images. This kind of image perturbation is called a fold-over artefact. Thus the phase-encoding direction is also called fold-over direction.

Since in the read-out direction the separation of points in k-space is only limited by the sample frequency of the signal detector, fold-over artefacts can be dealt with by extending the FOV in the read-out direction and discarding the parts of the image which are not required.

### 1.4 MR-sequences and contrasts

An MR-sequence is a certain arrangement in time between RF-pulses, gradient pulses and acquisition periods. The particular arrangement is responsible for the contrast and for the time requirements of each acquisition. There are different timing parameters which are used to characterise a sequence:

- **TR**: Repetition time, time between two identical RF-excitations.
- **TE**: Echo time, time between the RF-excitation, which produces the transverse magnetisation and the acquisition of the centre of k-space in the read-out direction.

Sequences are often illustrated using sequence diagrams, which display in different rows the RF-pulses, the strength of each of the gradients and the time of signal acquisition. There is a wide range of different MR-sequences. The sequences used for this thesis are explained in the following sections.
CHAPTER 1. MAGNETIC RESONANCE IMAGING

Figure 1.3: Sequence diagram of an MP-RAGE sequence (Sanchez [2009]). The longitudinal magnetisation is prepared using an inversion pulse with an inversion time $T_I$ before the beginning of a train of rapid GE acquisitions with the read-out gradient applied in the x-direction. The phase encoding is varied along the y-direction in between these acquisitions, while the phase encoding in the z-direction remains the same. The train is repeated $N_{3D}$-times but with different strength of the phase encoding gradient in the z-direction.

1.4.1 MP-RAGE

MP-RAGE stands for magnetisation prepared rapid gradient echo (Mugler and Brookeman [1990]), also known as 3D-FFE (3D fast field echo). This sequence is a 3D-sequence, which means that every slice selective RF-pulse excites more than one slice and the following phase encoding is applied in two orthogonal directions. The sequence consists mainly of fast consecutive RF-pulses with a low flip angle $\alpha$, each exciting the whole FOV. Each RF-pulse is followed by a GE-readout with a short TE. Typical values for TE, TR and $\alpha$ are 5 ms, 10 ms and 10 degrees respectively. The mixture of short TE and short TR (in this case the time between two RF-pulses) leads to a $T_1$-weighted image. The sequence is split into trains of these RF-pulses with a duration of typically several seconds. At a time $T_I$, before each train an $180^\circ$ RF-pulse is applied to prepare the magnetisation for contrast enhancement. The sequence diagram for this sequence is shown in Figure 1.3. Since this sequence is mostly $T_1$-weighted, tissues with longer $T_1$ relaxation times appear darker in the images because the z-component of the magnetisation requires more time to recover. Thus white matter ($T_1 \approx 840$ ms) appears brighter than grey matter ($T_1 \approx 1500$ ms) whereas signal from CSF ($T_1 \approx 4300$ ms) is very small. This sequence is therefore used for anatomical brain imaging with a medium to high resolution. The acquisition of a whole head image with 1mm$^3$ resolution takes
1.4.2 EPI

EPI, which stands for echo planar imaging, is an imaging method which was first proposed by Mansfield [1977]. The idea behind this technique is to acquire the whole k-space of a single slice after a single RF-excitation. This is achieved by applying a number of readout steps, which equals the matrix size in the phase encoding direction, after the excitation of the slice. The readout gradients are applied with alternating directions. Between two readout steps a phase encoding gradient is applied. During each readout, one line in k-space is filled and each phase encoding step shifts this line in the phase encoding direction in k-space. The advantage of this imaging technique is that it acquires a whole slice in a very short period of time (e.g. 50 ms). The image of a whole head can therefore be acquired within 3 seconds by repeatedly exciting and imaging successive slices. The period of acquisition after each RF-pulse typically lasts tens of ms, because each readout step requires some time. The TE in EPI is defined as the time between the RF-pulse and the acquisition of data at the centre of k-space. TR in EPI is the time between the acquisition of two identical slices, which is usually the time in which one volume is acquired. EPI has a long TR and a long TE. Therefore GE-EPI is $T_2^*$-weighted and SE-EPI is $T_2$-weighted.
EPI is sensitive to different artefacts. Asymmetries in the fast alternating readout gradients cause 'ghosting' artefacts, which appear as a copy of the image, shifted by half the FOV in the phase encoding direction. The long TE in GE-EPI causes a signal 'drop-out' in areas where there are inhomogeneities in $B_0$. This results from signal dephasing across the voxel.

These inhomogeneities also cause an additional local phase offset between readout steps. This leads to a shift of the voxels in the phase-encode direction, which is proportional to the offset in $B_0$ and to the duration of the acquisition train. In Section A.4 a method is presented, which simulates the acquisition and the image reconstruction of EPI. This method is also able to simulate the artefacts due to the causes described above.

EPI is often used, when it is required to acquire images rapidly and repetitively. One of the most important applications of EPI is functional Magnetic Resonance Imaging (fMRI) with Blood Oxygenation Level Dependent (BOLD) contrast. A typical resolution of EPI is $3 \times 3 \times 3\text{mm}^3$ (Jezzard et al. [2003]).

### 1.5 Special contrasts

MR-sequences can be used to produce contrasts, which are not related to the relaxation times of the different tissues. In the following some of these contrasts are explained.

#### 1.5.1 Perfusion imaging

MRI can be used to measure perfusion by using the magnetisation of blood as a tracer. This type of MR-imaging is called Arterial Spin Labelling (ASL). In ASL RF-pulses are used to modulate the state of the longitudinal magnetisation of arterial blood. This magnetisation recovers with a rate described by Equation 1.7. The value of $T_1$ for arterial blood is about 1660 ms at 3T (Lu et al. [2004]). This is also roughly the time-frame during which the labelling has a strong effect on a consequent image acquisition.

ASL sequences use inversion pulses to label the magnetisation of blood outside of the FOV and then acquire the image with a fast imaging technique such as EPI. Between the labelling and the acquisition there is a delay which allows the labelled blood to flow into the imaging area. The water in magnetically-labelled blood exchanges in the capillary bed and as a result the longitudinal magnetisation in the tissue is modified by an amount which depends on perfusion. The change
in magnetisation affects the amplitude of an acquired image. This acquisition is then repeated, but with a different area affected by the labelling. Subtracting the two images from one another reveals the blood which was labelled in one of the images and but not labelled in the other image. The difference image can then be used to determine the amount of cerebral blood flow (CBF). The signal change is usually small and averaging over several repetitions is usually required in order to achieve a reliable map of perfusion.

For the experiments described in Chapter 8 of this thesis we used a Flow sensitive Alternating Inversion Recovery (FAIR) sequence (Gardener et al. [2009]). For the labelling (Label) condition a non-selective inversion pulse is applied followed after a delay by an image acquisition of a relatively small area of the volume. The non-labelled (Control) condition is similar with the only difference being that a slice selective inversion pulse is applied which covers a little more than the extent of the imaged region in the slice select direction. Typical coverages of the Label and Control slabs are shown in Figure 1.5.

The signal intensity of the whole image is reduced because of the inversion pulse. The only contribution to the signal which is not affected by the inversion pulse is the inflowing blood from outside of the inverted area of the Control condition. This non-labelled blood produces a stronger signal in the Control images compared to Label images resulting in a higher signal from regions with more perfusion. The time between the inversion pulse and the acquisition, which is called the inversion time (TI), is important for the perfusion contrast. The inversion time must be

**Figure 1.5:** Coverage of the ASL sequence. The grey area is a sagittal view of the ASL image before subtraction. The areas covered by the large boxes are the areas affected by the inversion pulse of Label and Control respectively.
Figure 1.6: Diagram showing a FAIR-ASL sequence. The diagram presents the image acquisition which follows a non-selective inversion pulse. This is followed by the same sequence, but with a selective inversion pulse. The only difference between both parts is the strength of the slice selection gradient used during the inversion.

long enough to allow the blood to flow into the small vessels of the brain where exchange occurs. Making it too long decreases the effect of the labelling since the longitudinal magnetisation recovers to equilibrium.

This type of sequence was introduced by Kim [1995], who also described how it can be used to quantify CBF.

The sequences used in this thesis used a double-echo GE-EPI acquisition. Although the second echo of the acquisition produces a significantly weaker signal than the first one, it has a longer TE and therefore it can be used for BOLD-contrast (Section 1.6.1). A simplified diagram of the sequence is shown in Figure 1.6.

1.5.2 $B_0$-mapping

The $B_0$-field is not entirely uniform and any materials with a magnetic susceptibility $\chi_m \neq 0$ cause additional field perturbations. It is possible to measure these inhomogeneities using the phase of GE-images. In the following the different steps needed for this process are outlined.
CHAPTER 1. MAGNETIC RESONANCE IMAGING

Theory

The frequency of precession depends on the external magnetic field $B_0$ and the gyromagnetic ratio $\gamma$:

$$\omega_0 = B_0 \gamma.$$  \hfill (1.22)

Directly after the RF-pulse in the sequence all the transverse magnetisation is in phase, but because of inhomogeneities $\Delta B_0(r)$ of the external magnetic field this magnetisation in different regions precesses with slightly different frequencies.

The signal is measured at a time $T_E$ after the RF-excitation. The phase difference at time, $T_E$ of the signals from a point $r$ relative to a reference point $r_0$ can be calculated from:

$$\Delta \phi(r) = T_E (\Delta B(r) - \Delta B(r_0)) \gamma.$$  \hfill (1.23)

The phase of the reconstructed image gives $\Delta \phi(r)$. The phase is only defined in the range $-\pi$ to $\pi$, so values outside this range are wrapped back inside it.

Under ideal conditions the phase is only dependent on $T_E$, the magnetic field $B_0 + \Delta B$ and the gyromagnetic ratio $\gamma = 2.675 \times 10^8 s^{-1} T^{-1}$. The relationship between $\Delta B$ and the phase $\phi$ is relative to a reference location with $\Delta B_0 = 0$ is given by

$$\Delta B(r) = \frac{\Delta \phi(r)}{\gamma T_E}$$  \hfill (1.24)

Data Processing

In the first step the phase-maps must be unwrapped which means that the borders where the value of the phase-image jumps from $-\pi$ to $\pi$ must be eliminated to achieve a well defined map. Therefore first the regions of the original image where the phase lies within a range of $(-\pi$ to $\pi)+2\pi$ must be identified. Afterwars a different multiple of $2\pi$ is added to each of them so that the whole phase map in all 3 dimensions becomes smooth with no phase wraps (Figure 1.7). A C-program was used to generate these unwrapped images (Mougin [2007]).

A double echo GE sequence, which takes for every RF-pulse the same line in k-space with different $T_E$ ($T_{E1}$ and $T_{E2}$) can be applied. By taking the difference in phase between the two images and evaluating $T_{E2} - T_{E1} = T_{ED}$ a reliable map of $B_0$ can be generated.

The unwrapped phase maps of two images of the same object with different $T_{ED}$ are taken and subtracted. The resulting value after a division by $T_{ED}$ multiplied by $2\pi$ is the shift in the Larmor-frequency in Hz.
To determine the influence of an additional object on the $B_0$-field, a reference phase map is first produced without the object. Afterwards, the object is introduced and a second image is made. The difference between the two phase maps allows additional disturbances to be identified.

1.5.3 $B_1$-mapping

The field of the RF-pulses is also called the $B_1$-field. This field becomes increasingly inhomogeneous at higher $B_0$ field strengths. The strength of the $B_1$-field dictates the flip angle and therefore has an effect on images.

It is possible to measure the flip angle by comparing the signal strength of different images. In the following section it will be shown how this can be done. The sequence which was used is a pulsed steady state sequence with two different repetition times $TR_1$ and $TR_2$ (Figure 1.8), (Yarnykh [2007], Yarnykh [2010]).

The calculation of the steady state solution and the acquired signal intensities is based on the assumption that:

$$TR_{1,2} \gg T_2^*$$  \hspace{1cm} (1.25)

First we look at the longitudinal magnetisation at the points in the sequence where:

$t = \tau_{1-}, \ t = \tau_{1+}, \ t = \tau_{2-}$ and $t = \tau_{2+}$. 

\[Figure 1.7: \] Left: wrapped phase image with values from $-\pi$ to $\pi$. Right: corresponding unwrapped image is shown.
Figure 1.8: Pulse sequence used to measure the flip angle, which is related to the strength of the RF-field. It uses of two identical RF-pulses with a flip angle $\theta$. The signal is acquired at time $TE$ after each of the pulses. The repetition time between two RF-pulses is $TR_1$ or $TR_2$. The relation between the time constants is as follows: $T_2 \ll TR_1 < TR_2 \ll T_1$. The signal strength can be calculated with a steady state solution.

For the magnetisation before the beginning of a cycle we assume:

$$M(\tau_{1-}) = (M_0 - M_b) \begin{pmatrix} 0 \\ 0 \\ 1 \end{pmatrix}$$  (1.26)

Since the transverse component of the magnetisation is zero (with Equation 1.25), $M$ can be treated as a scalar and we can calculate only the the $z$-component of the magnetisation. The following substitutions are made in the formulae:

$$K = e^{-\frac{TE}{T^*_2}}$$ \hspace{1cm} (1.27)

$$E_{1,2} = e^{-\frac{TR_{1,2}}{T_1}}$$ \hspace{1cm} (1.28)

After the first RF-pulse with the flip angle $\alpha$ the longitudinal magnetisation becomes

$$M(\tau_{1+}) = \cos(\alpha)(M_0 - M_b)$$  (1.29)

and after the relaxation time $TR_1$

$$M(\tau_{2-}) = M_0 - E_1(M_0 - \cos(\alpha)(M_0 - M_b)).$$  (1.30)

By repeating these two steps with $TR_2$ we get again to the beginning of the sequence

$$M(\tau_{2+}) = \cos(\alpha)(M_0 - E_1(M_0 - \cos(\alpha)(M_0 - M_b)))$$  (1.31)

$$M(\tau_{1-}) = M_0 - E_2(M_0 - \cos(\alpha)(M_0 - E_1(M_0 - \cos(\alpha)(M_0 - M_b)))) = M_0 - M_b.$$  (1.32)
Therefore the steady state solutions for the longitudinal magnetisation at the times $\tau_1$ and $\tau_2$ are:

\begin{align*}
M(\tau_1) &= \frac{(1 - E_2) + (1 - E_1)E_2 \cos \alpha}{1 - E_1 E_2 \cos(\alpha)} \tag{1.33} \\
M(\tau_2) &= \frac{(1 - E_1) + (1 - E_2)E_1 \cos \alpha}{1 - E_1 E_2 \cos(\alpha)} \tag{1.34}
\end{align*}

The signal intensities become

\begin{align*}
S_1 &= K \sin(\alpha) M(\tau_1) \tag{1.35} \\
S_2 &= K \sin(\alpha) M(\tau_2) \tag{1.36}
\end{align*}

and their quotient is

\begin{equation}
\frac{S_1}{S_2} = \frac{(1 - E_2) + (1 - E_1)E_2 \cos(\alpha)}{(1 - E_1) + (1 - E_2)E_1 \cos(\alpha)}. \tag{1.37}
\end{equation}

$TR_1 = R \cdot TR_2$ using the assumption $TR_{1,2} \ll T_1 \tag{1.38}$

results in

\begin{align*}
E_{1,2} &\approx 1 \tag{1.39} \\
(1 - E_1) &= R(1 - E_2). \tag{1.40}
\end{align*}

Solving the equation for $\alpha$ leads to:

\begin{equation}
\alpha = \cos^{-1} \left( \frac{R \frac{S_1}{S_2} - 1}{R - \frac{S_1}{S_2}} \right) \tag{1.41}
\end{equation}

With the assumptions described in Equations (1.25) and (1.38), the flip angle can be calculated by finding the quotient of the two different signals and the measurement is independent of $T_1$.

### 1.5.4 SNR-maps

SNR maps can be calculated from times-series made up of a number of repetitions of an EPI-sequence. The time-series are corrected for movement of the subject and high-pass filtered so as to take out long-term drifts. The SNR of each voxel is the temporal mean divided by the temporal standard deviation. The absolute value of the SNR depends on a range of factors. Important factors are for example the NMR relaxation times of the studied object, the parameters of the EPI-sequence and the coils used for signal reception.
1.6 Functional Magnetic Resonance Imaging

Functional Magnetic Resonance Imaging (fMRI) is a sub-field of MRI, which uses series of repeated MR-images to investigate brain function. The acquisition of a single volume is carried out in typically less than 3 s. A number of volumes is acquired in one scan using exactly the same MRI-sequence for each volume. The results are images, which are identical apart from contributions of noise and of physiological changes. The data are arranged in a 4-D array where the 4th dimension represents the time domain. In this thesis the single 3-D volumes of a 4-D array are called ‘dynamics’.

Usually the subjects who are scanned are asked to perform tasks or they are exposed to stimuli at certain times. Local signal changes between different volumes of the fMRI-data indicate brain activity if the changes show a correlation with the timings of the stimuli (Jezzard et al. [2003]). Not all MRI contrasts are sensitive to brain activity. Perfusion contrast can be used, because active brain areas require more oxygen and therefore the CBF in these areas is increased.

1.6.1 BOLD fMRI

Blood Oxygenation Level Dependent (BOLD) contrast is the most commonly used contrast for fMRI. This contrast takes advantage of the fact that oxygenated haemoglobin is diamagnetic whereas deoxygenated haemoglobin is paramagnetic. The magnetic susceptibility of the surrounding brain tissue is more similar to oxygenated haemoglobin compared to deoxygenated haemoglobin.

Since local field inhomogeneities are stronger if the concentration of deoxygenated haemoglobin is higher this leads to a reduced $T_2^*$ relaxation time. Therefore $T_2^*$-weighted images are sensitive to the amount of oxygen in the blood. A higher concentration of oxygenated haemoglobin leads to a stronger signal intensity due to the longer $T_2^*$ relaxation time.

Increased neural activity comes with higher oxygen demands, which leads to an increase in blood-flow that over-compensates for the increased oxygen demand. Therefore the concentration of oxygenated blood increases in brain areas which are active during the task or the stimulus. An increase in signal intensity in $T_2^*$-weighted images can be observed, when they are acquired shortly after the onset of the stimulus or task (Jezzard et al. [2003]).

GE-EP-images are commonly used for fMRI because they offer a strong $T_2^*$-contrast and they allow volumes to be acquired with a high repetition rate. Typically images which cover the whole brain
Figure 1.9: Characteristic HRF. After an initial latency period of about 1.5 seconds the signal increases and peaks around 5.5 seconds after the neural activity. After about 10 seconds the signal drops below the level before the neural activity resulting in an undershoot for about 5 seconds. Between 15 and 20 seconds after the neural activity the signal recovers back to the resting level.

are acquired in 2 - 3 seconds using an isotropic resolution of 3 mm. At 3T, echo times between 30 and 50 ms offer a good compromise between signal strength and $T_2^*$-contrast.

The increase in signal intensity due to the BOLD effect is not immediate. Instead, the timecourse of neural activity is convolved with a characteristic function called the Hemodynamic Response Function (HRF) (Glover [1999]), which represents the response of the oxygenation of blood to an infinitesimal short event which causes neural activity. The typical shape of this function is shown in Figure 1.9. The Figure shows that the peak response is delayed by about 5 seconds. Furthermore the response function causes a temporal smoothing with a full width at half maximum of about 5 seconds. It is therefore difficult to distinguish between events which are close to each other in time using the BOLD-response.

1.6.2 General Linear Model

In most fMRI experiments either the subject is asked to perform one or more different tasks or the subject is exposed to one or more stimuli at defined times. An assumption commonly used for
fMRI analysis is that during these tasks or stimuli certain areas of the brain show an increase in activity. This activity leads to a local signal increase in $T_2^*$ weighted images as described in the previous section. A model is created to identify the contribution of each stimulus to the signal variation. This model is a function representing the task or stimulus in time (1 when active, 0 when inactive) convolved with the canonical HRF. It is used to localise brain areas, which are active during the task or stimulus.

The analysis is usually carried out for each voxel independently. The applied method is called the General Linear Model (GLM) (Friston et al. [1995]) in which $y(t, r)$ describes the signal of the voxel at location $r$ over time, $t$ and $x_1(t)\ldots x_n(t)$ are the models for $n$ different tasks or stimuli. These models can be fitted to $y(t, r)$:

$$y(t, r) = \sum_{i=1}^{n} \beta_i(r)x_i(t) + c(r) + e(t, r)$$  \hspace{1cm} (1.42)

$c(r)$ is a constant value over time, $e(t, r)$ is the remaining part of the function, which cannot be described by a linear combination of the models $x_1(t)\ldots x_n(t)$. The parameters $\beta_1(r)\ldots \beta_n(r)$ describe the contribution of each model to the timecourse at location $r$. These parameters indicate the strength of the brain activity in this voxel related to each of the stimuli. The fitting algorithm determines the values $\beta_1(r)\ldots \beta_n(r)$ which minimise $\sum_te(t, r)^2$. It also calculates the standard error ($SE$) for echo of the parameters $\beta_i(r)$.

To convert the parameters to values which indicate the statistical significance of the results, the parameters are converted to T-values, which are calculated using

$$T_i(r) = \frac{\beta_i(r)}{SE(\beta_i(r))}.$$  \hspace{1cm} (1.43)

The results of the GLM are maps $T_i(r)$ and $\beta_i(r)$, which indicate where task $i$ induces significant brain activity.

### 1.6.3 Pre- and Postprocessing

Usually fMRI data requires some pre- and postprocessing to produce useful results and to allow comparison between subjects. In the following some of the most important processing steps are summarised.

1. **Movement correction**: The different volumes can be slightly shifted relative to each other due to head movement of the subject during the scan. The movement correction procedure
corrects for this movement by translating and rotating each volume slightly in order to achieve the best match of volumes.

2. High-pass filtering: High-pass filtering is applied to eliminate unwanted long-term drifts in the signal, which can, for example, be related to the scanner hardware. The cut-off frequency should be low enough to ensure that the filtering does not attenuate the stimulus-related contribution to the functional data.

3. Smoothing: In most cases brain activity is not restricted to isolated voxels. Larger connected areas show activation. Smoothing is the easiest way to average between adjacent brain areas. It effectively decreases the spatial resolution, but also decreases the contribution of noise to the data.

4. Clustering: Isolated voxels with significant T-values are often false positives. Clustering eliminates voxels which don’t have a certain number of adjacent voxels with significant T-values.

5. Co-registration: In most cases the results of fMRI experiments are presented as overlays on high resolution anatomical scans. The fMRI-data are co-registered to the anatomical image in order to do this. Consequently the transformation matrix determined from this co-registration is also used for transforming the results into the high resolution space. Often a second co-registration step is applied which transforms the anatomical images and the fMRI-results to a standard image space such the standard MNI-brain (Evans et al. [1993]). This allows the results to be compared across subjects.

1.7 MRI-system

The main scanner unit of whole body MR-system is displayed in Figure 1.10. Not displayed is the equipment, which is accommodated outside of the magnet room. The scanner environment is made up of the following elements:

- Screened Room: The scanner is accommodated in a room which is screened in order to avoid artefacts due to external RF-interference. An electrically conducting metal sheet in the walls all around the room prevents RF from entering the room. Waveguides which are passed through the metal sheet allow equipment from outside to be connected to devices inside the
room without violating the screening. This only works flawlessly as long as the connection between inside and outside is non-conductive. Access to this room is restricted due to the potentially dangerous magnetic field inside. Any person who enters the room must be checked for metallic objects beforehand.

- **Main Magnet:** The main magnet is responsible for the \( B_0 \) field. Modern high-field MR-scanners use superconducting wires to produce a strong magnetic field. To maintain the wires in the superconducting state, the wires have to be cooled with liquid helium. The main magnet is the largest part of the scanner. The field strength it produces is the most commonly used value to characterise MR-scanners.

- **Shim Coil:** Shim coils are used to improve the homogeneity of the \( B_0 \) field. Inhomogeneities can be measured at the beginning of each scan and then adjusted for each subject or even dynamically during scanning.

- **Gradient Coils:** Three sets of coils produce gradients in \( B_0 \). The induced gradients of each coil are perpendicular to each other. Use of a linear combination of the three gradients allows a gradient to be applied in any direction in space. Strong currents are passed through the gradients during operation and they cause strong Lorentz forces between the wires of the gradients and the \( B_0 \)-field. As a result, switching of the gradients causes vibrations in the gradient coils. These vibrations are responsible for the loud noise during MR-scans.

- **RF Coils:** RF-coils are used for the transmission of RF-pulses and for signal reception. A body coil is integrated into the bore of the scanner. This body coil is often used for transmission while a coil with a smaller bore is used for reception. Most scanners have a range of RF-coils available for different purposes. For head imaging, multi-channel receiver coils are used, which are just large enough to accommodate a human head. Other coils are often designed to scan a specific part of the human body.

- **Operator terminal:** The operator controls the scanner through a computer which is positioned in the control room adjacent to the magnet room.

- **Equipment room:** The equipment room accommodates electrical equipment, which is required to run the scanner. Examples of this equipment are RF amplifiers, gradient amplifiers and cooling units.
Figure 1.10: Cut through a scanner-unit for whole body MR-imaging.
Chapter 2

Transcranial Magnetic Stimulation

Introduction

Transcranial Magnetic Stimulation (TMS) is a technique for stimulating the brain non-invasively using a pulsed magnetic field. The principles of this technique have been known for a long time and the history of transcranial brain-stimulation reaches back to the times of the Roman empire (Pascual-Leone and Wagner [2007]). Nevertheless the first successful experiments using TMS were carried out by Barker et al. [1985] in 1985 in Sheffield and involved stimulating the motor cortex. Since then interest in TMS has increased constantly.

In neuroscience, TMS offers a new method to explore cortical circuits which are responsible for motor function, but also for cognition and perception. Used in combination with functional brain imaging, TMS has the potential to contribute greatly to the understanding of the function of the human brain.

In this chapter, I explain the fundamental ideas behind the TMS technique, describe the construction of a typical TMS-stimulator and outline the different technical, physical and physiological steps, which lead to the stimulation of the brain. I also give some examples of experiments employing TMS.
2.1 Stimulating with magnetic fields

2.1.1 How to access the brain

A big problem in neuroscience and in medicine is the complexity of the brain since it consists of many highly interconnected structures of which many parts have important functions for the operation of the human body. Any incision into the tissue cuts thousands of pathways with a high probability of causing permanent damage to certain brain functions. Therefore interventions in the human brain are only acceptable in exceptional circumstances such as surgery to remove cancerous tumours.

For diagnostics and for research purposes it is necessary to image the brain. Ideally it would even be possible to influence the brain function temporarily. But how can this be achieved without damaging it?

There are several different kinds of field and radiation which interact with the tissue of the brain or body in different ways. Several of these fields can be used for imaging, as well as for manipulative purposes. Table 2.1 gives an overview of these fields. Of these fields, electric or temporally changing magnetic fields are the most appropriate for the manipulation of brain function because they can directly interfere with the electrical nature of neuronal activity.

2.1.2 Methods of electrical stimulation

The nervous system exploits a combination of electrical and chemical processes. Electric fields therefore have the potential to alter these processes. In contrast to drugs, electrical stimulation can be applied non-invasively to a spatially restricted area. This gives methods of electrical stimulation a large potential for the development of new therapies and means that they form an important approach for understanding how the human brain works.

Besides TMS there are currently a number of different techniques of electrical brain stimulation in use:

- **Deep Brain Stimulation (DBS):** An electrode is implanted into the patient’s brain. A voltage applied to the electrode can efficiently inhibit the activity of adjacent brain areas. This is used to suppress the effects of disrupted brain function in neurodegenerative diseases such as Parkinson’s disease. This highly invasive method is only used in severe cases, when other treatments have failed (Kringelbach et al. [2007]).
Table 2.1: Overview of different fields and their potential for manipulating the brain non-invasively. Static or near static electric or magnetic fields can affect the neuronal activity, but it is difficult to cause focal effects non-invasively. Higher frequencies can be focused up to a point of the order of their wavelength, but they heat up the tissue, rather than directly affecting neuronal activity. Radio frequencies have a wavelength, which is too long to focus. Shorter wavelength radiation is absorbed by the tissue before reaching the brain. Hard radiation passes through tissue in a straight line, but damages the tissue. Mechanical waves can be focused inside the tissue, causing local heating.
• **Direct Current Stimulation (DCS):** For this technique conducting patches are positioned at different locations on the surface of the head of a subject. If a voltage is applied to these patches, a current flows through the brain from one patch to the other. The patch electrodes need to have a reasonably large area so as to distribute the current over a large surface and therefore to overcome the electrical resistance of the skull. Observable effects are for example correlations between the applied current and the performance of the subject in a specific task (Kincses et al. [2004]). The technical requirements for this method are relatively low and it is non-invasive. On the other hand it has a rather poor spatial and temporal specificity (Nitsche et al. [2007]).

• **Transcranial Magnetic Stimulation (TMS):** A strong magnetic field (>1 tesla) is applied to the subject’s head over a short period of time (<1 ms). This changing magnetic field induces an electric field in the conducting tissue of the brain. The spatial distribution of this field is mainly dependent on the shape of the coil, which produces the magnetic field. With a figure-of-eight coil, a focal region of about 2 cm extent can be achieved. The electric field can activate or alter the function of the underlying brain area. A disadvantage of this method is the low depth of penetration of the magnetic field, which decays rapidly with distance from the coil.

In comparison to DCS, TMS has a smaller focal region and a high temporal resolution. The stimulated area is much better localised and therefore brain areas can be investigated more precisely. With the high temporal resolution it is also possible to measure signal transit times in pathways of the brain.

As a result of its non-invasive nature, TMS provides unique opportunities to study brain function in healthy subjects. In combination with methods of functional brain imaging such as functional MRI, TMS has the potential to give new insights into brain function.

### 2.1.3 Using magnetic fields

In Section A.1.1 the relationship between electric and magnetic fields as well as the interactions of electric and magnetic fields with matter, such as the human head, are explained. The basic idea behind TMS is to use a magnetic field, which penetrates nearly freely through the human head. If this field is varied over time, it induces an electric field in conducting tissues. To make a useful
application out of these ideas, several questions need to be answered:

- What strength of electric field is required to produce an effect on the neurons. At what intensity will this approach become dangerous? → Section 2.1.4

- What strength and what rate of change of the magnetic field can induce an electric field of the required strength? → Section 2.1.5

- What spatial distribution of the magnetic field can be generated? How can this field be used to create a spatially restricted electric field? Section 2.3

- What current source is needed to achieve the required magnetic field? Which properties are important for the coil? Section 2.2

- How safe is brain stimulation using magnetic fields in practice? Section 2.8

These questions will be answered in the following sections so as to give a complete picture of how TMS works.

### 2.1.4 Brain tissue in an external electric field

In Section A.3 the basic concept of electro-chemical communication between neurons is explained. The fact, that the signal transfer is triggered by changes in the intracellular electric field makes it susceptible to the effects of externally applied fields. To understand the relationship between field strength and the effect on the brain, we first look at the microscopic processes that occur in a single neuron.

**Microscopic view (effect on a single neuron)**

The voltage change required to trigger an action potential (Section A.3) is about 15 mV (Barnett and Larkman [2007]). Once triggered, the action potential propagates through the whole axon. If an external electric field across the cross section of the axon is strong enough, it can trigger an action potential on one side of the axon. We assume that the axon has a thickness of 2µm and a required potential difference of 30 mV because it has to pass through 2 membranes. This corresponds to an electric field with a strength of 15000 V/m. However a field of that strength would cause all axons to fire and cause a complete overload of the whole brain area at once. However the electric field is microscopically inhomogeneous because of charge accumulation at
tissue boundaries between tissues of different conductivities. This can lead to local spots with much higher electric fields.

Another question is, if there are other points at which an extracellular electric field can have an effect on the neuron. An example is the initial trigger for the action potential, which is initiated in the axon terminal. The voltage for the trigger is generally caused by the input from several synapses working together. If the output voltage is just below the trigger level, a rather small extracellular electrical field can activate the action potential.

To understand fully the effect of an extracellular electric field a very detailed model would be required. This model must include assumptions about the shape and the electrical properties of the neuron. Furthermore a profound and extensive model of the electrochemical processes inside the neuron is necessary.

An analytical approach to this problem has been described by Tranchina and Nicholson [1986], who concluded that the soma or the nodes of Ranvier are the most likely sites for action potential initiation by applied electric fields. A review of studies addressing this question has been written by Basser and Roth [2000], but so far only simplified models have been developed.

**Macroscopic view**

Another approach is to assume that a brain area is composed of homogeneous tissue with certain electric properties and that a stimulating field above a certain strength and orientation over this area can activate neurons. A strong enough effect can elicit a response such as a muscle movement.

In the case of peripheral nerve stimulation (PNS), where axons are stimulated directly, the elicited action potential induces a motor response directly. If the brain is stimulated, the brain function is altered in an uncontrolled way and it brings the activity of the brain slightly out of balance. If the stimulation exceeds a threshold, the uncontrolled activity can provoke for example a muscle response.

There are two values, which are used to characterise the threshold for the stimulation of nerves:

- **Rheobase**: Minimum amplitude of stimulation of infinite duration needed to elicit a response.
- **Chronaxie**: duration above which a stimulation of the strength of twice the rheobase elicits a response.
In most of the literature, the value for the rheobase is assessed for a specific experiment e.g. a voltage applied between two electrodes at clearly defined positions. With TMS it is also difficult to determine the chronaxie because the duration of a TMS pulse is not adjustable in most stimulators. Nevertheless if the rheobase is determined with the unit of electric field strength (V/m) in tissue, these two values can be the key to a quantitative approach to brain stimulation. Values for the rheobase and chronaxie in brain matter of $32 \text{ V/m}$ and $406 \mu s$ respectively are mentioned in Davey [2008].

### 2.1.5 From a magnetic field to an electric field

Equation A.3 describes the connection between a time-varying magnetic field and an induced electric field. To estimate the requirements for the magnetic field and how it can be achieved, we start with the rheobase value of $E = 32 \text{ V/m}$ described in the previous section. To form the equation we assume a homogeneous tissue with no charge accumulation. For a simple approach a wire loop as the creator of the magnetic field and vector potential (Figure 2.1) is assumed.

For the given example the result is a required rate of change $dI/dt$ of the current through the wire of about $1.8 \cdot 10^8 \text{A/s}$. If we take a chronaxie value of $t = 408 \mu s$ as the rise time and twice the rheobase, the required maximum current would be $I = dI/dt \cdot t = 7.3 \cdot 10^4 \text{A}$. This value can be reduced by about one order of magnitude by using a more efficient coil design e.g. multiple wire loops. The value increases if the target area is located deeper in the brain and if inhomogeneous
tissue has a weakening effect on the achieved electric field. A shorter rise time can lead to more efficient stimulation.

In conclusion, an increase in current from zero up to the order of $10^4\, \text{A}$ is required over a time of less than 1 ms to stimulate. This value is fairly high, but it lies within the range of what can be generated and controlled with standard high voltage equipment.

### 2.2 Construction of a TMS-stimulator

At this point an overview of the electrical circuits, which can be used to create a magnetic pulse with the right strength and the right temporal characteristics to stimulate neurons in the head, is provided. This information helps us to understand, quantify and improve the interactions between TMS and fMRI. The information about the electrical circuits was taken from Davey [2008].

#### 2.2.1 Basic considerations

A fundamental requirement for the generation of strong electric fields using induction is a magnetic field (or vector potential) with a high rate of change. The magnetic field produced by a given current is dependent on the spatial arrangement of the wires. The inductance is dependent on the energy stored in this magnetic field. The strength of the magnetic field $\mathbf{B}$ and the associated vector potential $\mathbf{A}$ are proportional to the current $I$:

$$|\mathbf{A}| \propto |\mathbf{B}| \propto I. \quad (2.1)$$

To demonstrate the factors limiting the rate of change, we assume a constant voltage, $U$, is applied
to an inductance, $L$. We also include a resistance, $R$, that usually comes with the inductance (Figure 2.2). As a starting condition we assume the current to be zero $I(t = 0) = 0$. The solutions for the resulting differential equation for the current and its rate of change are:

$$I(t) = \frac{U}{R} \left(1 - e^{-\frac{R}{L} t}\right), \quad (2.2)$$

$$\frac{dA}{dt} \propto \frac{dI}{dt} = \frac{U}{L} \cdot e^{-\frac{R}{L} t}. \quad (2.3)$$

If we assume that a $\frac{dI}{dt} = 2 \cdot 10^8$ As$^{-1}$ which decays in $t_S > 400\mu$s to half the value and we apply a voltage of $1000$ V, we get a value for the inductance of $L < \frac{U}{\frac{dI}{dt}} = 5 \cdot 10^{-6} VsA^{-1}$ and for the resistance of $R < \frac{\ln(2) \cdot L}{t_S} \approx 0.09\Omega$.

This does not represent the whole circuit of a TMS-stimulator, but it gives a good estimate of the requirements for efficient stimulation. A high voltage and a low inductance are needed to get a high maximum stimulation and a treatment coil with a high inductance-resistance quotient maximises the duration of the stimulation.

Other problems are related to the voltage source, the shape of the field induced by the coil, the energy requirement for every pulse and issues with coil heating.

### 2.2.2 Stimulator circuits

The requirements in constructing a TMS-stimulator are therefore a high-voltage power supply and a low-resistance circuit which includes the cable and the stimulation coil. Furthermore a capacitor to store the energy and an electrical switch to trigger the stimulation are required.

**Monophasic Stimulator**

Figure 2.3 shows the circuit of a monophasic TMS-stimulator. Additional to the mentioned components it includes a diode placed in parallel with the capacitor that short-circuits the capacitor, if the voltage is reversed. The thyristor is a semiconductor switch which allows current to flow in one direction, when it receives an external trigger pulse. It remains conducting even if the trigger is removed, until the voltage has dropped to zero. Once the current is interrupted, it blocks again in both directions. A discharge of this circuit consists of the following steps:

1. Charging/Rest ($<0$ ms). The voltage supply charges the capacitor.
Figure 2.3: Basic circuit of a monophasic TMS-stimulator

Figure 2.4: Current and voltage of a monophasic TMS pulse at the coil. The curves are simulated using values for the electrical components from Figure 2.3. The actual stimulation lasts less than 0.05 ms.
2. Firing (0 ms - 0.06 ms). The trigger activates the thyristor and the capacitor discharges itself into the TMS-coil. During this period the circuit acts like an LCR-resonator and it can be described with a quarter cycle of Equation 2.4.

3. Decay (>0.06 ms). When the voltage at the coil drops below 0, the direction of the current is reversed and the diode shorts the whole circuit. The energy stored in the magnetic field of the coil decays with $e^{-\frac{Rt}{L}}$. After the TMS pulse the capacitor is discharged completely and has to recharge again.

**Biphasic Stimulator**

Biphasic stimulation can be achieved using a slightly modified circuit as shown in Figure 2.5. The additional diode is used to bypass the thyristor in the blocking direction and the additional inductance acts like a high-frequency filter for currents to protect the voltage supply. A pulse can be described by the following steps:

1. Charging/Rest (<0 ms)

2. Building up the magnetic field (0 ms - 0.2 ms). The thyristor is activated and the magnetic field in the coil builds up. After the maximum, the magnetic field decays again and energy stored in the coil charges the capacitor with a reversed voltage.

3. Reversed magnetic field (0.2 ms - 0.4 ms). When the current direction is reversed, the thyristor blocks again, but the diode allows a back-flow of current so that the energy stored in the coil partially recharges the capacitor.

4. Charging/Rest (> 0.4 ms). As the thyristor is blocked now, the charge is trapped in the capacitor. This charge can be used for the next pulse and therefore reduces the total energy requirement.

A pulse consists therefore of a full resonance cycle of a weakly damped LCR-circuit. This is represented by the following differential equation:

$$I(t) = \frac{U_0}{L\omega} e^{-\frac{R}{2L}t} \sin(\omega t) \quad \text{with} \quad \omega = \sqrt{\frac{1}{LC} - \frac{R^2}{4L^2}} \quad (2.4)$$

Figure 2.6 shows, that this agrees to a high degree with the real behaviour of the circuit of a TMS-Stimulator. The measurement is explained more in detail in Section 3.3.
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Figure 2.5: Circuit of a biphasic TMS-stimulator. Compared to the monophasic TMS-stimulator (Figure 2.3) the thyristor is bypassed in the insulating direction with a diode and the voltage supply is shielded against fast current changes by an additional inductance.

Figure 2.6: Current and voltage of a Biphasic TMS pulse at the TMS-coil. The voltage was measured indirectly through a wire loop which was attached to the TMS-coil and then scaled to a maximum voltage of 1.6 kV. The current is based on the voltage integrated over time.
Monophasic vs biphasic

The main difference between monophasic and biphasic stimulation is the temporal variation of the voltage at the TMS-coil which is proportional to the stimulation intensity.

As shown in Figures 2.4 and 2.6, the coil-voltage $U_{\text{Coil}}$ shows a short ($< 0.1 \text{ ms}$) peak and afterwards a decay with a low $\left| \frac{dU}{dt} \right|$. If we assume that TMS just has an effect if the induced electric field is above a specific threshold, then the induced effect has just one orientation. With the biphasic circuit the voltage has the shape of a whole cosine period. Therefore it induces an oscillating electric field in the tissue during the pulse. The monophasic pulse produces a temporally sharper stimulation with a clearly defined direction of the electric field.

The power consumption of the monophasic circuit is higher. As the time of the stimulation is just limited to the build-up time of the magnetic field of the coil, the stimulation intensity must be higher compared to the longer stimulation time of the biphasic circuit. The capacitor must also be charged with a higher voltage because the period of stimulation is four times shorter compared to the biphasic stimulation (assuming the same values for $L$ and $C$). Furthermore with every discharge the whole energy, that was stored in the capacitor, is dumped. In a biphasic circuit the voltage is lower and after a pulse the capacitor is partially recharged for the next pulse. The total energy consumption is significantly lower in a biphasic stimulator. This also reduces heating problems of the TMS-coil because the current through the coil shows a sharp cutoff instead of decaying slowly to zero.

An ideal TMS stimulator

The two presented circuits for TMS stimulators are based on simple electronic circuits and they are very limited in changing the temporal characteristics of the stimulation pulse. An amplifier with a sufficiently high range in the voltage output (between -2 kV and 2 kV) could deliver a wide range of temporal shapes of TMS pulses. To illustrate this, we can take the circuit from Figure 2.2 with $U$ as the output voltage of the amplifier. We assume that $S = \frac{dI}{dt}$ is proportional to the strength of the stimulation which we want to control and find

$$U(t) = U_L + U_R = L \cdot \frac{dI}{dt} + R \cdot \int \frac{dI}{dt} dt = L \cdot S + R \cdot \int S dt,$$

(2.5)

with the starting condition $I = 0$, the required voltage is defined. A limitation is that after the pulse the field should drop to 0. This can be achieved by applying an opposite stimulation with a
low intensity over a long period of time.

An amplifier would need to be high power and have a good temporal response. As an example we assume that an increase in the current of \( \frac{dI}{dt} = 10^8 \text{As}^{-1} \) is required over a period of \( t_S = 4 \cdot 10^{-4} \text{s} \). The assumed inductance is \( L = 10 \mu \text{H} \) and the resistance is 0.01\( \Omega \). The voltage would have to start at 1 kV and increase linearly over \( t_S \) up to 1.4 kV. Then the voltage has to drop slightly below 400 V and decrease slowly to 0.

Even if it is not easy to build a device like this, the requirements are similar to gradient amplifiers of MR-scanners.

### 2.3 TMS-coil design

The other important part of a TMS system is the treatment coil (TMS-coil) which is used to apply the stimulation. As mentioned in the previous section, the inductance and the electrical resistance of the coil are important, but they are not directly associated with the stimulation. For the stimulation itself it is important to consider the size and the position of the target site. For this it is relevant to consider, how focal the stimulation is and how the field decays with distance from the coil. The best predictor of the electrical field is the spatial distribution of the magnetic vector potential, which can be calculated by integration over the coil (Section A.1.3).

\[
A(\mathbf{r}, t) = \frac{I(t) \mu_0}{4\pi} \int_{\text{loop}} \frac{d\mathbf{l}(\mathbf{r}')}{|\mathbf{r}' - \mathbf{r}|}
\]  

(2.6)

Here \( I(t) \) describes the current in the coil and \( d\mathbf{l}(\mathbf{r}') \) describes an infinitesimal element of the coil.

The magnetic field and the magnetic vector potential always decay with the distance from the wires. This is an intrinsic limitation and it is not possible to produce a larger field inside the brain than at the surface (Heller and van Hulsteyn [1992]). As a consequence, the maximum of the stimulation is always located at the surface in the area directly beneath the coil. If deeper areas of the cortex are targeted, side effects from areas closer to the coil are always possible.

In addition there are some other general rules of thumb, which should be taken into account when designing a TMS-coil.

- Thick wires should be used to reduce the electrical resistance.
- The field is proportional to the the number of windings of the coil. The inductance is proportional to the square of the number of windings. The resistance increases rapidly with
the number of windings (greater length and reduced cross-section).

- Smaller coils allow production of larger and more focal fields.
- The field produced by larger coils decays more slowly with distance from the coil. Larger coils must therefore be used to stimulate deeper target areas.
- The inductance and the resistance of the leads and the electronics of the stimulator are not negligible in comparison to that of the coil.

An analytical approach to the design of TMS-coils has been described by Davey [2008]. Furthermore it has been shown that the efficiency of a TMS-coil can be improved by using a ferromagnetic core Epstein and Davey [2002], such cores are not discussed further in this thesis because of their intrinsic incompatibility with MRI.

### 2.3.1 Coil Types

The two main types of TMS-coils are circular and figure-of-eight coils (Figure 2.7).

Circular coils consist generally of a flat spiral of wire with typically about 10 windings. An average loop diameter between 5 and 10 cm is commonly used. Such coils have their strongest effect in cortical regions where the wires come closest to the head. The focality is poor and a large region of the brain may be stimulated.

Figure-of-eight coils consist of two flat spirals, which are arranged to form the shape of the figure 'eight' (Figure 2.7). The currents in both rings flow in the same direction in the centre. Therefore their effects sum up to produce a large magnetic vector potential near this point. This type of coil is usually positioned with its centre over the target site. It provides better focality than a circular coil with a typical focus size of the order of 1 cm. A rough measure that can be used to estimate the depth at which the stimulation can have effects, is that the achievable depth is approximately equal to the radius of each of the rings (Ravazzani et al. [1996]; Thielscher and Kammer [2004]).

Beside these two types of TMS-coil there are other more specialised treatment coils, but all require a tradeoff between focality and penetration depth.

To prevent coil heating, the resistance of the coil is kept low by using wires with a cross section that is as large as possible. Therefore a large proportion of the volume inside the coil is copper. Some commercial coils have an active cooling system. Coil heating is also a safety issue, because
overheating can damage the coil. Commercial stimulators often include circuits to control the coil temperature. These switch the system off in the case of overheating.

2.4 TMS in practice: Modes of stimulation

There are several different modes of application of TMS, each of which induces different effects in the brain. The main difference between the modes is the chronology of the TMS pulses.

2.4.1 Single-pulse TMS

In single-pulse TMS, each TMS pulse can be considered as a single event. This is the case if the time between pulses is much longer than 1 second. This mode of application is considered to be safe in terms of the risk of producing seizures (Wassermann [1998]). This mode is used to probe the impact of TMS pulses on a single action or to observe the immediate response to TMS (See for example Pascual-Leone et al. [1994]).

Multiple-pulse TMS

Some paradigms use a short sequence of two or more pulses with adjustable inter-pulse delays. Examples are paired-pulse TMS (Ziemann et al. [1998]) or triple-pulse TMS (Rösler et al. [2002]). These paradigms offer a wider range of stimulation parameters because the time between the pulses can be adjusted. Using more than one TMS-coil, the individual pulses can be applied to different
parts of the brain. Modulating the delay between the pulses can for example reveal temporal characteristics of brain function.

2.4.2 Repetitive TMS (rTMS)

In repetitive TMS, pulses are applied multiple times, often in a train or burst with gaps in between bursts. rTMS can induce cumulative effects, which means that lasting effects are caused by the repeated application of TMS over the same area. The frequency of the stimulation is an important factor in dictating the effects on the stimulated brain area.

**Low-frequency rTMS**

Repetition frequencies of 1 Hz or lower are characterised as low-frequency rTMS. Frequencies around 1 Hz are associated with inhibitory effects on the stimulated brain area (e.g. Chen et al. [1997a]).

**High-frequency rTMS**

TMS with repetition rates above 1 Hz is called high-frequency TMS. Higher frequency pulsing (>5 Hz) is usually applied in trains of pulses with durations of less than 10 s and intervals between successive trains. In contrast to 1 Hz rTMS, frequencies around 20 Hz are associated with excitatory effects on the stimulated brain area.

For example, in a study by Speer et al. [2000] the effects of 1 Hz rTMS was compared directly with that of 20 Hz TMS. The number and the strength of the pulses and the times at which the pulses were delivered were roughly the same (1600 pulses, 100% motor threshold (MT), 20 minutes (20 Hz), 26 minutes (1 Hz)). The study showed inhibitory effects for the low-frequency rTMS and excitatory effects for the high-frequency rTMS, indicating that changing the mode of stimulation can strongly modify the impact of TMS on brain function.

**Patterned rTMS**

Patterned rTMS refers to the application of short bursts during which TMS pulses are applied with a very high frequency (≥ 50 Hz). These bursts are repeated with a lower frequency. The idea behind this application is, that the bursts induce a more reliable stimulation of the neurons (Lisman [1997]). Theta burst stimulation (TBS) protocols are frequently used. These typically
consist of bursts of three TMS pulses applied at 50 Hz, which are repeated with a frequency of 5 Hz. Examples of such experiments were summarised by Lazzaro et al. [2005], [2008].

2.5 TMS in practice: problems and solutions

To achieve reliable results in TMS experiments, there are several aspects of the experimental set-up which must be considered independent of the particular paradigm or type of the experiment.

2.5.1 Positioning of the TMS-coil

A consistent way of positioning the TMS-coil is crucial for achieving reliable results. Otherwise different brain areas will be stimulated in different subjects, yielding variable effects. As described in Section 2.3 the areas, that are closest to the coil, are stimulated. A small displacement of the TMS-coil can cause a strong change in the stimulating field in the target region. Furthermore the orientation of the TMS-coil is important, because it controls the orientation of the induced electric field. The dominant direction of the electric field is parallel to the nearest wires. Figure-of-eight shaped TMS-coils are usually positioned adjacent to the subject’s head with the coil centre, where the two rings join each other, over the target region. At this position the induced electric field is parallel to the coil-surface and perpendicular to the long axis of the coil. Strongest stimulation is produced under the centre of the coil. To achieve a good reproducibility of the positioning, several different methods can be used:

- **For stimulation of the primary motor cortex**
  The position and orientation of the TMS-coil, which can be found that elicits a motor response at the lowest intensity of TMS can be found. The way to find this position is to stimulate by trial and error and to monitor the motor response. The position and orientation of the coil is adjusted to maximise the response. A good strategy is to move the coil along a line in the coronal plane over the top of the head which connects both ears, starting 5 cm to the left or to the right from the centre. When the target is found, the motor threshold (see Section 2.6.1) can be determined.

- **Using landmarks to position the coil**
  Anatomical landmarks including the ears, the nasion, the topmost point of the vertex, the most posterior point of the skull or the ‘hot-spot’ for motor activation can be used to define
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the site of stimulation. For example the somatosensory cortex is slightly posterior to the primary motor cortex, so a recipe for coil positioning for stimulation of the somatosensory cortex can be as follows:

*Find the hot-spot of the motor activation and then move the coil 2 cm in the posterior direction.*

This approach assumes, that the brain anatomy is similar in different subjects.

- **Using MR-images and a stereotactic system to position the TMS-coil**

  A stereotactic system makes use of a three dimensional coordinate space in order to localise a target in the brain. The localisation is based on three or more anatomical landmarks which are accessible from outside and on prior knowledge about where the target area is positioned relative to these landmarks in space. This knowledge can for example be extracted from MR-images. A stereotactic system defines a coordinate system in the space of the subject. The coordinates of the landmarks are measured on the subject. The coordinates describing the location of the target in real space can be calculated by co-registering these landmarks with the same landmarks defined in the MR-image. For TMS a stereotactic system can be used to position the TMS-coil over a location which has been identified in an MR-image. The site of the stimulation is identified individually for each subject. This can be done by identifying the site directly using the gyri and sulci of the brain or by translating the coordinates from a standard space into the native space.

  Standard space means the coordinates in a standardised brain formed from a large number of brain scans such as that developed by Evans et al. [1993]. The native space is the space of the images, taken of the subject.

  A more reliable way of identifying the target location is to use the results of fMRI applied with a task that activates the target area. The target site can be identified from the measured site of peak activity. This method requires an extra MRI-session to identify the target site and therefore it makes the experiment more extensive.

  Clearly defined landmarks on the head (tip of the nose, nasion...) must be identified in the MR-image and also on the the subject. This allows the coordinates of the target area to be transformed from the anatomical MR-image into the real space. The stereotactic system can be used to identify the position of the coil relative to the target site.
2.5.2 Unwanted effects

TMS stimulation cannot be restricted just to the target site. Adjacent areas also experience an electric field. The extent and strength of this field depends on the coil used and on the position of the target site. In the case of stimulation of deeper areas, the tissue lying between the target brain region and the skull experiences a stronger electric field than the target region. These effects have to be taken into account, when studying the results of the stimulation, since the unwanted stimulation of other brain areas can contribute to the measured effects.

Another problem is the sensation that the subject experiences during the stimulation. Every pulse produces a click-sound resulting from vibrations of the coil and also often stimulates nerves in the scalp. These effects mean that the subject is aware of the TMS procedure and also that the sensations produced can influence the results. An example of this effect is the blinking of the eye which decreases the performance in recognising a visual stimulus when it is delivered 70 ms after the TMS pulse (Amassian et al. [1989]). Another example is the activation of auditory and somatosensory areas, when TMS is combined with fMRI.

2.5.3 Controlling for TMS-effects

A consistent set-up is required in order to generate reliable data from experiments with TMS, but this only ensures that the induced effects are comparable between subjects. It is also necessary to consider how to separate the interesting, direct effects of TMS on the brain from the side effects resulting from the acoustic noise, scalp sensation and other factors.

This can be done by using a control condition which should induce as many of the side effects as possible, but not the stimulation itself and should not allow the subject to distinguish between true TMS and the control condition. The gold standard is a double-blind treatment where neither the experimenter, nor the subject can distinguish between real treatment or control. The information about this is recorded separately and only in the last step of the statistical analysis between the two groups is this information included. This kind of study eliminates the possibility that the experimenter can directly influence the subject and also the chance, that the results are is influenced during analysis. Because of the range of different side effects that TMS has, it is difficult to achieve a perfect control condition, but there are several strategies which can be used:

- **High intensity vs. low intensity:** The noise, the vibrations and the scalp sensation all increase
with TMS-intensity, but they remain qualitatively the same. In comparison, the effect of TMS can change strongly for small changes in the intensity. For example stimulation of the motor cortex doesn’t have much effect if it is applied with 90% of the motor threshold (MT), but at the 120% level it induces a significant muscle response. For the subject, the side effects will be very similar, but the TMS-effect (muscle response in the hand) is significantly different. This kind of control is relatively easy to implement in the same session because the TMS-coil can stay in the same position. However it is not an ideal control method, because the side effects are also dependent on the intensity.

- **Timing in single- or paired pulse studies:** If the purpose of the study is to explore the effect of the timing of a TMS pulse relative to another event, variations of the timing can be used to control for side effects. However in some circumstances side effects can also depend on the timing of the TMS pulse. One example is eye blinking, which is produced at a characteristic time after a TMS pulse.

- **Control sites:** TMS can be applied over a second site which generates no direct effects of TMS. The difference between the effects from both sites shows just the direct TMS-effects of the stimulation of the first site. A problem with this approach is that the side effects often are not independent of the site of the stimulation.

- **Sham TMS:** There is a possibility to deliver sham TMS pulses using special sham-coils. These coils are designed so that the magnetic field in the brain is attenuated, but the vibrations and noise are similar to that produced by a standard coil. Some of these systems are electronically switchable and therefore they don’t require a change of the coil to produce a sham stimulation (Hoeft et al. [2008]). It is more difficult to simulate the sensation in the scalp. This problem has been addressed by Rossi et al. [2007] or Borckardt et al. [2008], who used a smaller coil to induce the skin sensation without inducing a field which penetrates deeply into the brain.

It is difficult to simulate exactly the sensation of a real stimulation and therefore all approaches are only approximations. The availability of a reliable placebo TMS is essential for clinical double-blind studies of the efficiency of TMS-treatments. This is an important step, before TMS can be used routinely in addition to or even as a replacement for drugs to treat neurodegenerative disorders.
Chapter 2. Transcranial Magnetic Stimulation

In general the quality of the control data is equally important as that of the data produced with stimulation applied to the target site. All significant results must be checked for effects, which are not directly TMS-related or for effects from the stimulation of sites other than the target site.

2.6 Applications of TMS

Since the first application of TMS the concept of the stimulator has remained largely unchanged, with modifications mainly relating to the details of stimulators and changes such as the introduction of figure-of-8 coils and stimulators which allow high repetition rates.

In contrast to this, a lot of progress has been made in understanding the effects of TMS. This progress has been driven on one hand by clinical applications and on the other hand by the general progress in neuroscience where TMS provides an unique approach for studying the brain.

In this section I will give a short summary of the different ways in which TMS has been applied.

2.6.1 TMS on the primary motor cortex

The first experiments using TMS by Barker et al. [1985] showed that the stimulation of the primary motor cortex (M1) can elicit a muscle response in the hand. Subsequently this effect has been studied extensively and it is still a core element of many experiments carried out with TMS. The main advantage of this effect is that it is directly observable.

Measuring the motor response

For quantitative measurements of the motor response a standard electromyography (EMG) system is used. An EMG system basically consists of electrodes, a sensitive amplifier and a recording system. The electrodes are attached to the skin above the belly and the tendon of the muscle of interest. To decrease the contact resistance, a conductive paste is applied between the skin and the electrode. The voltage across the electrodes is then amplified and displayed with a recording bandwidth of typically 1 kHz. Detectable changes are of the order of 10 $\mu$V and the maximum amplitude of a muscle response can reach values of 10 mV.

When used in combination with TMS, the EMG recording must be synchronised with the stimulator. A recording time of 500 ms after the TMS pulse is sufficient to measure the immediate effects (Rossini et al. [1994]). Often the TMS pulse can be observed directly in the EMG-data in
the form of a single spike. This allows precise localisation of the pulse in time.

**Motor Threshold**

The motor threshold (MT) is the lowest stimulus intensity which produces a detectable muscle response. A common definition of the threshold is the stimulus intensity required to elicit a recordable response in the EMG-signal with a peak amplitude of 100 µV in 50 % of 10 to 20 trials (Rossini *et al.* [1994]). The definition can be slightly different such as a response in 3 of 6 trials (Conforto *et al.* [2004]) or a visible motor response in 5 of 10 trials (Reid [2003]). The last definition allows the determination of the MT without EMG recording but instead by observing movement of the subject’s hand.

The MT is usually determined at the beginning of a TMS experiment after positioning of the TMS-coil over M1. The intensity is then increased in steps of 5% until a response is visible. The threshold is adjusted in 1% steps to find the stimulation strength, which causes a response in accordance to the MT definition. An interstimulus interval of >3 s has been recommended to avoid crossover effects on the subsequent stimulation (Rothwell *et al.* [1999]).

Although the MT only measures the excitability of M1, it is commonly also used as a reference strength for other target sites. The MT can vary across subjects, because of differences in skull thickness or in the brain anatomy. There can also be effects of the environment or of the state of the subject. Nevertheless the MT is a useful indication of the strength of the stimulation.
because it gives an estimate of the power of the combination of the stimulator and the coil. If other hardware is used, the induced field distribution in the head would be different in shape and in strength. Stimulation intensities with less than 100% of the MT are called subthreshold and intensities above MT are called suprathreshold.

**Motor evoked potential**

The motor evoked potential (MEP) is the peak-to-peak amplitude of the signal recorded by the EMG. This amplitude usually increases with the intensity of the stimulation. An example MEP elicited by a TMS pulse is shown in Figure 2.8.

**Latency times**

There is a latency between the TMS pulse and the MEP, which can be explained by the transit times of the neuronal signals between the motor cortex and the muscle.

**Using MEP, MT and time measurements to study the brain**

The MT, the MEP and the latency time are useful measures, because they are affected by external influences which can have a facilitatory effect or an inhibitory effect on cortical excitability. Together with changes in latency times, these influences can give an insight into brain function. In the following I give some examples of experiments where this effect has been used.

**Voluntary muscle contraction**

The MT decreases and the MEP increases during voluntary muscle contraction of the target muscle. This has been shown in many experiments (e.g. Hess et al. [1986], Ugawa et al. [1997]). This effect must be considered when determining the MT. The MT during muscle contraction is known as the active motor threshold (aMT). This is in contrast to the resting motor threshold (rMT) measured with relaxed muscles.

This muscle contraction is also interrupted by the TMS pulse for a short period of time. In the EMG signal this can be observed as a silent period compared to the signal with a high amplitude during the contraction. This period is known as the cortical silent period (cSP). The cSP is typically of the order of 150 ms in duration but this time is dependent on the intensity of the
CHAPTER 2. TRANSCRANIAL MAGNETIC STIMULATION

Figure 2.9: Example of facilitatory effects for different ICI. A suprathreshold conditioning pulse was followed by a subthreshold (90% MT) test pulse. The y-axis indicates the MEP size in % of the MEP size produced by the conditioning pulse alone. Strongest facilitation occurs for ICI’s of 1.1-1.5 ms and for 2.3-2.9 ms (Ziemann et al. [1998]).

stimulation. Different groups have studied the cSP (e.g. Kessler et al. [2002] (stroke) or Wu et al. [2000] (using a conditioning TMS pulse)).

**Paired pulse TMS**

In paired pulse experiments, a conditioning TMS pulse is given over another brain region prior to the main pulse over M1. This conditioning pulse can induce changes in the motor cortical excitability in the form of an increased (facilitatory) or decreased (inhibitory) MEP. Such experiments can demonstrate a connection of remote brain areas to M1 and measure the temporal characteristics of the connections between these areas. The effects are classified in terms of short intracortical inhibition/facilitation (SICI/SICF) ISI <10 ms and long intracortical inhibition/facilitation (LICI/LICF) ISI >10 ms. An example of SICF with a conditioning and a test pulse applied over the same site is shown in Figure 2.9. Similar effects for LICI and LICIF were studied e.g. by Valls-Sol et al. [1992].
MEP and drugs

Many studies of the effects of drugs on the MEP have also been carried out, often using paired pulse TMS. These studies can reveal more specifically the effect of drugs on the cortical excitability and connectivity. A summary of the hitherto existing findings was written by Ziemann [2008].

Other application of MEPs

- Measurement of conduction times between the brain and different muscle groups (Dvork et al. [1991]).
- In clinical neurodiagnosis (Sandbrink [2008]).
- Changes due to attention, training or sensory influences OxT [2008].

2.6.2 TMS in perception and cognition

Methods to observe functional activity in the brain, such as fMRI or EEG can reveal brain areas which are active in a specific task. Use of correlation methods and a variety of tasks can deliver a sophisticated and reliable picture of the involved areas, but the contribution of each area is difficult to determine. A reliable way to study this, would be to deactivate each brain area and consequently study the effects. In animal experiments invasive methods can be used to achieve this effect, but animal brains are obviously not entirely comparable with human brains. Patients with lesions can offer a similar insight but they are restricted to case studies. TMS can provide another way to approach this problem by temporally disrupting the brain function of a selected area (Walsh and Pascual-Leone [2003]).

Direct disturbance of ongoing brain function

The immediate influence of a TMS pulse can disrupt the processing of brain signals. One of the first demonstrations of this effect was by Amassian et al. [1989] (Figure 2.10), who showed that a single TMS pulse applied over the primary visual cortex can inhibit the correct identification of a visual stimulus. The effect was found to be strongest when TMS was delivered between 80 ms and 100 ms after the visual stimulus. Similar effects were found by Corthout et al. [1999] and Cowey [2004]. These experiments show, that that the visual cortex is involved in the identification of the stimulus. The experiments also show the range of time over which the stimulated area is required
Correct letters per trial

Interval between visual and TMS stimuli

Figure 2.10: Effect of TMS on the perception of three letters. The letters were shown for about 18 ms. If TMS was applied between 80 ms and 100 ms after the letters were shown, a significantly lower proportion of the letters was identified correctly (Amassian et al. [1989]).

for the correct perception, also demonstrating clearly how the high temporal resolution of TMS can be used.

2.6.3 Virtual lesion approach

Another way to use TMS is called the ‘virtual lesion’ approach. This expression was first introduced by Pascual-Leone et al. [1999]. Since then this expression has been accepted widely in the TMS literature and many articles discuss this approach (Pascual-Leone et al. [2000], Ziemann [2009], Siebner et al. [2009]). It assumes that TMS introduces temporary functional lesions in the brain. The function of the affected brain area is unnaturally increased or decreased and the performance in associated tasks can be improved or degraded. These lesions can last between tens of ms for single pulse TMS up to long lasting (>5 minutes) effects for rTMS. The strength of the effect depends on the intensity and the frequency of stimulation.

2.6.4 Therapeutic applications of TMS

In addition to its use in neuroscience one of the most promising applications for TMS is in the treatment of brain-related disorders or diseases. The idea behind this is to suppress or stimulate brain functions which are involved in the disorder. The big advantage is, that TMS is non-invasive, relatively safe to use and only locally effective, while the effect of most drug treatments cannot be restricted to a certain brain area.
For the treatment of patients long lasting effects are desirable. Basically the brain should ‘memorise’ the effects of TMS. This effect on the brain is called long term potentiation (LTP). LTP is the enhancement of the signal transmission between two neurons which results from stimulating them synchronously (Cooke and Bliss [2006]). When used for treatment, TMS must be applied in a way that induces permanent or long-lasting changes which oppose the disorder. A more detailed summary of the potential of TMS-induced plasticity was written by Vorel and Lisanby [2008]. The field which has been explored most extensively, is the treatment of depression. The progress in this field has been reviewed by Loo and Mitchell [2005]. Several well controlled studies have reported clinically significant results, which show that TMS has the potential to become a tool for treating depression. Most importantly in 2008 TMS has been approved in the USA as a method to treat depression in medication-resistant patients (Millet [2009]).

There are also other disorders for which TMS forms a promising treatment modality. These include dipolar disorder, migraine, schizophrenia, Parkinson disease and chronic pain (Wassermann and Lisanby [2001], Lisanby [2008]).

### 2.7 TMS and Brain Imaging

Most experiments with TMS involve observation of direct responses such as MEPs or investigation of behavioural changes, such as in the performance in a specific task. Consequently such studies can be used to investigate the relationship between cause and effect, but the underlying neuronal activity is like a black box in between. To overcome this limitation TMS can be combined with methods, which allow the spatially resolved observation of brain activity. TMS also extends the range of these methods because of its ability locally to perturb the brain activity (virtual lesion). This allows mapping of the effect that a virtual lesion in one location has on the whole brain network.

Techniques which have been combined successfully with TMS are positron emission tomography (PET) (Paus et al. [1997]), electroencephalography (EEG) (Ives et al. [2006]) and functional magnetic resonance imaging (fMRI) (Bohning et al. [1998]).
2.7.1 TMS combined with PET

PET imaging uses radioactive isotopes, which undergo $\beta^+$-decay. During each $\beta^+$-decay a positron is created, which then annihilates with a nearby electron. During this annihilation two $\gamma$-photons are emitted in directions which make an angle of 180° to each other. An array of $\gamma$-detectors around the region of interest is used to detect these photons. If two detectors detect $\gamma$-photons at the same time it is likely that the origin of the photons is identical and that the location of the origin is somewhere on a straight line between the detectors. Using this approach a spatial map of the concentration of the tracer can be created. Commonly used isotopes in PET include $^{15}$O, $^{11}$C and $^{18}$F, which can be used to create a wide range of radioactive compounds as tracers. These isotopes have half-lifes of tens of minutes and must be produced at a location close to the scanner. This makes the application of PET expensive. PET can be used to quantify changes in cerebral blood flow (CBF) in general or the cerebral metabolic rate of the applied tracers.

The main direct influence of TMS on PET results from the magnetic field which can perturb the photomultiplier tubes that are commonly used for $\gamma$-detection (Thompson [1998]). The application of TMS itself can also be restricted by space limitations inside the PET-scanner.

Compared to fMRI, PET provides a lower spatial and temporal resolution. On the positive side PET provides quantitative measurements of regional cerebral blood flow, which makes it suitable for the detection of cumulative changes in blood flow. The use of tracers allows investigation of the uptake of specific neurotransmitters such as dopamine. The combination of TMS and PET is technically less challenging than concurrent TMS/fMRI. However the radioactive dose, the high price of the tracers and the limited availability of PET-scanners restricts the application of this technique on healthy subjects.

The first experiments with concurrent TMS/PET were carried out by Paus et al. [1997], who showed a dose-dependent decrease in CBF in the sensorimotor cortex. Other examples of experiments were for example presented by Siebner et al. [2000], who used fluorodeoxy-D-glucose to visualise synaptic cortical activity after rTMS.

2.7.2 TMS combined with EEG

An EEG system consists of a cap with many electrodes, a very sensitive multi-channel amplifier and a recording system. The cap is pulled tightly over the subject’s head, so that the position of the electrodes is relatively stable. The electric resistance between the electrodes and the scalp is
minimised using a conductive gel. The electrical potential between electrodes is measured with a sampling rate of the order of 5kHz.

Changes or oscillations in the local electric potential can indicate ongoing electrophysiological processes in brain areas below the electrodes. EEG has a poor spatial resolution, which is limited by the number of electrodes and the smearing out at the scalp of potentials produced by neuronal current flow in brain tissue. The localisation of the sources of measured voltages is difficult, especially for processes occurring in deep brain areas. On the positive side, EEG has a high temporal resolution and the measured signal provides a more direct indication of neuronal activity than signals used in fMRI or PET.

A TMS pulse has a strong effect on the measured EEG signals, which spoils the signal for the duration of the pulse and a short period afterwards (Veniero et al. [2009]). TMS pulses can also cause movement or heating of the electrodes (Virtanen et al. [1999]). An important requirement is, that the amplifier is protected against high voltage, so that it is not damaged by a TMS pulse and that it produces reliable data after a short latency time. Apart from potential heating of the electrodes, EEG recording does not restrict TMS as the cap is generally thin enough to allow the TMS-coil to be freely positioned. EEG-data from concurrent TMS/EEG must be analysed and interpreted very carefully, because TMS can produce artefacts, which lead to false positive results during the most interesting periods directly after the pulses (Veniero et al. [2009]).

Concurrent EEG/TMS can be used to measure temporal characteristics of the spread of brain activity after a pulse stimulation (e.g. Ilmoniemi et al. [1997], Paus et al. [2001]). Also long-term effects of rTMS can be measured using EEG (Schutter et al. [2001]).

2.7.3 TMS combined with fMRI

fMRI has been discussed in Section 1.2 and the technical challenges arising from the combination of TMS and fMRI are discussed in detail in Part II of this thesis. Combining these two techniques is challenging, mainly because of the strong interactions between the field of the TMS pulses and the field of the MR-scanner. Synchronisation of TMS and fMRI is required to avoid artefacts and the range of applicable TMS-paradigms is limited by the MRI-sequence. Combining the advantages of both techniques allows an insight into the brain activity with a higher spatial and temporal resolution than can be produced using PET. Also MRI does not involve any harmful radiation and MR-scanners are more common, more accessible and cheaper to run than PET-scanners.
The first experiments with concurrent TMS/fMRI were carried out by Bohning et al. [1998]. Since then only a few groups in the world have carried out experiments using both techniques. A large contribution to this field has been made by the Wellcome Trust Centre for Neuroimaging at University College London. A review paper about the combination of TMS and fMRI was written by Bestmann et al. [2008].

2.8 TMS and Safety

The voltage and the current inside the coil during a TMS pulse is high enough to be potentially lethal and far higher compared to what is present in electrical devices that are in daily use. Appropriate insulation of all high voltage leads and a safety circuit, which protects the stimulator against incorrect handling, reduces this risk to a minimum. Heat sensors disable the stimulator, when the coil gets too warm.

The risks arising from the effects of TMS are more problematic and cannot be eliminated easily by changing the design of the equipment, since reducing the field of TMS inside the brain also reduces the effect of TMS.

Is Transcranial Magnetic Stimulation harmful to the brain?

The answer to this question can only be answered empirically based on all the experiments which have been carried out with TMS so far. For this purpose leading researchers in the field of TMS gathered together in 1996, to set up guidelines for the range of parameters for which TMS is safe. The results of the workshop were published by Wassermann [1998] and Chen et al. [1997b]. These guidelines were updated during another workshop in 2008 (Rossi et al. [2009]). Furthermore a detailed review paper about the effects of applying TMS to cortical areas other than the motor cortex was written by Machii et al. [2006]. In the following text the risks and the application guidelines are summarised.

Seizure Risk

The induction of seizures is the most acute severe adverse effect of rTMS. It occurs, when rTMS decreases the intrinsic inhibitory neural activity so much that hypersynchronised discharges between groups of neurons occur. In some therapeutic studies seizures have been triggered intentionally (e.g. Lisanby [2002]), but also in a very small number of cases seizures were induced accidentally.
Since no other comparably strong side effects were reported, the tables in the guidelines give values, which are considered to be safe in terms of seizure induction. Since the introduction of the safety guidelines a large number of papers on TMS have been published. Therefore the tables from the safety guidelines show parameters, which are based on a huge database. Only four cases of accidental seizures have been reported to have occurred with operation within the safety guidelines. Three of these seizures occurred in patients taking pro-epileptogenic medication and two of them may not have been directly TMS-related seizures. Table 2.2 shows safe protocols for a single train of TMS pulses and Table 2.3 for series of 10 trains. Safe means the absence of a seizure. A few remarks have to be made in order to complete the picture about stimulation paradigms and safety.

- Single pulse TMS is considered to be safe.

- There are currently no safety guidelines for theta burst stimulation (TBS) because the technique is relatively new. One seizure caused by TBS has been reported.

- The determination of the MT only by a visual twitch can lead to an overestimation of the MT and therefore to a higher dose of TMS. Using EMG to measure the MT is more reliable.

- Several factors can increase the risk of inducing an epileptic seizure.
  
  Related to the protocol:
  - A 'novel paradigm' which goes beyond classical methods, e.g. a new coil or a new temporal distribution of the TMS pulses.
  - Intensities beyond the safety guidelines.

  Related to the patient’s condition:
  - Personal history of epilepsy
  - Lesions in the brain
  - Administration of certain drugs. A list is included in the guidelines.
  - Sleep deprivation, alcoholism

Other side effects

There are other potential hazards or side effects related to TMS. The following list gives a short description of their relevance.
Table 2.2: Maximum safe number of pulses in a single rTMS train. Numbers preceded by ‘>’ show the maximum number of pulses which was tested.

<table>
<thead>
<tr>
<th>Frequency /Hz</th>
<th>90</th>
<th>100</th>
<th>110</th>
<th>120</th>
<th>130</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&gt;1800</td>
<td>&gt;1800</td>
<td>&gt;1800</td>
<td>&gt;360</td>
<td>&gt;50</td>
</tr>
<tr>
<td>5</td>
<td>&gt;50</td>
<td>&gt;50</td>
<td>&gt;50</td>
<td>&gt;50</td>
<td>&gt;50</td>
</tr>
<tr>
<td>10</td>
<td>&gt;50</td>
<td>&gt;50</td>
<td>&gt;50</td>
<td>42</td>
<td>29</td>
</tr>
<tr>
<td>20</td>
<td>41</td>
<td>41</td>
<td>32</td>
<td>20</td>
<td>11</td>
</tr>
<tr>
<td>25</td>
<td>32</td>
<td>32</td>
<td>21</td>
<td>10</td>
<td>6</td>
</tr>
</tbody>
</table>

Table 2.3: Safety recommendations for number of pulses per train for 10 trains of TMS pulses with inter-train intervals of 5 seconds.

<table>
<thead>
<tr>
<th>Frequency /Hz</th>
<th>100</th>
<th>110</th>
<th>120</th>
<th>130</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>270</td>
<td>270</td>
<td>180</td>
<td>50</td>
</tr>
<tr>
<td>5</td>
<td>50</td>
<td>50</td>
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<td>50</td>
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<tr>
<td>10</td>
<td>50</td>
<td>50</td>
<td>32</td>
<td>22</td>
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<td>20</td>
<td>30</td>
<td>24</td>
<td>16</td>
<td>8</td>
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<tr>
<td>25</td>
<td>25</td>
<td>17</td>
<td>7</td>
<td>5</td>
</tr>
</tbody>
</table>
• **Noise/Mechanical impact**
  During the discharge the forces inside the coil cause an intense noise. Therefore hearing protection is recommended during TMS and patients with hearing problems should only be stimulated under certain circumstances.
  Noise and vibrations are much more intense in concurrent TMS/fMRI and therefore they will be discussed separately (Section 6.3).

• **Headache/local pain**
  This problem occurs frequently for rTMS. The origin is unclear but possibly linked to TMS-related muscle contraction or to the posture of the patient or pressure from the coil against the head. The effects vanish rapidly in the majority of cases.

• **Cognitive/neurophysiological changes**
  In experiments in cognitive neuroscience TMS can produce desired (short lasting) changes in the cognitive domain, which can be detected through changes in the performance of subjects in a given task. These changes are usually small and they do not raise particular safety issues. They disappear within tens of minutes.
  Possible hazards regarding long-lasting cognitive changes are related to cumulative effects of repeated sessions of TMS for the treatment of psychiatric diseases. Only a few cases have been reported and it is possible that they were related to a placebo effect.

• **Magnetic and electric field exposure to the subject and the operator**
  The magnetic and electric field exposure to the subject appears to be safe and in all aspects far below the threshold of what must be considered as harmful. Single patients have received up to 420,000 pulses with no side effects. Nevertheless many aspects of long-term exposure to pulsed magnetic fields are still unclear.
  A directive from the European Parliament (directive 2004/40/EC) introduced exposure levels for non-ionising electromagnetic fields for the operator. Karlstroem et al. [2006] addressed this problem for TMS and concluded, that the limits are transgressed at distances of about 70 cm from the coil. However the start of the directive has currently been postponed in part because of its incompatibility with MRI.

• **Interaction with electrical circuits, surface electrodes or implants**
  TMS can induce significantly stronger currents in metallic objects and thus heat them up
significantly. Skin electrodes can cause burning of the scalp and implants inside the brain can damage the tissue. Besides this, TMS can cause a malfunction of electronic devices such as cochlear implants or internal pulse generators. TMS should only be used on subjects with implants if the site of the stimulation is at a significant distance from the implant.

**Standard questionnaire**

In the safety guidelines a standard screening questionnaire was suggested, which should be filled out by candidates for TMS. Because of its high relevance this questionnaire it is reproduced here.

1. Do you have epilepsy or have you ever had a convulsion or a seizure?
2. Have you had a fainting spell or syncope? If yes, please describe in which occasion(s).
3. Have you ever had severe (i.e., followed by loss of consciousness?) head trauma?
4. Do you have any hearing problems or ringing in your ears?
5. Are you pregnant or is there any chance that you might be?
6. Do you have metal in the brain/skull (except titanium)? (e.g., splinters fragments, clips, etc.)
7. Do you have cochlear implants?
8. Do you have an implanted neurostimulator? (e.g., DBS, epidural/subdural, VNS)
9. Do you have a cardiac pacemaker or intracardiac lines or metal in your body?
10. Do you have a medication infusion device?
11. Are you taking any medication? (Please list)
12. Did you ever have a surgical procedure to your spinal cord?
13. Do you have spinal or ventricular derivations?
14. Did you ever undergo TMS in the past?
15. Did you ever undergo MRI in the past?
CHAPTER 2. TRANSCRANIAL MAGNETIC STIMULATION

Affirmative answers to one or more of questions 1-13 do not represent absolute contraindications for TMS, but the risk/benefit should be carefully balanced by the investigator. The guidelines can be used to estimate the risk.

The only absolute contraindication to TMS is the presence of metallic hardware close to the discharging coil. Besides this, the induction of a seizure is the greatest risk. This can be nearly eliminated by following the guidelines for dosing of rTMS and by making sure, that the patient is not in a condition, which is associated with a decreased seizure threshold.
Chapter 3

Set-up for combined TMS/fMRI

3.1 MRI-system

Philips Achieva 3T (Figure 3.1) and Philips Achieva 1.5T MR-systems, operating at 3 tesla and at 1.5 tesla respectively, were used for the experiments described in this thesis. Both scanners are very similar apart from their field strength. They have the same user terminal and the accessories and the environment around the scanner are nearly identical. Most tools or pulse sequences which are developed for one scanner can be implemented with only minor changes on the other. The majority of the experiments were carried out on the 3 T system. The following information refers to this scanner.

- **Bore**: The scanner has a bore with a diameter of 60 cm inside the body RF coil.

- **Gradients**: The maximum gradient amplitudes are 40 mTm$^{-1}$ with slew rates of up to 200 Tm$^{-1}$s$^{-1}$

- **Shimming**: The scanner is equipped with second order room-temperature shim coils.

- **RF-coils**: A range of RF-coils is available for the scanner. The following RF-coils were used in the work described in this thesis:
  - Body coil. Integrated in the scanner bore, used mainly for RF transmission, but can also be used for signal reception.
  - 8-channel head coil (Figure 3.2), used for signal reception for standard brain scans.
CHAPTER 3. SET-UP FOR COMBINED TMS/FMRI

Figure 3.1: Philips Achieva 3T MR-system for whole body imaging.

Figure 3.2: 8-channel head coil

Figure 3.3: FlexL-coils

Figure 3.4: FlexS-coils
Figure 3.5: Nova coil

- FlexL coils (Figure 3.3). Pair of flexible surface coils which have a circular shape. The average diameter of each ring is 20 cm.
- FlexS coils (Figure 3.4). As FlexL, but with a diameter of 11 cm.

The scanner is sited inside a screened room. A wave-guide allows equipment inside the screened room to be connected to equipment in the control room.

3.1.1 Nova-coil

A special receiver coil (Figure 3.5) became available during the last year of my PhD project. It was manufactured by Nova-Medical-Ltd company (Boston, USA). In the following I will call this coil the Nova-coil. The Nova-coil was previously used by the group of Daryl E. Bohning at the Medical University of South Carolina, where they carried out the first successful experiments with concurrent TMS/fMRI (Bohning et al. [1998]).

This coil is a 6-channel receiver array. It has a cylindrical shape with an inner diameter of 300mm, outer diameter of 352mm and a length of 330mm. The coil is open at its superior end and it consists of front and back parts, each compromising 3 receiver elements. The front part can be detached, providing a better access to the subject. Cables from both parts of the coil join in an
acquisition box, which has to be accommodated on the scanner bed.

The software of the scanner was modified, so that the scanner could recognise the coil under the name 'Test1' in the coil option when setting up a sequence. Some initial tests were carried out which proved that the coil does not overheat during scanning and that it can be used safely to scan human subjects.

Two rails are attached to the scanner bed which have an indentation, which matches the outer diameter of the coil. These rails hold the coil stably in place. An insert, which matches the inner diameter of the coil is used to accommodate the head of the subject. The acquisition box is placed on the scanner bed and covered with a foam mattress. When the subject is placed on the scanner bed, special attention is paid, that there is no direct contact of skin to the cable, which connects the coil to the acquisition box. Otherwise there is a small chance that accidentally circuits is created which are in resonance with the transmitted RF and therefore they could heat up during the scanning.

3.2 TMS System

3.2.1 Stimulator

A Magstim Rapid² (Magstim Company, Whitland, Wales) stimulator was used for TMS. It consists of a power supply unit (PSU), a main unit and touch screen as a user interface.

The following information describing this TMS system was either extracted from the manual (Mag) or the values were given to us by verbal communication with Magstim employees:

The stimulator sends out pulses with the shape of a full cycle of a cosine wave with a length of 400 $\mu$s. The voltage at 100% of the output power is 1670V. The maximum repetition rate for the pulses ranges from 50 Hz at 30 % of the maximum stimulation output power to 15 Hz at 100 % of the stimulation output power. The stimulator should only be used together with certified coils, which have an inductance of at least 15 $\mu$H.

The user interface can be used to adjust the pulse strength, to send out pulses and to program basic TMS pulse sequences. The sequence can be triggered using a button on the user interface of the stimulator or by using a footswitch. Alternatively it can be triggered by sending a TTL-pulse to the trigger port. Instead of using the interface port, all parameters of the stimulation can be
Figure 3.6: Picture of the main parts of the TMS-system (left). The lower box is the power supply and the upper box is the main unit of the stimulator with the connection for the coil-lead. On the top is a touch-sensitive display which is used to control the stimulator and to program pulse sequences. The MR-compatible TMS-coil is shown on the right.

controlled through the 26-pin port at the back of the main unit. This option was not used in the work described in this thesis.

3.2.2 MR compatible TMS-coil

The coil used in the experiments is a figure-of-eight coil specially designed for use in concurrent TMS/MRI experiments. All ferromagnetic materials have been removed from the coil. It is used together with the Rapid² coil adapter (model 3110-00) and a temperature sensor box that is introduced between the coil and the stimulator. According to Magstim staff, the Temperature Sensor Box simulates the heating characteristics without actually measuring the temperature of the MR-compatible coil.

The coil itself consists of two identical circular coils with an average diameter of 70 mm. Each coil is made of 10 turns of flat copper-wire with a cross section of 1.75×6mm². The diameter of the turns ranges from 53 to 93 mm. The two coils are attached together in the middle with a distance of 95 mm from centre to centre. The internal arrangement of the wire is identical to the 70 mm Magstim figure-of-eight-coil model 9925. The coil inductance is 25µH (Mag [2003]). From correspondence with Magstim, the peak of the magnetic field ranges between 0.8 Tesla and 1 Tesla on the Rapid² stimulator and 200 shots per hour are possible with 100% stimulator output. Our
experience shows that a higher maximum number of pulses ($\approx 700$) with 80 % stimulator output can be applied before the stimulator indicates overheating.

3.2.3 Safety when using the TMS-stimulator

The stimulator has safety circuits which monitor the temperature of the coil and which automatically disarm the stimulator if the coil overheats. Furthermore another circuit discharges the stimulator automatically if the TMS-coil is disconnected. Nevertheless the greatest risk when using the stimulator arises from the high voltage combined with the relatively large amount of charge which is stored in stimulator unit. The following rules must be observed when using the stimulator:

- Never disconnect the coil while the stimulator is charged.
- Regularly check the coil including the coil adapter and the temperature sensor box for any kind of damage. Examples are a crack in the coil or corroded pins of the connector. Any damaged equipment must not be used
- The first thing to be done under any unusual occurrence is to disarm the stimulator.

3.3 Characterisation of stimulator and MR-compatible coil

3.3.1 Temporal shape of a TMS pulse

The rate of change of the magnetic field produced by the TMS-coil can be measured by connecting a simple wire loop (acting as a search coil) to an oscilloscope. The amplitude of the result is not calibrated, but the temporal variation and relative differences in the fields produced by TMS pulses can be measured with a high precision. In Figure 3.7 the induced voltage for a single pulse is shown. As the measured voltage is proportional to $\frac{dB}{dt}$, the integral of the measured voltage shows the evolution of the magnetic field over time. This is also proportional to the current through the TMS-coil. The function from Equation 3.1 which describes a damped LCR-circuit agrees well with the measured pulse shape.

$$I(t) = \frac{U_0}{L\omega} e^{-\frac{R}{2L}t} \sin(\omega t) \quad \text{with} \quad \omega = \sqrt{\frac{1}{LC} - \frac{R^2}{4L^2}}$$  \hspace{1cm} (3.1)

Assuming an inductance of $L = 25 \mu H$ leads to values of 147 $\mu F$ for $C$ and 0.095 $\Omega$ for $R$. The corresponding circuit is shown in Figure 2.5. Together with the given maximum voltage of 1670
Figure 3.7: Voltage at the TMS-coil (top). The ‘measured’ line is the induced voltage in the conducting loop which was attached to the TMS-coil. This voltage is proportional to the voltage at the TMS-coil. The maximum voltage was adjusted to 1.67 kV in order to match the voltage which is delivered by the stimulator. Current through the TMS-coil (bottom). The measured line is the integral over time of the induced voltage in the conductor loop. The fitted curve is a single cycle of a damped sinus curve which describes the current through an LCR-circuit.
V, the current through the TMS-coil is clearly defined using Equation 3.1. After the main TMS pulse, there are still currents flowing through the TMS-coil over a period of up to 90 ms. The effect of these currents on MR-images is discussed in Chapter 5.

### 3.3.2 Spatial shape of the field of the TMS-coil

To calculate the spatial distribution of the magnetic field produced by the coils, the wire-paths are approximated as follows:

- The figure-of-eight coil consists of two identical circular coils.
- Each of the circular coils consists of 10 loops of flat wire with a width of 6 mm.
- The inner loop has a radius of 27.55 mm and the increment in radius for each loop is 2.1 mm.
- All the loops are connected in series.
- To approximate the width of the wires, they are separated into 6 thin wires with a separation of 1 mm relative to each other and carrying of 1/6th of the total current.
- The spatial distribution of the magnetic field for each of these wire loops was calculated using the Biot-Savart law (Equation 3.2).
- The whole magnetic field was obtained by calculating the vector-sum of the field’s produced by the 60 wire loops.

\[
B(r, t) = \frac{I(t)\mu_0}{4\pi} \int_{\text{loop}} \frac{dl \times (r' - r)}{|r' - r|^3}
\]  

(3.2)

- The same wire distribution was also used to calculate the vector potential \( A \) which is more directly related to the electric fields induced by TMS. It is calculated using Equation 3.3.

\[
A(r, t) = \frac{I(t)\mu_0}{4\pi} \int_{\text{loop}} \frac{dl(r')}{|r' - r|^3}
\]  

(3.3)

Maps of the field variation produced by a current of 4000 A in the coil are shown in Figure 3.8. The strongest magnetic field can be found close to the wires at the inner side of the two rings and not exactly in the centre of the figure-of-eight coil. The region with the strongest magnetic field is butterfly-shaped.
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Assumed wire-paths in the TMS-coil
| B | in a plane that is parallel to the coil and located 10 mm away from the surface
| B | in a plane perpendicular to the coil over the middle of the coil

Figure 3.8: Assumed wire distribution (left), magnetic field produced by a current of 4000 A in the coil: Absolute value of $B_{TMS}$ in a plane 10 mm away from the surface of the TMS-coil (middle) and through the long axis of the coil (right). The colour-bars show the field strength in tesla.

| A | in a plane parallel to the coil, 10 mm away from the surface
| A | in a plane perpendicular to the coil, parallel to the middle axis

Decay of $|A|$ with the distance from the coil.

Figure 3.9: Absolute value of the magnetic vector potential produced by a current of 4000 A in the coil. The focality of $A$ is much better than of $B_{TMS}$. In the graph it can be seen, that a displacement of the coil by 10 mm decreases $|A|$ about 10 %.
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The vector potential $A$ is calculated, assuming the same current. The maps shown in Figure 3.9 demonstrate that $A$ is much more focal than $B$. The focal region of $A$ is around 20 mm in size which means that a precision of $\pm 10\, \text{mm}$ is required in coil positioning.

This estimation is only correct under the assumption that the electric field produced by the TMS pulse is approximately proportional to $|A|$. However to calculate the $E$ properly, a model for the conductivity of the head is required (Thielscher and Kammer [2002]).

The results of the field calculations of $A$ and $B$ are used for simulations in several sections of this thesis.

3.4 Equipment for concurrent TMS/MRI

3.4.1 Mounting for the MR-compatible TMS-coil

A 'home-built' mount is used to fix the TMS-coil inside the MR-scanner. In producing this design, the weight of the coil and the limited space inside the magnet bore had to be taken into account. The mounting also needed to be designed to allow easy positioning of the coil over most head areas. This coil mounting was designed so as to allow the coil to be positioned over the target area outside the scanner, and to also allow some minor adjustments to be made from the back end of the scanner when the volunteer is positioned inside the scanner.

The mounting is described in Figure 3.10. This concept for the mounting has proven to be satisfactory. It is possible to position the TMS-coil in a reasonable time ($< 5$ min) so that its centre is positioned over a wide range of points anterior to, at the left or the right or on the top of the head of a human subject. Nevertheless the screws must be tightened strongly to deal with the vibrations of the TMS-coil which occur when TMS is applied inside the scanner. Since some force is needed to tighten the screws it becomes more difficult to position the TMS-coil. Another approach for mounting a TMS-coil inside the MR-scanner has been described by Bohning et al. [2003].
Figure 3.10: Mounting for the TMS-coil. It consists of a baseplate, which is fixed to the scanner bed and a second baseplate, which can slide forward and backward on the first baseplate to allow easy movement of the TMS-coil in the foot-head direction. On the top plate a column is installed which has on its top a bearing (3) to hold a rod (4). One end of the rod is fixed in a bushing (5) which gives the possibility to adjust its length and to rotate it around the axis of the rod. It is connected to an adjustable plate for the left-right and for the posterior-anterior positioning (6). Both, the column and the adjuster can be positioned in seven different holes (7) to cover a wide range of positions range in the left-right direction. On the other end the TMS-coil (8) is fixed with two independent screws (9) allowing two more rotational degrees of freedom. The whole mount can be screwed to the scanner bed.
3.4.2 Head rests

Insert for the Nova-coil

A head-rest was built in order to accommodate the head inside the Nova-coil. The head-rest consists of a curved PVC-plate with an inner radius of 93 mm and an area of about $160 \times 170$ mm$^2$. On the top end of the plate, the corners are cut off to provide more space for the TMS-coil. The head-rest rests on two bars with cut-outs to form a precise fit. These bars are curved on the bottom with a radius of 150 mm and the surface on the bottom is rubberised. Therefore the bars fit tightly into the Nova-coil and the whole construction can be rotated along the inner walls of the coil. At the centre, the bars are narrow to keep the plate for the head as low as possible. For a higher head position there are spacers of 10, 20 and 40 mm thickness, which can be used to lift the plate.

The construction is designed to provide a range of different possible head positions inside the Nova-coil. This allows access to a wide range of target areas. Additionally foam pillows are used to fill the empty spaces between the head and the coil and to provide a comfortable and stable head position.

Head holder for the use with flexible receiver coils

A problem that occurs when flexible receiver coils are used is that the head of the subject is not surrounded by something solid onto which it can be fixed. This problem is solved with a holder for the head that can be screwed to the bed of the Philips scanners. It consists of a curved plate to lay the head on and two rods that can be adjusted and clamped perpendicular to the ears of the subject.

The subject is equipped with a cap, which is described in Section 3.4.4. The head is fixed by clamping it between the ear-shells of the cap using the two rods. The mount is shown in Figure 3.11.

3.4.3 Triggering

The MR-scanner sends out a trigger pulse at the beginning of every TR period. This pulse is detected by a PC with a program written in the "presentation" programming language. After receiving a trigger this program sends out a sequence of trigger pulses through its parallel port to
the trigger port of the TMS-system with adjustable delays.

The cable used for triggering connects a 25-pin parallel adapter to the 26-pin connector of the trigger-port. Pin number 5, which corresponds to number 16 (or $2^5 - 1$) is used for triggering.

Alternatively a National Instruments data acquisition card in combination with a Matlab program was used to send out the trigger pulses. In this case the signal was sent through a BNC-cable with an adapter to the 26-pin connector.

### 3.4.4 Miscellaneous tools

**Cap for the head**

In all experiments on human subjects a cap (www.speeddiving.de/uwr, Kappen) for the head, which normally would be used in water polo to protect the ears from impact or pressure, was used. It consists of a thin sheet of fabric over the head and of sturdy plastic shells over the ears. On the bottom it has a strap to tighten it. The cap has different purposes for the experiment.

- To reduce the acoustic noise, small foam pillows are placed between the ear-shells and the ears. The space occupied around the head by these ear-shells is much smaller compared to the ear defenders, which are normally used for MRI.

- The cap allows the head to be stabilised by applying pressure on the shells over the ears. The
cap is required for the use together with the head holder, when a volume coil is not available.

- For most subjects the cap has a fairly tight fit. It can be used to mark target areas for positioning of the TMS-coil.

### 3.4.5 Positioning with Brainsight System

A common way to do the positioning is to acquire an fMRI activation map based on a task, which reveals brain activity in the area that has to be stimulated. The resulting activation map is used to find and mark the right position in a structural image. Alternatively the target site can be defined just on the basis of certain landmarks in the brain. This structural image is then used with a Brainsight System (Rogue Research Inc, Montreal, Canada) (Figure 3.12). This system allows precise positioning of the TMS-coil at a defined location on the head-surface. For this, a 3-D infra-red camera is used and reflective spheres are fixed to the TMS-coil and to the subject’s head. The tip of the nose, the ears and nasion are identified as landmarks in the MRI data. The positions of these landmarks and of the TMS-coil are also registered in the real space to align the head and the image data. The camera uses the information to show the centre of the TMS-coil relative to the brain. It can now be placed over the marked structure and fixed in position.

To apply this system in experiments with concurrent TMS/fMRI the scanner bed is taken out of the scanner room. The subject must be rested in a stable position on the bed. One set of reflective spheres are attached to the MR-compatible TMS-coil while another set is fixed the head holder. For this method it is crucial to ensure that any movement of the head of the subject is suppressed, as the position of the markers is stable only relative to the head holder. The ears, which would normally be used as landmarks, are not accessible. Instead, the outer edges of the eyes and points at a distance of 100, 150 and 200 mm away from the nasion over the middle of the head are used as landmarks.

Once the coil has been fixed in position, the markers must be removed. The position of the head relative to the TMS-coil must then be maintained while the bed with the subject on is moved into the scanner.
CHAPTER 3. SET-UP FOR COMBINED TMS/FMRI

Figure 3.12: Positioning with the Brainsight system. In the left picture, the reflective spheres on the TMS-coil, on the subject and on the pen which is used for marking positions are visible. These markers must be visible at all the times to the camera during the positioning process. The position of the camera can be seen on the right picture. Permission for adding the photos was given by Andre Atunes.

Figure 3.13: Different ways of visualising MR-visible parts of the TMS-coil. The first three pictures show the maximum intensity projected along the y, x and z-axes. The last image shows a 3D-surface image, which was created using FSLview. All four pictures are based on the same MRI data.
Figure 3.14: Interface of the program which is used to determine the position of the TMS-coil. Four pictures on the right allow navigating through the image. The buttons on the left are used to mark points, to delete the previously marked point, to fit the shape of the coil to the marked points and to tell the program that the fit was successful. The white dots in the images show the marked points, the black curve the shape of the coil. It can be seen that in this case the fit was successful.
3.4.6 Verifying the position of the TMS-coil

A Matlab-based tool has been written to determine the exact position of the TMS-coil based on MRI data. It takes advantage of the MR-visible parts of the TMS-coil, which mostly consist of the rubber ring running around the coil. These visible parts are displayed in Figure 3.13.

The program allows the user to navigate through the data to change the image contrast. These options can be used to detect points on the rubber ring around the coil. If three or more points have been detected, the program displays a cut along a plane through the image. The plane is determined by a least-squares fit to the distance to all marked points. This cut helps finding more points.

When four or more points have been marked, the program can adjust the shape of the TMS-coil to these points using a matrix with 6 variable parameters (for 3 translational and 3 rotational degrees of freedom). The shape is represented by the parameterised form of the rubber ring around the TMS-coil. The fitting process can be repeated with different outcomes because the procedure has random starting values. Using more points increases the accuracy of the fit. The tool is optimised to work with an MP-RAGE image with a FOV of 256×256×256 mm³ and 2 mm isotropic resolution.

The main output of this tool is the matrix, which defines the transformation parameters between the space of the parameterised rubber ring around the coil and the coil position on the head. Using this matrix other distributions, which are defined in the space of the coil can be transformed into the image space and then be written into an image file. In the following some examples of these distributions are given:

1. **Distance to the coil surface:** This map can for example indicate how far the target area was away from the coil.

2. **Distance from a line, which is perpendicular to the TMS-coil and which passes through the centre point of the TMS-coil:** The map gives information about the exact position of the coil. For example the point, where the centre line perpendicular to the coil hits the brain surface, can be taken to display the coil position on the brain surface.

3. **Magnetic vector potential caused by a given current through the TMS-coil:** The vector potential inside the brain can be used together with a conductivity map of the brain to calculate the induced electric field. Since the vector potential is a vector field, the direction of the vector is also taken into account during the transformation process.
CHAPTER 3. SET-UP FOR COMBINED TMS/FMRI

4. Magnetic field caused by a given current through the TMS-coil: The local direction of the magnetic field is also rotated during the transformation. For MRI the z-component of the field in the coordinate system of the scanner has the dominant influence. This component was used for simulations of the effect of currents through the TMS-coil on EP-images (Section 5.2).
Part II

Compatibility between TMS and MRI
Introduction

The first question one has to answer before combining TMS and MRI is the extent to which the two techniques are compatible. Consideration of the fact that MRI requires a very uniform and stable magnetic field while TMS uses a strong and rather uncontrolled magnetic field suggests that the two techniques are intrinsically incompatible. However the successful experiments combining TMS and fMRI (Bohning et al. [1998] and Baudewig et al. [2000]) have disproved this assumption. To make this combination possible, the TMS pulses had to be synchronised with the MR-scanner in a way that they occur only during ‘silent’ periods of the MR-sequences. This avoids most of the interference on the imaging process which is caused by TMS.

Despite the fact that several groups have successfully carried out experiments involving the combination of TMS and fMRI, the problems involved in combining these techniques have been addressed in the literature in only a few papers. Bohning et al. [1997] measured the pattern of field perturbation produced by an MR-compatible TMS-coil by passing a small current through the coil and then using a B₀-mapping sequence. Baudewig et al. [2000] studied the effect of an MR-compatible coil on T₂*-weighted echo-planar (EP)-images. They concluded that the coil can cause severe artefacts, which may however not be too strong inside the brain because of the distance between the coil and the cortical surface. Bestmann et al. [2002] analysed the effect of TMS pulses on T₂*-weighted EP-images investigating the dependence of the timing of the TMS pulse relative to the imaging sequence. Their conclusion was that artefacts due to the TMS pulse can be avoided if the TMS pulse is applied at least 90 ms before the start of the EPI-sequence. If the time between the TMS pulse and the EPI-sequence is reduced, effects on the images can be detected and if the TMS pulse is applied between the RF-excitation and the acquisition, the image is highly corrupted. These findings are consistent with other statements in the literature (e.g. Bohning et al. [1998]). The suggested explanations of these findings are mostly that either leakage currents from the stimulator or vibration of the TMS-coil cause image perturbations when the TMS pulse is applied too close in time to the RF-excitation.

Weiskopf et al. [2009] approached the problem of leakage currents from the stimulator and developed a tool which eliminates this problem. This consists of a switch which bypasses the TMS-coil when no pulses are being applied.

In the following chapters a more complete picture of the artefacts and other problems specific to concurrent TMS/MRI is given.
Chapter 4

Influence of the presence of the TMS-coil on MR-images

In this chapter the influence of the presence of the TMS-coil on MR-images is analysed. This does not include the effect of the TMS pulses themselves. The following effects are discussed:

- $B_0$ inhomogeneities caused by the TMS-coil.
- $B_1$ inhomogeneities caused by the TMS-coil.
- Foldover from visible parts of the TMS-coil into the image.
- Ghosting artefacts from eddy currents in the TMS-coil.
- Radio frequency noise brought into the scanner room from outside by the TMS-coil lead.

4.1 $B_0$ inhomogeneities caused by the TMS-coil.

A uniform magnetic field is essential for MRI. Field perturbations cause MR signal dephasing and thus decrease the effective $T_2^*$ which leads to the production of a weaker signal in gradient echo images. This is a particular problem in gradient echo EPI sequences, where the echo-time, $TE$, is long. Field inhomogeneities can also cause spatial distortions in EP-images.

The magnetic susceptibility $\chi_m$ of any material which is introduced into the magnetic field causes field perturbations. Although this effect is weak for most non-ferromagnetic materials, it can
disturb images in MRI. Objects with a complex surface shape can also cause local gradients of the magnetic field. These field perturbations can be measured by analysing the phase of the signal generated using gradient echo techniques. The method and the sequence used for $B_0$-mapping is described in Section 1.5.2.

**Method**

In order to measure the $B_0$ inhomogeneities caused by the TMS-coil, $B_0$ field maps were taken without the TMS-coil and with the TMS-coil positioned close to the region of interest (either the head of a subject or a phantom).

A double-echo, GE-sequence was used for measuring the field offset (Section 1.5.2). A matrix size of 64x64x64 with a voxel size of 3x3x3 mm$^3$ gave an adequate resolution. The values of the timings were $TE_1=2.3$ ms, $TE_2=20$ ms and $TR=23$ ms. The acquisition time of this sequence was 3:08 minutes.

The shimming settings were important for these measurements. In auto-shimming the scanner measures the field inhomogeneities during the preparation steps of a scan in order to determine the ideal current settings for the shim coils. These settings are applied during the subsequent scan.

Volume shimming allows to define the area over which the field is optimised.

In these experiments, the first field map was acquired without the TMS-coil using auto-shimming. The TMS-coil was then positioned close to the ROI. For the second field-map, the automatic readjustment of the shims was turned off, so that a subtraction from the first field map revealed the contribution of the TMS-coil to the $B_0$ inhomogeneities. For the third field map, the shims were readjusted for the new field distribution which includes the inhomogeneities caused by the TMS coil. This field map reveals to what extent the TMS-coil related field inhomogeneities can be eliminated using shimming.

Two arrangements which produce different forms of field variations were considered. These arrangements are illustrated in Figure 4.1.

EP-images ($TE=35$ ms, phase-encoding BW = 28 Hz per pixel) were taken after the acquisition of each field-map using the same shimming settings. The EP-images were acquired with the same matrix size and the same resolution.

The simulator described in Section A.4 was used to calculate the signal reduction and the spatial deformation an EP-images acquired with the parameters described above. The spatial extent of
CHAPTER 4. INFLUENCE OF THE PRESENCE OF THE TMS-COIL ON MR-IMAGES

Figure 4.1: Effects of a diamagnetic object such as the TMS-coil on the $B_0$-field. The $B_0$-field is decreased where it hits the TMS-coil, but increased in areas where it passes around it. When the TMS-coil is positioned either inferior or superior to the ROI, this results in an increased field underneath the TMS-coil (left picture). If positioned anterior, posterior, left or right, the field is decreased in the ROI (right).

the phantom, which was used for the simulations, was defined using an MP-RAGE image.

Results

Figure 4.2 displays field maps acquired from a human head without and with the TMS-coil in position. Without the TMS-coil, strong field inhomogeneities in the $B_0$-field are visible, which can be explained by air/tissue interfaces such as those found in the sinuses. This figure shows that most of the moderate increase of the field in the area under the TMS-coil could be eliminated using shimming.

Figure 4.3 shows field maps of a phantom and without the TMS-coil attached. Here the TMS-coil is responsible for strong inhomogeneities in $B_0$, but also in this case most of these inhomogeneities could be eliminated using shimming. Figures 4.2 and 4.3 both follow the prediction which has been illustrated in Figure 4.1.

In Figure 4.4 the real and the simulated effects of the field inhomogeneities on EP-images are displayed. Good agreement between the measured and the simulated effects could be achieved. There are spatial distortions in the images in the area under the TMS-coil. The beneficial effect of shimming is less pronounced than one would expect from the improvement in the field-maps.
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**Figure 4.2:** Comparison of $B_0$-maps acquired from a human head without the TMS-coil (left), with the TMS-coil and without extra shimming (centre) and with the TMS-coil and full shimming (right). The TMS-coil was positioned on the left side of the head. The scale shows the frequency offset in Hz. In the image acquired without adjusting the shimming settings there is a significant increase in the $B_0$-field inhomogeneity, but after adjusting the shimming the distortions are reduced to a level comparable to the level without the TMS-coil.

**Figure 4.3:** Field maps similar to those shown in Figure 4.2, but acquired from the phantom and with the TMS-coil superior to the phantom. The field perturbations are stronger than in the head, but in this case also could be reduced by shimming.
Figure 4.4: Comparison of $B_0$-maps acquired from an elliptical gel-phantom with a diameter ranging between 11 and 16 cm. A coronal slice without the TMS-coil, with the TMS-coil and without extra shimming and with the TMS-coil either using a (150mm)$^3$ centrally positioned box for shimming or with shimming over the whole phantom. The TMS-coil was positioned on the top left side of the phantom as can be seen in the first image. 

- **a)** The frequency offset in Hz is shown.
- **b)** The effects on an EP-image (TE=35 ms, BW 2.46 kHz, 64×64×64 matrix, (3mm)$^3$ resolution) are simulated. The shape of the phantom used in the simulations was represented by the MP-RAGE image shown on the left.
- **c)** Spatial perturbations in measured EP-images show a good agreement with the simulation. The strong intensity variations in the EPI data are in this case related to problems with the receiver coil and they do not affect the measured distortions in the geometry.
Conclusion

It can be concluded, that most of the effects of the TMS-coil on the homogeneity of the $B_0$-field can be eliminated using shimming. The susceptibility effects of the coil after shimming are still present and they cause small distortions close to the TMS-coil.

In a human head only rather weak additional artefacts from the effects of the TMS-coil on the $B_0$-field should be expected because of the separation of the TMS-coil and the brain. The general $B_0$-inhomogeneities from air/tissue interfaces in the head are stronger and are more rapidly varying with position. $B_0$-perturbations due to the TMS-coil are small compared to these effects (Wilson et al. [2002]).

4.2 Effect on the homogeneity of the RF-field

In MRI, a radio-frequency (RF) pulse with a specific flip angle excites the protons in the selected slice. The flip angle is proportional to pulse strength $\times$ pulse duration. The applied RF fields are not necessarily homogeneous in space, as the fields are perturbed by the dielectric and weak conducting properties of the tissue. Good conductors can shield out the RF completely. It is important to control the flip angle, $\theta$, because the signal strength is (in the case of a single excitation) proportional to $\sin \theta$.

Higher magnetic fields produce higher Larmor-frequencies, meaning that the RF has a shorter wavelength and the inherent inhomogeneities tend to be greater.

In our case, the focus of interest lies on the influences of the TMS-coil on the flip angle. Influences can be expected because the TMS-coil consists mainly of copper wires which shield or strongly perturb the RF.

Methods

Measurements at 3T were carried out on an agar-filled, elliptical phantom with a diameter ranging between 11cm and 16cm. At 1.5T a spherical water-filled phantom with a diameter of 16cm was used. The method which was used to measure the RF-field is described in Section 1.5.3. The flip angle is calculated from Equation 1.41 by taking the ratio of the signal amplitudes in the two images. The flip angle was measured with and without the TMS-coil positioned close to the phantoms.
CHAPTER 4. INFLUENCE OF THE PRESENCE OF THE TMS-COIL ON MR-IMAGES

Figure 4.5: Comparison of $B_1$-maps acquired from an elliptical, agar-filled phantom at 3T. The maps are displayed in coronal and transverse orientations. The scale used relates to the percentage of the targeted flip angle. On the right the relative difference of the flip angle with compared to without the TMS-coil is shown. The area indicated by the white arrows is an artefact, which is caused by a foldover of signal from the MR-visible parts of the TMS-coil.

Figure 4.6: $B_1$-map of a phantom in the 1.5 Tesla scanner. The flip angle was set to 60°. Without the TMS-coil (left) and with the TMS-coil positioned over the superior-left position of the phantom. A clear reduction in the flip angle can be seen close to the TMS-coil.
CHAPTER 4. INFLUENCE OF THE PRESENCE OF THE TMS-COIL ON MR-IMAGES

Results

The results obtained at 3 T are shown in Figure 4.5 and at 1.5 T in Figure 4.6.

There is an influence of the TMS-coil on the homogeneity of the $B_1$-field. In the $B_1$-maps acquired at 1.5 T, the flip angle is reduced in the region close to the coil (Figure 4.6). At 3 Tesla the flip angle is already inhomogeneous without a TMS-coil (Figure 4.5). Nevertheless there is a moderate local decrease in the flip angle just underneath the TMS-coil.

At both field strength the effect is so weak, that only sequences which require a high degree of RF homogeneity would experience a significant effect. The signal in images acquired using GE-EPI with long TR ($> T_1$) is roughly proportional to $\sin \theta$. If $\theta = 90^\circ$ is used, the signal reduction due to a reduction of 5% in $B_1$ is less than 0.4%. Therefore in GE-EPI, which is most commonly used for fMRI, the effects are negligible.

4.3 Fold-over artefacts from MR-visible parts of the TMS-coil

Parts of the TMS-coil which consist of rubbery materials are visible in MR-images. Specifically these form parts of the sheaths of the lead connecting to the coil, the rubber ring around the coil and some parts inside the coil housing. These parts which are shown in Figure 3.13, disappeared, when GE-images were acquired with a TE of 10 ms or longer, which indicates that their $T_2^*$ values are low. They do not therefore appear in images produced using sequences with a long TE such as GE-EPI used for producing BOLD-contrast. In $T_1$-weighted images produced using structural sequences such as the MP-RAGE sequence (Section 1.4.1) they can be visible and thus can be used to determine the position of the TMS-coil as described in Section 3.4.6. These parts can also appear as fold-over artefacts in the images if they are located outside of the FOV in the phase-encoding direction. Often the TMS-coil is located close to the receiver-coil array and therefore in an area for which the coil has a higher sensitivity to the MR-signal compared to the area where the imaging FOV is located. This can amplify the effect and locally cause either a complete loss of signal or a massive increase in intensity.

The effects of a fold-over of the signal from the TMS-coil into the image are demonstrated in Figure 4.7. The effect is clearly related to the signal coming from the material in the coil.

This artefact can be neglected in BOLD-fMRI-studies where the data is acquired with long echo-
CHAPTER 4. INFLUENCE OF THE PRESENCE OF THE TMS-COIL ON MR-IMAGES

GE image, TE=2.3 ms, 192×192 mm² / MP-RAGE, TE=2.3 ms, 256×256 mm²

Figure 4.7: Fold over artefacts from the TMS-coil. On the left a GE-image with a 192×192 mm² is shown. A strong artefact can be seen on the left side in the image. On the right an image covering an area of 256×256 mm² is shown. In this image, parts of the TMS-coil are visible. The position of the artefacts on the left agrees exactly with location where the fold-over of these parts would occur.

It can be necessary to run sequences with a short TE (< 5 ms) in the same session together with concurrent TMS/fMRI. In this case there are two straightforward ways to eliminate the fold-over artefacts. The fold-over-direction can be chosen to be parallel to the surface of the TMS-coil. In this case the MR-signal originated from the TMS-coil is not eliminated, but it appears outside of the brain. The other way is to leave these sequences to the end of the session and to remove the TMS-coil before running them.

4.4 Ghosting artefacts caused by eddy currents in the TMS-coil

In some cases, when the TMS-coil is positioned close to the head of the volunteer or to a phantom, strong ghosting artefacts can be observed in EP-images. These ghosting artefacts are usually asymmetric and the ghost appears mostly on the opposite side of the image to the TMS-coil (Figure 4.8). A similar effect can be observed if instead of the TMS-coil a sheet of several layers of aluminium foil was placed close to the phantom. From this observation it can be deduced that the artefacts are caused by eddy currents in the coil.
In EPI, a switched read-out gradient is applied with a polarity which alternates between consecutive phase-encoding steps. This gradient consequently induces alternating eddy-currents in any conducting structures. These currents will produce a magnetic field perturbation in the area close to the TMS-coil. This produces a local offset in the NMR frequency, which in turn causes a phase variation. In the readout direction this causes only a slight stretching or squeezing of the image due to the change in frequency. In the phase encoding direction it adds to the effect of the blips gradients with an opposite sign for even and odd echoes respectively. This leads to ghosting. The strength of the ghosting is dependent on the strength of the asymmetry in the phase between odd and even echoes. A phase difference of $\pi$ moves all the signal from the affected voxel into the ghost, which is shifted by exactly half the FOV in the fold-over direction.

**Ghost correction of the scanner**

The data processing of the scanner already includes a method to correct for ghosting artefacts by acquiring an EPI-echo-train of a whole volume without the phase encoding gradients. It measures the difference in phase of even and odd echoes and then subtracts this from the phase of even echoes during the acquisition of the images (Bruder *et al.* [1992]). The method works well for asymmetries in the read-out gradients and for other variations which are constant in the fold-over-direction. However this method cannot compensate for field-variations which are inhomogeneous in the fold-over direction.

**Read-out gradient strength**

The induced eddy currents are proportional to the rate of change of the read-out gradient. The resulting phase shift is proportional the the integral of the eddy currents over time. Therefore the phase shift is proportional to the strength of the gradients. The strength of the readout gradient is determined by Equation 1.15. Given a resolution in the readout-direction of $Res_x = 3\text{mm}$ and a bandwidth of 3.8 kHz this leads to a gradient strength of

$$G_x = \frac{\Delta \nu}{Res_x} \frac{2\pi}{\gamma} = 30\text{mT/m}.$$  \hspace{1cm} (4.1)

If the coil is positioned about 0.1m away from the centre in the readout direction, it experiences a change in the magnetic field of about 3 mT. The switching time of the gradient is about $t_s=280\mu s$ as measured by reading out the settings from the MR-scanner.
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Figure 4.8: Comparison of ghosting artefacts in a coronal view of volumes acquired using EPI. The image was acquired with different slice orientations and different fold-over directions. The white lines indicate the area where the ghosts occur. 

a) The TMS-coil was placed superior and to the left of the phantom. 
b) MP-RAGE image 
c) Transverse slice orientation with a fold-over direction L-R. A moderate ghost is visible in superior parts of the image. 
d) Coronal slice orientation with fold-over direction L-R. The ghost is significantly stronger compared to c). 
e) Coronal, but now fold-over direction F-H. The ghost is reduced significantly compared to c). 
f) Sagittal slices, fold-over direction F-H. The ghost is less pronounced than in the other examples. These examples show that the ghosting can vary strongly with slice orientation and the fold-over direction.
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4.4.1 Coil, lead and stimulator as an LCR-oscillating circuit.

A changing magnetic field, which is perpendicular to the coil surface, induces a voltage along the wire of every turn of the coil. A coil with \( n = 10 \) turns and with an average radius of each turn of \( r_c = 35 \) mm is assumed. The induced voltage is

\[
|U_{\text{ind}}| = \left| n \frac{dB}{dt} \cdot A \right| = n \frac{B_x}{l_s} \pi (r_c)^2 = \frac{10}{2.8 \cdot 10^{-4}} \pi (3.5 \cdot 10^{-2} m)^2 \approx 0.41 \text{V.} \quad (4.2)
\]

where \( A \) is the coil area. In an homogeneous field the voltage across the two halves of the coil would cancel out, but if the gradient is along the long axis of the coil the two halves of the coil experience different fields and the difference in the voltage would be similar to the result of \( U_{\text{ind}} = 0.41 \) V. The voltage is induced in the coil only during the switching of the gradient. An oscillatory LCR-circuit with a driving voltage \( U_{\text{ind}} \) can be used to describe the circuit (Figure 4.9). This model accounts for the fact that the connection to the coil in the stimulator is an open circuit. When the gradient strength reaches its target value \( U_{\text{ind}} \) drops to zero. According to information from the Magstim company, the capacitance of the TMS-coil lead is between 375 pF/m and 530 pF/m resulting in a total capacitance of about 3 nF for the lead. The maximum charge which flows through the coil would therefore be about 1.5 nAs for \( U_{\text{ind}} = 0.5 \) V which is several orders of magnitude below a level which could cause significant effects (see Section 5.2). The resonance frequency of the circuit is \( \omega_0 = \sqrt{\frac{1}{LC}} \approx 4 \cdot 10^6 \text{rad s}^{-1} \) which is well below the Larmor frequency of about \( 8 \cdot 10^8 \text{s}^{-1} \) and well above the gradient switching frequency. In conclusion the properties of the coil as an LCR-circuit are not responsible for ghosting artefacts in EP-images. This finding is supported by the observation that these artefacts are more likely to occur when the coil surface is tilted instead of being perpendicular to main axis of the scanner.
Figure 4.10: Induced field in the coil from a changing magnetic field (blue arrow) perpendicular to the coil surface. The component perpendicular to the coil causes a considerable electric field along the wire. Only a small amount of current can flow because the two ends of the wire in the coil are not connected and therefore the loop is not closed.

Figure 4.11: Induced field in the coil from a changing magnetic field (blue arrows) parallel to the coil surface. The component parallel to the coil surface, has a component perpendicular to the surface of the flat wire. This causes a small electric field in the wire. Current can flow in closed loops inside the layer of each wire.

Figure 4.12: Left: model of a section of wire (Cyan rectangle) which is approximated as a ring wire (black) in which eddy currents can occur. The dimensional measures are in mm. Right: Variation of induced phase shift with distance from the wire along the dashed line. We assume that a charge of $U_{ind} = 1.38 \cdot 10^{-3}$ As flows through the coil. The units are mm (x-axis) and rad (y-axis). Only the component of the field parallel to the z-axis of the scanner is relevant. To calculate this field component assumptions about the orientation of the TMS-coil are required. Instead therefore the modulus of the magnetic field was taken to calculate the phase shift. This leads to an overestimation of the effect.
4.4.2 Eddy currents inside the wire

Inside the TMS-coil, the wire consists of a flat copper cable with a width of \( a = 6 \text{ mm} \) and a thickness of \( b = 1.75 \text{ mm} \) and it is wound into \( n = 10 \) turns on each side of the figure-of-eight coil. Each half turn of the coil can be approximated as a flat, straight piece of this wire with a length of 70 mm. For a further reduction in complexity this is replaced by a rectangular shaped wire with a cross section of \( A_W = 2 \times 1.75 \text{ mm}^2 \) and a surface area of \( A_C = 350 \text{ mm}^2 \). The electric resistance around the circumference of wire in sums up to

\[
R_W = \rho_C \times \frac{l}{A_W} = 1.78 \times 10^{-8} \times 2 \times (5 + 70) \times 10^{-3} / (2 \times 1.75 \times 10^{-6}) \Omega = 7.6 \times 10^{-4} \Omega
\]

with the specific resistivity \( \rho_C \) of copper as taken as \( 1.78 \times 10^{-8} \Omega \cdot \text{m} \). Considering a change in the magnetic field perpendicular to the rectangle from zero to \( 3 \text{ mT} \), the total charge which has flown through the coil during the switching of the gradient gradient is calculated using

\[
Q_{\text{ind}} = \int_{\Delta t} \frac{U_{\text{ind}}}{R} dt = -\int_{\Delta t} \frac{dB}{dt} \cdot \frac{A}{R} dt = \frac{B \times A}{R} = 1.38 \times 10^{-3} \text{ As}.
\]  

(4.3)

In Figure 4.12 the phase shift induced by a coil of the assumed rectangular shape is shown.

For the simulation of these ghosting artefacts, the position of the TMS-coil is detected and only the distance of each voxel to the plane of the TMS-coil and the charge flowing through the coil are used as parameters. The asymmetric phase offset is calculated using the decay over distance which is shown in Figure 4.12.

These simulations are based on a model which is too simple to reproduce precisely the measured artefacts. For this a better model of the coil and the gradient field would be required and also the orientation of the different components of the field that arises from these current to the \( B_0 \) field would have to be taken into account. Furthermore it has not been taken into account that the ghost correction from the scanner partially balances out the phase offset. This doesn’t eliminate the ghosting. Instead it occurs in a weaker form, but on both sides of the image.

Nevertheless the fact that the simulations and the measurements show ghosting artefacts with a comparable strength, provides some support for the hypothesis that the ghosting artefacts are caused by eddy-currents inside the flat wires of the TMS-coil.

4.4.3 Reducing the ghosting artefacts

Experience shows that the ghosting artefacts are less significant if the fold-over direction is parallel to the coil-surface. In this case most of the ghost image occurs in a part of the image which would
Figure 4.13: Simulated ghosting artefacts caused by eddy currents in the wire of the TMS-coil. On the top coronal images with fold-over direction L-R and on the bottom transverse images with fold-over direction A-P are shown. 

a) An elliptical phantom with a realistic position of the TMS-coil was taken as a model. For the phase offset caused by eddy currents a model based on the curve illustrated in Figure 4.12 was taken with the charge that has flown through the coil and the distance to the plane of the coil as parameters. 

b) On the right a charge of 1 mAs was assumed. The simulation showed a moderate ghost in the coronal image and a weak ghost in the transverse image.

c) A charge of 3mAs was used for the calculation. The ghosting artefact is now strong in both images.
normally be empty and therefore these artefacts are easy to eliminate. Using a read-out direction which is parallel to the coil surface has the advantage, that the change in the magnetic field during gradient switching is small around the centre of the coil with the result that the eddy currents are smaller.

In the brain, ghosting artefacts are less significant than in phantoms because of the distance between coil and brain.

The ghosting effect could also be reduced by using a narrower wire inside the TMS-coil. Using a bundle of insulated wires instead of a single flat wire should eliminate the effect nearly completely.

### 4.5 RF interferences from the scanner

In MRI the receiver coils are used to detect a weak and highly controlled radio-frequency field. RF signals from external sources, whose frequency is close to the Larmor frequency can cause artefacts in the image. A single frequency corresponds to one position in the readout-direction. In most sequences using phase encoding this means that RF interference produces lines showing an increased signal running in the phase encode direction.

In EPI the phase encoding is coupled with the readout and therefore each external frequency corresponds to two adjacent frequencies and to a constant phase, which is added between two readout steps. Because of the reversal between odd and even echoes, artefacts or at least an increased noise level can be detected at two points which are arranged symmetrically.

To avoid influences from external sources, the scanner room is completely screened. It is possible to introduce cables or other narrow objects from outside into the scanner room through a waveguide. The waveguide is constructed so that it blocks RF in the range of the Larmor frequency of the scanner (Section 3.1).

For concurrent TMS/MRI, the lead of the TMS-coil is passed through this waveguide. This violates the screening and allows RF to travel along the copper cable into the scanner room and directly to the TMS-coil near to where the RF-coil is located. The part of the lead which is located outside the scanner room can work like an antenna which receives RF. The resulting RF interference can cause image artefacts which scale with the amount of RF which has been received. The level of interference depends on the orientation and length of the lead outside of the screened room and it scales with strength of the RF in the relevant frequency band inside the control room.
In this section, the amount of RF-noise which is brought into the scanner through the lead of the TMS-coil is measured and analysed.

**Method**

External RF leads to an increased level of noise, which can be detected by creating maps which show the spatially resolved signal to noise ratio (SNR) of EP-images. For each measurement an EPI-sequence (TE = 35 ms, TR = 4 sec, 64×64×64 matrix size, (3 mm)$^3$ resolution) was used and 30 dynamics were acquired. The standard deviation of the signal over time in each voxel was taken as a measure of the noise. To determine an SNR-map the mean signal value over all dynamics and voxels was calculated and then divided voxel by voxel by the noise-map (Section 1.5.4).

The measurements were repeated with different configurations:

- No TMS-coil attached.
- No TMS-coil, door of the screened room open thus violating the screening.
- TMS-coil attached, door closed, lead completely inside the screened room.
- TMS-coil positioned close to the ROI, a long part of the lead outside of the screened room.
- TMS-coil close to the ROI, a short part of the lead outside of the screened room.
- TMS-coil close to the ROI and connected to the stimulator, the stimulator is charged.

**4.5.1 Results**

The results of the noise measurements can be seen in Figure 4.14, and Table 4.1. They show clearly that the connection of the lead between the inside and outside of the screened room increases the RF-noise. This increases the noise level of the images in large areas. The noise shows peaks in several different points of the image.

The noise level is not increased significantly while the door is open and the the screening of the room is violated. It can be concluded that the lead forms an antenna which conducts the RF directly to the receiver coils. The strongest interference occurs when the lead is connected to the stimulator.

The noise cannot come from the electrical properties of the lead or the coil, because they are
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<table>
<thead>
<tr>
<th></th>
<th>No Coil</th>
<th></th>
<th>Coil positioned close to the ROI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Door closed</td>
<td>Door open</td>
<td>in screened room</td>
</tr>
<tr>
<td>SNR</td>
<td>100</td>
<td>97</td>
<td>98</td>
</tr>
</tbody>
</table>

Table 4.1: Values for the average SNR for different configurations with or without the TMS-coil and with the coil connected or not connected.

![Comparison of SNR- (top) and noise (bottom) maps acquired with different configurations for the TMS-coil and how it is connected.](image)

Figure 4.14: Comparison of SNR- (top) and noise (bottom) maps acquired with different configurations for the TMS-coil and how it is connected. The scale on the right shows values of the SNR. The noise is displayed with an arbitrary scaling. Red indicates a high and blue a low amplitude. The noise is notably increased when the lead is guided through the waveguide and even further when it is connected to the stimulator.

identical if the lead is passed through the waveguide or not. Furthermore the distribution of the increase in noise shows very little relationship to the position of the TMS-coil. Only a slight decrease in SNR can be observed at the top of the image where the TMS-coil was positioned and this can be related to the effect of $B_0$ and $B_1$ inhomogeneities.

Other data relating to the mean values of the SNR measurements are displayed in Table 4.2 and the images can be seen in Figure 4.15. In this case the maps are based on measurements which were carried out using flexible receiver coils. The large differences between the head and the phantom are caused by the long TE of saline compared to the average in brain tissue and by the noise introduced by physiological fluctuations in the brain data. Other differences can be caused
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<table>
<thead>
<tr>
<th></th>
<th>3T Phantom</th>
<th>3T Head</th>
<th>1.5T Phantom</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>left</td>
<td>top</td>
<td>left</td>
</tr>
<tr>
<td>No coil</td>
<td>84.5</td>
<td>107.8</td>
<td>38.4</td>
</tr>
<tr>
<td>Coil con.</td>
<td>84.7</td>
<td>84.1</td>
<td>29.1</td>
</tr>
<tr>
<td>Coil unc.</td>
<td>76.4</td>
<td>80.4</td>
<td>28.6</td>
</tr>
</tbody>
</table>

Table 4.2: Average SNR over the volume with different configurations (no TMS-coil; Coil connected to the stimulator; coil unconnected and lead left in screened room).

by different positions of the flexible RF coils in different measurement series, but the behaviour is consistent across the different samples.

At 3 T a decrease of the SNR could be observed in some of the measurements after putting the TMS-coil in place. However in this case there was no obvious sign, that keeping the TMS-lead in the scanner room made a strong difference. This is in contrast to the observation of the results presented in Table 4.1.

Images acquired at 1.5 Tesla showed strongly elevated noise levels when the TMS-lead was pulled out of the scanner room. In Table 4.2 it can be seen, that the SNR was reduced by more than 80%. This was independent of whether the cable was connected to the TMS-system or not, but the influences were slightly reduced when the length of the cable outside of the scanner room was reduced.

There was neither a significant reduction in the SNR observed, when the coil was placed adjacent to the phantom nor when the cable was led from inside to outside of the scanner room, but not attached to the phantom.

Conclusions

As expected, no strong increase in the level of RF-noise is produced just by the presence of the TMS-coil.

The problem is that the lead of the TMS-coil disturbs the screening of the scanner room and picks up RF-frequencies, especially in the 1.5 T scanner, and leads them directly to the receiver coils. A reason for the stronger influences at 1.5 T compared to 3 T could be that there are lots of other cables from computers close to the waveguide in the control room. They might act together with
CHAPTER 4. influence of the presence of the tms-coil on MR-images

<table>
<thead>
<tr>
<th>Image</th>
<th>No coil</th>
<th>Coil unconnected</th>
<th>Coil connected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head</td>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
<td><img src="image3.png" alt="Image" /></td>
</tr>
<tr>
<td>3 T</td>
<td><img src="image4.png" alt="Image" /></td>
<td><img src="image5.png" alt="Image" /></td>
<td><img src="image6.png" alt="Image" /></td>
</tr>
<tr>
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<td><img src="image9.png" alt="Image" /></td>
</tr>
<tr>
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<td><img src="image12.png" alt="Image" /></td>
</tr>
<tr>
<td>Phantom</td>
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<td><img src="image14.png" alt="Image" /></td>
<td><img src="image15.png" alt="Image" /></td>
</tr>
<tr>
<td>1.5 T</td>
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<td><img src="image17.png" alt="Image" /></td>
<td><img src="image18.png" alt="Image" /></td>
</tr>
</tbody>
</table>

Figure 4.15: Results from the noise-measurements made at 3 T on a human head (top), a phantom (centre) and at 1.5 T from a phantom (bottom). The TMS-coil was placed on the left. In the first column the temporal mean of the images are shown. The other rows display the SNR-maps without the TMS-coil, with the TMS-coil but with the cable pulled back into the scanner-room and with the coil connected to the stimulator which was outside the scanner room. The scale on the right gives the SNR value. At 3 T the SNR seems to be slightly reduced when the TMS-coil is in place. At 1.5 T the SNR is strongly reduced, when the TMS-coil is connected to the outside of the scanner room.
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Figure 4.16: Left: Survey image acquired with a flip angle of 15° with the TMS-coil unconnected. Right: Survey image acquired with a flip angle of 1° and with the TMS-coil connected. Arrows indicate the lines in the survey which come from certain RF-noise frequency.

the TMS-lead as a transmitter. Most likely there is also a larger amount of interference present at 64 MHz compared to 128 MHz.

At 1.5 T the reduction in SNR is so strong that the quality of the data in fMRI experiments would be greatly reduced and small BOLD-related signal changes would be nearly impossible to measure.

At 3T a reduction in SNR could be observed, but less significant than at 1.5 T.

In general the amount of RF-noise tends to be stronger if the lead of the TMS-coil outside of the screened room is longer. Connecting the TMS-coil to the stimulator increases this level further. The worst results were achieved when the stimulator was activated. The exact position of the cable can change the amount of the RF-noise.

Without further measures, using our current setup for combined TMS/fMRI in 1.5T would produce data with a significantly reduced SNR. The quality of the data would be too low to produce results which justify the effort. This is the main reason, why the great majority of experiments in this thesis were carried out at 3T.

At 3T the SNR was reduced in our measurement in the maximum by 70%. In most cases the reduction in SNR was small enough to produce suitable data.

4.5.2 Detecting and avoiding RF-noise

For a quick estimation of how strongly the data are affected by RF-noise, a standard survey scan can be run with a flip angle of 1° instead of 15°. This generally decreases the MR-signal from the sample which leads to a relative increase in the effect of external RF-noise. Bright lines in the image indicate an elevated level of RF at certain frequencies. This can be seen in Figure 4.17.
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Figure 4.17: Comparison of surveys with a flip angle of 1° (top) and noise-maps acquired from the standard deviation of an EPI-sequence with a flip angle of 10°. The length of the lead refers to the length of the lead between the waveguide and the stimulator outside the screened room.

If these lines are very significant, the length of the TMS-lead outside of the screened room must be reduced or the lead must be repositioned. The survey with the TMS-lead pulled back into the screened room can be used as a reference.

A promising approach is to position the stimulator as close as possible to the waveguide to reduce the length of the cable outside the screened room. There are also other strategies which can work, but which were not applied during the work of this thesis:

- The stimulator can be placed inside the screened room. This makes it more difficult to operate and it must be kept away from the magnet.

- An RF-filter can be installed in line with the TMS-lead. The main problem is that the filter must handle the strong currents and the high voltages during the TMS pulses (e.g. Blankenburg et al. [2008]).
Chapter 5

Effect of TMS pulses on MR-images

The influence of TMS pulses on MR-images and in particular on EP-images is analysed in this chapter. First the Bloch equations are used to approach the problem theoretically. The results are used to simulate the effect of TMS pulses on the longitudinal and transverse magnetisation. The properties of TMS pulses are also studied in detail. The results are compared with experiments in which the effects of TMS pulses on MR-images were measured. The results allow a conclusion to be drawn about the origin of the effects and how they can be suppressed.

5.1 Simulation of the effect of the TMS pulses on the magnetisation

The effect of TMS pulses is assessed by analysing the action of the additional magnetic field on the evolution of the longitudinal and transverse components of the magnetisation.

5.1.1 Approach

The influence on the evolution of the magnetisation is calculated using the Bloch-equations.

\[ \frac{dM}{dt} = \gamma M \times B \]  

(5.1)
The relevant magnetic field here is a combination of the field, $B_T(t)$, of the TMS-coil and $B_0$ of the MR-scanner. The field of the TMS-coil is not stationary, but it scales linearly with the strength of the time-varying current through the TMS-coil, $I(t)$. The combined field therefore changes its orientation and its absolute value, but for a single voxel it stays in the same plane. The coordinate system in the laboratory space can be orientated so that $B_0$ is aligned with the z-axis and $B_T$ lies in the x-z-plane. The combined field can then be expressed as

$$B(t) = B_0 + B_T(t) = \begin{pmatrix} B_{Tx}(t) \\ 0 \\ B_0 + B_{Tz}(t) \end{pmatrix},$$

and for the temporal derivative as

$$\frac{dB}{dt} = \begin{pmatrix} \dot{B}_x \\ 0 \\ \dot{B}_z \end{pmatrix}.$$  (5.3)

The ratio of the components of $B_T$ is constant

$$B_{Tx} \propto B_{Tz} \propto I(t).$$  (5.4)

The absolute value of the magnetic field is calculated from

$$B(t) = |B(t)| = \sqrt{(B_0 + B_{Tz})^2 + B_{Tx}^2}.$$  (5.5)

The angle between the resulting magnetic field and the $B_0$-field is

$$\theta = (B \cdot B_0) = \arctan \left( \frac{B_{Tx}}{B_0 + B_{Tz}} \right).$$  (5.6)

and the resulting rate of change of this angle with time is

$$\Omega = \frac{d\theta}{dt} = \dot{B}_{Tz} \frac{1}{(B_0 + B_{Tz})} \left( 1 + \left( \frac{B_{Tx}}{B_0 + B_{Tz}} \right)^2 \right) - B_{Tz} \frac{B_{Tx}}{(B_0 + B_{Tz})^2} \left( 1 + \left( \frac{B_{Tx}}{B_0 + B_{Tz}} \right)^2 \right).$$  (5.7)

The Bloch-equations are now transformed to a rotating coordinate system with the z-axis always aligned with $B(t)$. The coordinate system is rotated relative to the initial system by an angle, $\theta$.
around the y-axis. In the new coordinate system the magnetic field becomes

$$ B(t) \rightarrow B'(t) = \begin{pmatrix} 0 \\ 0 \\ B(t) \end{pmatrix}, $$

(5.8)

with a transformed magnetisation

$$ M \rightarrow M' = \begin{pmatrix} M'_x \\ M'_y \\ M'_z \end{pmatrix} = \begin{pmatrix} M_x \cos(\theta) + M_z \sin(\theta) \\ M_y \\ -M_x \sin(\theta) + M_z \cos(\theta) \end{pmatrix}. $$

(5.9)

If the magnetisation does not change in the original coordinate system, the temporal derivative in the rotating coordinate system must be expressed as

$$ \left( \frac{\partial M'}{\partial t} \right)_M = \begin{pmatrix} -\Omega M'_x \\ 0 \\ \Omega M'_x \end{pmatrix}, $$

(5.10)

and in this case the Bloch equations become

$$ \left( \frac{\partial M'}{\partial t} \right)_B = \gamma B(t) \begin{pmatrix} M'_y \\ -M'_x \\ 0 \end{pmatrix} = \omega \begin{pmatrix} M'_y \\ -M'_x \\ 0 \end{pmatrix}, $$

(5.11)

with

$$ \omega = \gamma B(t). $$

(5.12)

The subscripts $B$ and $M$ indicate the component which is assumed to be constant in the partial derivatives. The result is a set of differential equations (Equation 5.13) with $\omega$ as the Larmor-frequency and $\Omega$ as the angular speed of the rotating coordinate system. These can be solved analytically for given $B(t)$ and $\dot{B}(t)$.

$$ \frac{dM}{dt} = \left( \frac{\partial M'}{\partial t} \right)_M + \left( \frac{\partial M'}{\partial t} \right)_B = \begin{pmatrix} 0 & \omega & -\Omega \\ -\omega & 0 & 0 \\ \Omega & 0 & 0 \end{pmatrix} M $$

(5.13)
\[ M(t) = \begin{pmatrix} \cos \omega_0 t & -\frac{\omega}{\omega_0} \sin \omega_0 t & -\frac{\Omega}{\omega_0} \sin \omega_0 t \\ -\frac{\omega}{\omega_0} \sin \omega_0 t & 1 - \frac{\omega^2}{\omega_0^2} (1 - \cos \omega_0 t) & \frac{\omega_0}{\omega_0^2} (1 - \cos \omega_0 t) \\ \frac{\Omega}{\omega_0} \sin \omega_0 t & \frac{\omega_0 \Omega}{\omega_0^2} (1 - \cos \omega_0 t) & 1 - \frac{\Omega^2}{\omega_0^2} (1 - \cos \omega_0 t) \end{pmatrix} M(0) \] (5.14)

with
\[ \omega_0 = \sqrt{\Omega^2 + \omega^2}. \] (5.15)

To calculate the effect of a TMS pulse on the magnetisation the spatial and temporal variation of \( B_T \) has to be calculated. The spatial distribution of \( B_T \) can be calculated by applying the Biot-Savart law (Equation A.13) to an approximated version of the wire distribution inside the coil. How this field is determined is described in detail in Section 3.3. The exact position of the TMS-coil can be detected in the image and the resulting transformation matrix is then applied to move the simulated field into the same space. This procedure is described in Section 3.4.6. Based on this information, the equations are applied to each voxel, in order to determine the local change in the state of the magnetisation.

### 5.1.2 Influence on the longitudinal magnetisation

The longitudinal component of the magnetisation is one of the determining factors of the signal strength. RF pulses influence this component and during most MR-sequences, it reaches a steady-state after several TR-periods. Any effect on the longitudinal magnetisation causes a change in the level of the MR-signal until the steady state is restored. It is therefore important to estimate, how strongly a TMS pulse affects the longitudinal magnetisation.

The longitudinal component of the magnetisation relaxes with a function
\[ M_z(t) = M_0 \left( 1 - \left( 1 - \frac{M_i}{M_0} \right) e^{-t/T_1} \right). \] (5.16)

In this formula \( M_0 \) is the equilibrium magnetisation and \( M_i \) is the magnetisation at time, \( t = 0 \). The time constant \( T_1 \) is typically of the order of 1 second in brain tissues. The TMS pulse has a duration of shorter than 1 ms and therefore the effect of \( T_1 \) relaxation during the TMS pulse can be neglected in any simulation. To simulate the effect of the TMS pulse the Equation 5.14 is applied step-by-step with the simulated spatial distribution of the magnetic field. This is done using values describing the time variation of the current over the whole TMS pulse. After the TMS pulse has been applied it is assumed that the field of the coil is negligible and the coordinate space of the calculation is identical with the laboratory space.
5.1.3 Influence on the phase information

The phase of the magnetisation increases at a rate $\omega_0$ during a TMS pulse compared to the value $\gamma B_0$ under normal conditions. The contribution of $\Omega$ to $\omega_0$ is negligible because $\Omega < 10^{-4} \omega$. The phase-shift is caused by the field $B_T$ of a TMS pulse which is proportional to the current $I$ which flows through the wire of the coil. The phase shift is calculated as

$$\Delta \phi = \gamma \int_{t_0}^{t_1} \left( B_{Tz} + \frac{1}{2} \frac{B_{Tz}^2}{B_0} \right) dt$$

$$\approx \gamma \frac{\partial B_T}{\partial I} \int_{t_0}^{t_1} \left( B_{Tz} \frac{B_{Tz}}{B_T} + I^2 \frac{1}{2} \frac{\partial B_T}{\partial I} \frac{B_{Tz}^2}{B_T^2} \right) dt$$

where $B_{Tz}$ is the component of $B_T$ parallel to $B_0$ while $B_{Tx}$ is the perpendicular component. The signal reduction in EP-images due to TMS pulses is mostly dependent on the spatial gradient of the phase shift. A simple way to estimate the signal reduction $\Delta S_p$ is shown in Equation (5.18) where the vector $e_r$ stands for the resolution in the three directions. In this case the additional intravoxel dephasing of the gradients of the MR-scanner are ignored.

$$\Delta S_p/S = 1 - \text{sinc}(\nabla \phi \cdot e_r/2)$$

(5.18)

For a better approximation this phase shift is calculated over the image and then used in the EPI-simulator (Section A.4) in order to calculate the influence on EP-images.

Inhomogeneities in the $B_0$-field during the acquisition of EPI can also cause spatial distortions, but at this point, it is assumed here, that there are no remaining residual currents at the onset of the EPI acquisition-train. The image experiences the same spatial distortions as in the absence of a TMS pulse.

5.1.4 Influence on the slice selection

An additional magnetic field that is present during a slice selective RF-pulse shifts the position and shape of the excited region. The local displacement $\Delta z$ can be quantified using

$$\Delta z = \Delta B_z/G_z.$$ 

(5.19)

Here $G_z$ is the strength of the slice selection gradient and $\Delta B_z$ the additional field in the z-direction. Any shift in the slice position is relevant, not only for the affected slice, but also for the adjacent
slices. If the excited area then overlaps adjacent slices, the steady state of the magnetisation is

disturbed. This also has an effect also on the following images acquired with subsequent excitations.

This effect therefore has a special importance because it can persist over a significant number of

repeated image acquisitions.

5.1.5 Influence of leakage currents through the TMS-coil

After each TMS pulse the whole TMS-system needs a certain time to recharge. During this time,

it is possible, that currents are still present in the TMS-coil. These currents are small compared to

the currents during the TMS pulse, but because of the low resistance of the TMS-coil, they still can

be of the order of tens of mA. If TMS is applied briefly before the RF-excitation, these currents can

influence the slice selection and the phase of the signal. For the slice selection the current during

the RF-pulse is relevant. Considering the influence on the phase information, Equation 5.17 for

small currents translates into

\[
\Delta \phi = \gamma \frac{\partial B_T}{\partial t} \frac{B_T z}{B_T} \int_0^{T_E} I(t) dt .
\]  

(5.20)

The integral \( \int I(t) dt \) of the current over the time between the RF-excitation (t=0) and the acqui-

sition (t=TE) is the relevant measure.

5.1.6 Example calculations

Longitudinal magnetisation

The change in the longitudinal magnetisation is calculated using the approach which was described

in Section 5.1.2 and which is based on Equation 5.14. The following example describes a conser-

vative estimate where the strength of the TMS pulse is similar in strength to the \( B_0 \)-field.

It is assumed that \( B_0 = 3 \, T \) (\( \omega = \gamma B_0 = 128 \, MHz \)), and a TMS pulse with a rise time of 100 \( \mu s \) and

a maximum field strength of 1 \( T \) is applied perpendicular to \( B_0 \), then \( \Omega = \frac{\Omega}{B_0} = \frac{10^{14} T / s}{1.3 T} = 6.6 \, kH z \).

No initial transverse magnetisation \( (M_x(0) = M_y(0) = 0) \) is taken as a starting condition.

Under the assumption of a constant \( \Omega \) the transverse magnetisation oscillates at a frequency \( \omega_0 \)

with an amplitude of \( \Omega / \omega \times |M| \approx 5 \times 10^{-5}|M| \). The longitudinal magnetisation is only reduced by

a factor of less than \( 10^{-8} \). If a smooth non-linear increase and afterwards the same decrease over a

similar period of time is taken into account the integration has to be carried out numerically. The

overall result however doesn’t change significantly. The longitudinal magnetisation always follows
the current field direction and when the TMS-field is turned off, the longitudinal magnetisation
returns to the state it was in before the TMS pulse.

Phase Information

A monophasic pulse of a duration of $t_1 - t_0 = 100\mu s$ and with a relatively weak peak magnetic
field of $B_T = 0.01$ Tesla parallel to $B_0$ is assumed (based on Equation 5.17).

$$\Delta \phi = \gamma \int_{t_0}^{t_1} |B_T| dt = 265\text{rads} \quad (5.21)$$

Assuming a resolution of $(3\text{ mm})^3$ and a moderate relative inhomogeneity in $B_T$ of 2% over 3 mm,
results in a $\nabla \phi$ of 5.3 rads across a single voxel and thus in a strong reduction of the MR-signal
$\Delta S_p$ from this voxel according to Equation 5.18.

The TMS-stimulator sends out biphasic pulses which should ideally be symmetric. Under this
assumption the first term of equation (5.17) is zero. Therefore we make a new estimation. We
assume that $B_\perp = \sin \alpha B_T = \pm 0.01T$ and $B_0 = 1.5T$ and we assume that the two lobes of the
TMS-pulse each last for $100\mu s$ in both directions. Equation 5.17 then becomes:

$$\Delta \phi = \gamma \left( \int_{0}^{100\mu s} \frac{1}{2} \frac{(0.01T)^2}{1.5T} dt + \int_{100\mu s}^{200\mu s} \frac{1}{2} \frac{(-0.01T)^2}{1.5T} dt \right) = 1.67 \quad (5.22)$$

Even under these circumstances, in spite of the weak assumed field of the TMS pulse a significant
image distortion can be expected. When applying TMS, the field would be of the order of 0.1 T
in regions close to the TMS-coil, so that the effect on the transverse magnetisation would be 100
times larger.

In Figure 3.7 it has been shown, that the pulses from the Magstim Rapid system are not balanced
and that the assumption of equal lobe areas is not realistic.

Therefore it can be concluded that a TMS pulse influences the transverse magnetisation so strongly,
that large areas of the affected slices would be completely spoiled. The effect occurs when TMS is
used at any time from the start of the RF-excitation until the end of the following acquisition. In
EPI this leads to the loss of a whole slice.
Figure 5.1: Simulation of the effect of a current through the TMS-coil on EP-images. 
a) Position of the TMS-coil. 
b) z-component of the field of the TMS-coil as it was determined using the procedure described in Section 3.4.6. 
c) Relative decrease of the MR-signal due to dephasing caused by a current of 100 mA over 10 ms through the TMS-coil between RF-excitation and acquisition in an EPI sequence. 
d) Shift in slice position caused by a current of 100 mA during the RF-excitation assuming a slice selection gradient strength of 30 mT/m.
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Slice selection

A field $B_T$ of 0.01T parallel to $B_0$ and a gradient strength of the slice selection of $3mT/m$ causes according to Equation 5.19 a shift of 33 cm in the slice position. This basically means that the slice selection does not work at all during an TMS pulse.

Effect of leakage currents

In Figure 5.1 simulations of the effects of moderate leakage currents through the TMS-coil on the signal strength in EP-images and on the slice selection are shown. The results demonstrate that even relatively low currents through the TMS-coil can cause significant distortion on the images.

5.2 TMS pulses during EPI acquisition

The influence of a TMS pulse on the magnetisation has been analysed theoretically in Section 5.1. According to these calculations a TMS pulse has a large influence on the phase of the transverse magnetisation, but the longitudinal magnetisation is not significantly affected. If a TMS pulse is carried out during an RF-excitation, it changes the effect of the RF-excitation strongly. In this case the TMS pulse influences the longitudinal magnetisation indirectly.

To verify these calculations, the results they produce are now compared with experimental measurements of the influence of TMS pulses on images with a controlled timing between pulses and different parts of the imaging sequence.

Method

For these measurements single slice time-series were acquired using a GE-EPI sequence (TE = 35 ms, TR = 5 sec, phase-encoding BW = 28 Hz per pixel, 64×64 matrix size, (3 mm)$^3$ in-plane resolution). They were carried out on an approximately head sized phantom. The TMS-coil was positioned adjacent to the phantom.

The TMS pulse strength was set as a variable percentage of the maximum stimulator output. The TMS pulses were applied at variable times relative to the acquisition of the EPI-slice.
Figure 5.2: Direct effect of a TMS pulse (30% stimulator output) on an echo-planar image. The image sequence timing diagram (evolution of the three gradients and RF) is shown in the middle section. Underneath the timescale in ms and a description of the parts of the sequence are displayed. On the top, a series of images with numbers can be seen. The number gives the time in ms when the TMS pulse was applied relative to the slice-selective RF-excitation. The images that are shown are the results of the corresponding pulse timing.
A quick survey

Figure 5.2 gives an overview of the effects of TMS with 30% of the maximum pulse strength on a single EP-image. The dependence on the time of application of the TMS pulse is evident. Little influence on the images is visible when the TMS pulse is applied before the start of the EPI sequence or when it is applied after the sequence. However, when the TMS pulse is applied during the RF-excitation used for fat suppression, there are significant perturbations.

If the TMS pulse was applied between the slice selective RF-excitation and the acquisition a similar region of the image is always spoiled. When applied at different points during the acquisition the image changed. When TMS was applied during the later portion of the acquisition train, the image was nearly undistorted.

These results agree well with the predictions of the theoretical analysis in Section 5.1. If a TMS pulse is applied at a time which does not overlap with the the RF-excitations or the period when transverse magnetisation is present, the magnetic field produced by the TMS has no significant influence on the images. This is the case when the pulse is applied before the sequence, directly after the fat-suppression and after the EPI acquisition has finished. If the pulse is applied during the fat suppression or the excitation of the slice, the state of the longitudinal magnetisation is modified and the image is changed over a large region.

If a TMS pulse is applied between the slice selective excitation and the acquisition, the phase of the signal of a large region of the image is spoiled and no signal can be acquired from this region. If the TMS pulse is applied during the acquisition, the k-space is acquired normally before the TMS pulse and acquired with the spoiled information after the TMS pulse. Therefore if TMS is applied at the end of the acquisition, only higher spatial frequencies are lost. These make only a small contribution to the overall signal of the image. Therefore the images get better the later TMS is applied during the acquisition.

A question of particular interest is how close the TMS pulse can be applied to the start of the sequence without corrupting the image. Other studies showed that influences can be observed if a TMS pulse was applied up to 90 ms before the start of the sequence (Bestmann et al. [2003]). The data presented in Figure 5.2 are insufficient to answer this question, so in the following section the topic is approached in detail.
5.2.1 What is the minimum delay between the TMS pulse and EPI acquisition?

To study the effect of varying the timing of TMS pulse application, TMS was synchronised with a single slice of EPI acquisition (TE = 35 ms, TR = 5 s, phase-encoding BW 28 Hz, 64×64 matrix size, (3 mm)$^3$ in-plane resolution). Fat suppression was turned off. The experiment was carried out on an approximately head-sized phantom with four segments, which were filled with agar, that had been doped to produce different relaxation times. The TMS-coil was positioned on the superior-left of the phantom and the slice orientation was coronal.

TMS was applied in every second acquisition, starting with a delay of 200 ms before the slice selective RF-pulse of the EPI-sequence. After each acquisition the delay was decreased until the TMS pulse was applied 80 ms after the RF-pulse. TMS was applied with pulse strength of 100%, 70% and 30% of the maximum stimulator output. Additionally, a structural image was acquired to allow the position of the TMS-coil to be identified. A $B_0$-map (64×64×3 matrix, (3 mm)$^3$ resolution) and an MP-RAGE image (128×128×128 matrix, (2 mm)$^3$ resolution) were also acquired.

The mean signal decrease was taken as a measure of the influence of the TMS pulses. This was calculated from the sum of the absolute value of the difference of two consecutive dynamics (one with TMS, one without TMS) divided by the sum over the image without TMS. The results are shown in the Figures 5.3, 5.4 and 5.5. Examples of the images acquired at different time-points are also shown.

Images were also simulated using the EPI-simulator (Section A.4). The z-component of the field from the TMS-coil was determined using the procedure described in Section 3.4.6, and the temporal and spatial field distribution of the TMS-coil (Section 3.3). The phase offset was calculated by Equation (5.20) and then used in the simulator. The simulator accounts for the spatial distortions and signal loss on an EPI sequence with the same parameters as were used for the measurements. The MP-RAGE image was used to provide the initial signal distribution for the simulations.

The only parameter that was changed between different simulation runs was the accumulated charge $\int I(t) dt$ that had passed through the TMS-coil. This simulates the effect of the phase-offset which is induced by the field of the TMS-coil. The simulation of the influence of the TMS pulses when applied between RF and acquisition, was based on charges of 250 mAs for 100%, 168 mAs for 70% and 68 mAs for 30% TMS intensity. These agree roughly with the charge determined by the temporal shape of the TMS pulse, which was discussed in Section 3.3.
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![Figure 5.3: TMS with 100% of the maximum stimulator output. The graph shows the average signal decrease induced by TMS when it was applied relative to the start of the acquisition process at the time shown on the x-axis. The signal reduction caused by TMS starts appearing at about 90 ms before the sequence and it increases linearly until 49 ms before the sequence. Then it remains nearly constant until at 0 ms the main TMS pulse overlaps with the imaging and destroys most of the signal. At the top right, the images produced when TMS was applied at different times relative to the sequence are shown. At the bottom right the results from simulated images are shown under the assumption that an accumulated charge of 0 mAs, 1.6 mAs or 250 mAs had flown through the TMS-coil. The signal loss is mostly caused by intra-voxel dephasing. The assumed charges produce results similar to the acquired images.

For TMS before the RF-excitation the charge could not be based on independent measurements. Instead the charge flowing through the coil was varied in the simulations so as to produce a best match of simulated and measured data.

The results clearly show that there is a period after every TMS pulse in which EPI images are affected. The period increases with the intensity of the TMS pulses. For 70% and 100% the strength of the effect increases over a time of 30-40 ms and then remains constant. The maximum signal loss is only slightly influenced by the pulse strength. At 30% the effect increases constantly over a period of 23 ms and there is no period with a constant signal loss. The simulations show signal loss which has a very similar spatial distribution to the experimental measurements. The results indicate that at a pulse intensity of 100% a charge of about 1.6 mAs must flow through the TMS-coil. This must happen in the period between the RF-excitation and a time of TE (35 ms) afterwards, when the centre of k-space is acquired. A corresponding constant current is 28 mA.
Figure 5.4: As in Figure 5.3, but with 70% of the maximum stimulator output. The plot is similar to Figure 5.3, but the period of the increasing signal loss is slightly reduced (30 ms) and the period of constant signal loss is significantly shorter (25 ms). The artefacts at -3 ms are similar to the artefacts which occur with 100% TMS-strength.

Figure 5.5: As in Figure 5.3, but with 30% of the maximum stimulator output. Here the signal loss increases from 23 ms before the sequence and there is no period with a constant signal loss. The artefacts at -3 ms are smaller compared to the two previous examples (Figures 5.3, 5.4). When TMS was applied during the imaging, not all of the image is destroyed.
Figure 5.6: Measurements of the voltage induced in a search coil following the application of a TMS pulse triggered at t=0. The different measurements were carried out with different ranges in amplitude and time. A dominant pulse over 0.4 ms and an amplitude of 70V peak-to-peak is followed by oscillations over 85 ms which have an amplitude about 500 times weaker than the pulse itself. The rather random amplitude in the bottom two measurements is caused by aliasing effects between the sampling frequency of the oscilloscope and high frequency oscillations of the signal.
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The strong difference can be explained by frequencies, which are close to multiples of the sampling rate which was 20kHz. With normal sampling this leads to interference.

5.2.2 Studying the leakage currents after a TMS pulse

To understand what causes the TMS pulse-related artefacts in EP-images, it is necessary to find out what happens in the TMS-coil directly after the pulse. The spatial distribution of the artefacts agrees with the simulation of the effect of a charge flowing through the TMS-coil on the phase of the transverse magnetisation. Therefore leakage currents, which occur during the recharging time of the stimulator, are likely to cause these artefacts.

In order to investigate this leakage current, the following measurements were carried out outside of the scanner. A coil consisting of 7 turns of wire with a diameter of about 5cm was attached to the TMS-coil and connected to an oscilloscope. The stimulator was fired and the voltage induced in the coil was measured. This was repeated using different sampling rates of the scope and different pulse strengths.

In Figure 5.6 the induced voltage from a TMS pulse with 100% of the stimulator output is shown. The dominant voltage with a peak-to-peak amplitude of about 70V occurs during the pulse itself which lasts 0.4 ms and afterwards the voltage on the search coil returns to a nearly zero value. If the acquisition period is increased and the voltage scale is expanded, oscillations with a peak-to-peak amplitude of about 160 mV over a period of 85 ms can be observed.

Figure 5.7 shows what happens during this period of 85 ms after the TMS pulse. If this period is measured with the ‘peak-detect’ setting of the oscilloscope it reveals that this period consists of oscillation with a higher frequency and the observed amplitude can be related to interferences of the underlying frequency with the sampling rate. Sampling with a higher sampling rate reveals that the oscillations consist mainly of frequency bands between 0.3-0.9 MHz and 7-10MHz (Figure...
Induced voltage 42 ms after a TMS pulse

Figure 5.8: Left: Voltage induced in a search coil following the application of a TMS pulse with a delay of 42 ms. The voltage was measured at different sampling rates. Right: Fourier transformation of the timecourses, which show that the oscillations consist mainly of frequencies between 0.3-0.9MHz and 7-10MHz.
Figure 5.9: Comparison of $\frac{dU}{dt}$ measured after TMS pulses of different strengths. The length of the period of time after the pulse, over which the TMS-system shows activity, increases with the pulse strength.
5.8). These frequencies are in a range where they should not affect the imaging process. It is possible that there are further frequencies, but these would be too high to be picked up by the oscilloscope which was used for the measurements. The bandwidth of the oscilloscope was 40 MHz. The search-coil method measures the rate of change of the induced magnetic field. Changes on a long timescale (> 1 ms) would be overlayed by the amplitude of the fast oscillations. These changes on a long timescale are likely to be the major contribution to the current flowing through the TMS-coil and therefore to the induced magnetic field.

Due to the sharp cut-off of the oscillations at a definite time after the TMS pulse, it can be assumed that the stimulator is only active during that period. Most likely the period corresponds to the recharge time of the stimulator. Any slowly changing leakage currents would also occur during this period.

The peak-to-peak measurements were repeated using different TMS pulse strengths. The results are shown in Figure 5.9. The amplitude of the leakage currents increases slightly with the pulse strength. More significant is that the period over which the leakage currents occur is nearly linear with the pulse strength with a rate of about 0.9 ms/(% stimulator output). Furthermore the amplitude of the induced voltages is at a similar level throughout the period and in all cases it shows a sharp cut-off after this period.

5.2.3 Interpretation of the results

For each TMS pulse strength there is a period in which EP-images are corrupted if they are acquired briefly after a TMS pulse. The duration of this period depends on the strength of the TMS pulse and during the first 30 - 40 ms of this period the effect builds up and afterwards it does not increase further. The spatial form of the artefacts is similar to that which would be induced by a magnetic field resulting from currents through the TMS-coil. The total length of the period agrees well with the period of leakage currents which were measured after every TMS pulse (Figure 5.9). The same effect would occur if during the recharge-period an average current of between (26±12) mA flowed through the TMS-coil.

The period, during which the artefacts build up, is similar to the echo time of the EPI-sequence. If this period covers the whole time between the RF-excitation and the echo time, the centre of k-space experiences the maximum dephasing. If the TMS pulse is applied closer to the RF-excitation, no further increase in the artefacts would occur. This is illustrated in Figure 5.11.
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Figure 5.10: Length of the period after a TMS pulse during which a voltage induced in the search coil can be measured. It increases proportionally with 0.9 ms/(% pulse strength). The red crosses show the timespan after TMS pulses, which had an effect on an EP-image. This timespan was measured as shown in Figures 5.3, 5.4 and 5.5. There is an excellent agreement between the two periods.

The effect of the leakage currents on the selective excitation has not been approached with these experiments. However in Figure 5.1 a shift in the slice position of up to 0.5 mm under the assumption of a current of 100 mA was estimated. For leakage currents of about 26 mA, the shift in the slice position would be up to 0.13 mm, which is about 3% of a 3 mm slice. This is enough to cause a signal change, during the following TR-periods. This can lead to false positives in the results of the fMRI analysis.

5.3 Conclusions

In agreement with the theory, no direct influence of a TMS pulse on the longitudinal magnetisation was found. The longitudinal magnetisation can be altered if TMS is applied during RF-pulses. This can also happen if TMS is applied during RF-pulses which produce no net transverse magnetisation (e.g. fat suppression, rest slabs). In this case the field from the TMS-coil changes the shape and the extent of the region which is excited by the RF-pulse. If applied between the RF-excitation and the acquisition, TMS pulses spoil the signal in a large area of the image.

After every TMS pulse there is a period during which the TMS-system recharges. In this period
EPI-sequence time
Accumulated dephasing

Effective Dephasing

Leakage−current Period

TMS−pulse

Centre of k−space

RF Acquisition−period

TE

Figure 5.11: Effect of leakage currents on the phase of the signal. The currents induce a magnetic field which either reduces or increases the local Larmor frequency. \( t_{TMS} \) is the time between the TMS pulse and the RF-excitation of the EPI-sequence. If the leakage period \( t_L \) is longer than \( t_{TMS} \) the phase offset is roughly proportional to \( t_L - t_{TMS} \) (left). If \( t_L - t_{TMS} \) exceeds TE, then the effective dephasing remains constant and proportional to TE. The currents at the end of the leakage period then have no significant effect on the image.

leakage-currents of the order of 20mA flow through the TMS-coil. The length of this period is about 0.9 ms/(% stimulator output) on the Magstim Rapid² stimulator and it therefore has a maximum duration of about 90 ms. Overlaps of active parts of an MR-sequence during this period can lead to artefacts.

To avoid artefacts, the application of TMS must be synchronised with the scanner so that the active parts of the imaging sequence do not overlap with time-periods in which leakage currents flow. The most straightforward way to achieve this in EPI, is to introduce a gap of at least 90 ms between the TMS pulse and the slice selective excitation. Another option is deliberately to spoil single slices which are then discarded in subsequent data analysis. It is important that RF-pulses are not applied during the recharge period, because this can change the longitudinal magnetisation and therefore affect more than one dynamic. Another option would be to isolate the TMS-coil from the stimulator immediately after the TMS pulse. This would remove the leakage currents and allow the acquisition of the images very shortly (\( \approx 1 \) ms) after a TMS pulse. A relay box which was presented by Weiskopf et al. [2009] should provide this option, but this would require further testing.

The artefacts which were observed in the experiments can be explained. Nevertheless, it is possible that there are other smaller effects which superposed onto the effect of dephasing due to leakage currents. If the leakage currents are removed, these effects might still contribute significant artefacts. An example of such effects could be vibrations of the TMS-coil.
Chapter 6

TMS in the MR-scanner

Introduction

The effects of TMS on MR-images were analysed in the previous chapters, but there are other difficulties which are specific to the combination of TMS and MRI. Some of these difficulties are discussed in the following sections. They include:

- Accommodation of the TMS-coil in the MR-scanner.
- Performance of different receiver coils that are compatible with the use of a TMS-coil.
- Forces on the TMS-coil.
- Synchronisation of the TMS system and the MR-scanner.

6.1 Accommodation of the TMS-coil

Correct positioning of the coil is crucial for producing reliable results in TMS experiments. Different methods of positioning the TMS-coil are described in Section 2.5.1. These methods can be used for combined TMS/fMRI experiments as is discussed in Section B.4, but the special environment of the MR-scanner makes their application more difficult.

For brain-imaging using MRI, the subject’s head is usually accommodated inside an RF-coil which is used for signal reception. RF-receiver-coils have a sensitivity which peaks close to the wires of the coil and decreases with the distance from the origin of the signal.
Concurrent TMS/MRI experiments are restricted to RF-coils which provide enough space for the TMS-coil. Most RF-coils which are optimised for head imaging don’t fall into this category as they provide just enough space so that patients with normal sized heads can fit comfortably in the coil. Other receiver coils therefore have to be used for concurrent TMS/fMRI, which means a compromise in MR-image quality. This topic is discussed in the next section.

Furthermore the TMS-coil must be mounted in a stable way. Commercially available systems to hold the TMS-coil are not designed for use inside the MR-scanner. A mount for the TMS-coil in concurrent TMS/fMRI must therefore be specifically designed for the scanner which is to be used. It must consist of non-magnetic materials and it must permit positioning of the TMS-coil with all the required degrees of freedom. The mount which was used for this thesis is described in Section 3.4.1.

The RF-coils, the TMS-coil and the mount must be positioned around the head of the subject. The positioning varies in difficulty depending on the target site for TMS. Detailed instructions, indicating how to position the TMS-coil for combined TMS/fMRI experiments in the Phillips 3 T using the set-up developed in the work of my thesis, are given in Section B.4.

### 6.2 Comparison of receiver coils

The 1.5 T and 3 T Philips-scanners, used for the work described in this thesis, provide a range of RF-coils for different purposes. For head imaging a volume 8-channel array coil, which surrounds the head, is generally used. This coil is highly optimised and provides a high sensitivity for RF-reception, which covers most of a human head, including the whole brain.

In addition, there are flexible surface coils of different sizes which must be placed close to the imaging region. These have a high sensitivity close to their wires, which decreases rapidly with distance. These scanners also have a body-coil integrated in the scanner bore which provides a very homogeneous $B_1$-field, but a rather low sensitivity for signal reception. This coil is also used for RF-transmission for most purposes. It is possible to acquire images by combining different RF-coils simultaneously. The coils which were used for this thesis are described more in detail in Section 3.1. Of these coils the Nova-coil is most suitable for the specific requirements of concurrent TMS/fMRI.
Figure 6.1: SNR maps using generated different coils for signal reception. A coronal slice through the middle of the phantom is displayed. The 8-channel head-coil provides a high SNR over the wholephantom. The FlexL coils were positioned anterior and posterior to the phantom. In the slice shown they provide a homogeneous coverage but a significantly lower SNR compared to the head-coil. The FlexS coils were positioned on the left and right of the phantom. In these areas they also show an SNR, which is even higher compared to the the head coil, but the overall coverage is poor. The Nova-coil shows the most homogenous coverage. The overall SNR is low compared to the head-coil, but higher than that provided by the FlexL coils.

6.2.1 Image quality

To compare the image quality of the different coils, SNR maps were acquired as described in Section 1.5.4. Identical EPI-sequences (TE=35 ms, TR=3500 ms) were acquired using a matrix size of 64x64x64 with (3mm)$^3$ isotropic resolution. The results produced using four different receiver coils are shown in the Figures 6.1 and 6.2. An elliptical, agar-filled phantom (with major and minor axes of 11 and 16 cm) was used for these experiments.

6.2.2 The optimal RF-coil for use in concurrent TMS/fMRI

In the following, the advantages and disadvantages of different RF-receiver coils for concurrent TMS/fMRI are discussed.

- **8-channel head-coil.** The standard 8-channel head-coil does not provide enough space to accommodate the TMS-coil and it is closed at its superior end. This coil is therefore not suitable for concurrent TMS/MRI, but it is the best choice for images which can contribute to a TMS/fMRI study, but which can be acquired in a separate session (e.g. anatomical images).

- **FlexL coils.** The large flexible surface coils provide a reasonably homogeneous coverage of the
Figure 6.2: Histogram of SNR-maps from the different receiver coils. A mask was applied to each map, which includes only voxels with an intensity of at least 10% of the maximum intensity (The image was corrected for coil sensitivity). The histogram has been cut off at 250. The results reflect what can be seen in the Figure 6.1. The majority of the voxels from the head coil show an SNR of $>150$. The FlexL coils and the Nova-coil reach an SNR of between 100 and 170 for most voxels, but do not show any voxels with an SNR of $>250$. The SNR of most voxels acquired using the FlexS coils is between 50 and 120, but there is also a considerable number of voxels with a high SNR ($>200$).
whole head, but the sensitivity of these coils is rather low. The coils can be positioned either on the anterior and posterior of the head or on the left and on the right sides. Both cases can cause conflicts with the positioning of the TMS-coil. Usually it is possible to accommodate the FlexL coils together with the TMS-coil, but it can take some time and it can cause some discomfort for the subject. In addition to the head of the subject the RF-coils must also be stabilised. If the subject moves relative to the coils or the coils change in shape or orientation, then the sensitivity profile of the coils superposed onto the head will change and as a result the local image intensity will vary. The image quality provided by the FlexL coil is good enough to detect large signal changes for fMRI experiments, but in many cases not for identifying subtle differences.

- **FlexS-coils.** The small flexible receiver coils have a high sensitivity directly under the coil, but they provide poor whole head coverage. Therefore they should be positioned directly over the regions which are most interesting in the study. The problems with accommodating these coils in conjunction with the TMS coil are very similar to the FlexL coils. Our experience shows that they produce better results than the FlexL-coils. Nevertheless with these coils the image quality is only adequate in restricted regions.

- **Combining the FlexS and FlexL coils.** It is possible to combine the FlexS and the FlexL-coils, but there is limited space to accommodate four RF coils and the TMS-coil around the head of a subject. Experience also shows that the image quality improved only marginally compared to the case when the FlexS-coils only were used.

- **Nova 6-channel coil.** The Nova-coil provides sufficient space for the head of the subject together with the TMS-coil. An insert for the head gives additional flexibility to access large areas of the head surface with the TMS-coil. The head can be stabilised by adding pillows between the head and the sides of the coil. It is much easier to set up TMS/MRI experiments using this coil compared to the surface coils. The measured SNR is slightly higher compared to the FlexL coils. Since the Nova-coil is rigid, movement of the coil can be excluded as a cause of changes in the signal intensity. The six independent channels of this coil allow, parallel imaging techniques such as sensitive encoding (SENSE) (Pruessmann et al. [1999]), to be used.

In general, the Nova-coil has significant advantages compared to the FlexL or FlexS coils.
The experiments are easier to setup and the set-up is more comfortable for the subject. The overall SNR of the images is higher on average and the images are more stable. The FlexS coils can produce better images in the situation where the region of interest is restricted to just a small area.

6.3 Forces and Torques on the TMS-coil

A TMS-pulse outside of the MR-scanner causes a small clicking noise. This noise originates from Lorentz-forces (Equation A.17) between the magnetic field produced by the TMS-coil and the currents inside the coil. The process of MR-imaging produces strong acoustic noise, which is caused by the Lorentz forces between the currents in the gradient-coils and the $B_0$-field. When TMS is applied inside the MR-scanner, the same effect occurs but in a stronger form because the current in the the TMS-coil also interact with the $B_0$-field. These currents are significantly larger than those of the gradient coils.

The forces on an infinitesimal piece of wire described by the vector $dl$ carrying current, $I$ in a field $B_0$ can be expressed as

$$dF = -IB_0 \times dl$$

(6.1)

and the absolute value of this force is given by

$$dF = |IB_0 \times dl| = IB_0 dl \sin \alpha$$

(6.2)

where $\alpha$ is the angle between $B_0$ and $dl$. The maximum current during a TMS-pulse is about $I = 5kA$. The force on 1 cm of wire which is perpendicular to a field of $B_0=3$ T is therefore 150 N. Each half of the MR-compatible TMS-coil consists of 10 loops with an average radius of 3.5 cm resulting in a total length of the wire inside the coil of about 440 cm. Every cm of this wire experiences a force of up to 150 N resulting in huge mechanical stresses inside the TMS-coil.

Another approach is to calculate the torque on each half of the TMS-coil. The effective dipole moment of each half of the coil is given by

$$m = nIA$$

(6.3)

where $A$ is the surface area, which is encircled by each loop of the coil. The dipole moment of one half of the TMS-coil results as $|m| = 192 Am^2$. The resulting torque between one half of the
TMS-coil and the $B_0$-field is

$$\mathbf{M} = \mathbf{m} \times \mathbf{B}_0 = 576 N m \sin \beta.$$  \hspace{1cm} (6.4)

where $\beta$ is the angle between $\mathbf{A}$ and $\mathbf{B}_0$. The torque causes either bending or torsion forces at the connection between the two halves.

In Figures 6.3, 6.4 and 6.5 the three fundamentally different positions of the coil inside the scanner are displayed. All other positions can be described by a combination of these positions.

In the first two cases, the two halves of the coil experience a torque. In the third case, there are no forces perpendicular to the coil surface. Instead there are forces which force the windings inside the coil either together or apart. If the flat copper wires inside the coil are packed tightly together, these forces are compensated well inside the windings. The audible noise that is produced is significantly smaller compared to the two other orientations.

In all cases the forces over a figure-of-eight-shaped coil cancel out each other, because the coil forms a closed loop in a homogeneous field. Furthermore the torques experienced by the two halves of the coil cancel out each other. This is only the case if the housing is rigid enough to assimilate the internal forces.

### 6.3.1 Movement of the coil during experiments

The movement of a TMS-coil, which has been pulsed inside the MR-scanner, is in most cases too fast and too small to be detected by eye. With a hand on the coil, one can feel a short and strong ‘knock’ of the coil. This ‘knock’ is accompanied by a loud 'crack' noise. The effect is much stronger if the coil orientation is as shown in Figure 6.3 or Figure 6.4, compared to the orientation shown in Figure 6.5. If the coil is just placed flat on the scanner bed with the long axis parallel to the scanner axis, the coil performs a small jump when pulsed.

In experiments with subjects, this knocking of the coil can cause some discomfort, especially if the TMS-coil presses against the skull. Discomfort is more likely for a higher pulse strength and if the coil axis makes a small angle to the scanner axis. To reduce the discomfort, a small gap ($\approx 1$mm) can be introduced between the TMS-coil and the subject’s head.

If the TMS-coil is well positioned, the subject can feel some movement, but no direct impact on the skull.

The crack noise is comparable in intensity with the noise from the gradient switching during EPI,
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Figure 6.3: Forces experienced by the TMS-coil when its long axis is parallel to the $B_0$-field. The blue arrows indicate the directions of the forces. The blue circles indicate zero force. The two halves of the coil experience an equal and opposite torques. These torques cancel out each other, but they lead to strong bending forces at the connection between the two halves of the coil. There are no forces in the plane of the coil.

Figure 6.4: As Figure 6.3, but with the long axis perpendicular and the surface of the TMS-coil parallel to the $B_0$ field. In this case, there is a strong torsion force at the connection between both halves of the coil.

Figure 6.5: Forces, when the surface of the TMS-coil is perpendicular to the $B_0$-field. There are no forces perpendicular to the coil surface. The forces cause an expansion or contraction of the coil loops.
1. Circular coil
2. Flat Figure-of-eight
3. Figure-of-eight with 120° angle
4. Three rings

Figure 6.6: Torques experienced by TMS-coils with different shapes. 1. The circular coil experiences a torque of \( F_l \). 2. In the flat Figure-of-eight coil, each half of the coil experiences a torque of \( F_l \), but with opposite signs, which cancel out each other. 3. In Figure-of-eight coil with the 120° angle both halves experience different torques and the torques are no longer balanced. 4. The previous coil can be extended with a third wing. The third wing as shown could restore the balance of the torques over the whole coil.

so that when the subject wears earplugs, the noise does not require any additional measures.

The ‘shocks’ experienced by the TMS-coil can destabilise the mounting of the coil. In this case, the TMS-coil can change its position slightly with every pulse. The shocks can also loosen the screws which are used to clamp the coil in position. In some experiments, especially when the coil orientation was similar to Figure 6.3, the coil orientation changed completely after a series of pulses. Unwanted changes in the coil-position make the TMS unreliable. These changes can also cause additional image artefacts because the \( B_0 \)-inhomogeneities due to the TMS-coil change while the shimming setting still remain optimised for the initial coil position.

In the long-term run, the force of repeated TMS-pulses can damage the structure of the coil. A crack in the coil can be a hazard and therefore the coil should be checked after every experiment.

6.3.2 Conclusion and how to reduce the movement

Strong forces on the wires inside the TMS-coil are an intrinsic problem in concurrent TMS/fMRI. Several factors reduce the impact of the forces, so that concurrent TMS/fMRI is possible. Especially at 3 T the forces on a current TMS-coil are close to what it can support and all of these factors are therefore important. In the following the importance of the different factors is explained.
and ways in which they can be controlled are described.

1. **Short duration of TMS-pulses.** The impact of the forces is easier to control, because the forces are only present during the short duration of a TMS pulse. Shorter pulses can be achieved using a smaller capacitor in the TMS-system or a lower inductance of the TMS-coil. The duration of the pulse has an impact on the effect of TMS. This limits the range of pulse durations, which can be used, but in a certain range it might still be possible to compensate a decrease in the TMS efficiency by change in intensity.

2. **Biphasic TMS-pulse balances out the forces.** The forces during a biphasic TMS-pulse partially cancel out each other if integrated over time, because during each of the two half cycles, forces in opposing directions are produced. An asymmetry between these half cycles reduces this effect. The asymmetry is caused by the electrical resistance of the coil and the lead (See Equation 2.4). This resistance can be reduced using thicker wires or a shorter lead. Monophasic TMS-pulses are not suitable to be used inside an MR-scanner, because the current in the wire is present over a longer period and produces forces, which are unidirectional.

3. **Each ring inside the coil experiences only a torque and no resulting force.** The two wings of a flat Figure-of-eight-coil experience torques which oppose each other. A flat Figure-of-eight-coil provides a complete balance of forces and torques over the whole coil. Most other coil-shapes do not satisfy this condition. E.g. a circular coil experiences a strong torque which makes it difficult to prevent it from moving with every pulse. During the design of MR-compatible TMS-coil, the balance of the forces must be considered. Examples of coil shapes with balanced and not-balanced torques are shown in Figure 6.6.

4. **A rigid housing allows the internal forces to compensate each other.** The housing of the coil must take the internal forces and distribute them over the structure, so that they can cancel out each other. Therefore an ideal outer layer of the housing would be perfectly rigid. As the internal forces are huge, a damping material could help to distribute them over the whole coil. The construction of the housing is an essential factor to control the forces.
6.4 Synchronisation of TMS and MRI

In Section 5.2 the influence of TMS pulses on MR-images was discussed. It was shown that after each TMS pulse there is a period, $t_I$, during which there is still some current flowing through the TMS-coil. This current can influence active parts of an MRI-sequence. The period $t_I$ was found to last for up to 90 ms. If the period overlaps with a slice selective RF-excitation, the position of the excited slice is shifted. Adjacent slices and also the following dynamics can be affected. Silent periods are not affected.

This influence is caused by leakage currents during the recharge period of the TMS-stimulator. If this current can be suppressed, it might be possible to restrict the duration of this period to basically the duration of a TMS pulse ($t_I \approx 1$ ms).

6.4.1 Strategies to avoid artefacts

To avoid artefacts, TMS pulses must be applied during silent periods, which last for at least a time $t_I$ after the pulse. Alternatively TMS can be applied during periods of no RF, which means for GE-EPI directly after the RF-excitation. As a result one slice is heavily affected and it must be discarded when analysing the data, but consecutive volumes and adjacent slices are not affected.

There are different strategies for satisfying these conditions. All these strategies have in common, that the application of TMS is restricted to certain periods. In the following, different examples are discussed. All the examples assume EPI sequences with a duration of a complete single slice acquisition of 50 ms. For the recharge period a value of $t_I = 90$ ms was assumed.

1. *Sequences without silent periods*

Most MR-sequences are optimised to use the scanning time efficiently. This means, that most of the scanning time is filled with active elements or with periods during which the transverse magnetisation evolves. Therefore many sequences do not provide silent periods, during which TMS can be applied. An example of a standard multi-slice EPI-sequence is shown in Figure 6.7. The TR is determined by the time required for the acquisition of a single slice times the number of slices. Therefore there are no silent periods in this sequence and the application of TMS pulses would inevitably cause image distortions.

2. *Sequences with inherent silent periods*

Some sequences contain inherent silent periods. These silent-periods occur after RF-pulses
1. **Regular EPI**

![Figure 6.7](50 ms T_A=1.8 s TR=1.8 s)

**Figure 6.7:** A typical EPI sequence with 36 slices acquired in $T_A=1.8$ s. Slices are acquired during the entire $TR$ period and there are no silent periods during which TMS can be applied.

2. **Silent period at the end**

![Figure 6.8](50 ms t_A=1.8 s TR=2 s t_T=0.1 s 0.2 s)

**Figure 6.8:** A similar EPI sequence to that shown in Figure 6.7. The slice spacing and the number of slices are the same, but a silent period of 0.2 s (red) has been added at the end of the acquisition. During the first 0.1 s of this period, TMS can be applied safely (blue area). In this scenario TMS paradigms with continuous TMS at 0.5 Hz or short bursts which last less than 0.1 s are possible. About 90% of the TR period is taken up with scanning.

3. **Sequence split into packages**

![Figure 6.9](50 ms t_T = 0.05 s t_A = 0.85 s TR=2 s)

**Figure 6.9:** The EPI sequence is split into two packages of 1 s each. Each package compromises half of the volume and is acquired in 850 ms. A silent period after each package provides a time window of 50 ms during which TMS can be applied. This allows continuous TMS at 1 Hz instead of 0.5 Hz. For higher repetition rates, the sequence can be split into more packages. About 85% of the TR-period is taken up with scanning.

4. **FAIR ASL**

![Figure 6.10](Inversion pulse Inversion time 1.4 s Acquisition 0.3 s TR=2 s)

**Figure 6.10:** Example of a FAIR ASL-sequence (see Section 1.5.1). The inversion pulse is followed by a long inversion time of 1.4 s, which is required to allow the labelled blood to flow into the FOV. This period is a silent period, during which TMS can be applied (blue area). Only during the relatively short EPI-part, is TMS forbidden. This sequence can be combined with TMS without any further changes.
Figure 6.11: Every slice acquisition is followed by a silent period of 100 ms. TMS can be applied during a short period after each slice acquisition. Therefore during each TR-period there are 15 short periods which allow the application of TMS. Continuous TMS with up to 6.6 Hz frequency can be accommodated. Only 33% of the scanning time is taken up in the MRI-sequence.

Figure 6.12: Similar to the sequence shown in Figure 6.11, but with a gap of only 50 ms after the slice acquisitions. In this case, TMS can be applied between 2 ms and 7 ms after each RF-excitation. This spoils a single slice, but it does not affect the following slices or the same slice of the following dynamics. The spoiled slice must be excluded from the data analysis. TMS can be applied with frequencies of up to 10 Hz. 50% of the scanning time is used for the MR image-acquisition.

Figure 6.13: Here it is assumed the the effects after a TMS pulse, which influence MR-images can be suppressed, such that any silent period of more than 5 ms allows the application of a TMS pulse. In this example a silent period of 10 ms is introduced after each slice. TMS can be applied every 60 ms without affecting the image. The restrictions on MR-sequences are reduced greatly.
which are used to prepare the longitudinal magnetisation for contrast enhancement. Examples of this type of sequences are inversion recovery (Hajnal et al. [1992]) or arterial spin labelling (Kim [1995]) sequences. An example showing the compatibility of TMS with ASL is illustrated in Figure 6.8. The long labelling time of 1.4 s provides plenty of time to accommodate TMS pulses. Even bursts of 10 pulses at 10 Hz can be applied without any adjustment of the sequence.

3. **Silent period at the end of every TR**

In fMRI, a silent period can be introduced at the end of every TR-period. This silent period can be used to accommodate one or more TMS pulses. In Figure 6.9 a single TR-period of an EPI-sequence is shown. The acquisition of a volume requires 1.8 s, but the TR is set to 2 s. To make sure that the silent period occurs in a block at the end of the dynamic, the parameter ‘temporal slice spacing’ is set to ‘shortest’ on the Philips scanner. During the first 100 ms of the silent period, a TMS pulse can be accommodated.

4. **Several silent periods during the acquisition of each volume**

Silent periods can also be accommodated at several times during each TR-period. For each TR-period these silent periods must occur exactly at the same times relative to the start of the acquisition of the volume, otherwise the steady state of the magnetisation is affected. In Figure 6.10 an example of an EPI-sequence with two silent periods is shown. A volume requires a total time of 1.7 s to be acquired. The time per dynamic is 2 s which includes two silent periods of 150 ms duration each. TMS pulses can be accommodated at times of between 850 ms and 900 ms or between 1850 ms and 1900 ms after the start of each dynamic. The sequence could be implemented easily by starting with an EPI-sequence which requires 1.7 s to acquire one volume. In the Philips scanner if TR is set to 1 s using this sequence, the scanner automatically splits each volume into two packages resulting in a time of 2 s being required for every volume acquisition. Each of the packages contains one half of the slices. This, together with setting ‘temporal slice spacing’ to ‘shortest’, produces two silent periods occurring at the end of each half acquisition. This sequence can, for example, be combined with 1 Hz TMS.

5. **Silent period after each slice acquisition of a multi-slice EPI sequence**

It is also possible to use a temporal gap between individual slice acquisitions, which is long...
enough (≈100 ms) to accommodate TMS pulses. In Figure 6.11 an EPI sequence with 13 slices is shown. Between the end of the acquisition of each slice and the beginning of the next slice acquisition, there is silent period of 100 ms. A TMS pulse can be placed at the beginning of each silent period. This example allows the application of TMS pulses with a frequency of up to 6.6Hz. For a fixed imaging time, the number of slices, which can be acquired, is however reduced by a factor of 3.

6. **Spoiling single slices**

If TMS is applied only during the signal acquisition period of an EPI sequence, only a single slice is spoiled leaving the adjacent slices in the spatial and temporal domain unaffected. If TMS is directly applied after the slice selective RF-excitation the time required for an additional silent period can be reduced. In Figure 6.12 an example for this approach is shown. Compared to the previous example, the sequence can use the scanning time more efficiently. The spoiled slices must be excluded from the analysis, but the total share of lost data is limited. For example if every 5 dynamics every 2nd slice is spoiled (TMS at 5 Hz) it leads to a total of loss of 10% of the slices.

In these examples the periods in which TMS pulses can be applied are identical for every dynamic. Long blocks of TMS with a high repetition frequency are thus difficult to accommodate. For blocks with frequencies around 10 Hz, the main limiting factor is the time $t_I$ after the TMS pulse. This can be seen clearly in the example in Figure 6.11 where the time usage during the sequence is reduced significantly to accommodate TMS pulses applied at a frequency of 6.6Hz. If $t_I$ can be reduced to a period which is only slightly longer than the TMS pulse itself, the limitations could be reduced greatly. In Figure 6.13 an example is presented, which shows the gain in flexibility if $t_I$ can be reduced to 5 ms, so that silent periods of less than 10 ms only are required to accommodate TMS pulses. In this example a TMS pulse can be applied after every slice acquisition and more than 80% of the scanning time can be used for active parts of the MRI-sequence.

### 6.4.2 Choosing the right MRI-sequence

Given a certain TMS-paradigm, an MRI-sequence can generally be constructed to allow the application of TMS pulses. In most cases this requires compromises with the MRI-sequence, because silent periods have to be introduced. Of the presented strategies the most versatile is Option 4
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(Figure 6.10), with silent periods inserted during the MRI-sequence only when they are necessary.
In most cases this requires designing a special sequence for every paradigm.

Different aspects have to be considered:

1. The periods during which TMS is allowed are chosen in a way, that the TMS pulse does not have any effect on the images. When designing a paradigm it is not required to fill all the silent periods with TMS pulses.

2. The possible positions of TMS pulses have to have a periodicity which agrees with the time per dynamic. Therefore the TMS paradigm or the time per dynamic has to be adjusted. An entirely randomised timing of the TMS pulses is not possible although pseudo-randomised timings can be used.

As an example consider the situation where TMS with blocks of 10 pulses applied at 2Hz has to be combined with an EPI-sequence in which 30 slices are acquired with a time of 50 ms required for every slice. Each block of TMS is followed by a period of rest with a random length between 20 and 40 s.

The EPI can be reorganised to provide the compatibility with 2Hz TMS using the following sequence for every dynamic:

8 slices 400 ms, silent 100 ms, 7 slices 350 ms, silent 150 ms, 8 slices 400 ms, silent 100 ms, 7 slices 350 ms, silent 150 ms.

The sequence has a TR of 2s and TMS can be applied at 400 ms, 900 ms, 1400 ms and 1900 ms after the start of the acquisition of each volume. The TMS-paradigm has to be changed in a way that TMS pulses can only occur at the right times during each TR. The rest period between the blocks must therefore have a duration which is a multiple of 500 ms, instead of a completely random value between 20 and 40 s.

In this example the time for the acquisition of a volume is increased by 33% in order to accommodate the TMS pulses. If instead of 2 Hz TMS, blocks of 10 Hz TMS need to be applied, a silent period with 1 s duration would be required to accommodate all of the pulses. The resulting TR would be 2.5 s (1.5 s for the acquisition and 1 s for the TMS pulses). The time from one train of TMS pulses until the next then has to be a multiple of 2.5 s.

3. The MRI-sequence is taken as the reference in time and the timing of the TMS pulses must be adjusted according to position in time of silent periods of the MRI-sequence. If a precise
timing between an additional stimulus and a TMS pulse is required, the position in time of the external stimulus has to be adjusted, rather than the position of the TMS pulse.

4. An important parameter is the interference time \( t_I \), which is mostly dependent on the TMS pulse strength (see Figure 5.10). For lower pulse strengths, \( t_I \) is shorter (see Figure 5.10) and the silent periods in the MRI-sequence can be made shorter in duration.

Based on these considerations, an MRI-sequence can be constructed. The starting points should be the optimal fMRI-sequence without taking TMS into account and the optimal TMS pulse sequence without taking the fMRI-sequence into account. In most cases, the time per dynamic of the fMRI-sequence can be increased or the number of slices can be reduced to introduce silent periods that will accommodate the TMS pulses. The TMS-paradigm can also be adjusted to minimise the total duration of the silent periods during the MRI-sequence. For most combinations it is possible to find a solution that does not require a significant compromise of imaging performance.

Long blocks (> 1 s) of high frequency TMS (≥5Hz) are the most difficult to combine with fMRI, because they require silent periods with a duration which is of the order of the TR of a typical fMRI-sequence. This can result in a strong decrease in the performance of fMRI. Reducing \( t_I \) would solve this problem.

6.4.3 Implementation of the synchronisation

The Philips scanner generates a single TTL-pulse at the start of each dynamic. To implement the synchronisation between the MRI-sequence and TMS pulses it is most convenient to detect the TTL-pulses from the scanner and use them as the starting point for the timing of the TMS pulses. In the set-up used in the experiments described here, a computer program measures the time since the TTL-pulse from the scanner arrived and sends out a TTL-pulse to the stimulator to trigger each TMS pulse after a pre-set delay. It is also possible to use only the first TTL-pulse from the scanner, to trigger a whole sequence of pulses. In this situation an array is loaded with the timing delays of all TMS pulses and every time the system-clock arrives at one of these values, a TMS pulse is triggered. The basic structure of the program is presented in Figure 6.14.

This requires a high degree of consistency between the scanner clock and clock of the computer used to control the timing of the TMS, in order to ensure that TMS pulses and silent periods of the MRI sequence remain in synchrony as the experiment progresses.
% Create array with an entry of the timing of every TMS pulse in an increasing order
TMSp=[ pulse1, pulse2, .... ,pulse last]

% Wait for the first TTL-pulse from the scanner
while TTL-scanner==false
    wait(0.1 ms)
end

% Save the time, when the first TTL-pulse occurred
\[ t=\text{currenttime} \]

% loop for with one turn for every TMS pulse
for n=1 until n=last
    % Wait the next TMS pulse must be triggered
    while currenttime-t<TMSp(n)
        wait(0.1 ms)
    end
    % Send TMS pulse number n
    trigger(TTL-TMS)
    % Go to pulse number n+1
    n=n+1
end

\textbf{Figure 6.14:} Structure of a program for the synchronisation of TMS and fMRI. The value \( TMSp(n) \) represents the time between the first TTL pulse produced by the scanner and TMS pulse number \( n \).
Another option is to use multiple TTL-pulses from the scanner to control the time of application of TMS pulses. In this case the timing of every TMS pulse relative to the last TTL-pulse from the scanner is required, and the requirements on the consistency between the scanner clock and the computer clock are reduced as the errors sum up only over the duration of a single dynamic. In some experiments we found that TMS pulses produced electrical interference which was detected by the computer used to control the timing as a false-positive TTL-pulse from the scanner. This problem could be solved by ignoring pulses which are detected during a period of 10 ms after each TMS pulse.

### 6.4.4 Hardware requirements and accuracy

The 5V TTL-pulses from the scanner are sent out through a BNC-port. These pulses can be detected using an interface card in the computer. A 5 V output channel is also required to trigger the stimulator. This can be either a BNC-port or an IEEE1284 parallel port. The following pins of the trigger I/O port of the stimulator can be used for trigger reception:

<table>
<thead>
<tr>
<th>Pin number</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>GND</td>
</tr>
<tr>
<td>5.</td>
<td>+ Trigger In</td>
</tr>
<tr>
<td>6.</td>
<td>- Trigger In</td>
</tr>
</tbody>
</table>

A BNC-adaptor, which connects to pin number 5 of the trigger port, is sufficient for triggering. For most of the experiments described in this thesis, a parallel port was used to send out trigger pulses. A cable connected pin number 5 of a male IEEE1284 connector to pin number 5 of the trigger port of the stimulator. Sending number 16 (or 00010000 binary) for 5 ms to the parallel port triggers the stimulator. The stimulator responds to trigger pulses, when it is charged and the screen of the user interface displays the green sign and the text 'Ready'.

The temporal precision of the trigger pulses which is required to avoid imaging artefacts is dependent on the interference time, $t_I$, and the duration of the silent periods, $t_S$, of the MRI-sequence. If $t_I=90$ ms and $t_S=100$ ms, then TMS pulses must be applied in the first 10 ms of $t_S$.

The software used for triggering can add unwanted latency times to the trigger output. When a high precision for the timing is required, these delays are likely to cause problems.
Part III

Application on human subjects
Introduction

In the final part of this thesis three studies are presented which are based on concurrent TMS/fMRI and which were carried out using the set-up described in Chapter 3. These studies show examples for how the the set-up can be used in a neuroscience-focused study. The following studies are presented:

- *Measuring the strength of the connectivity through the corpus callosum*
  TMS was applied over different brain areas in the left hemisphere during fMRI. The aim of this study was to explore effects on the activity of the corresponding site in the right hemisphere. Several problematic aspects of concurrent TMS/fMRI are discussed in this chapter.

- *Combining ASL and TMS over the motor cortex*
  This study is a proof of principle, that it is possible to combine TMS and ASL concurrently.

- *TMS over the primary motor cortex during hand movement*
  In this study the effect of TMS on the activity of an active motor network is studied.

All experiments on human subjects were carried out in agreement with the local ethics approval.
Chapter 7

Probing the connectivity between hemispheres

This study involved using concurrent TMS/fMRI to investigate the connection between brain regions in the left and right hemispheres. It took advantage of the local nature of TMS, which directly stimulates only a restricted area. Our hypothesis was that all other areas which show changes in activity due to the stimulation must be connected to this restricted area.

7.1 Aim of the study

Histology of the corpus callosum of the human brain has shown a variation in the average diameter of the axons along the structure in the anterior-posterior direction (Aboitiz et al. [1992]) in which fibres in the centre of the corpus callosum have the largest average diameter. The variation in fibre diameter might be linked to the strength of connection between corresponding areas of the left and right hemispheres, where larger fibres provide either a stronger or a weaker connection. Boorman et al. [2007] combined diffusion tensor imaging (DTI) and TMS to demonstrate that differences in white matter microstructure can reflect variations in connectivity. They used paired pulse TMS to examine the connectivity between motor areas of the left and the right hemisphere. Individual difference in connectivity during action selection showed highly specific correlations with fractional anisotropy in localised regions of white-matter interconnecting regions.
Using concurrent TMS/fMRI and DTI, we wanted to explore if axon diameter correlates with the strength of trans-callosal connectivity. In the following a short outline of how the techniques could be combined, is given:

- TMS is applied over different locations in the left hemisphere.
- DTI is used to detect the areas in the corpus callosum and in the other hemisphere which show the strongest interconnection with the TMS target site.
- fMRI is used to determine the brain areas which are affected by TMS.
- Interconnected brain areas should show a significant response to TMS.
- Ideally the strength of this response correlates with the fibre composition of the corpus callosum at the point which shows the strongest interconnection with the target site. For example if larger fibres can be associated with a larger trans-callosal response to TMS, it would indicate that these fibres create a stronger connection.

### 7.2 Methods

DTI was not part of the preliminary experiments described here since the DTI acquisition and the analysis would be based on standard techniques which were not expected to require much developmental work.

The aim of the preliminary experiments was to identify a paradigm for TMS applied over different target sites which would produce reliable BOLD responses in remote areas. A main problem to address was how to achieve consistent positioning of the TMS-coil.

#### 7.2.1 Set-up

For imaging, a Philips Achieva 3T scanner and for TMS a Magstim Rapid\(^2\) stimulator were used. The stimulator was positioned in the operator room of the scanner, close to the waveguide, so that the length of the TMS-lead between the stimulator and the waveguide was less than 50 cm.

For the synchronisation of TMS and MRI parallel ports were connected to the trigger ports of the scanner and of the stimulator to send and receive TTL-pulses. The TTL pulses from the scanner indicate the start of the acquisition of a new volume. TMS pulses were triggered 1850 ms after
every 5th TTL pulse that came from the scanner. TMS pulses were delivered through an MR-compatible TMS-coil, which was introduced from the back of the scanner. A custom built coil holder, which was screwed onto the scanner bed was used to hold the coil in place over the target site (Section 3.4.1). The Philips Flex-S coils were used for signal reception, because the Nova 6-channel RF coil was not available at the time when these experiments were carried out. The head was stabilised using the head rest as described in Section 3.4.2. In this experiment, the Brainsight Frameless Stereotaxic system was used for the localisation of the target site and positioning of the TMS-coil. The procedure is described in Section 3.4.5.

7.2.2 MR-sequences

For fMRI an EPI-sequence with 32 slices, TE=35 ms TR=2 s, resolution (3 mm)$^3$, matrix size 64x64 and FOV was 192x192x96 mm$^3$ was used. The first 1700 ms of each TR were required for imaging and the remaining 300 ms silent period was used to accommodate the TMS pulses. During each sequence 450 dynamics with a total duration of 15 minutes were acquired. Additional MP-RAGE images with (1 mm)$^3$ isotropic resolution and a FOV of 192x192x96 mm$^3$ and with (2 mm)$^3$ isotropic resolution and a FOV of 256x256x200 mm$^3$ were acquired.

7.2.3 TMS-paradigm

TMS was applied during the whole 15 minutes with a frequency of 0.1 Hz and a strength of 100% of the maximum stimulator output. This corresponds to 130% MT on average. TMS was always applied 1850 ms after the start of the acquisition of an fMRI volume. 90 pulses were delivered during each sequence of 15 minutes. The synchronisation of TMS with the EPI-sequence is shown in Figure 7.1.

7.2.4 Target sites

Three different target sites were chosen and defined using coordinates in MNI standard space (left-right/posterior-anterior/inferior-superior) in mm:

- Dorsolateral prefrontal cortex (DLPC), (-40/32/30)
- Premotor cortex, (-32/-2/52)
7.2.5 Procedure

The paradigm was applied to 9 different volunteers (3 female, average age 34), who were familiar with TMS and fMRI. Nevertheless all the required safety measures were taken and special attention was paid to the comfort of the subjects.

The MT was measured by taking the lowest intensity of TMS pulses, which elicited a visible motor response. For positioning the TMS-coil, the subject was placed on the scanner bed outside of the scanner room. The subject was equipped with earplugs and a padded water polo cap. Movement of the head was suppressed by applying a small amount of pressure on the shells of the cap using the head rest (Section 3.4.2.)

Prior to the experiment the target sites were marked on an anatomical image of the subject. These image data were loaded onto a computer, that ran theBrainsight software. The 3-D camera was installed at the side of the demounted scanner bed with visual access to the subject’s head position. Since the subject was stabilised relative to the bed, the reflective spheres used for marking could be attached to the head-rest. The head of the subject was then registered in the Brainsight system.

For registering the TMS-coil, it had to be aligned with the calibration plate for at least 5 s, while
the camera had a free view of the markers on the calibration plate and on the coil. Here, aligned means that the centre pin of the calibration is lined up with the centre of the coil, that the surfaces of the plate and coil are parallel and that the short edge of the calibration plate is parallel to the long axis of the TMS-coil. The rod, which connected the TMS-coil to the set of reflective spheres was about 15 cm long and had a sharp bend of 90°. This was necessary to give the camera a free line of sight to the markers of the coil and to the markers of the subject at the same time. The TMS-coil was then positioned over the target site (see Section 3.4.5).

Once the TMS-coil had been fixed in position, the subject was moved carefully into the scanner room on the bed and then into the scanner. Rapid movements were avoided as much as possible during this process, in order to prevent changes in the position of the TMS-coil relative to the subject.

Once the subject was in position, the scanning was started. Prior to the main experiment with TMS, a short test run of 30 seconds with 15 dynamics of EPI and three TMS pulses was delivered to the subject to test whether the subject was comfortable and to look for unexpected artefacts in the images. The procedure was then repeated for each target site.

7.3 Results

7.3.1 Problems during the experiment

The main problem when running the experiment was the positioning of the TMS-coil, which is discussed later. We also encountered the following problems during the experiments:

- *TMS-coil moved during the scan due to inadequate fixation.* The coil was found to be no longer positioned over the target area after the experiment. These data were excluded from the analysis.

- *Stimulation of the prefrontal cortex caused a painful sensation because of the stimulation of facial nerves.* This effect could not always be eliminated when positioning the TMS-coil over DLPC. The sensation causes additional side effects which show up as false positives in the fMRI analysis.

Apart from the positioning, most of the experiments could be carried out without any major problems. None of the subjects showed any adverse side effects after the experiment.
7.3.2 Positioning

In most cases the positioning of the TMS-coil took the majority of the time required for the whole experiment. This is a result of the amount of equipment that had to be set up and the significant number of preliminary steps which were required when using the Brainsight system. The other main problem for the positioning was that it was often difficult to accommodate both the flexible receiver coils and the TMS-coil around the head of the subject. In these cases the subject had to be repositioned to provide enough space for the TMS-coil over the target site. Another difficulty was that the reflective spheres of the Brainsight system had to be visible to the 3-D camera. The time required to position the TMS-coil over one target site varied between 15 minutes and one hour.

Verification of the coil position

The MP-RAGE image with the large FOV was used to verify the position of the TMS-coil using the Matlab program described in Section 3.4.6. This program allows the location of the TMS-coil to be identified in MR-images based on MR-visible parts of the coil. Using the information about the coil position, the program can calculate the distance of each voxel to the coil surface and the distance to a virtual centre line which passes perpendicular to the coil surface through the centre of the TMS-coil. These values were written into MR-images with the same dimensions as the MP-RAGE image.

The MP-RAGE image was co-registered to the MNI-brain and the transformation matrix was applied to the image which shows the distance to the centre line through the TMS-coil. The coordinate where this centre line crosses the brain surface of the MNI-image was defined as the coil position.

The error of the measured coil position in MNI space can be estimated as

$$
\Delta r_C = \sqrt{\Delta r_T^2 + \Delta r_\alpha^2 + \Delta V^2}
$$

where \(\Delta r_T\) represents the error of the position of the centre of the coil, \(\Delta r_\alpha\) the error due to the coil angulation and \(\Delta V\) the error due to the voxel size in MNI-space. The quality of the MP-RAGE for this purpose was relatively poor, because of the low sensitivity for signal reception of the FlexS-coil in the regions of the TMS-coil. The MNI-brain used in this study had a low resolution of (3 mm)³.

The errors for the centre of the coil can be estimated as \(\Delta r_T = 4\) mm. For the angulation we assume that two sides of the coil are 100 mm apart and that the location of the sides can be estimated with an error of \(\Delta r_T\) relative to each other. Assuming that the brain surface has a distance of 50 mm
to the plane of the rubber ring results in $\Delta r_\alpha = 2$ mm. With $\Delta V = 1.5$ mm (half the voxel size) the resulting total error for the coil position is $\Delta r \approx \pm 5$ mm or about $\pm 3$ mm in each direction.

The measured coil positions are shown in Figure 7.2 and in Table 7.1. The measured location at the three different coil positions has a standard deviation over subjects of roughly 1cm in each direction. The position over S1 shows the largest variation. This is probably related to the fact, that the space available for positioning the TMS-coil over S1 was most restricted. There are also large differences between the average target location and actual coil position, especially in the x-direction.

The target site was marked using a coordinate in MNI-space. Individual differences were not taken into account. The variability of the coil position therefore cannot easily be explained by differences in the brain anatomy between subjects.

We modified the details of the TMS-coil positioning procedure several times between experiments on different subjects, which could be one reason for the inconsistent coil positions between subjects. In conclusion, there was a significant uncertainty in the position of the TMS-coil in this experiment. Brain areas which were adjacent to the target site were also potentially therefore affected by TMS. This can have a strong negative effect on the comparability of the results of the fMRI-analysis.

### 7.3.3 fMRI analysis

The analysis of the functional data was carried using FSL and Matlab. The preparatory steps included movement correction, high-pass filtering (0.05 Hz cut-off frequency) and spatial smoothing (5 mm FWHM). A general linear model was used to detect TMS-related brain activity. Each TMS pulse was taken as a single event and then convolved with the canonical hemodynamic response function. The resulting model was similar to a sine wave with a frequency of 0.1 Hz. T-maps without clustering showing the average percentage signal change in each voxel were created. The average signal change had the advantage of forming a measure that is not strongly affected by the inhomogeneous sensitivity of the receiver coils. All results were transformed into MNI-standard space.

In Figure 7.3 the T-map and the average BOLD change of a single subject are shown. The figures show a clear similarity between T-map and the average signal change and they indicate that T-values of 2 correspond roughly to a peak BOLD response of 0.2% in average.
Figure 7.2: Coil positions projected on sagittal, coronal and transverse slices of the MNI brain. The three black points mark the target for DLPC, premotor cortex and S1. The measured coil positions are colour coded for different target sites: left S1 (green), left premotor cortex (blue) and left DLPC (white). The results show large variations in the coil positions for each target area.
<table>
<thead>
<tr>
<th>Target area</th>
<th>Coordinates x / y / z (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DLPC (target)</td>
<td>-40/32/30</td>
</tr>
<tr>
<td>DLPC (measured)</td>
<td>-40.5/15/52.5</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>(±3/±3/±3)</td>
<td>-37.5/18/52.5</td>
</tr>
<tr>
<td></td>
<td>-52.5/12/40.5</td>
</tr>
<tr>
<td></td>
<td>-49.5/30/28.5</td>
</tr>
<tr>
<td></td>
<td>-58.5/21/19.5</td>
</tr>
<tr>
<td></td>
<td>-43.5/30/37.45</td>
</tr>
<tr>
<td>mean</td>
<td>47/21/38.5</td>
</tr>
<tr>
<td>std</td>
<td>8/7.6/13.1</td>
</tr>
<tr>
<td>mean distance to target</td>
<td>7/-11/8.5</td>
</tr>
<tr>
<td>Premotor cortex (target)</td>
<td>-32/-2/52</td>
</tr>
<tr>
<td>Premotor (measured)</td>
<td>-58.5/-21/6</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>(±3/±3/±3)</td>
<td>-52.5/6/43.5</td>
</tr>
<tr>
<td></td>
<td>-40.5/6/55.5</td>
</tr>
<tr>
<td></td>
<td>-55.5/-3/43.5</td>
</tr>
<tr>
<td>mean</td>
<td>-51.8/-3/47.3</td>
</tr>
<tr>
<td>std</td>
<td>7.9/12.7/5.7</td>
</tr>
<tr>
<td>mean distance to target</td>
<td>-19.8/-1/-4.7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Target area</th>
<th>Coordinates x / y / z (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1 (target)</td>
<td>-39/-31/57</td>
</tr>
<tr>
<td>S1 (measured)</td>
<td>-22.5/-15/70.5</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>(±3/±3/±3)</td>
<td>-31.5/-24/67.5</td>
</tr>
<tr>
<td></td>
<td>-16.5/54/70.5</td>
</tr>
<tr>
<td></td>
<td>-61.5/-42/43.5</td>
</tr>
<tr>
<td></td>
<td>-58.5/-45/46.5</td>
</tr>
<tr>
<td>mean</td>
<td>-52/-21/52.5</td>
</tr>
<tr>
<td>std</td>
<td>-46.5/-27/58.5</td>
</tr>
<tr>
<td>mean distance to target</td>
<td>-58.5/-30/46.5</td>
</tr>
<tr>
<td></td>
<td>-52.5/6/43.5</td>
</tr>
<tr>
<td></td>
<td>-46.5/-36/58.5</td>
</tr>
<tr>
<td>mean</td>
<td>-45.5/-30.5/55.8</td>
</tr>
<tr>
<td>std</td>
<td>14.4/16/9.9</td>
</tr>
<tr>
<td>mean distance to target</td>
<td>-6.5/0.5/-1.2</td>
</tr>
</tbody>
</table>

Table 7.1: Coordinates of the target sites and of the measured coil positions in MNI-space. The average variation of the coil position was the largest for S1. For the premotor cortex the results shows a large difference in x-direction between target and coil position. The measured position in the x-direction is more lateral than the target site for the premotor cortex and S1.
The averaged results of the three different brain areas are displayed in the Figures 7.4, 7.5 and 7.6. In all three cases the pattern of activation are dominated by a BOLD response in the superior temporal lobe which can be related to the noise of the TMS pulses. None of the results indicate brain activity, which can clearly be related to the site of stimulation.

The differences between these pattern of activity are displayed in Figures 7.7, 7.8 and 7.9. There is a tendency in the results that the BOLD response due to TMS over DLPC is stronger in large areas of the brain, but this can be explained with stronger side effect because the coil orientation was more parallel to the $B_0$ which results in a louder noise from the TMS pulses. Furthermore TMS over this area is more likely to induce a painful sensation in the face.

We can conclude, that most of the activity was caused by non-TMS specific effects such as the noise of the coil or the sensation of the vibration of the coil. This can also be seen on an individual subject in Figure 7.3 where TMS-related activity can be identified.

In Figure 7.10 the average signal change of all different conditions is displayed. This can be used as a reference for non-TMS specific brain activity in studies with concurrent TMS/fMRI.

### 7.4 Discussion and Conclusion

This study shows clearly the need for a good control condition in experiments with concurrent TMS/fMRI. The side effect of TMS is so dominant in the results, that they even can contribute the major part to the detected effects after subtracting the control condition (as shown in Figures 7.7 and 7.8). There are also other aspects, which can explain the negative outcome of this study:

1. Is the TMS-coil positioned over the target area? Are there other areas affected?
2. Does TMS have an effect on the brain function. How can these effects be observed?

As shown previously the position of the TMS-coil was in most of the experiments roughly over the target site, but the uncertainty in the position is so large, that in most cases adjacent brain areas would have received TMS of a similar strength. Therefore the significance of the group analysis was greatly reduced. Individual data as shown in Figure 7.3 however did not show clearly TMS-related effects either.

The TMS-paradigm was designed to evoke brain activity with an event related design using single strong TMS pulses applied to S1, pre-motor cortex or DLPC. According to our results it is
Figure 7.3: Comparison between T statistics (left) and average signal change (right). The data is from a single subject and TMS was applied over the DLPC. The thresholds are $T > 2$ and for the average signal change $> 0.2\%$ of the modulus signal. The pattern and the size of the activated areas is in both cases very similar apart from some false positives around the edges of the images where the average signal change is elevated due to the low modulus signal in these regions.
Figure 7.4: BOLD response due to TMS over S1, averaged over 10 subjects. The colour overlay indicates the percentage change thresholded to values $> 0.1\%$. The most significant changes in brain activity due to TMS can be found in the left and right temporal lobes.
Figure 7.5: BOLD response due to TMS over left DLPC, averaged over 6 subjects. The colour overlay indicates the percentage change thresholded to values > 0.1%. The pattern of the TMS-induced brain activity is similar to the pattern from TMS over S1 (Figure 7.4).
Figure 7.6: BOLD response due to TMS over the left premotor cortex, averaged over 4 subjects. The colour overlay indicates the percentage change thresholded to values $> 0.1\%$. The pattern of activation is similar to that produced by TMS over S1 or DLPC. The data are likely to show a larger contribution of noise, because they are based on only 4 subjects.
Figure 7.7: Difference in fractional signal change due to TMS over DLPC compared to TMS over S1. Left: DLPC > S1. Right: S1 > DLPC. The threshold in both cases is a difference in BOLD response of >0.06% in average. The data for TMS over DLPC are based on 6 subjects and for TMS over S1 on 10 subjects.
Figure 7.8: As Figure 7.7, but comparing DLPC > premotor cortex (left) and premotor cortex > DLPC (right). The data for TMS over the premotor cortex are based on 4 subjects.
Figure 7.9: As Figure 7.7, but comparing S1 > premotor cortex (left) and premotor cortex > S1 (right).
Figure 7.10: BOLD response due to TMS averaged over all stimulation sites and subjects. The colour overlay indicates the percentage change thresholded to values $> 0.1\%$. 
questionable if this paradigm influences the brain activity in a way, which is detectable using BOLD-contrast. We don’t know this for sure, since there were no previous studies using concurrent TMS/fMRI with a similar paradigm. The most likely case is that there was some effect, but the effect was too small to be detected using our setup for fMRI.

Another factor is that we were using small flexible receiver coils in this experiment, which come with a significantly lower coverage of the whole brain and a lower average sensitivity. With a higher sensitivity it might have been possible to detect significant BOLD-effects, which can be related to TMS.

Choosing the right TMS paradigm is crucial in studies with concurrent TMS/fMRI. Furthermore a consistent positioning of the TMS-coil is required, because otherwise the results are not reliable. The method described in Section 3.4.6 can be used to verify the position. Running this program takes currently less than 5 minutes and the program can give a clear feed-back of how exactly the coil must be adjusted in order place it exactly over the target site. This would speed the up-set of experiments up and also provide a more reliable coil position.
Chapter 8

Combining TMS with Arterial Spin Labelling

8.1 Aim of the study

The aim of this study was to demonstrate that TMS can be combined with concurrent Arterial Spin Labelling (ASL). ASL has a range of potential advantages compared to BOLD fMRI for use in studies employing simultaneous TMS. It provides quantitative measurements of cerebral blood flow, which is a contrast that is not dependent on the parameters of the MRI-sequence and which is therefore readily comparable between studies carried out on different scanners. Furthermore, ASL has advantages for studying TMS-induced effects, which persist over times of minutes because blood flow is determined by taking difference images between consequently acquired volumes. This means that for the analysis of the time-course of each voxel no high pass filtering is required because the subtraction already eliminates any slow drifts in signal strength.

In many TMS-studies TMS is applied over a considerable amount of time and afterwards behavioural changes in the subject are evaluated (Pascual-Leone et al. [2000]). This kind of study focuses on the effects of TMS, which last over a time-scale of minutes. Combining TMS and ASL would allow effects of TMS on the brain to be measured on this time-scale using paradigms which have proved to be effective in previous studies with using only TMS.
CHAPTER 8. COMBINING TMS WITH ARTERIAL SPIN LABELLING

8.2 Methods

8.2.1 ASL sequence

The ASL technique which was used in the experiments is the Flow sensitive Alternating Inversion Recovery (FAIR) method (Kim [1995]). The sequence used here was implemented by Gardener et al. [2009] and it is described in detail in Section 1.5.1. For this study the following parameters were applied:

- **Image Dimensions**
  Matrix: 64×64
  6 slices
  Resolution: 3×3×5 mm³
  FOV: 192×192×30 mm³

- **Acquisition**
  Double echo GE-EPI acquisition
  $T_{E1}=10 \text{ ms}$
  $T_{E2}=33 \text{ ms}$
  TR=4 s (for each pair of Label and Control images)

- **Perfusion parameters**
  Inversion time $T_I=1400 \text{ ms}$

Figure 8.1: Coverage of the ASL sequence. Area covered by the inversion pulse of the Label and Control acquisitions.
Label slab thickness: 100 mm  
Control slab thickness: 40 mm  

The coverage of the image slab in the foot-head direction was restricted to 30 mm because only a small number of slices could be acquired. The centre of the slab was positioned over M1 as shown in Figure 8.1. The second echo image, which had a TE of 33 ms, provided BOLD-sensitive contrast. BOLD-contrast could therefore be measured simultaneously with perfusion contrast using this sequence.

8.2.2 MRI sequences  

In addition to the ASL measurements, a study using conventional GE-EPI for BOLD-contrast was also carried out to provide results for comparison with the ASL-data. 28 slices were acquired in 1.8 s with a TR of 2 s, leaving a silent period of 0.2 s at the end of each volume acquisition. The resolution was 3x3x4 mm$^3$ and the matrix was 64x64. The resulting FOV was 192x192x112 mm$^3$. The TE was set to 35 ms.

Three MP-RAGE sequences were also run, two with 1 mm$^3$ resolution and the same FOV as the ASL-sequence or the conventional EPI respectively. The other sequence, which had a FOV of 256x256x256 mm$^3$ (2mm)$^3$ resolution) was used to detect the position of the TMS-coil and to provide data that would allow the vector potential produced by the TMS-coil inside the brain to be calculated.

8.2.3 TMS paradigm and synchronisation  

A simple diagram of the FAIR sequence is shown in Figure 8.2. The inversion time, which is required for the in-flow of labelled blood into the capillaries, forms a silent period without RF, gradient switching or any transverse component of the magnetisation. This allows great flexibility in the application of TMS during the ASL sequence. The timeframe during which TMS can be applied, is indicated with green bars in Figure 8.2.

In this experiment, TMS pulses were delivered with a repetition rate of 0.1 Hz and 130% of MT. The high TMS intensity was chosen to produce a reliable motor response from each pulse. The repetition rate of 1 pulse every 10 s allowed easy analysis of the data using an event related design. The paradigms can also be treated as a homogeneous train of TMS pulses. This train might cause
Cumulative effects on the brain, which then can be detected in the form of changes in perfusion.

The MRI part of the experiment consisted of the following sequences:

1. **ASL**, 16 minutes, 240 pairs of label and control images, 3 minutes rest then 10 minutes TMS at 0.1 Hz, then 3 minutes rest.

2. **MP-RAGE**, 3:30 minutes, to determine the position of the TMS-coil

3. **MP-RAGE**, 40 s, FOV as in ASL data, for coregistration

4. **BOLD-EPI**, 28 slices, 5 minutes, 150 dynamics, acquired during 0.1 Hz TMS.

5. **MP-RAGE**, 4 minutes, FOV as in BOLD EPI, for coregistration

During the ASL sequence the TMS pulses were delivered either 100 ms or 2100 ms after the trigger pulses, which were produced by the scanner just before each inversion pulse was applied to the label region. The synchronisation is illustrated in Figure 8.2.

During the BOLD-EPI-sequence, TMS was applied 1850 ms after the trigger pulses from the scanner. Software written in the Presentation package was used for synchronisation of the scanner and TMS-stimulator.
8.2.4 Procedure of the experiment

Before the experiment, the motor threshold MT of each subject was determined by applying TMS over left M1 and observing the muscle response in the right hand. This was done while the subject lay on the scanner bed with their head resting inside the Nova-coil (Section 3.1.1). The TMS-coil was then fixed in position over left M1 using the coil holder which is described in Section 3.4.1. To make sure that the position of the TMS-coil was correct, TMS pulses were again applied at MT, and the coil position was adjusted until a muscle response could be observed. The subject was then moved into the scanner and the scans were started.

Four healthy subjects were studied who were all familiar with TMS and fMRI. No side effects were reported after the experiments.

8.2.5 Data analysis

ASL data

Each ASL data-set consisted of 4 different parts: 1st Echo Label, 1st Echo Control, 2nd Echo Label and 2nd Echo Control. The data from each echo time were arranged in a 4-D format with alternating Label and Control volumes (Label first). The two datasets were corrected for movement of the subject and then transformed into the MNI-image space. The MP-RAGE images with 30 and 112 mm coverage in the foot-head direction were used as intermediate steps for the coregistration.

Perfusion contrast event related

Data from the two echoes were added together for the analysis of perfusion effects. Difference images were created using an interpolation method, which takes the difference between each image volume and the average of the preceding and following image volumes. The result of the subtraction was negated for alternate volumes (i.e. those corresponding to subtraction of control from label volumes) so that signal changes were always positive. The interpolation increased the temporal resolution to 2 s. Each volume was divided by the temporal mean of the sum of both echoes. The result was an image times-series with values representing the relative signal change due to perfusion-related differences between Label and Control.

The time-course of the data was analysed using FSL-software (Smith et al. [2004]). A general linear model was applied using every TMS pulse as a single event.
BOLD contrast from the ASL sequence. For BOLD contrast only the data from the 2nd echo with TE = 33 ms was used. The temporal mean of the difference between Label and Control volumes was added to every single Control volume. This eliminated the perfusion component from the time-course of the data. These data were also analysed using a general linear model with each TMS pulse used as a single event.

Perfusion TMS vs no-TMS.
The difference of the mean perfusion-difference signal of each voxel during the 10 minutes of 0.1 Hz TMS and during the 6 minutes (3 minutes at the beginning and 3 minutes at the end) with no TMS was calculated. Statistical parametric maps were created by using this difference divided by the standard error of the difference.

Other sequences
BOLD contrast of the conventional EPI sequence
The data from the conventional EPI-sequence were corrected for movement and transformed into the same space as the ASL-data. These data were analysed in the same way as the ASL data with every TMS pulse forming a single event.

Position of the TMS-coil
The position of the TMS-coil was determined using the procedure described in Section 3.4.6 based on the MP-RAGE image with the large FOV. This information was then used to determine the strength of the vector potential produced by the TMS-coil.

Timecourses over different ROIs
Two different ROIs were defined in the ASL-data of each subject:

1. Voxels with positive activation in the BOLD-weighted (2nd echo) images (z>3) produced in the ASL study.

2. Vector potential $A$ per current $I$ in the TMS-coil: $A/I > 2.4\mu TmA^{-1}$. 
CHAPTER 8. COMBINING TMS WITH ARTERIAL SPIN LABELLING

Figure 8.3: Images from the ASL-sequence. The raw data from the ASL sequence data looks similar to EPI-data with low structural contrast. Subtraction of a single pair of Label- and Control images results in a noisy image. Averaging over 150 difference images produces an image which clearly shows the same shape of the grey matter white matter boundaries which are evident in the MP-RAGE image.

The threshold for the vector potential per current was chosen so that the area of this strength penetrates into brain on average by 2 cm. Since the strength of the vector potential is proportional to the current through the TMS-coil, the vector potential per current unit was chosen as a measure for the local effect of TMS. The corresponding maximum induced electric field under the assumption of $\frac{\partial I}{\partial t} = 5 \times 10^7 \text{As}^{-1}$ is $120 \text{Vm}^{-1}$, based on Equation A.11 and neglecting any charge accumulations at tissue boundaries.

The averages of the perfusion and BOLD sensitive data were calculated over these ROI. The results are time-courses showing the temporal variation of the different contrasts over the particular ROIs. The relative signal change from the BOLD contrast was extracted by dividing the time-course of the BOLD-data with the mean value of the time-course and subtracting 1. The ASL-data were already normalised as described earlier.

To form an average time-course showing the average BOLD and perfusion-related signal change produced by a TMS pulse, the time-courses were segmented into 60, 10 seconds periods each following a TMS pulse which then were averaged together.
8.3 Results

8.3.1 Image quality

No direct influence of the TMS pulses on the MR-images could be observed. As described in Section 6.2 there was a small reduction in signal quality because data were acquired using the Nova-coil instead of the standard 8-channel head coil.

Images from the ASL-data are shown in Figure 8.3. This figure shows that the difference image from a single pair of Label- and Control volumes has a low SNR. Nevertheless the average over 150 of these difference images provides a map, which can be used to quantify perfusion with high SNR. There is excellent agreement between the features seen in this perfusion map and grey and white matter structures seen in the anatomical image (MP-RAGE) of the same slice.

8.3.2 Comparison of activation patterns from fMRI different contrasts

The results from a single subject are shown in Figure 8.4 and a comparison between all four subjects is shown in Figure 8.5.

In three of the four subjects a significant positive BOLD-response was found in M1 in the ASL-data and in the data from the conventional EPI-sequence. The area identified was very similar for both sets of data for each of the subjects. The data from the ASL-sequence showed a higher statistical significance, which can be explained by the higher number of volumes and the longer duration of the experiment.

The event-related analysis of the perfusion contrast showed a less significant pattern, but there was some activity in M1 which was slightly shifted relative to the area with the strongest BOLD-response.

For the three subjects, who showed a significant BOLD-response, statistically significant activation could also be detected in the area where the vector potential was strongest. This is also true for the results from the event-related perfusion analysis. The subject who didn’t show any BOLD-response in left M1 also showed no similarity between the the area with the strong vector potential and the main activity which was detected from the BOLD- or the perfusion contrast. Furthermore for this subject the position of the TMS-coil was more anterior compared to the other subjects. Although we didn’t observe the muscle response during the experiment, it is likely that TMS was not eliciting reliable motor responses on this subject.
Figure 8.4: Comparison between different contrasts on one subject. The BOLD-contrast from the conventional EPI-sequence (a) and from the ASL sequence (b) show similar significant activations in left M1. The event related analysis from the perfusion contrast (d) shows the main activity in a slightly shifted area. Some areas show a significantly increased perfusion during the 10 minute period with TMS compared to the periods of rest. However these areas seem to be rather randomly distributed and they are possibly false positives. The vector potential which indicates where TMS has the strongest effect, shows a maximum over M1.
Figure 8.5: Perfusion and BOLD-contrast. Comparison between different subjects. Four different contrast are overlayed on the images with the following order from foreground to background Perfusion increase during TMS, Perfusion (event related), BOLD (standard fMRI) and BOLD (from ASL). The colour scale ranges for each of the contrasts starts at $z=3$ and saturates at $z=6$. The white line indicates a vector potential per current of $A/I = 2.4 \mu Tm A^{-1}$ and the area inside the white line has a higher vector potential. The first three subjects showed a significant BOLD-activation due to TMS in the area with the strongest vector potential.
8.3.3 Timecourse analysis

The average of the time-courses from the three subjects, who showed activity in M1 was calculated. The results are shown in Figure 8.6. The time-courses of the perfusion and BOLD signals are similar in form for the two ROI’s.

The peak-to-peak amplitude after averaging over all significant voxels from the BOLD-contrast results in a time-course with a peak-to-peak amplitude in the BOLD-contrast of 0.6% of the total signal the amplitude, while the perfusion data show a change of 15% of the perfusion in the ROI.

When the area with a high vector potential was taken as an ROI, the values were 0.5% and 5% respectively.

The ratio of the signal change (perfusion contrast)/(BOLD contrast) was about 25 when the voxels with values z>3 in the BOLD data were used to form an ROI and about 10 when the area with the strongest vector potential was used to define an ROI.
8.4 Conclusion

The experiment shows that TMS and ASL can be combined concurrently. The difference of a single pair of Label- and Control is noisy, but after averaging over 150 pairs, a clear map showing a perfusion related contrast could be produced.

One advantage of combining ASL with TMS is that most ASL sequences have silent periods between the inversion pulse and the acquisition. This allows the application of a variety of TMS-paradigms without any changes to the MRI-sequence.

The data from the second echo in the ASL sequence (TE=33 ms) gives reliable BOLD-contrast which is similar to the contrast from a conventional GE-EPI sequence which was optimised for BOLD-contrast. The drawback of the ASL-sequence is the low coverage (6 slices compared to 28 slices for the conventional GE-EPI sequence which was used).

Maps of event related changes in perfusion could be produced. These maps show some similarity for the event related changes in BOLD contrast. No significant average change in perfusion during TMS compared to perfusion before and after TMS was found.

One reason for the low significance of the results from the data is the relatively low dose of TMS. The TMS-related changes of the brain metabolism are just too low to induce strong effects. Increasing the dose for example by applying bursts with a high stimulation intensity would be a promising approach to overcome these problems (Ruff et al. [2006]).

The results show clearly, that ASL is less sensitive to short term changes than BOLD-contrast. Therefore BOLD-contrast is the fMRI technique of choice for most studies with concurrent TMS/ASL. Use of ASL is recommended when the expected changes are difficult to detect with BOLD contrast. This is the case in the following situations:

1. When quantitative results are required such as in longitudinal studies.
2. When a TMS-paradigm is used, which cannot be split into single events or blocks.
3. When looking at long term effects of TMS.
4. When looking explicitly at changes in perfusion.
In some cases it might be an option to combine ASL with offline TMS outside of the scanner. In this case there is no compromise in the image quality and experiments with TMS are less difficult to carry out.
Chapter 9

Effect of TMS on an active motor network

The following study was conducted together with Ms JeYoung Jung, who is a PhD-student and her supervisor Professor Steven Jackson from the School of Psychology at the University of Nottingham. The first experiments started in January 2010 and preliminary results are presented here. Data analysis was carried out by Ms Jung.

9.1 Aim of the study

In this study TMS was applied during execution of different hand movements. The aim of the study was to explore the effect of TMS on brain activity which is induced by the hand movement tasks.

9.2 Methods

9.2.1 Set-up

The set-up used in this experiment was very similar to that used for the study described in Chapter 7. The differences in the set-up compared with that described in Section 7.2.1 are listed below.

- The Nova 6-channel RF coil with a bore of 30cm diameter was used for signal reception. An
insert for this coil allowed flexible positioning of the subject’s head inside the coil. Ear-plugs and a cap with padded ear-shells were used for additional ear protection.

- For the synchronisation between TMS and MRI a National Instruments data acquisition card was connected to the trigger ports of the scanner and of the stimulator. This card was controlled by a Matlab program. Only the first TTL-pulses at the start of the fMRI sequence was used as a reference event. All subsequent TMS pulses and visual instructions were applied with different timings relative to this event.

### 9.2.2 MR-sequences

For fMRI, a GE-EPI sequence with 30 slices and TE=35 ms was used. The resolution was (3 mm)\(^3\) with a 64x64 matrix. The slice orientation was transverse and the fold-over direction was anterior-posterior. The FOV of 192x192x90 mm\(^3\) was enough to cover most of an average brain, excluding only the lower half of the cerebellum.

The acquisition of each slice required about 52.6 ms, which led to a minimum time for acquisition of each volume of 1580 ms. TR was set to 1000 ms and temporal slice spacing to shortest. The scanner then automatically splits the acquisition of each volume into two packages, whose acquisitions each required 1000 ms. The time required therefore for the acquisition of a complete volume was 2000 ms. During the first 790 ms of each of these package acquisitions, the scanner acquires 15 slices. During the remaining 210 ms the scanner is passive. A silent period of 90 ms is required after every TMS pulse to avoid production of artefacts in the images due to leakage currents through the TMS-coil during the recharge period of the stimulator (Section 5.2). TMS can therefore be applied safely at times ranging from 800 ms to 900 ms and 1800 ms to 1900 ms during each volume acquisition.

Each scan was preceded by 3 dummy scans. The number of repetitions was 135 resulting in a total acquisition time of 4:30 minutes.

An MP-RAGE sequence with (1mm)\(^3\) resolution and a FOV of 192x192x140mm\(^3\) was used to acquire structural images for co-registration purposes. An MP-RAGE image with (2mm)\(^3\) resolution and a large FOV of 256x256x256mm\(^3\) was also acquired. This was used to determine the position of the TMS-coil. All images were acquired with the same angulation and with the FOV centred over the same position.
9.2.3 Paradigm of the experiment

Each paradigm consisted of blocks with durations of 30 seconds. The instructions for hand clenching were changed after each block. Each of these blocks included a period during which 12 TMS pulses were delivered at a frequency of 1Hz and each specific hand clenching therefore consisted of 18 seconds of hand clenching without TMS and 12 seconds of hand-clenching during TMS. TMS pulses were delivered either at 850 ms or at 1850 ms after the start of each volume acquisition (Figure 9.1). The start of the TMS-block was jittered randomly, so that the first TMS pulse could occur between 0.85 s and 19.85 s after the beginning of each block.

TMS with 100% MT was delivered to left M1 and right M1 while the subject executed a visually-cued hand-clenching task. The subject was given simple instructions on a visual display screen with visual cues used to direct the subject to open and close at a comfortable rate either the right hand only ('R'), the left hand only ('L'), both hands simultaneously ('B') or to rest ('N'). After each block of 30 seconds the instruction changed. Each fMRI-sequence consisted of 9 blocks,
spanning 135 TR periods corresponding to a total acquisition time of 4:30 minutes. The sequence of the blocks was:

- \textit{N-R-L-B-N-B-R-L-N}

In total 108 TMS pulses were delivered during each sequence.

The same sequence was run twice for each target site on each subject with a period of 5-10 minutes without TMS in between. During this period the MP-RAGE images were acquired. Each experiment consisted of the following MR-sequences:

- Survey (1min)
- Reference (1min)
- EPI 135 repetitions with TMS and motor task (4:30 min)
- MP-RAGE high resolution (4 min)
- MP-RAGE large FOV (3:30 min)
- EPI 135 repetitions with TMS and motor task (4:30 min)
- \textit{Subject moved out of the scanner to change coil position}
- Survey (1min)
- Reference (1min)
- EPI 135 repetitions with TMS and motor task (4:30 min)
- MP-RAGE large FOV (3:30 min)
- EPI 135 repetitions with TMS and motor task (4:30 min)

The time spent inside the scanner by each subject was between 40 and 50 minutes.

12 healthy subjects (8 female, average age 25, all right handed) were studied using this paradigm. The starting coil position was alternated between either left or right M1. The whole experiment is illustrated in Figure 9.2.
9.3 Procedure

9.3.1 Experiment

After explaining the experimental protocol to the volunteer, TMS was demonstrated, first on the hand and then on the head in order to introduce the subject to the stimulation. The subject was asked to put on earplugs and the cap with foam pillows. They were then positioned on a chair outside of the scanner room in order to determine the MT.

The starting position for this was to apply stimulation at a position about 5 cm to the left from the centre of the top of the head along a circumferential line running between both ears. Initially the long axis of the TMS-coil was held parallel to this line. A starting intensity of 75\% of the maximum stimulator output was used. The intensity and the position of the coil were adjusted to find the site, where a response of muscles of the right hand with the lowest stimulation intensity could be observed. The intensity which elicited a visible motor response in 5 of 10 repetitions was taken as MT. The circumference of the coil was marked on the cap. The same procedure was repeated for the other hemisphere.

After marking the target sites, the subject was positioned on the scanner bed and their head was stabilised inside the Nova-coil. The TMS-coil was then fixed over the first target site. We made sure that the coil was very close to the head surface, but not pressing against the head. One or more TMS pulses at 100\% MT were delivered to test for a motor response. In some cases the coil position had to be readjusted. The subject was then moved carefully into the scanner. Inside the scanner a few TMS pulses were delivered to the subject to test whether the subject would be comfortable during the experiment.

The experiment was then started with the survey and the reference scan. The imaging slab was positioned with transverse orientation but with a slight angulation, so that the FOV covered as much of the brain as possible. Before and after every sequence involving TMS, the subject was asked if they were comfortable. After the first half of the experiment, the bed was moved out of the scanner and the TMS-coil was positioned over the new target site. In most cases it was possible to reposition the coil without adjusting the position of the head of the subject. After the experiment, the subject was asked to fill out a form containing questions about the experience of TMS in the scanner.
9.4 Results

In general the experiments could be carried out without any major problems. After the scan there were no adverse side effects and all subjects reported, that they would participate in this type of experiments again.

9.4.1 Problems during the experiment

There were different problems, which occurred in single cases:

- *Finding site of M1, high MT*
  Two subjects showed a high MT (>75% stimulator output). For these subjects it was also more difficult to determine the best TMS-coil position for evoking a muscle response. On stimulation, one of these subjects reported an uncomfortable sensation in the face which was caused by peripheral nerve stimulation.
  
  In general for subjects with a lower MT it was easier to find the right target site and the side effects were less significant.

- *Not enough space for the TMS-coil*
  Despite the relatively easy access to the chosen target sites, in some cases there was not enough space to position the TMS-coil with the desired orientation over the target site. In these cases the head of the subject had to be repositioned.

- *Coil moved during the scan.*
  In one case the TMS-coil was found to have moved during the scan. This could have been avoided by tightening all screws once more, before the subject was moved into the scanner.

- *Subject moved during the scan.*
  The data of one subject were excluded because he moved more than 5 mm during the scan.

- *Discomfort of the subject*
  In one of the preliminary experiments one subject felt very uncomfortable during TMS inside the scanner. The subject was our youngest participant and had never participated before in any experiment with TMS or MRI.
  
  This example shows, that it is sensible to use only subjects who have participated earlier in experiments involving TMS or MRI. It should be explained clearly to the subjects what
happens during the scan and TMS inside the scanner should be demonstrated before the experiment starts. The subject must be encouraged to press the panic button during the scan, if they feel uncomfortable.

In total the data from one stimulation site in two subjects were excluded from the analysis.

9.4.2 Image quality

The image quality of the scans varied to some extent between subjects. This was mostly related to the amount of RF-noise. The larger bore of the receiver coil resulted in a decreased SNR compared to that provided by the the standard eight-channel head-coil. Altogether the image quality was however satisfactory.

9.4.3 Coil position

The coil position was determined using the procedure described in Sections 3.4.6 and in Section 7.3.2. The results are shown in Table 9.1. Apart from subject number 6, the two coil positions are relatively symmetric for each subject. These data are also presented in the in Figure 9.3 where most of the lines connecting both target sites are close to parallel to the left-right direction. This is an indication, that the method for coil positioning was reliable.

9.5 FMRI analysis and results (by Ms JeYoung Jung)

Data analysis

The SPM5 software package (Wellcome Department of Imaging Neuroscience, UK) was used to analyse the fMRI data. The functional images were realigned, co-registered with the anatomical image, spatially normalised to the Montreal Neurological Institute (MNI) space, and spatially smoothed using a Gaussian kernel (8 mm, full-width half-maximum). Individual contrast images were calculated using a general linear model (GLM) in SPM5. A design matrix was defined comprising TMS condition and No-TMS condition (See Table 9.2). T-contrast images were defined for each participant and the data were analysed at the group level using random effects analysis. The contrast images were entered into a one sample T-test for the experimental conditions (TMS vs. No-TMS and No-TMS vs. TMS). Statistical significance was set to a height threshold of p <
**CHAPTER 9. EFFECT OF TMS ON AN ACTIVE MOTOR NETWORK**

<table>
<thead>
<tr>
<th>Subject</th>
<th>Left (MNI) x/y/z (in mm)</th>
<th>Right (MNI) x/y/z (in mm)</th>
<th>Distance (mirrored)/mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-40/-12/66</td>
<td>34/-8/68</td>
<td>7.5</td>
</tr>
<tr>
<td>2</td>
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</tr>
<tr>
<td>3</td>
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<td>34/-4/68</td>
<td>20.2</td>
</tr>
<tr>
<td>4</td>
<td>-36/-2/66</td>
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<td>2</td>
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<tr>
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<td>40/-26/68</td>
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<td>30/0/70</td>
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</tr>
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<td>2</td>
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<td>36/-14/68</td>
<td></td>
</tr>
<tr>
<td>11</td>
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</tr>
<tr>
<td>12</td>
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<td>30/-4/68</td>
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<td>6.8/8.2/3.6</td>
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</tr>
<tr>
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<td>39/-17.2/61.6</td>
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<tr>
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<td>2.8/5.1/4.5</td>
<td>4.5/4.3/5.4</td>
<td></td>
</tr>
</tbody>
</table>

**Table 9.1:** Coil position from the different subjects in MNI space. The position was defined as the point, where a virtual line, perpendicular to the surface and through the centre of the TMS-coil, hits the brain. In general, the variations between subjects are greater along the y-axis compared to the x- or z-axis. The last column indicates the distance between the two coil positions, if one position would be mirrored along the mid-plane of the brain. In 7 of 12 subjects, this difference is smaller than 11mm. Subject 6 is an outlier. The literature values represent the coordinates which show the peak of activation in fMRI data during index finger movement (Kobayashi et al. [2003]). These coordinates are located inside the brain, which can explain the differences to the measured values.
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Figure 9.3: Coil positions on the different subjects over left and right M1 projected onto sagittal, coronal and transverse cuts through the MNI brain. The displayed brain is a standard in MNI space. The coil position was defined as the point, where the virtual line through the centre of the coil and perpendicular to its surface hits the standard brain. Points connected with lines indicate the two coil positions used on the same subject.
### Table 9.2: Overview over the conditions during this experiment.

For each TMS-coil positions there were four hand clenching conditions: left (hand clenching), right, both, rest. Each of these conditions included a period with and a period without TMS. Each experiments was carried out with TMS over left and the right M1, resulting in a total number of 16 conditions.

<table>
<thead>
<tr>
<th>TMS/Hand</th>
<th>Left (L)</th>
<th>Right (R)</th>
<th>Both (B)</th>
<th>Rest (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMS left</td>
<td>LH TMS/left</td>
<td>LH TMS/right</td>
<td>LH TMS/both</td>
<td>LH TMS/rest</td>
</tr>
<tr>
<td>No TMS left</td>
<td>No TMS/left</td>
<td>No TMS/right</td>
<td>No TMS/both</td>
<td>No TMS/rest</td>
</tr>
<tr>
<td>TMS right</td>
<td>RH TMS/left</td>
<td>RH TMS/right</td>
<td>RH TMS/both</td>
<td>RH TMS/rest</td>
</tr>
<tr>
<td>No TMS right</td>
<td>No TMS/left</td>
<td>No TMS/right</td>
<td>No TMS/both</td>
<td>No TMS/rest</td>
</tr>
</tbody>
</table>

0.005 (uncorrected, T > 3) and the resulting statistical parametric maps were assessed for clusters comprising twenty or more simultaneously activated voxels.

### Results

The results of the fist clenching task indicated that for each hand condition there was significant contralateral motor cortex activation, and that the both hands condition evoked significant bilateral motor cortex activation (Figure 9.4). TMS produced a significant activation bilaterally within the insula and the second somatosensory cortex (SII), and deactivation in the precuneus and superior parietal lobe (SPL) bilaterally across all task conditions. We conducted an analysis to obtain overlapping areas through all condition. The result indicates that TMS on motor cortex causes increased activation in insula and SII and decreased activations in precuneus and parietal lobe (PL) (Figure 9.5). The effect size ROI analyses revealed that the activations within each ROI were largest in the rest condition (9.6). The analyses also showed that the deactivation of bilateral PL varied as a function of task. Specifically, deactivation were stronger in the left hemisphere (TMS on left M1) during left hand movements and stronger in the right hemisphere (TMS on right M1) during right hand movements.
**Figure 9.4:** The result of the task condition shows that each hand condition caused strong contralateral motor cortex activation and that the both-hand condition evoked significant bilateral activation in motor cortex.

**Figure 9.5:** Brain areas which show different levels of activity during different tasks.
Figure 9.6: Results from a region of interest analysis over different areas and during different conditions. The areas analysed are left and right SII (l_SII, r_SII) left and right insula (l_insula, r_insula) and left and right superior parietal lobe (l_SPL, r_SPL). In all regions the effect of TMS is stronger during the rest condition than during any other condition.
Conclusion

TMS on motor cortex during the fist clenching task induced increases in SII and insula bilaterally and decreases in bilateral superior parietal lobe (SPL). Increased activation in SII and insula may be a re-afferent feedback from peripheral system, or SII and Insula may play a role in monitoring movement intention signals. Thus, their activation might be linked to distinguishing self-generated movements from those induced by TMS. The decrease in bilateral SPL might indicate inhibitory process evoked by TMS on the motor cortex. This study demonstrates that the activations induced by TMS can be modulated by current brain states. The effect size in each ROI differs according to task condition. The largest activation was found in the rest condition. SPL deactivations show reversed patterns for left hand and right hand movements.
Chapter 10

Overall conclusion and outlook

In this PhD project the problems and the limitations, which are specific to the concurrent application of TMS and fMRI, have been discussed. It has been shown that it is possible to combine these techniques successfully without any major changes to either the TMS-system or the MR-scanner. The problems related to concurrent TMS/fMRI have been identified and solutions to overcome them have either been implemented or proposed. Experiments using concurrent TMS/fMRI have been carried out successfully on human subjects. A brief summary of the results of this PhD project is given below.

10.1 Equipment

Given an MR-scanner and a biphasic TMS-stimulator, the necessary equipment required for carrying out experiments with concurrent TMS/fMRI consists of the following parts:

1. MR-compatible TMS-coil
2. Coil holder which screws onto the scanner bed
3. RF-receiver coil which allows access to the subject’s head
4. Computer with a parallel port to synchronise the TMS pulses with the MR-scanner

This is a rather short list and the most costly part is the RF-receiver coil. The financial demands for setting up concurrent TMS/fMRI are moderate and as such this is an affordable research option
for many neuroscience laboratories.

The equipment that was used during this PhD leaves room for improvement. An RF-filter for the lead of the TMS-coil would improve the fMRI data and reduce fluctuations of the level of noise between sessions. An improved coil-holder, that is more straightforward to use, would reduce the time requirement for setting up each experiment in the scanner and would make the positioning of the TMS-coil more reliable. The same applies to the methods for localising the target site. For example it might be possible to change the Brainsight-System in a way that the positioning of the TMS-coil is carried out in the scanner room with the camera at a safe distance from the main magnet.

Changes to the design and construction of the TMS-coil could reduce static artefacts in MR-images and also attenuate vibrations of the coil inside the scanner. However these changes would have to be made by the coil manufacturer due to safety reasons.

The method which I have developed for determining the position of the TMS-coil is reliable and can be used just before an fMRI scan in order to verify the coil position. Furthermore knowing the precise coil position allows the MR-images to be overlaid with maps of the vector potential and magnetic field generated by the coil. Combining the map of the vector potential with a conductivity map of the head of each subject would allow the calculation of a map of the TMS-induced electric field, thus providing a better prediction of where in the brain TMS is likely to have an effects. This method has contributed to the analysis of the experiments on human subject. In the future, it could be integrated into the scanner environment in order to use it as a part of a guided positioning system for the TMS-coil.

10.2 Artefacts in MR-images

Different artefacts in MR-images have been observed, analysed and simulated. There are three main types of artefacts that result from the presence of the TMS-coil, which can be observed in EP-images.

1. $B_0$ inhomogeneities. The non-zero magnetic susceptibility of the TMS-coil causes additional inhomogeneities in the main magnetic field, $B_0$. The effects on EP-images are signal drop-out in the area under the TMS-coil and spatial distortions, but these effects can be reduced by shimming. The artefacts are significant in phantoms, but tolerable in human subjects due to
the distance between human brain and skull. Decreasing the effect of the TMS-coil on the
$B_0$ field would reduce these artefacts. This would require changes to materials of which the
TMS-coil is composed.

2. **Ghosting.** Eddy currents induced in the wires of the TMS-coil by the applied field gradients
cause ghosting artefacts. In some cases these ghosting artefacts can contain locally more
signal than the main image. The choice of the frequency encoding direction can have a major
influence on the strength of the ghost. Ghosting artefacts are more pronounced in images of
phantoms compared to images of human brains. Thinner wires inside the TMS-coil would
reduce the eddy current and thus the artefacts.

3. **RF-noise.** RF-noise is transported from the control room to the bore of the scanner through
the lead of the TMS-coil. This results in a higher level of noise in entire EP-images with
several hot-spots in each slice, where the level of noise is greatly elevated. The elevated noise
level results in a lower SNR of the data and thus in a lower significance of the results of fMRI
analysis. The length of the lead of the TMS-coil which is located outside of the screened
room has an influence on the amount of RF-noise. In general reducing this length helps to
reduce the level of RF-noise. Introducing an RF-filter into the lead of the TMS-coil would
eliminate these artefacts.

Since these artefacts are either identical or in the case of RF-noise random between volumes, they
are not likely to cause false positive results in the fMRI analysis. If the extent of these artefacts is
not too large, they can be tolerated when applying fMRI. Changes to the TMS-coil can potentially
eliminate these artefacts.

There are two main effects on the images which occur after TMS pulses.

1. **Direct effects of TMS pulses.** The magnetic field of the TMS pulse is strong enough to
spoil the MR-signal in a large area of the image. If TMS is applied after the slice selective
RF-excitation, the signal acquired after the TMS pulse is spoiled.

2. **Effects from leakage currents during the recharging period of the TMS-stimulator.** Local
signal decrease in EPI-slices which were acquired in a period of up to 90 ms after a TMS
pulse could be detected. This period corresponds to the time over which electrical activity in
the TMS-coil could be measured following the application of a TMS pulse. The conclusion is
that leakage currents during the recharge period of the TMS-stimulator cause image artefacts. These artefacts could be eliminated by suppressing leakage currents.

These artefacts have to be eliminated since they can have effects which the analysis of the functional data would recognise as a strong direct effect of TMS pulses on the brain. The main measure which has to be taken to eliminate these artefacts is to apply TMS pulses during silent periods of the MRI-scanning sequence. Only sequences with silent periods of a sufficient duration can be used. Designing MR-sequences specifically for each TMS-paradigm can help to avoid unnecessary silent periods. Since the required duration of a silent period for safely accommodating a TMS pulse is dependent on the duration of the period with leakage currents, eliminating these leakage currents would allow a much greater flexibility in choosing the sequences which can be used. Precise synchronisation between TMS and the fMRI-sequences is essential.

It can be concluded that strictly speaking concurrent TMS and fMRI is impossible, because the direct influence of a TMS pulse spoils the MR-signal. In reality typical sequences used in fMRI require 2 seconds or more for the acquisition of a whole volume. A TMS pulse lasts for 400\(\mu\)s. Especially in EPI where all slices are acquired independently, it is possible to introduce silent periods for the TMS pulses without any major compromises in the performance of the sequence or the temporal resolution of fMRI. It is even possible to accept that single slices are affected and to discard them during the analysis of the data. It is important that TMS pulses or leakage currents must not be present during an RF-pulse, otherwise it is possible that a different area is affected by the RF-pulse, resulting in artefacts which can range over several slices and several TR-periods.

Several other sources of artefacts such as \(B_1\) inhomogeneities due to the TMS-coil were also discussed in this work, but their influences on the images in our case were small compared to the effects which were described above.

### 10.3 Applying TMS inside an MR-scanner

Several reasons, why it is more difficult to apply TMS inside and MR-scanner, have been discussed. During TMS pulses there are strong forces between the wires of the coil and the \(B_0\)-field of the scanner. These cancel out each other in space if they are summed over the whole figure-of-8-coil.
Furthermore in a biphasic TMS pulse the forces are partially cancelled over time. The remaining forces are mostly absorbed by the structure of the TMS-coil. Coil vibrations and a loud cracking noise are notable and they contribute to the discomfort of the subject. These forces are potentially a safety risk and after each experiment the TMS-coil must be checked for any signs of structural damage. The forces restrict the application of TMS in an MR-scanner currently to biphasic TMS pulses, which are delivered through a figure-of-8-coil.

Positioning the TMS-coil on the head of a subject requires space around the head, which is not available in the standard 8-channel, RF-receiver coils that are often used for head imaging. We used the Nova-coil and flexible surface coils to avoid this problem. There is a reduction in the SNR of the images when acquired with these coils when compared to the standard 8-channel head-coil. This reduction is the main contributor to the performance loss of the EPI-data due to the set-up required for concurrent TMS/fMRI. The Nova-coil provides advantages compared to the flexible receiver coils, mostly because it provides a more stable set-up that is also more comfortable for the subject.

The coil-holder which was developed and used during this PhD project allowed a wide range of the head-surface to be accessed with the TMS-coil. The more restricting problem was accommodating the head of the subject in a way that the target area is accessible with the TMS-coil. Developing a method which allows the head to be positioned anywhere inside an RF-coil while maintaining space around the target area would extend the range of TMS experiments which can be carried out inside an MR-scanner.

Three different ways of locating the target site in the MR-scanner were tested during this project. Finding the hot-spot of excitability in primary motor cortex (M1) by monitoring hand movements showed reliable results in most of the subjects. However this method is restricted to the stimulation of M1. Use of frameless stereotaxy (Brainsight System) produced large differences between the target site and the actual coil positions, but at least we could show that using the Brainsight System for concurrent TMS/fMRI is possible. The time requirements for the experiment were increased significantly when using the Brainsight System. Using anatomical landmarks for identifying the target site is another option for localising the target site. The reliability of this approach has not been assessed in this thesis. Positioning the TMS-coil over the target site was difficult in some cases. Improving the coil-holder so that it allows a more precise and tunable positioning would solve this problem.
10.4 TMS/fMRI on human subjects

The results of three different studies on human subjects were presented in this thesis. They showed the feasibility of using concurrent TMS/fMRI with the set-up that was developed during this project. These studies were also used to demonstrate a range of problems which are related to concurrent TMS/fMRI.

Probing the connectivity between both hemispheres

This study was not successful in getting results which allowed conclusions about the connection between both hemispheres of the brain to be drawn, but helpful in demonstrating the major problems with concurrent TMS/fMRI. The localisation of the target areas, namely left premotor cortex, left primary somatosensory cortex (S1) and left prefrontal cortex was carried out using the Brainsight System. Small flexible surface coils (FlexS) were used for signal reception. This resulted in a time-consuming preparation phase which usually took longer than the experiment in the scanner itself.

The results of the fMRI analysis showed very consistent patterns of brain activity. Unfortunately these patterns were independent of the brain area which was stimulated by TMS. Subtracting the patterns from different target sites from each other didn’t produce results which could be related to the site of the stimulation. The analysis of the coil position showed a large spread around the target site.

Three conclusions could be drawn from this study:

1. The TMS paradigm (130% MT at 0.1 Hz) was inefficient for producing a strong BOLD response. The BOLD response due to side effects of TMS was dominant.

2. The positioning of the TMS-coil was inconsistent

3. Using different target sites as mutual control conditions can work, but only if the direct BOLD response due to the stimulation is larger than differences in the BOLD response due to side effects produced by stimulation over different target sites.
Combining TMS and Arterial Spin Labelling (ASL)

We have shown that it is possible to combine TMS and ASL. The presence of a long inversion time in the FAIR sequence allows the application of TMS without any changes to the sequence. Perfusion contrast could be achieved during the application of TMS over M1 at 0.1 Hz with 130% MT. Changes of perfusion after every TMS pulse could also be detected, but the contrast to noise ratio was much lower compared to BOLD-contrast. Together with the restricted FOV of this sequence this leads to the conclusion that BOLD-contrast provides a more promising approach for observing immediate effects of TMS pulses on the brain.

TMS over M1 during hand clenching

The analysis of the data and the interpretation of the results of this collaborative study are still in progress. As this was not primarily my own work, the results are not discussed further here. The application of the experiments was efficient with a time requirement of about 1 hour for each subject in which TMS was applied over M1 on both sides of the head. A range of minor problems which occurred during the experiment were described, but in general the experiments were successful. The positioning was more reliable compared to other experiments, mainly because of the direct feedback that is available when the TMS-coil is positioned over M1.

10.5 Final conclusion

TMS in the MR-scanner causes a range of different artefacts, but it is possible to reduce these artefacts to a degree which makes concurrent TMS/fMRI possible without serious drawbacks. The static artefacts due to the presence of the TMS-coil occur at a tolerable level. Changes to the TMS-system, especially to the TMS-coil offer a promising approach for further reducing these artefacts.

Dynamic artefacts which occur after each TMS pulse must be eliminated by applying TMS pulses only during silent periods of MR-sequences. Eliminating the leakage currents after each TMS pulse would reduce the required length of these silent periods and reduce the requirements on MR-sequences for use with concurrent application of TMS.

The space which is required for the accommodation of the TMS-coil restricts the usable RF-receiver coils to surface coils or to coils with a large inner diameter which are open at their superior end.
This restriction is responsible for the main loss in quality of the fMRI data compared to a standard set-up where optimal RF-coils can be used.

It can be concluded that combining TMS and fMRI is feasible. The image artefacts caused by TMS can be reduced to a minimum, but the space which is required for the TMS-coil has an indirect negative impact on the image quality. There are three outstanding issues in concurrent TMS/fMRI which need to be addressed when designing experiments:

1. *Localising and reaching the target site.* Localising the target site is a general problem in many studies with TMS. Tools which are used for the localisation are often not compatible with the MRI-environment. Furthermore the subject is always lying on their back with limited space around their head. In many cases it is difficult to reach the target site. Consistent positioning of the TMS-coil is crucial because otherwise TMS-related effects are not comparable between subjects.

2. *Finding a TMS paradigm which is efficient for both, TMS and fMRI.* Experiments incorporating fMRI based on BOLD contrast must be optimised for the temporal characteristics of the hemodynamic response function. TMS paradigms are required which cause observable changes in the brain activity on the order of tens of seconds. This is in contrast to other methods of observing TMS related effects such as EEG and EMG (tens of ms) or behavioural changes of the subject (minutes). Just reproducing offline experiments inside the MR-scanner would in most cases result in a very inefficient design for fMRI.

3. *Correcting for TMS-related side effects in the fMRI-data.* TMS inside the scanner is loud and the subject can feel the coil vibration. When the coil is attached too close to the head of the subject, the coil knocks on the head which can even cause a painful sensation. TMS can induce a wide variety of sensations to the subject, such as an audible noise, anxiety, the sensation of movement or pain. These sensations are linked to wide range of brain areas which potentially show activity correlated with TMS pulses. Finding a control condition which causes similar sensations, but a different direct effect of TMS is essential for designing experiments with concurrent TMS/fMRI.

If these problems can be solved, concurrent TMS/fMRI provides a unique approach for studying the brain by perturbing and measuring brain activity simultaneously with a high spatial resolution. The technical constraints of concurrent TMS/fMRI are solvable.
Part IV

Appendix
Appendix A

General background information

A.1 Equations describing electric fields

A.1.1 Maxwell equations

The formulae which describe the properties of electromagnetic fields are the Maxwell equations
which were described in their final form in 1864 by James Clerk Maxwell. This set of four differ-
ential equations describes the connection between the electric field $E$, the magnetic field $B$, the
electric displacement field $D$ and the magnetising field $H$ (Jackson [1999]).

\begin{align}
\text{Gaussian law} & \quad \nabla \cdot D = \rho \tag{A.1} \\
\text{Gauss’ law for magnetism} & \quad \nabla \cdot B = 0 \tag{A.2} \\
\text{Faraday’s law of induction} & \quad \nabla \times E = -\frac{\partial B}{\partial t} \tag{A.3} \\
\text{Ampere’s circuital law with Maxwell extension} & \quad \nabla \times H = J + \frac{\partial D}{\partial t} \tag{A.4}
\end{align}
In addition to these equations there are formulae which describe the relationship between $B$ and $H$ and between $E$ and $D$ including the material constants $\chi_e$ and $\chi_m$.

\[ D = (1 + \chi_e)\varepsilon_0 E \quad \text{(A.5)} \]
\[ B = (1 + \chi_m)\mu_0 H \quad \text{(A.6)} \]

Here, $\chi_e$ is the electric susceptibility which describes the relationship between the electric field and the dielectric polarisation in a non-conducting material. $\varepsilon_0 = 8.854 \times 10^{12} \text{As}(\text{Vm})^{-1}$ is a universal constant called the 'Vacuum Permittivity' or 'Electric Constant'.

$\chi_m$ is the magnetic susceptibility which describes the relationship between an external magnetic field and the magnetisation. $\mu_0 = \pi 10^{-7} \text{VsA}^{-1} \text{m}^{-1}$ is also a universal constant called the 'Vacuum Permeability' or 'Magnetic Constant'.

For explaining the connection between electric fields $E$ and the current density $J$ another material constant, $\sigma$, is required, which describes the is the conductivity of the material.

*Ohm’s law*

\[ J = \sigma E \quad \text{(A.7)} \]

### A.1.2 Vector potential and electric potential

Other relationships, which characterise the connections between electric and magnetic fields, can be derived from the Maxwell equations.

**Vector Potential**

Since the magnetic field has zero divergence (Equation A.2), it can be fully described by a vector potential, $A$.

\[ B = \nabla \times A \quad \text{(A.8)} \]

**Electric Potential**

An electric field $E$ can be described using a scalar potential, $\Phi$:

\[ E = -\nabla \Phi \quad \text{(A.9)} \]
with
\[ \nabla^2 \Phi = -\frac{\rho}{\varepsilon_0} \] (A.10)
where \( \rho \) is the charge density. If a time-varying magnetic field is present, an additional term is required to describe the electric field. The additional term can be derived from Equations A.3 and A.8.
\[ \mathbf{E} = -\frac{\partial \mathbf{A}}{\partial t} - \nabla \Phi \] (A.11)
This equation describes the electric field for a given magnetic field and a given charge distribution.

### A.1.3 Biot-Savart-Law

Based on Ampere’s Law (Equation A.4) and assuming negligible effects of time-varying electric fields, the magnetic field, \( \mathbf{B} \), can be calculated for a given current distribution, \( \mathbf{J}(\mathbf{r}) \) as
\[ \mathbf{B}(\mathbf{r}) = \frac{\mu_0}{4\pi} \int \frac{\mathbf{J}(\mathbf{r'}) \times (\mathbf{r'} - \mathbf{r})}{|\mathbf{r'} - \mathbf{r}|^3} dV'. \] (A.12)
For a loop, consisting of a thin wire carrying current, \( I \), this equation can be written as
\[ \mathbf{B}(\mathbf{r}) = \frac{\mu_0 I}{4\pi} \oint_{\text{loop}} \frac{d\mathbf{l}(\mathbf{r'}) \times (\mathbf{r'} - \mathbf{r})}{|\mathbf{r'} - \mathbf{r}|^3}. \] (A.13)
Similar, but slightly less complicated formulas can be derived for the vector potential, \( \mathbf{A} \).
\[ \mathbf{A}(\mathbf{r}) = \frac{\mu_0}{4\pi} \int \frac{\mathbf{J}(\mathbf{r'})}{|\mathbf{r'} - \mathbf{r}|} dV'. \] (A.14)
\[ \mathbf{A}(\mathbf{r}) = \frac{\mu_0 I}{4\pi} \oint_{\text{loop}} \frac{d\mathbf{l}(\mathbf{r'})}{|\mathbf{r'} - \mathbf{r}|^3}. \] (A.15)

### A.1.4 Lorentz forces

The Lorentz Force is the force on a charge, \( q \), which is moving with velocity, \( \mathbf{v} \), in an electric field, \( \mathbf{E} \), and a magnetic field \( \mathbf{B} \):
\[ \mathbf{F} = q(\mathbf{E} + \mathbf{v} \times \mathbf{B}) \] (A.16)
This equation can be used to describe the force produced by a magnetic field on a current carrying wire:
\[ \mathbf{F} = I(\mathbf{I} \times \mathbf{B}), \] (A.17)
where \( \mathbf{I} \) describes the length and the direction of the wire and \( I \) is the current flowing through the wire.
A.2 Human Anatomy and Physiology

In this section an insight is given about selected aspects of human anatomy and physiology in particular of the brain. It is necessary to understand these aspects in order to develop a complete picture of the underlying processes during TMS stimulation.

In MRI most of the contrasts depend on the tissue parameters $T_1$, $T_2$, $T_2^*$ and on the proton density. Nevertheless the interpretation of images requires an understanding of the underlying structure. Every change in contrast or in signal intensity, which is not technical in nature, must have an origin in a physiological change.

A.2.1 The composition of the brain

The human brain is the most complex organ of human body. Although it has a similar structure to the brain of other mammals, it is much larger in comparison to body size. Unlike most other organs, each part of the brain has a different function. The brain is the control centre of the body, where nearly all the information is processed.

The brain is surrounded and protected by the skull and a series of membranes called the meninges. The outer layer of the meninges contains larger blood vessels which supply the brain with blood. The inner layer encapsulates a liquid called cerebrospinal fluid (CSF) which helps to protect the brain against mechanical impact from outside. Inside the brain there are also fluid-filled spaces called ventricles, which have a similar purpose and which are interconnected through
APPENDIX A. GENERAL BACKGROUND INFORMATION

Figure A.2: Transverse slice through a post-mortem human brain. The difference between white and grey matter is clearly visible. (Image: www.answers.com/topic/nervous-system, 08/2010)

Figure A.3: Transverse slice of a structural MR-image. The structural features are similar to those that can be seen in the dissected brain (Figure A.2).

The brain itself is nearly symmetrical about a central sagittal plane. It consists of several large scale structures namely the cerebral cortex, cerebellum, thalamus, hypothalamus, hippocampus and brain stem (Figure A.1). The cerebral cortex, which is the largest part, is split into two hemispheres, which are connected through a bundle of nerve fibres called the corpus callosum. All these structures consist of sub-structures which play different roles in the operation of the brain. For example the cerebral cortex has an area which is associated with the execution of motor tasks and which is called the motor cortex. This area can be split further into areas which are responsible for controlling different muscle groups such as those of the tongue or the hands. These characterisations are made to distinguish the functions of different brain areas.

The cerebral cortex and the cerebellum are folded into gyri and sulci and this folding significantly increases the surface area of these structures. The gyri can be used as landmarks to identify sub-structures in the brain.

If a brain is dissected and cut into slices, it shows a darker layer at the cortical surface while the inner regions appear lighter in colour. The same sort of contrast can be achieved invivo by using an appropriate MRI-sequence. These two different types of brain tissue are called grey and white matter and they are composed of different cell types which are responsible for the appearances of the tissues. Grey matter contains all parts of neurons including the cell body while white matter
APPENDIX A. GENERAL BACKGROUND INFORMATION

Figure A.4: Drawing of a single neuron (Jarosz [2009])

consists of myelinated axons. The grey matter is mostly responsible for information processing while the white matter consists of data pipeline which interconnect nerve cells.

A.2.2 Neurons

Neurons are the core components of the nervous system and therefore also of the brain. They are cells which can process information by electrochemical signalling. Neurons exists in different shapes and sizes and can also be classified by their functions. The body of a neuron consists of the cell nucleus and the surrounding soma. Around the body of the neuron are the dendrites which are split into many branches. The dendrites receive signals from other neurons (Figure A.4).

Also connected to the soma is the axon hillock, which in turn connects to the long and thin projecting axon. The axon itself is often covered by a myelin sheath. At its end it splits into multiple branches with axon terminals at their end which are connected to other neurons through synapses.

Through the axons, neurons can send signals to other neurons over long distances. The longest axon reaches from the brain stem to the big toe and therefore it has a length of over one meter.

If a neuron fires (activates) an axon, an electrochemical wave called the action potential is transmitted along the axon. There the electrical pulse triggers a release of neurotransmitters (Figure A.5). These are received by the neurotransmitter receptors at the dendrites. This can trigger the neuron to fire (excitatory) or it can prevent it from firing (inhibitory).
Figure A.5: Electrochemical processes in a synapse (Nrets [2006])

Figure A.6: Action Potential (Shores [2009])
A.3 Action potential

An axon consists of a long tubular membrane, with different ion concentrations inside and outside. The membrane prevents the free flow of ions between the inside and outside. It also contains ion pumps, which elevate the concentration of sodium ions on the outside and of potassium ions on the inside of the membrane. The number of charges is not symmetrical and leads to a resting potential of typically -70 mV between the inside and the outside the membrane.

There are also ion channels embedded in the membrane, which are activated when the voltage at the membrane changes sufficiently. An elevation of typically 15 mV is enough to open channels which allow sodium ions to pass to the inside of the membrane. This elevates the potential even further by equalising the sodium ion concentration on both sides of the membrane, thus reversing the resulting polarisation state. The potassium ion channels then open for a short time and the sodium channels close, which lets the voltage drop again and after an undershoot it recovers to the resting potential. The change in the voltage through the membrane is called the action potential. Once the process is triggered at one point, the elevation of the potential triggers the opening of sodium ion channels in adjacent regions of the membrane. The action potential propagates along the whole axon and induces a neurotransmitter release at the axon terminals.

The cause of the action potential comes from the body of the neuron when the input in form of neurotransmitters triggers a sufficiently strong initial stimulus. The amplitude and the speed of propagation of the action potential are not dependent on the strength (if above the threshold) of the initial stimulus. An axon has only the conditions: resting and firing.

A.4 EPI-Simulator

In order to achieve a better representation of simulated artefacts in EP-images, a simulator for EPI has been written, which is based on the simulator presented by Yoder et al. [2004]. It was extended to include some additional parameters which allow us to take TMS-specific effects into account. The phase and the amplitude of the transverse magnetisation for a single voxel for every sample point is evaluated. The received signal is the sum of the signals over voxels. The signal for a single slice containing $N \times M$ voxels can be described as

$$M(t) = \sum_{n=1}^{N} \sum_{m=1}^{M} M_0(n,m)e^{-\frac{t}{2\tau_0(n,m)}}e^{i\varphi(n,m,t)}D(n,m,t), \quad (A.18)$$
where $n$ and $m$ denote the voxels’ coordinates. The first factor represents the $T_2^*$-decay. $\varphi(n, m, t)$ is the phase at the timepoint, $t$ and $D(n, m, t)$ takes the dephasing inside a single voxel into account. The phase is the integral of $\gamma|B|$ over time. The magnetic field is made up of contributions from of the main field, $B_0$, field inhomogeneities, $\Delta B_0$ and the readout and the phase encoding gradients, $G_x$ and $G_y$. The z-component of the field from the TMS-coil is calculated using the simulated field of the TMS-coil (Section 3.3) and a way to overlay this field over an MR-image as described in Section 3.4.6. This component is multiplied by the estimated charge which flows through the TMS-coil in the time between the slice selective RF-excitation and the measurement time, $t$, and added in order to estimate effects of residual currents through the TMS-coil.

$\mathfrak{M}$ phase encoding steps are assumed. The total time is split into the central echo time $T_E$ and multiples of the time for every phase encoding step, $T_P$, and the time per sample, $T_S$. Therefore the time at which the sample point $n$ (of $\mathfrak{M}$) is acquired during the phase encoding step $m$ of $\mathfrak{M}$ is:

$$t_{nm} = T_E + (n - \mathfrak{M}/2)T_S + (m - \mathfrak{M}/2)T_P \quad (A.19)$$

The phase shift at voxel $(n, m)$ due to the gradients at the $n$th sample point during the $m$th phase encoding step is given by:

$$g_x(n, n) = \int B_x(n)dt = \frac{2\pi(n - \mathfrak{M}/2)(n - N/2)}{\mathfrak{M}} \quad (A.20)$$
$$g_y(m, m) = \int B_y(m)dt = \frac{2\pi(m - \mathfrak{M}/2)(m - M/2)}{\mathfrak{M}} \quad (A.21)$$

The effects of susceptibility artefacts add to the phase a term of the form

$$\varphi_{B_0}(n, m) = \Delta B_0(n, m)t_{nm} \quad (A.22)$$

and an additional factor which represents the phase shift induced by the field from the currents through the TMS coil

$$\varphi_{TMS}(n, m) = B_{TMSx}(n, m) \cdot \int I_{TMS}dt \quad (A.23)$$

Ghosting can be simulated by adding an asymmetric phase offset $\varphi_{Gh}(n, m)$ which is positive for even $m$ and negative otherwise (i. e. taking the value $(-1)^m$). The resulting phase sums up to:

$$\varphi_{nmnm} = (B_0 + \Delta B_0) \cdot t_{nm} + g_x(n, n) + g_y(m, m) + \varphi_{TMS}(n, m) + (-1)^m\varphi_{Gh}(n, m) \quad (A.24)$$

Gradients in the phase of the magnetisation are associated with intra-voxel dephasing. The resulting decay of the signal can be expressed as:

$$D(n, m, n, m) = \text{sinc}(e_x \cdot \nabla \varphi_{nmnm}/2)\text{sinc}(e_y \cdot \nabla \varphi_{nmnm}/2)\text{sinc}(e_z \cdot \nabla \varphi_{nmnm}/2) \quad (A.25)$$
with \( \text{sinc}(x) = \frac{\sin(x)}{x} \), where \( e_i \) describes the voxel’s dimension in along axis \( i \). The gradients of the phase in the x- and y-direction can be calculated based on the phase described by Equation A.24. For gradients in the z-direction information about the \( \Delta B_0 \) and \( \varphi_{TMS} \) in \( \Delta B_0 \) and \( \varphi_{TMS} \) is needed.

The image is reconstructed by applying a fast Fourier Transformation to the calculated matrix \( M_{nm} \). This simulator has been implemented in Matlab.
Appendix B

Setting up experiments with concurrent TMS/fMRI

This chapter describes how to design experiments with concurrent TMS/fMRI. It can be taken as a guideline for implementing experiments, although prior knowledge of TMS and fMRI is required.

B.1 Is concurrent TMS/MRI the right choice for your experiment?

Concurrent TMS/fMRI is a technique which combines the complementary capabilities of the two techniques. TMS allows manipulation of brain function in cortical areas with a spatial accuracy of about 1 cm and a high temporal resolution (1 ms). fMRI allows the detection of changes in blood oxygenation in the whole brain with high spatial (mm) and moderate temporal resolution (less than 1 s). The idea behind concurrent TMS/fMRI is to use TMS to manipulate one brain area and then to use fMRI to measure changes in the BOLD-signal which indicate increases or decreases in brain activity. Some problems which arise from the application of each of the techniques on their own can be more significant, when they are applied concurrently.

The sensitivity of fMRI is limited by the weakness of signal changes linked to brain function and the relatively low SNR of functional images. Furthermore, BOLD contrast which is exploited in most fMRI experiments is best suited to measuring signal changes occurring on time-scales of a few
APPENDIX B. SETTING UP EXPERIMENTS WITH CONCURRENT TMS/FMRI

seconds to a minutes. This is because BOLD contrast is usually used to identify changes, which are correlated with a certain task, but long-term changes are difficult to detect because they can be confounded by other effects which cause slow signal variations, such as scanner drift. The achievable temporal resolution is restricted by the effect of the delayed and dispersed hemodynamic response function. In general alternatives to BOLD contrast yield a lower sensitivity to brain activity in fMRI.

TMS potentially has a very high temporal resolution of up to a few ms. This resolution can be achieved by blocking a brain area at exactly the right moment, when a stimulus is being processed. For other experiments rTMS is used to induce virtual lesions, which can persist over several minutes. During this period, the performance of certain tasks can be facilitated or impeded for the subject.

B.1.1 Prior knowledge

Experience with carrying out fMRI experiments and analysing the results is needed before implementing TMS/fMRI studies. Furthermore a basic understanding of fMRI-sequences, is required, in order to introduce silent periods to accommodate the TMS pulses.

Experience with TMS is also essential, because concurrent TMS/fMRI involves the application of TMS under difficult circumstances. It is important to have a clear idea of how TMS can be applied and what effects it can have on the brain.

Extensive knowledge of the target area and the brain network to which it is linked is important, because otherwise it is difficult to interpret the results of the fMRI analysis.

Ideally, prior knowledge includes experience with TMS on the target site, as well as experience with fMRI-studies on brain networks which are expected to be affected by the application of TMS.

B.1.2 TMS and BOLD-contrast

The main question, which can be addressed with concurrent TMS/fMRI, is:

*What is the effect of TMS on brain function?*

One aspect is the timescale, on which TMS-related changes can be expected. For most fMRI experiments, blocks with stimuli or a series of events are used to activate the same brain areas
several times, alternating with periods of rest or other tasks.

To increase the probability that TMS induces directly detectable changes in brain activity, it can be applied in blocks, in single pulses or in bursts, which are well separated from each other. A higher TMS pulse strength is likely to induce a stronger BOLD-response. Direct effects can be detected with a simple first analysis (TMS vs. rest) using a GLM (Section 1.6.2).

Another option is to combine TMS with a task. In this case the TMS-related modulation of the brain activity during the task can be studied. In most cases a task can be organised into a block design. Combining TMS with a task inside the MR-scanner can give a deeper insight into the effect of TMS on the same task carried out outside of the MR-scanner. Furthermore it is not necessary to optimise the TMS-paradigm for a good BOLD-contrast. A disadvantage is that only a higher level analysis (activation with TMS vs. activation during control) can reveal TMS-related effects.

Concurrent TMS/fMRI has drawbacks for the quality of the fMRI data (Sections 5, 4 and 6). Stronger BOLD-contrasts are required to achieve the same significance of the results compared to studies, where a standard set-up can be used for brain imaging.

B.1.3 Limitations for MRI and TMS in combined TMS/fMRI

As shown in Chapter 6.4, a wide range of TMS-paradigms can be combined with EPI-sequences, some compromises have to be made when designing compatible MR-sequences. These compromises are generally more restrictive for long blocks of rTMS with frequencies above 5 Hz compared to the situation when low frequency TMS is used.

The SNR of fMRI-data (Section 6.2) is generally reduced in combined TMS/fMRI experiments. This is mostly related to the limited choice of receiver coils. RF-noise can further reduce the SNR and the presence of the TMS-coil can also cause artefacts.

For TMS the main limitation is the accessibility of the head of the subject. It is relatively straightforward to position the TMS-coil over superior regions, but accessing occipital or parietal areas can be difficult, because the subject is usually lying on their back and the space inside the RF-coil is limited. Positioning the TMS-coil in a reliable way is also more difficult because of the limited space inside the scanner. The special requirements of the MR-environment also restricts the coil positioning methods that can be used. Also movement of the subject relative to the TMS-coil can happen after positioning, especially when the scanner bed is moved into the scanner. TMS is much louder inside the scanner and the coil vibrates slightly. This can cause discomfort for the subject.
and unwanted side effects on brain activity. In general an experiment with concurrent TMS/fMRI is less comfortable for subjects and more challenging for the experimenter compared to the stimulation where each technique is used on its own. On the other hand concurrent TMS/fMRI has the potential to give a detailed insight into the effects of TMS.

### B.2 Preliminary steps

An experiment with concurrent TMS/fMRI requires a specific planning phase where different questions must be answered.

1. What is the aim of the study?

2. Which equipment is required?
   
   (a) Stimulator and TMS-coil?
   
   (b) TMS coil-holder for the scanner bed?
   
   (c) Which MR-scanner?
   
   (d) Receiver Coil?
   
   (e) Optional equipment (EMG, projector, response buttons...)?

3. What is the target site for stimulation?
   
   (a) How to determine the exact position of the target area?
   
   (b) How to accommodate the TMS-coil over the target area in the scanner?

4. Which TMS pulse sequence should be used?
   
   (a) How can this sequence be combined with an EPI-sequence?
   
   (b) How will TMS be synchronised with the scanner?
   
   (c) Is the dose safe according to the TMS-safety guidelines?

5. Which sequences are required?
   
   (a) Which fMRI-sequence (TR, coverage, contrast)?
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(b) Are additional images required (e.g. MP-RAGE data for coregistration)?

6. Is TMS going to be combined with an additional task/stimulus?

7. How will a control condition be implemented?

8. What BOLD-responses are expected?

   (a) Which conditions will be used to form the first level analysis?

   (b) How will these conditions be compared in higher level analysis?

After answering these questions, preliminary experiments can start. If these produce promising results, the study can be run with the same set-up for a larger number of subjects.

In the following sections, different aspects of the preliminary steps for experiments exploiting concurrent TMS/fMRI are discussed in detail.

B.3 How to use BOLD-contrast in concurrent TMS/fMRI?

This section describes how experiments can be designed to detect TMS-related changes of brain activity using fMRI. Either the effect of TMS can be detected directly or TMS can be combined with an additional task.

B.3.1 Detection of the direct effects of TMS on brain activity

Periods with TMS pulses and rest periods must be alternated in a way, which makes the effects of TMS detectable in the fMRI-contrast, which in most cases would be BOLD-contrast. To best exploit BOLD signals, the rest periods between TMS pulses should not be much shorter than 10 s and the total length of a block should not exceed 1 minute.

TMS can be applied as single pulses, in short bursts (Ruff et al. [2006]) or in longer blocks of low frequency rTMS (Bohning et al. [1998]). To increase the chance of detecting a significant BOLD-response, the TMS-dose can be increased by using more pulses or pulses of a higher intensity.

In many recent studies, compact blocks of high-frequency TMS have been used (Bestmann et al. [2008]).

The main contrast for this type of experiments is TMS vs rest. Higher level contrasts can for example involve identifying changes in the BOLD response from TMS, which are dependent on the
TMS intensity.

This approach can be used not only for the detection of the changes in the stimulated area, but also for changes in remotely connected areas. It therefore potentially allows measurement of the strength of connection from the target area to other areas of the same brain-network. An example of this type of approach is described in Chapter 7.

A problem of using only TMS as events is that the changes in brain activity have to be strong enough to be detected with BOLD-contrast. Even if previous studies have shown excitatory or inhibitory effects induced by TMS on the same target area using a similar paradigm, there is no guarantee that the induced changes in brain produce significant results using BOLD-contrast.

### B.3.2 Combining TMS with a task or an additional stimulus

When TMS is not used together with brain imaging, the options for detecting the effects of TMS are limited. In many experiments the effect of TMS on the performance of the subject in a specific task is used. A wide range of literature is available on studies in which TMS has been combined with a task (Silvanto et al. [2008]). These experiments have the advantage that the presence of an effect of TMS has already been proven and many of these experiments can also be carried out inside an MR-scanner. fMRI can then be used to detect brain activity which is related to the task. A higher level analysis can also be used to investigate how TMS modulates the task-related brain activity.

Some studies have used this approach to show significant performance changes in a task. For example Chambers et al. [2004] showed that TMS over the right parietal cortex can perturb spatial orientation if TMS is applied between 90 ms and 120 ms after presentation of a visual stimulus. Combining this experiment with fMRI could reveal, how the activity in different brain areas spreads after a stimulus.

In general combining concurrent TMS/fMRI with a task has the advantage that the TMS-sequence is not restricted to a paradigm, which is optimised for producing immediate BOLD-contrast. Long trains of rTMS, which increase or decrease the excitability of a brain area, can be used as well as single-pulse TMS. In many cases the task itself produces a good first level contrast. Significant TMS-related effects can be observed if the modulation of this task by TMS is strong enough. The disadvantage is that with this approach the TMS-related effects can only be detected in the higher level analysis.
B.3.3 Side effects and fMRI

TMS has a wide range of side effects, most of which are more difficult to deal with, when TMS is applied inside the scanner. Outside the scanner each TMS pulse causes a clearly audible, but not very loud clicking-sound. Inside the scanner, this sound changes into a very loud ’crack’. The increase in intensity is caused by the forces between the current in the TMS-coil and the main field of the scanner. The sound tends to be significantly louder when the surface of the coil is orientated parallel to $B_0$, compared to when it is orientated perpendicular to $B_0$. The forces experienced by the coil also cause a small cyclic movement through the TMS-coil with every pulse. If the TMS-coil is touching the head of the subject, they feel a hit with every pulse.

TMS pulses also cause electric stimulation of peripheral nerves in the scalp, which is perceived as an electrical shock. When stimulating frontal areas, TMS can also cause an uncomfortable twitching of facial muscles.

All these effects contribute to the discomfort of the subject, potentially giving risk to feelings of anxiety, pain and an increased probability of claustrophobia. Furthermore discomfort makes it more likely, that the subject will move or modulate their breathing during TMS, thus compromising the fMRI data. In experiments involving periods of TMS and rest, the subject has no further distraction and it is possible that the attention of the subject will differ significantly between resting periods and periods of TMS. Head movement or breathing leads to signal changes, which are temporally correlated with the application of TMS. The fMRI-analysis can therefore show usually a range of false-positive results that are not directly linked to the effect of TMS on brain activation. The most consistent is activation in auditory areas of the brain resulting from the noise produced by the pulses. In many experiments the auditory areas areas show the strongest activation.

By using prior knowledge, the false positive networks can be detected and discarded from the analysis. Some changes can be eliminated by monitoring breathing and movement. To limit the possibility that the subject synchronises their behaviour with application of TMS, the timing of the blocks of TMS and rest can be jittered.

B.3.4 Control conditions

A control condition can be used to distinguish side effects from direct TMS-related effects on the brain. A good control condition produces side effects which are very similar to the main condition, but significantly different direct effects of TMS. Comparison of the results of the two conditions
allows the brain activity which is induced directly by TMS to be identified. There are several different ways that a control condition can be implemented.

**Modulation of the intensity**

TMS often has to be applied at a level above a certain threshold to be effective. For example stimulation of M1 has to be above MT to cause muscle movement. The effect of TMS does not therefore scale proportionally with the intensity of the stimulation. On the other hand, most side effects increase with the pulse strength in a less significant fashion. If the same paradigm is run with different TMS-intensities, the areas activated by the side effects show a smaller variation, when the intensity is increased, while TMS-induced brain activity only occurs above a certain threshold. Comparing data acquired with stimulation above and below this threshold thus allows direct TMS effects and side effects to be distinguished.

This method is easy to implement, as only the TMS-intensity needs to be changed. Completely subtracting out the side effects can be difficult, as they also may scale to some extent with the intensity.

**Different stimulation sites as mutual control sites**

Different stimulation sites can be used to provide control conditions at the same stimulation intensity. In this situation, if the side effects are similar at the different sites, the difference in the activation patterns shows the difference in the effects of TMS between the two target sites. Using prior information allows in some cases to relate the difference in the activation patterns to one of the target sites. Alternatively a target site that produces no activation through brain stimulation can be chosen. However the noise and the vibrations produced by TMS pulses can vary for different coil orientations in the scanner. Also TMS over different target sites can cause different sensations to the subject. Using different target sites as mutual control sites is not always therefore reliable. In addition the coil has to be repositioned between the conditions, which increases the time required for the experiment. During the repositioning, the position of the subject and the intensity profile of the receiver-coil can potentially change. Good co-registration of the acquired data-sets is fundamental for comparison between the conditions.
**Combined with a task**

If the effects of TMS on a task are studied, instead of the TMS condition, the task condition can be modulated to produce a control condition. Different conditions during the fMRI can be for example: TMS only, TMS with task, task only. Different tasks can also be used as mutual control conditions. This approach uses exactly the same TMS-paradigm for the main condition and for the control condition so the direct effects of TMS are likely to be removed. It is still possible that the subject perceives TMS differently, when they are distracted by a task.

**B.3.5 Designing an experiment**

The induced changes in brain function must be detectable with BOLD-contrast. For this task and control conditions must be arranged in a way, which is optimised to give a good contrast when convolved with the hemodynamic response function. It should also be clear from the beginning, how different conditions can be separated in the analysis. Subsequently an fMRI-sequence, which is compatible with the TMS-paradigm, must be developed. On top of this, the sequence should provide a good compromise between high SNR, coverage, temporal and spatial resolution. Most TMS-paradigms can be combined with fMRI, but modifying the TMS-paradigm slightly can improve the performance of the fMRI significantly.

There are different strategies which can help to increase the contrast of the functional data. An optimised paradigm can produce better results, the signal reception can in some cases be optimised for the brain areas of interest. The same condition can be repeated more often or the TMS-intensity can be increased. The options are limited and they often have drawbacks such as an increased duration of the experiment.

Most importantly for more reliable results, the experiment should be kept simple. If the TMS-related effects are measurable more directly, the requirements for the first level contrasts in the functional data are decreased significantly. Using multiple different contrasts allows in theory better controlled conditions and more detailed insights into the effects of TMS. Nevertheless this is only possible if the induced BOLD-signal changes are significant. Before starting with complex studies the reliability of the results of the basic contrasts should be verified. Understanding when, where and how TMS induces a detectable BOLD-response is the most challenging aspect of studies using concurrent TMS/fMRI.
B.4 Positioning of the TMS-coil over the target site

Locating the target site and positioning the TMS-coil is an important part of any TMS experiment. In concurrent TMS/fMRI this procedure is especially challenging, because the head of the subject is difficult to access inside the receiver coil. Also most of the commercially available equipment which supports this procedure cannot be used inside the screened room of the scanner. After the positioning of the TMS-coil the subject must be moved into the scanner. During this process the TMS-coil can move away from its position over the target site. In any case a considerable amount of time is required for the positioning of the TMS-coil. Therefore testing and optimising this procedure is an essential preliminary step.

B.4.1 Space around the target area

Usually in combined TMS/fMRI, the subject lies on their back with their head resting on a padded support inside the scanner. The head is surrounded by coils for signal reception, either flexible surface coils or a rigid coil structure. The subject usually wears additional ear protection and the movement of the head is prevented by adding additional padding around it. All this restricts the space around the head. A rigid coil has a limited volume inside which leads in many cases to a lack of flexibility in positioning the TMS-coil over the target site. Areas at the top of the head, such as the motor areas, are comparably easy to reach whereas accessing lateral or occipital areas can be very challenging. There are different options, which can increase the amount of space around the target site so as to accommodate the TMS-coil.

- **Slim ear protection**
  
  Most ear protectors used during MR scans consist of two relatively large ear pieces, which are connected over the top of the head. Even without connection, the ear pieces can cause problems, when positioning the TMS-coil over the target area. Padding the ears with flat foam-pillows is an option, but support structures are needed to keep the pillows in position. A water-polo cap with two slim earshells woven into a thin material, which covers the top of the head was used in some of our experiments. A pillow can be introduced between the ear-shells and the ears for additional ear-protection.

- **Position of the head inside a rigid coil**
  
  Inside a rigid coil the space is limited. Under normal circumstance the head would be
positioned in the centre of the coil. Moving the head to the walls of the coil provides space on the other side for the TMS-coil. Also tilting the head can make it easier to reach the target site. It can be difficult to stabilise the head in the desired position and tilting the head can be especially uncomfortable for the subject during long scanning sessions.

- **Head rest**

The scanner’s head-rest has the purpose to provide a comfortable and stable support for the head. However the head-rest limits the possible head positions and restricts the space for the TMS-coil. The solution is to use a head-rest, which allows the head to be held in different positions. The head rest should be designed to be as thin as possible towards the top of the head, where space for the TMS-coil is required. A head-rest can be constructed in way which allows the position of the head to be adjusted inside the volume coil easily. Alternatively different head rests can be designed to allow different target area to be accessed. In each case, foam pillows around the head can be used for further adjustments. When accessing the back of the head, it can become necessary to support the head from both sides, leaving the back empty.

- **Scanning without a volume coil**

Instead of using a volume coil, flexible surface coils can be used for signal reception. This provides more space around the head to accommodate the TMS-coil. The different receiver coils were discussed in Section 6.2.

In our experience it is more difficult and it requires more time to set up TMS/fMRI experiments with flexible surface coils. Other drawbacks are the discomfort for the subject and a reduced image quality. Furthermore the images are less reliable, because any movement of these coils with respect to the head can change their sensitivity profile.

Accessing some target sites can be very difficult and it can take some time to get the coil into the right position, because the position of the subject has to be changed several times. This can be avoided by having a testing session, during which the ideal configuration can be determined.

First a head position must be found, which leaves enough space for the TMS-coil. Enough space means, that the TMS-coil can be placed comfortably over the target site. Ideally there is some additional space since the exact target site varies between subjects. When choosing a position for the head, it should be considered, that the subject has to stay in exactly this position for the whole
scanning session.
When the ideal position for the head has been found, it must be stabilised without restricting
the space around the target area. Eventually this requires the production of a specially designed
head-rest or foam pieces which are cut into the right shape.
For the main experiment, all subjects should be positioned in the same way, unless the way of
positioning proves to be unsuitable. Accessing the target area is different for every subject and
for every target area. The right preparation can facilitate this and reduce the time required for
setting up every subject substantially.

B.4.2 Localising the target area

We now consider that the target site for the TMS-coil is freely accessible. The ways to determine
the right position of the TMS-coil are basically the same as those which can be used outside of
the scanner (Section 2.5.1). Nevertheless there are some restrictions on the different methods, as
described below:

- **Motor cortex**
  It is more convenient and reliable to determine the MT outside of the scanner room. Therefore
  we usually find the 'hot-spot' for the stimulation of M1, mark it and then the position the
  TMS-coil over the same location inside the scanner.

- **Landmarks on the head**
  Some landmarks are not accessible inside the scanner. To solve this problem, the target
  position can be marked on the cap outside of the scanner for use as a guide when the subject
  is on the scanner bed.

- **Stereotaxy**
  Stereotactic systems can be used to position the TMS-coil. The application using the *Brain-
sight System* for concurrent TMS/fMRI is described in Section 3.4.5.

None of these methods stand out from the others. A stereotactic system provides the best way to
locate the target area, but it increases the time needed to set up the experiment.
Special attention has to be paid, when the subject is moved into the scanner. Any sudden move-
ments can change the position of the subject relative to the coil. Also movement during the scan
should be prevented as much as possible, because movement does not only affect the imaging, but also moves the TMS-coil away from the target area.

B.5 Experimental procedure

Here the important aspects of setting up an experiment with concurrent TMS/fMRI are explained.

B.5.1 Preparing the environment

- **TMS-stimulator**
  The lead of the TMS-coil can pick up RF-noise outside of the screened room. The longer the lead is, the more likely it is, that will cause a reduction of the SNR in the functional data (Section 4.5). The stimulator should therefore be placed as close as possible to the waveguide through which the lead is connected. We generally place the stimulator on the floor directly adjacent to the waveguide. This decreases the length of the TMS-coil lead outside the scanner room to about 30 cm.

  Alternatively the stimulator can be positioned inside the screened room. This can only be done after assessing in detail the forces on the apparatus, and defining operational methods, which prevent the equipment being pulled into the magnet bore.

  The strong current during each TMS pulse can have an effect on nearby electronic equipment. It is therefore recommended that other devices and cables are kept well away from the stimulator. A distance of 50 cm is usually sufficient.

- **TMS-coil and lead**
  To reduce the length of the lead outside the screen room, the temperature sensor box and the coil adaptor should be, if possible, also be kept in the screened room. The length of the lead inside the bore of the scanner should be kept as short as possible and the cable should be guided out in a straight line. Otherwise it is possible that substantial voltages are induced along the lead of the TMS-coil during gradient switching of the MR-scanner. We found that this can deactivate the stimulator.

- **Changes on the scanner bed**
  The receiver coil and the mount for the TMS-coil must be installed on the scanner bed. The
mattress and the required padding below and around the head should be ready in place. If it is required, the bed can be moved out of the scanner room.

- **Trigger tool**
  
  A computer with an interface port is required for the synchronisation of the scanner and the TMS-system. The interface must be connected to the TTL-output port of the scanner and to the TTL-input port of the stimulator. Eventually a pulse stretcher is required, to ensure that every TTL-pulse of the scanner is detected. The program, which is used for the synchronisation should be ready to use.

- **Scanner**
  
  A typical experiment consists of a survey, a reference scan, main fMRI-sequences, an anatomical scan and other sequences, such as those used for the detection of the location of the TMS-coil.

- **For the positioning**
  
  If the right location for the TMS-coil is determined using a stereotactic system, an anatomical image of the head of the subject is required prior to the experiment. This must cover the whole head including relevant landmarks, such as the tip of the nose. The landmarks and the target area must be marked in this image and loaded into the software used by the stereotactic system. The different parts of the system (3D camera, markers...) should be set up and ready to use.

- **Other items, form...**
  
  There are several additional items, which are required, such as earplugs, prism glasses, waterpolo cap or tape. Also a safety screening, the consent form and an information sheet are required for every new subject.

### B.5.2 Preparing the subject

After the arrival, the subject should be given some forms to fill out and some explanation about the experiment. These include the following:

- **Forms which need to be read, filled out and signed by the volunteer and the experimenter.**
  - Information sheet
– Safety screening form for TMS/MRI
– Consent form
– Abnormal scan form

• Ask the volunteer if he or she has previously undergone TMS or MRI procedures.

• Aspects which should be explained to the subject:

  – The basic idea of the experiment.
  
  – The procedure of the experiment: determination of the MT, localising the target area, lying on the scanner bed and positioning the TMS-coil, scanning with TMS.
  
  – How the volunteer should behave in the scanner: that they must not move during the scan and either they have to perform a task or they should just relax.
  
  – What happens during the experiment. This involves especially the noise and the vibrations of the TMS-coil, but also the noise of the MR-scanner.

• Ask the volunteer if they are comfortable and if they have any questions.

• Ask the volunteer to remove any metal from their body. This means in particular piercings and jewellery.

If there are any minor indications, that the subject might not be suited for the experiment, it is up to the competent person to decide if the experiment can be carried out. Some aspects can be more problematic for concurrent TMS/fMRI, because the experiment is less comfortable and the subject can become anxious.

The subject should be asked to put in earplugs, put on the cap and to sit on a chair. TMS can be presented to the volunteer by first showing the effect on a hand and then on the head. The MT can be determined. Afterwards the subject should lay down on the scanner bed. The head must be stabilised in the receiver coil, while leaving enough space for the TMS-coil. Then the TMS-coil can be positioned over the target site. The duration of this procedure can differ significantly across subjects and take between 5 and 60 minutes, dependent on the method used and on the target site. The time requirements also differ from subject to subject.

It is important, that the TMS-coil does not put pressure on the subject’s head, since this can
cause a painful sensation because of the vibrations of the TMS-coil. To release the pressure, the
coil can be pulled away slightly from the head, until the subject doesn’t feel it pressing anymore.
When the TMS-coil is in place, a pulse at the required intensity should be applied to make sure
that the subject is comfortable. The subject can then be registered and the bed can be moved
slowly into the scanner while avoiding sudden accelerations. The panic button must be given to the
volunteer and it should be explained, that the TMS and the scan would be stopped immediately,
if the button is pressed. The volunteer must be encouraged to do this, when he or she thinks that
something is going wrong or if TMS is uncomfortable. Before the scan starts, one or more test
pulses should be given to ensure that the subject is comfortable.
If the subject feels uncomfortable during the TMS pulses, the position of the head or the TMS-coil
can be modified slightly. If this doesn’t reduce the problem, it is worth considering, to abandon the
experiment, as in this case often the fMRI results are contaminated by a sensation of pain or other
effects, such as movement of the subject. Discomfort most commonly arises when the TMS-coil
knocks against the head of the subject or there is a painful stimulation of facial muscles as a side
effect of TMS.

B.5.3 In the scanner

Before the experiment

The preparation phase of an MR-scan usually involves acquisition of survey and a reference scans.
After the survey, the functional scans can be planned. If the centre of the FOV is too far from
the the axial centre bore of the magnet, the scanner moves the bed automatically. This should
be avoided, because it can cause stress on the lead of the TMS-coil. If repositioning the FOV
does not help, the subject must be taken out and registered again. These steps take together
about 2 minutes. Extending the preparation phase of the experiment can help to avoid additional
artefacts in concurrent TMS/fMRI. A survey with a flip angle of 1° is suitable for revealing RF-
noise (Section 4.5). The RF-noise can be reduced by changing the position and the length of
the lead of the TMS-coil outside of the scanner room. Running a short test run (< 1 minute) of
concurrent TMS/fMRI using the actual paradigm to be run helps to test whether the subject is
comfortable. Furthermore it can reveal artefacts caused by the presence of the TMS-coil.
During concurrent TMS/fMRI

During the scan, control over the subject and the TMS-conditions is limited. A relatively common problem is that the coil moves from the right position or that there is a problem with the timing of the TMS pulses. Sometimes the subject just feels seriously uncomfortable during TMS.

There are several indicators, which can show that something is going wrong during the scan.

- **Panic button**
  During concurrent TMS/fMRI, the TMS-system must be deactivated immediately, when the panic button is pressed and the scan should also be stopped. During sequences without active TMS, the procedure is identical to normal MR-scans.

- **Noise of TMS**
  The noise of the TMS pulses during the scan is an important indication, that the paradigm is running with the correct timing. When irregularities occur, the TMS-system must be deactivated immediately and the scan must be stopped.

- **Images (between dynamics)**
  Changes between different volumes of a dynamic study can indicate:
  
  - Incorrect temporal placement of the TMS pulses
  - Movement of the TMS-coil out of the original position
  - Movement of the subject
  - Instabilities of the scanner

  Changes can be observed using the auto-view option of the scanner, which shows every volume directly after the acquisition. Changes in the images can show effects, but they usually do not flag safety concerns. Therefore if they occur only at the end of a sequence, the scan should not be stopped, as some of the data might still be useful.

It is also recommended that the subject is asked between the different sequences if they are comfortable and that they are reminded of the next step in the procedure. After the experiment the subject must fill out a questionnaire to assess how they experienced the experiment.

In general for experiments with concurrent TMS/fMRI, special attention must be paid to the comfort of the subject and it should be observed constantly if the experiment runs as it should.
B.5.4 Data processing

The data analysis for data from concurrent TMS/fMRI can be carried out in the same way as for other fMRI datasets. When setting up the model, each TMS pulse can be treated as a single event. Periods in which TMS is applied at a frequency of 1Hz or higher can also be included in the form of blocks.

Additionally an analysis should be run, treating every TMS pulse as an event, but without convolving it with a hemodynamic response function. This reveals only the immediate effects of TMS on the images. These are not related to any brain function, but they indicate movement of the subject due to TMS or artefacts produced by TMS pulses. A very frequent example for this is the effect of eye twitching, which can be observed in the inferior frontal lobe.
Bibliography


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