Noise Reduction in fMRI Utilizing Concurrent Magnetic Field Monitoring

A dissertation submitted to
ETH ZURICH
for the degree of
DOCTOR OF SCIENCES

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2014
“Through seas of noise turned streams of consciousness – few Minds Reach Islands”
Für Mutti, Tante und Andreiuța
Functional magnetic resonance imaging (fMRI) is a unique measurement method to study the human brain at work. It is non-invasive and harmless, allowing healthy and diseased humans to be examined longitudinally. Its temporal resolution offers to follow learning processes in real-time (over seconds), while its spatial coverage and specificity can track brain dynamics at the systems level, i.e. interactions between regions of several millimeter extent.

However, the blood-oxygen level dependent (BOLD) signal of interest in fMRI is minuscule and buried in a vast landscape of noise, amounting to a few percent of the total signal maximally. With the recent advent of translational neuromodeling, which aims at a mechanistic understanding and treatment of psychiatric disorders, the need for higher, sub-mm spatial specificity in BOLD fMRI emerged, in order to investigate the neurotransmitter network architecture of the brain. Hence, at this stage, the overpowering impact of noise hinders fMRI from becoming a truly clinically relevant technique, and innovative ways for noise reduction are highly sought after.

This thesis takes a mechanistic stance on noise generation in fMRI, starting out from the MR image encoding process itself, in order to
Summary

develop more principled correction methods for the different noise-mediating components in fMRI. Specifically, the MR image encoding process can be separated into three stages: (1) the preparation of magnetization through radio-frequency (RF) excitation, (2) the spatial encoding of the magnetization through fast-varying spatial gradient fields and (3) the reception with one or more RF coils. Each of these stages is susceptible to multiple types of fluctuations, e.g. (1) noise in the RF excitation chain or slice selection gradients, (2) in-plane movement of the subject or gradient instabilities and (3) digitization noise, subject- and conductor-induced thermal noise or pre-amplifier gain fluctuations. In this work, three of these entry points of noise were considered as particularly important and assessed in the context of fMRI: (1) local alterations of the object magnetization through physiology, (2) fluctuations in the encoding magnetic fields, and (3) thermal noise added to the encoded signal by diffusive processes in the image object and receive chain.

The experimental pursuit of such a mechanistic perspective on noise generation was previously impossible, since field fluctuations as one of the three noise entry points were inaccessible to a comprehensive measurement. Only recently, the introduction of concurrent magnetic field monitoring using NMR field probes made it possible to measure encoding magnetic fields simultaneously to image acquisition and without any changes to the sequences employed. As part of this work, concurrent magnetic field monitoring was applied to fMRI for the first time. By using the collected field information in the inversion of the signal model, i.e. image reconstruction, field fluctuations can be effectively removed. Thus, concurrent magnetic field monitoring was most suited to address the perturbations through entry point (2). Furthermore, monitoring lifts constraints on encoding-field fidelity and reproducibility, thus broadening the scope of available MR imaging sequences. This work utilizes concurrent magnetic field monitoring as an enabling technique to implement more efficient acquisition schemes tailored to limit thermal noise propagation in fMRI processing, i.e. addressing noise entry point (3). Finally, for
complete coverage of the noise landscape, a model-based approach is implemented in this work to also address magnetization fluctuations (1). Concretely, localized tissue displacement and flow in the brain leads to magnetization changes locked to the cardiac and respiratory cycle. This physiological noise in the images is inferred on via peripheral measures and corrected by an image post-processing package developed here, the physIO Toolbox. Thus, each part of this thesis has its unique place in charting and leveling the three territories of the noise landscape in fMRI (cf. Fig. 1).

**Encoding Field Fluctuations**

The lion share of this work considers field fluctuations compromising the most prevalent imaging technique for fMRI, 2D echo-planar imaging (EPI). These field fluctuations were mapped out by concurrent magnetic field monitoring and used retrospectively to inform the signal model for image reconstruction. Overall, more than half of the overall noise in the image time series could be removed by concurrent magnetic field monitoring, thus doubling the signal-to-fluctuation noise ratio (SFNR) for fMRI. Few principal components drive the field fluctuations in the main field and gradient fields of both high (3 Tesla) and ultra-high (7 Tesla) field systems. By conducting a phantom as well as an in-vivo study at 3 T, the unique contributions of system-related and subject-induced physiological field fluctuations could be disentangled. Herein, system-inherent sources dominate, and mainly arose from heating-induced drifts of the main magnetic field. SFNR dropped by up to 50 %, when these drifts remained uncorrected. Fluctuations of the encoding EPI trajectory itself contributed to a lesser degree, but their correction still yielded an SFNR increase of several percent. Both effects critically depend on timing parameters of the acquisition sequence, and could be mitigated by avoiding mechanic resonance frequencies of the MR system in the choice of the EPI readout.
The second considerable source of field fluctuations arose from subject physiology, in particular breathing. These effects scaled with the main magnet strength amounting to just under 1% SFNR loss at 3 Tesla, and 2% at 7 Tesla. More than main field strength, subject behavior, e.g. breathing depth, altered the noise impact of physiological fields, and could triple the SFNR loss, reaching up to 5% at 7 Tesla. Importantly, the observed field fluctuations were highly unpredictable and could only be corrected for by real-time assessment, such as concurrent magnetic field monitoring. Moreover, field monitoring gave insight into the generating mechanisms of the fluctuations and their temporal evolution.

**Magnetization Fluctuations**

Besides head movement and system-instabilities in the excitation chain, magnetization fluctuations predominantly stem from local flow and subsequent tissue displacement in the brain. These fluctuations typically correlate with the cardiac and respiratory cycle and were thus termed physiological noise. In this work, model-based physiological noise correction was implemented using peripheral data into an easy-to-use software package, the physIO Toolbox. Herein, state-of-the-art models of image fluctuations were implemented and applied to several basic and cognitive neuroscience studies. The physIO Toolbox could remove up to 70% of the residual variance in the respective voxel time series, in particular related to the cardiac cycle. Major sites of noise correction were situated close to vessels and CSF reservoirs, but also near brain and tissue boundaries in general. In general, the physIO Toolbox corrected for magnetization fluctuations of higher spatial order, thus complementing the concurrent magnetic field monitoring approach employed here. Through the combination with magnetic field monitoring it could be shown that up to 25% of image fluctuations correlating with respiration – and hitherto assigned to be magnetization fluctuations – were in fact field-mediated and could be corrected by field monitoring-based image reconstruction.
Thermal Noise

To reduce the impact of thermal noise on fMRI, a matched-filter acquisition scheme was developed in this work, which incorporates prior knowledge on the fMRI analysis pipeline to tailor an acquisition-efficient measurement sequence, replacing standard 2D EPI. Overall, this trajectory realized up to 30% SFNR yield in the post-processed image time series, which translated into comparable gains for task-based fMRI. Specifically, matched-filter fMRI improves BOLD sensitivity by variable-density image acquisition tailored to subsequent image smoothing. Spatial smoothing is an established post-processing technique used in the vast majority of fMRI studies. This work shows that the signal-to-noise ratio (SNR) of the resulting smoothed data can be substantially increased by acquisition weighting with a weighting function that matches the k-space filter imposed by the smoothing operation. The work predicts the theoretical SNR advantage of this strategy and proposes a practical implementation of 2D echo-planar acquisition matched to common Gaussian smoothing. Phantom and in-vivo measurements confirmed reliable SFNR improvement on the order of 30% in a “resting-state” condition and proved robust in different regimes of physiological noise (cf. magnetization fluctuations). Furthermore, a preliminary task-based visual fMRI experiment equally suggested subsequent increases in terms of statistical BOLD sensitivity (average t-value increase of 30%). Field monitoring proved to be essential for the practical implementation of this trajectory, since the demanding velocity modulation of the gradient waveform was not realized as nominally specified. Image reconstructions employing concurrent field monitoring provided artifact-free image time series viable for practical use of matched-filter fMRI.

In conclusion, this thesis proposes a mechanistic framework to interpret and correct noise in fMRI via the fundamental MR image encoding process. To this end, different correction methods were developed to address three important noise mechanisms, i.e. encoding field fluctuations, thermal noise and magnetization
fluctuations. Specifically, concurrent magnetic field monitoring for fMRI comprehensively characterized and addressed encoding field fluctuations, matched-filter acquisition schemes increased acquisition efficiency against thermal noise, and the physIO Toolbox removed remaining physiological magnetization fluctuations. Overall, the combination of these noise correction methods improved sensitivity for BOLD fMRI by 100%, which could, in the future, help to advance fMRI to clinical relevance, particularly in the context of translational neuromodeling.
Figure 1  The unifying theme of this thesis. Building on a mechanistic model of MR image encoding, different pathways of noise propagation in fMRI are identified, characterized and suitable correction methods proposed in the corresponding chapters.

Allerdings ist das charakteristische Signal der fMRT, dessen Kontrast auf dem veränderlichen Blutsauerstoffanteil im Hirngewebe beruht, sehr klein im Vergleich zu anderen, nicht funktionellen Fluktuationen, und repräsentiert höchstens einige Prozent des gesamten gemessenen Signals. Die Entwicklung hin zu translationaler Neuromodellierung, die versucht, mechanistische Erkenntnisse und Behandlungsmöglichkeiten für psychiatrische Erkrankungen zu entwickeln, verdeutlicht die Notwendigkeit der Steigerung räumlicher Spezifizität für fMRT (hin zum Sub-Millimeter-Bereich), um Neurotransmitternetzwerke im Hirn zu erforschen. Dementsprechend ist die Dominanz des Rauschens,
d. h. unerwünschter und unerklärter Signalfuktuationen, einer der Hauptgründe, der der klinischen Relevanz der fMRT entgegensteht, was innovative Wege zur Rauschkorrektur notwendiger macht denn je.


Diese mechanistische Interpretation der Rauscherzeugung konnte bisher nicht experimentell untersucht werden, da Feldfluktuationen als einer der drei Hauptrauschmechanismen einer zeitlich hochauflösten Messung unzugänglich blieben. Mittels seit kurzem verfügbarer Magnetfeldsensoren, die selbst auf nuklearer Magnetresonanz (NMR) beruhen, ist es inzwischen möglich, simultane Magnetfeldmessungen während des Bildgebungsprozesses mit einer zeitlichen Auflösung im Mikrosekundenbereich durchzuführen. Diese Dissertation zeigt die erste umfassende Anwendung der simultanen Magnetfeldmessung für die fMRT. Hierbei fliesst die gesammelte Information über die kodierenden Magnetfelder in die anschliessende Bildrekonstruktion ein, und präzisiert das verwendete Signalmodell. Demnach wird der zweite oben erwähnte Rauschmechanismus, Magnetfeldfluktuationen, weitgehend eliminiert durch die simultane
Magnetfeldmessung mit NMR-basierten Feldsensoren. Darüber hinaus erweitert diese Messmethode auch das Arsenal an einsetzbaren Bildgebungsssequenzen, da die Anforderungen an Reproduzierbarkeit und Güte der kodiierenden Felder sinken, wenn entsprechende Abweichungen mittels Feldmessungen detektiert und korrigiert werden können. In diesem Sinn wird hier die gleichzeitige Magnetfeldmessung als Schlüsseltechnologie eingesetzt, um effizientere Bildgebungsmethoden für fMRI zu entwickeln. Durch höhere Aufnahmeeffizienz schwindet der Einfluss des thermischen Rauschens auf das Signal, was den dritten der oben erwähnten Rauschmechanismen eindämmt. Schliesslich, um eine vollständige Abdeckung aller Rauschmechanismen zu gewährleisten, wurde in dieser Arbeit eine modellbasierte Korrektur für physiologische Magnetisierungsfluktuationen umgesetzt: Lokalisierte Gewebe pulsationen und Strömungen von Blut und Hirnflüssigkeit erzeugen oftmals Störungen, die an den Herz- oder Atemrhythmus gekoppelt sind. Dieses „physiologische Rauschen“ kann aus peripheren Messungen modelliert werden, was das Fundament für die hier entwickelte Software physIO bildet, die fMRT-Bildzeitreihen nachträglich bearbeitet.

Insgesamt betrachtet nimmt also jeder Teil dieser Arbeit seinen eigenen Platz in der Vermessung und Nivellierung der drei Regionen der fMRT-Rauschlandschaft ein (s. Fig. 1).

**Fluktuationen der kodierenden Magnetfelder**

Der Löwenanteil dieser Arbeit beschäftigt sich mit Magnetfeldfluktuationen innerhalb des am häufigsten verwendeten fMRT-Messverfahrens: 2-D echo-planarer Bildgebung (engl. echo-planar imaging, EPI). Diese Feldfluktuationen wurden durch simultane Magnetfeldmessung aufgezeichnet und nachträglich in der Bildrekonstruktion verwendet, um das Signalmodell zu verbessern. Insgesamt konnte fast die Hälfte des Rauschens in den Bildzeitreihen auf diese Art entfernt, d.h. das Signal-zu-Fluktuation-Rausch-Verhältnis verdoppelt werden (engl. signal-to-fluctuation SNR). Nur wenige Hauptkomponenten bestimmen die Feldfluk-
Zusammenfassung

tuationen im Hauptmagnetfeld und den Gradientenfeldern bei hoher (3 Tesla) und Höchstmagnetfeldstärke (7 Tesla): Anhand je einer Phantom- und in-vivo-Studie wurden die eindeutigen Beiträge der systemspezifischen und probandeninduzierten physiologischen Feldfluktuationen getrennt. Systeminhärente Feldfluktuationen dominieren, und stammen hauptsächlich vom Drift des Hauptmagnetfelds infolge Aufheizens. Das SFNR sank um bis zu 50 %, sofern diese Fluktuationen unkorrigiert blieben. Fluktuationen in den kodierenden EPI-Trajektorien selbst trugen weniger zum Rauschen bei, ihre Korrektur verbesserte das SFNR um einige Prozent. Beide Effekte hängen stark von den konkreten Sequenzparametern der EPI ab, und konnten deutlich verringert werden durch das Vermeiden mechanischer Resonanzen im Gradientensystem durch Anpassung der Auslesefrequenz der EPI.

Als zweite Quelle für Magnetfeldfluktuationen wurde die menschliche Physiologie identifiziert, vor allem in Form atmungsinduzierter Felder. Diese Fluktuationen skalierten mit der Hauptmagnetfeldstärke und bedeuteten SFNR-Verluste von ca. 1 % bei 3 Tesla und mehr als 2 % bei 7 Tesla. Noch grösseren Einfluss als die Magnetfeldstärke übte das Probandenverhalten auf den Rauscheinfluss der physiologischen Felder aus; insbesondere tiefe Atemzyklen liessen den SFNR-Verlust bei 7 Tesla auf bis zu 5 % ansteigen. Umgekehrt liess sich mittels der hier vorgestellten auf NMR-Feldsensoren basierenden simultanen Echtzeitmagnetfeldmessung der Einfluss dieser Rauschquellen fast vollständig unterdrücken, und darüber hinaus ein Einblick in die Mechanismen, die zu Feldfluktuationen führen, gewinnen. Insbesondere die beobachtete Unvorhersagbarkeit der system- und physiologiebasierten Feldänderungen erfordert den Einsatz von Echtzeitfeldmessverfahren gegenüber modellbasierter Kalibrierung.

Magnetisierungsfluktuationen

Neben Kopfbewegungen und Systeminstabilität in der Anregungskette bilden lokale Flusseffekte und Gewebeververschiebungen die Hauptquellen für Magnetisierungsfluktuationen im Gehirn.

**Thermisches Rauschen**

Um den Einfluss thermischen Rauschens auf die fMRT zu reduzieren, wurde im Zuge dieser Arbeit eine Optimalfilter-Bildaufnahmestrategie (engl. *matched filter*) entwickelt, die Vorwissen über die Signalverarbeitung der fMRT-Daten in den Entwurf einer effizienten Messsequenz einbezieht. Gegenüber der dadurch ersetzen 2-D EPI-Sequenz konnte so ein SFNR-Gewinn von ca. 30 % in den weiterverarbeiteten Bildern erzielt werden, die in die statistische Analyse einfließen. Diese Verbesserung drückte sich ebenfalls in vergleichbaren Sensitivitätsanstiegen für das

Zusammengefasst umreißt diese Dissertation eine mechanistische Perspektive auf die Interpretation und Korrektur von Rauschen in der funktionellen Magnetresonanztomographie (fMRT), ausgehend von ihrem grundlegenden Bildgebungsprozess. Zu diesem Zweck wurden verschiedene Methoden der Rauschkorrektur entwickelt, die sich an drei Hauptursachenmechanismen orientieren: Fluktuationen der kodierenden Magnetfelder, thermisches Rauschen und Magnetisierungsfluktuationen. Im Einzelnen liefert die simultane Magnethfeldmessung mittels NMR-basierter Sensoren eine umfassende Charakterisierungs- und Korrekturmöglichkeit für Magnetfeldfluktuationen, Optimalfilter-fMRI erhöht die Aufnahmeeffizienz gegen thermisches Rauschen und die physIO Toolbox entfernt physiologische Magnetisierungsfluktuationen. Insgesamt
verspricht die Kombination dieser drei Rauschkorrekturmethoden
eine Verdopplung der Sensitivität der fMRT, die in der Zukunft
ihren Beitrag zur klinischen Relevanz dieser Messmethode leisten
könnte, insbesondere im Umfeld der translationalen
Neuromodellierung.
ACKNOWLEDGEMENTS

This is the part of my thesis I enjoy writing the most... not least because here – and only here – my stream of consciousness will not be bound by the ideal of academic conciseness. And conciseness indeed means concision of literary value in academic texts to me. They possess elegance and a cold beauty, but warmth and soul lie in the manifold of interpretations ambiguity allows for – so many of the words following will embrace people in a personal way, my way, and I will not let go of them, until all is expressed, however redundant it may seem.

There are only so many ways to say thank you, and I am thankful in so many more ways to so many more people. So my first thank you goes to all people that I will forget to thank in the following, or whom to thank would be inappropriate in public acknowledgements. Rest assured I thought of you as well writing this text. Likewise, I want to thank the readers unknown to me, who will overcome skimming the figures of this thesis and truly appreciate the months of contemplation in structuring and carefully writing it.
I will start by thanking the only people who ever read this thesis fully: my referees Prof. David G. Norris, Prof. Klaas E. Stephan and Prof. Klaas P. Pruessmann. In particular to David Norris, the external referee, I am indebted, since his thorough evaluation and deep understanding of my thesis helped to set off the efforts of writing it.

At ETH, I have scientifically grown up in a two-Klaas system, and I am equally grateful to both of my supervisors, for showing me a conjoint scientific ideal, and two distinct ways to thrive for it. My passion for science transcended into the conviction to become a scientist over the last years as a result of their steady, selfless, patient and incredibly insightful guidance.

To Klaas E., I remain forever grateful for introducing a plain physicist to the marvelous world of neuroscience, which keeps inspiring me for exactly 9 years now. He was the reason I came to Zurich, and I thank him for his support, patience and trust in me even in times when I didn’t have it myself, as well as for giving me freedom in conducting this work. Furthermore, it was a great experience to participate in his research vision, the Translational Neuromodeling Unit (TNU), from the beginning and witness its growth into a fantastic group of diverse scientists and students. Personally, I am boundlessly indebted to him for introducing Dr. Diaconescu to me, my soulmate.

To Klaas P., I feel immense gratitude for broadening and deepening my level of understanding of MR by orders of magnitude, and teaching me the importance of clear and stringent, relentless thinking. I value his uncompromising prioritization of science and the endless hours of discussion filled with his unwaning will to arrive at the core of a question and its solution – intertwined with little detours revealing a like-minded sense of humour and punning. In his role as head of the MR-Technology Group and the Institute for Biomedical Engineering (IBT), I am grateful to Klaas P. for creating a paradise for scientists, abundant in freedom, facilities and knowledge in an altruistic, collaborative atmosphere, and with
the luxury of time to pursue a scientific question until complete understanding.

I also had the immense luck to see the other side of a supervisory process during my PhD, and am indebted to my semester and master students Shu-Ting Wang, Marco Jauslin and Saskia Bollmann, nee Klein, who taught me a lot about guidance, scientific project management and MR. With Saskia in particular, I exchanged unprecedented scientific trust and without her, I could not have imagined writing a paper literally together – in your presence alone I feel comfortable to err.

Being both member of the TNU and the MR-Technology Group not only offered the pleasure of working with twice as many colleagues in two unique research environments, but now also justifies acknowledging them at (double) length: First and foremost, I have to compliment all members of the TNU and MR-Technology Group, and likewise the Cardio-, Spectro- and Neurogroup for the genuine interest and untainted collaborative spirit that I enjoyed in all our interactions. I benefitted tremendously through the (non-) scientific discussions in the coffee corner and over lunch in all these years.

My two offices at TNU and IBT in particular were protected places of inspiration, intellectual discourse and hilarious fun to me – populated by my gifted colleagues-turned-friends Max Haeberlin, S. Johanna Vannesjö and Giorgos Katsikatsos at Gloriastrasse, as well as Kay Brodersen, Christoph Mathys, Sandra Iglesias and Kate Lomakina at Bluemlisalp/Wilfriedstrasse. With Max, I shared humour and mindset, and I thank him for his tireless scientific curiosity, wit, warmth and charme that coloured so many of my days. Johanna has been a remarkable scientific role model for me, a truly intellectual friend, and left me a bit wiser and happier after each of our discussions. Similarly, I admire Christoph M. as the ideal Bayesian modeller, enjoyed his mathematical rigour as well as his open, giving personality and his uncanny knack of sensing what is important for a conscious life in science. I thank Sandra for
Acknowledgements
giving neuroscientific meaning to my work as my first and most loy
al collaborator, for her kindness towards people and natural inclusiv
eness and understanding.

Beyond these closest colleagues, Lilian Weber and Falk Lieder shaped m
y self-conception of a scientist the most, with their mix of determi
nation, lightness, optimism and occasional genius. Simon Gross and Ben
jamin Dietrich sparked similar excitement in me with their knowl
dge of physics, electronics, life...and the rest, being great friends and t
he altruistically helpful hardware-wizards who allowed me to probe mag
netic fields in the first place.

The Skope-ists – Christoph Barmet, David Brunner and Bertram Wilm – a
re at the foundation of field monitoring, and I am grateful I could mon
itor the evolution of various (research) fields in these last years through t
heir work; without them, my thesis would have taken a completely diffe
rent and unknown path.

Collaboration has been one of my greatest treats during this time, and I p
articularly thank my colleagues Jakob Heinzle, Yolanda Duerst, Steffen Bollmann and Tobias Hauser, Zina-Mary Manjaly and Michael Wyss for t
heir steady interest and motivation as well as the mutual exchange on o
ur research.

I was impressed by the professionality and smoothness that both IT an
administration exhibited at the IBT – which is the accomplishment of M
ianne Berg, Suzanne Wilde, Bruno Willi and Sebastian Grässli. On a sim
lar note, I think there can be no better person to manage our MR center t
han Roger Lüchinger, who has saved my data and experiments countless
times with his incredible knowledge, helpfulness and availability.

I also thank my third and unofficial office – Martina Zingg and Georg Linsi, the “Le Puys”: Their bistro provided the best food and most mind-refres
hing atmosphere to become the birthplace of half the thesis and a paper. T
hey especially cheered me up day by day in the final phase of writing t
is up.
This thesis is the culmination of my scholarly education, which started 25 years ago, when there was still a wall dividing the capital of my home country. It would be rude neglect to not mention the people and institutions that shaped my growth over this quarter of a century: foremost, the Studienstiftung and the Georg-Cantor-Gymnasium in Halle provided an environment my mind could flourish in. Apart from the supervisors mentioned already, I thank Michael Breakspear for guiding my first endeavor into terra australis and terra incognita fMRI; as well as Susann Boretius for her dedicated guidance during my master thesis in Goettingen. During high school, my teachers Herr Pannicke, Dr. Kramer und Frau K. Schmidt instilled the lasting enthusiasm about science in me.

My most loyal friends, who kept in touch with the worst of all mail- and phone-responders over all these years, I found in Sebastian, Stefan and Joerg back in Halle; I feel blessed by having friends like you, whom I can rely on and spend untroubled time with alike. I thank my globetrotter friends, Laura and Gerald, for not being the only weak responder, and deepening our bond though we couldn’t be further apart. During my studies, the MO-Team in Göttingen, especially Ulrike and Alex, made my life more significant, as well as Martin, Christian and Ansgar. Later, the akitiv theatre company, in particular Ursi and Sarah, helped me arrive in Zurich and kiss alive my dearest hobby.

Ich bin der Mensch, der ich bin, vor allem durch die Erziehung, bedingungslose Liebe und Unterstützung meiner Mutti und meiner Tante Christa – wofür ich euch ewig dankbar sein werde. Selbst in meiner Muttersprache kann ich nicht ausdrücken, was ihr für mich geleistet habt und ich nie aufzuwiegen vermag: dass ich optimistisch und glücklich leben kann.

And finally – though this is just the beginning: I thank Andreiuța, model and model scientist, lover, mentor and friend, crisis manager and life-(im)balancer – in short, the person who gives me a place in this world:
Cu fiecare bătaie a inimilor noastre îmi întărești pasiunea pentru știință și credința în oameni.

Lars Kasper

Zurich, 17\textsuperscript{th} of August 2014
# TABLE OF CONTENTS

Summary ........................................................................................................................................... 7

Zusammenfassung .......................................................................................................................... 15

Acknowledgements ......................................................................................................................... 23

1 **Introduction** ............................................................................................................................... 37
   1.1 Background .......................................................................................................................... 37
   1.2 Outline of the Thesis ......................................................................................................... 41

2 **BOLD fMRI and Noise Considerations** .................................................................................. 45
   2.1 The Contrast Mechanism of BOLD fMRI ....................................................................... 45
   2.2 Modeling the BOLD Signal ............................................................................................... 50
   2.3 Statistical Measures of Noise and BOLD Sensitivity ....................................................... 53
   2.4 MR Image Encoding and Acquisition .............................................................................. 57
   2.5 The Noise Landscape Limiting BOLD Sensitivity ............................................................ 63

3 **Concurrent Magnetic Field Monitoring** ............................................................................... 73
   3.1 NMR Field Probes ........................................................................................................... 73
   3.2 Field Estimation from Probe Phase Measurements ......................................................... 77
   3.3 Concurrent Monitoring Setups ......................................................................................... 82

4 **The PhysIO Toolbox for Localized Physiological Noise Correction** .................................. 87
   4.1 Physiological Noise in fMRI Data .................................................................................... 87
<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.2</td>
<td>Image-based Physiological Noise Correction</td>
<td>90</td>
</tr>
<tr>
<td>4.3</td>
<td>Implementation of Noise Correction in the PhysIO Toolbox</td>
<td>97</td>
</tr>
<tr>
<td>4.3.1</td>
<td>Overview</td>
<td>97</td>
</tr>
<tr>
<td>4.3.2</td>
<td>Read-in of Physiological Log files</td>
<td>100</td>
</tr>
<tr>
<td>4.3.3</td>
<td>Pre-Processing of Peripheral Physiological Data</td>
<td>105</td>
</tr>
<tr>
<td>4.3.4</td>
<td>Physiological Noise Modeling</td>
<td>108</td>
</tr>
<tr>
<td>4.3.5</td>
<td>Physiological Noise Correction</td>
<td>113</td>
</tr>
<tr>
<td>4.3.6</td>
<td>Assessment of Noise Correction Efficacy</td>
<td>115</td>
</tr>
<tr>
<td>4.4</td>
<td>Applications of the PhysIO Toolbox</td>
<td>117</td>
</tr>
<tr>
<td>5</td>
<td>Matched-Filter Acquisition for BOLD fMRI</td>
<td>125</td>
</tr>
<tr>
<td>5.1</td>
<td>Introduction</td>
<td>125</td>
</tr>
<tr>
<td>5.2</td>
<td>Theory and Methods</td>
<td>128</td>
</tr>
<tr>
<td>5.2.1</td>
<td>Theory: Matched-density acquisition for image post-processing filters</td>
<td>128</td>
</tr>
<tr>
<td>5.2.2</td>
<td>Theory: EPI-Trajectory Design for a Matched-filter Gaussian Density</td>
<td>134</td>
</tr>
<tr>
<td>5.2.3</td>
<td>Image Acquisition, Concurrent Field Monitoring and Image Reconstruction</td>
<td>138</td>
</tr>
<tr>
<td>5.2.4</td>
<td>Experiment 1: Assessment of SFNR gain for EPI Time Series in Different Noise Regimes</td>
<td>140</td>
</tr>
<tr>
<td>5.2.5</td>
<td>Experiment 2: fMRI Paradigm and Analysis</td>
<td>141</td>
</tr>
<tr>
<td>5.3</td>
<td>Results</td>
<td>143</td>
</tr>
<tr>
<td>5.3.1</td>
<td>Monitoring: Trajectories and k-Space Densities</td>
<td>143</td>
</tr>
<tr>
<td>5.3.2</td>
<td>Monitoring: Image reconstruction</td>
<td>149</td>
</tr>
<tr>
<td>5.3.3</td>
<td>SFNR Analysis</td>
<td>153</td>
</tr>
<tr>
<td>5.3.4</td>
<td>fMRI Analysis: t-Maps and Total Least Squares</td>
<td>157</td>
</tr>
<tr>
<td>5.4</td>
<td>Discussion and Conclusion</td>
<td>162</td>
</tr>
</tbody>
</table>
6 Monitoring, Analysis and Correction of Magnetic Field Fluctuations in EPI Time Series .................................. 169
  6.1 Introduction ............................................................................................................................. 169
  6.2 Methods ................................................................................................................................. 172
    6.2.1 MR Image Encoding and Field Fluctuations .................................................. 172
    6.2.2 Concurrent Magnetic Field Monitoring ......................................................... 174
    6.2.3 Data Acquisition ........................................................................................................ 177
    6.2.4 Image Reconstruction ............................................................................................ 180
    6.2.5 Reconstruction Schemes ....................................................................................... 181
    6.2.6 Statistical Analysis of Image Fluctuations ................................................ 182
    6.2.7 Data-Driven Time Series Analysis: Principal Component Analysis ............. 183
  6.3 Results .................................................................................................................................. 185
    6.3.1 Image Accuracy and Precision Losses Induced by Field Fluctuations ........ 185
    6.3.2 Fluctuations of Global Phase and Trajectory ...................................................... 189
    6.3.3 Analysis of Image Fluctuations using Image PCA .................................................. 195
    6.3.4 Reproducibility of Field Fluctuations for Calibration ........................................ 197
  6.4 Discussion and Conclusion ................................................................................................. 198

7 Assessment of Magnetic Field Monitoring for EPI Time Series in-vivo ......................................................... 203
  7.1 Introduction ............................................................................................................................. 203
  7.2 Methods .................................................................................................................................. 206
    7.2.1 MR Image Encoding and Field Fluctuations ................................................................. 206
    7.2.2 Concurrent Magnetic Field Monitoring ................................................................. 207
    7.2.3 Data Acquisition ........................................................................................................ 209
    7.2.4 Analysis of Field Fluctuations .................................................................................. 211
    7.2.5 Image Reconstruction ............................................................................................. 213
    7.2.6 Reconstruction Schemes .......................................................................................... 214
<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.2.7</td>
<td>Coil Data Simulations</td>
<td>216</td>
</tr>
<tr>
<td>7.2.8</td>
<td>Statistical Analysis of Image Fluctuations</td>
<td>217</td>
</tr>
<tr>
<td>7.3</td>
<td>Results</td>
<td>219</td>
</tr>
<tr>
<td>7.3.1</td>
<td>Characterization of Field Fluctuations</td>
<td>219</td>
</tr>
<tr>
<td>7.3.2</td>
<td>Reference Reconstruction: Concurrent Monitoring</td>
<td>225</td>
</tr>
<tr>
<td>7.3.3</td>
<td>Characterization of Field-mediated Image Fluctuations</td>
<td>228</td>
</tr>
<tr>
<td>7.3.4</td>
<td>BOLD Sensitivity Losses due to Field Fluctuations</td>
<td>229</td>
</tr>
<tr>
<td>7.4</td>
<td>Discussion</td>
<td>236</td>
</tr>
<tr>
<td>7.5</td>
<td>Conclusion</td>
<td>239</td>
</tr>
<tr>
<td>8</td>
<td>Physiological Noise in High-Field fMRI: Disentangling Field from Brain</td>
<td>241</td>
</tr>
<tr>
<td>8.1</td>
<td>Introduction</td>
<td>241</td>
</tr>
<tr>
<td>8.2</td>
<td>Methods</td>
<td>245</td>
</tr>
<tr>
<td>8.2.1</td>
<td>MR Image Encoding and Field Fluctuations</td>
<td>245</td>
</tr>
<tr>
<td>8.2.2</td>
<td>Concurrent Magnetic Field Monitoring</td>
<td>246</td>
</tr>
<tr>
<td>8.2.3</td>
<td>Data Acquisition</td>
<td>248</td>
</tr>
<tr>
<td>8.2.4</td>
<td>Analysis of Field Fluctuations using Principal Component Analysis</td>
<td>250</td>
</tr>
<tr>
<td>8.2.5</td>
<td>Image Reconstruction and Pre-Processing</td>
<td>251</td>
</tr>
<tr>
<td>8.2.6</td>
<td>Statistical Analysis of Image Fluctuations</td>
<td>253</td>
</tr>
<tr>
<td>8.3</td>
<td>Results</td>
<td>255</td>
</tr>
<tr>
<td>8.3.1</td>
<td>Fluctuations in Encoding Fields</td>
<td>255</td>
</tr>
<tr>
<td>8.3.2</td>
<td>Impact of Field Fluctuations on fMRI Time Series</td>
<td>269</td>
</tr>
<tr>
<td>8.3.3</td>
<td>Localization of Physiological Effects: Magnetization vs Field</td>
<td>275</td>
</tr>
<tr>
<td>8.4</td>
<td>Discussion</td>
<td>279</td>
</tr>
</tbody>
</table>
9 Conclusion and Outlook ........................................ 285
  9.1 Conclusion .................................................. 285
  9.2 Outlook ..................................................... 288

Appendices .................................................................. 295
  A Theoretical SNR Gain of Matched-Filter fMRI for
      Gaussian Smoothing ............................................. 295
  B Analytic Expression for a Gradient Waveform with
      Gaussian Acquisition Weighting .............................. 297

Bibliography .............................................................. 301

List of Publications ..................................................... 317

Curriculum Vitae ........................................................ 323
CHAPTER 1

INTRODUCTION

1.1 Background

Functional magnetic resonance imaging (fMRI) has revolutionized our ability to study brain function. Out of all neuroimaging techniques, fMRI embraces a unique combination of spatial and temporal specificity to investigate brain activity non-invasively at the systems level. fMRI assesses time-courses of metabolic activity on a millimeter scale, i.e. summarizing the processes of millions of neurons, with a sampling rate on the order of seconds. Thereby, fMRI captures the dynamics of interacting brain regions for up to hours.

Moreover, fMRI possesses a remarkable suitability for studying the healthy as well as the diseased human brain. It is a non-invasive and harmless technique, therefore individuals can undergo longitudinal measurements over years with fMRI, without dose-limitation. The suitability for human studies is further enhanced by the widespread availability of the technique. fMRI is performed on a medical device, i.e. the MR scanner, which is installed in a
significant portion of hospitals all over the world, improving the practical usability and robustness of the technique compared to methods that are only prevalent in pure research environments.

Through its accessibility to a diverse group of scientists beyond MR physicists and radiologists, fMRI has become the method of choice in a huge variety of neuroscientific research questions and applications. Over the past twenty years, the field has transitioned from studying large sensory and motor systems (Biswal et al., 1995; Boynton et al., 1996; Kanwisher et al., 1997; Rao et al., 1993; Tootell et al., 1995) to localized small subunits, such as cortical columns (Cheng et al., 2001; Yacoub et al., 2008) and subcortical nuclei (D’Ardenne et al., 2008; Iglesias et al., 2013) on the one hand, and distributed brain networks serving complex cognitive processes, on the other (Bressler and Menon, 2010; McIntosh, 2000; Stephan and Friston, 2010; Stephan et al., 2009b).

To a large extent, this transition became possible through numerous developments in MR methodology that increased the sensitivity of the fMRI measurement, like improved detection hardware (coil arrays), higher main magnetic field (available signal), or faster and more robust acquisition schemes (e.g. echo-planar and spiral imaging (Ahn et al., 1986; Mansfield, 1977) or parallel imaging (Griswold et al., 2002; Pruessmann et al., 1999). In boosting fMRI sensitivity, these developments pushed the limits of its spatial and temporal specificity, arriving at the state of the art: acquiring a snapshot of whole-brain activity with a 2 mm resolution in 2 seconds.

Today, advancing the sensitivity of fMRI further could conquer the next frontier by allowing for measurements on a sub-millimeter scale. This might initiate another transition of the research field into the realm of clinical relevance. In
particular, fMRI with sub-millimeter resolution enables the study of neurotransmitter sites in subcortical areas, such as the brainstem. This is highly relevant for studying disease mechanisms and evaluating candidate neuropharmacological treatments (cf. (Honey and Bullmore, 2004; Matthews et al., 2006). Ultimately, the impact of fMRI could reach beyond systems neuroscience to benefiting the individual patient with a psychiatric or neurological disorder (Owen et al., 2006; Ressler and Mayberg, 2007; Stephan et al., 2009a).

However, in order to achieve such advancements, the notoriously low sensitivity of fMRI has to be overcome. Sensitivity describes the relation between the signal of interest and the confounding noise it is embedded in. For fMRI, small signal changes due to brain function amount to at most a few percent of the signal intensity. Increasing spatial resolution, for example, reduces the signal in the smaller resolution elements, and shifts the proportion between detectable signal and noise unfavorably towards noise dominance. In principle, this imbalance can be rectified by increasing the signal of interest or reducing the noise content in the measurement.

This thesis takes an innovative perspective on the improvement of fMRI sensitivity by scrutinizing the different noise mechanisms confounding the fMRI time series. What is unique about this approach is that it does not treat MR image encoding as a black box by starting off to correct an image time series. Rather, the ideas proposed here incorporate a mechanistic model of signal generation and image reconstruction in fMRI. This leads to dedicated treatments of (1) the thermal noise in the receiver channels of the MR system, arising both from the object and the conducting elements of the receive chain (2) the magnetization fluctuations induced by subject-induced physiological noise and (3) fluctuations in the time-varying
magnetic fields – that form the basis of spatial encoding for MRI. In particular, while the landscape of thermal and physiological noise has been explored extensively for fMRI, the realm of encoding field fluctuations has remained uncharted territory thus far. The work presented here will shed light on the spatiotemporal structure of encoding field fluctuations present in fMRI acquisitions and their propagation into confounding noise of the image time series.

Methodologically, this anticipates the second unifying theme of this thesis: concurrent magnetic field monitoring using NMR field probes (Barmet et al., 2010, 2009, 2008; De Zanche et al., 2008). This method exhibits the unique capability to study reproducible as well as non-reproducible field fluctuations simultaneously to image acquisition. Furthermore, field monitoring allows for a comprehensive assessment and correction of encoding field fluctuations, without any changes to the imaging sequence or magnetization state of the object. This work constitutes the first full-fledged application of concurrent magnetic field monitoring in the context of fMRI.
1.2 Outline of the Thesis

Along the conceptual theme of studying the noise sources in fMRI by mechanistic scrutiny of MR image encoding, and the methodological theme of concurrent magnetic field monitoring, the thesis comprises the following chapters:

**FIGURE 1.1**  The unifying theme of this thesis. Building on a mechanistic model of MR image encoding, different pathways of noise propagation in fMRI are identified, characterized and suitable correction methods proposed in the corresponding chapters.
• Chapter 2 gives a general introduction to fMRI as a measurement technique to study brain function, with a special focus on the noise sources limiting the sensitivity of the measurement.

• Chapter 3 introduces the most important methodological aspect employed in this thesis: concurrent magnetic field monitoring, which can both characterize and correct comprehensively for field-mediated noise stemming from both system and subject physiology.

• Chapter 4 specifies a post-processing software developed within the scope of this thesis, the physIO Toolbox. This software implements a correction method for localized physiological noise in fMRI via retrospective image correction (RETROICOR, Glover et al., 2000). Since localized physiological noise is not field-mediated, but manifests in magnetization fluctuations directly, the physIO Toolbox offers a complementary noise reduction method to field monitoring (Chapter 3).

• Chapter 5 introduces Matched-filter Acquisition for BOLD fMRI, which targets the third noise mechanism, i.e. thermal noise in the receive coil signal. Specifically, matched-filter acquisition tailors the MR acquisition to subsequent image post-processing in fMRI, i.e. smoothing. This chapter comprises both the theoretical aspects of matched-filter acquisition and its experimental validation. The theoretical part includes the design of a matched-filter echo-planar imaging sequence (EPI), while the experimental part utilizes concurrent magnetic field monitoring for a robust realization of the designed matched-filter EPI acquisition scheme.

• Chapter 6 employs magnetic field monitoring to comprehensively characterize system-related magnetic-field fluctuations for a typical fMRI sequence, 2D EPI, on a standard MR system (3 Tesla main field). The study further focuses on the impact of these field fluctuations
on the stability of fMRI time series. Finally, the efficacy of concurrent magnetic field monitoring for restoring stability is demonstrated, when used as a correction method in image reconstruction.

- Chapter 7 extends the work of Chapter 6 for in-vivo measurements using a cognitive fMRI paradigm. In particular, the findings of Chapter 6 regarding system-related fluctuations in the encoding fields are replicated. Additionally, the occurrence of physiological field fluctuations is characterized and quantified by concurrent field monitoring. The study examines the distinct impact of system-related and physiological field fluctuations on BOLD sensitivity in measured and simulated image time series. The comprehensive capability of concurrent field monitoring for correcting both system-related and physiological field effects is confirmed.

- Chapter 8 culminates the innovations in noise correction to ultra high-field application, i.e. fMRI on a 7 Tesla system. Concurrent field monitoring is used to correct for the even more pronounced field fluctuations at 7 T. Additionally, the physIO Toolbox (Chapter 4) addresses the remaining magnetization fluctuations due to physiological noise. The impact of these correction methods is evaluated quantitatively and compared to the measured BOLD effect using an established sensory paradigm. The chapter concludes by exploring the potential of concurrent field monitoring for novel functional contrasts, namely phase fMRI.

- Chapter 9 summarizes the key findings presented in the thesis and speculates on the most promising future developments and applications of this work.
2.1 The Contrast Mechanism of BOLD fMRI

Functional MRI routinely relies on blood-oxygen level dependent (BOLD) contrast (Huettel et al., 2009; Ogawa et al., 1990). BOLD, in turn, builds upon the distinct magnetic properties of oxygenated and deoxygenated hemoglobin in the blood (Pauling and Coryell, 1936; Weisskoff and Kiihne, 1992). Through oxygenation, deoxyhemoglobin changes its magnetic susceptibility $\chi$, which describes how a material alters its internal magnetic flux $\vec{B}$ in response to an external magnetic field $\vec{H}$.

$$\vec{B} = \vec{H} + \vec{M} = \vec{H} + \chi \cdot \vec{H}$$  

(2.1)

Oxygenated hemoglobin is slightly diamagnetic, reducing magnetic flux, while deoxyhemoglobin is paramagnetic and increases magnetic flux compared to the external magnetic field. The difference is tiny, amounting to only 0.18 parts per million (Weisskoff and Kiihne, 1992). Nevertheless, it implies that the local
fraction of deoxy- to oxyhemoglobin in tissue influences the magnetic field in the vicinity.

What makes BOLD fMRI possible, is that this fraction of deoxy- to oxyhemoglobin can be linked to brain metabolism, too. Hemoglobin, found in the red blood cells, is the oxygen transporter within the blood. Cells, and in particular neurons, rely on oxidative glucose metabolism to meet their energy demands. The details of the local response of the brain towards a higher energy demand are still matter of debate. One of the most established theories of the vascular consequences of elevated brain activity is provided by the balloon model (Buxton et al., 1998; Stephan et al., 2007). Herein, the active regulatory process is an increase in blood flow following increased oxygen consumption (Huettel et al., 2009). This blood flow increase supplies more oxygenated blood to the oxygen extraction site in the capillary bed, close to the neurons. However, the transit time of red blood cells through the capillary bed decreases with higher blood flow. Therefore, the probability of oxygen extraction from each individual red blood cell decreases. To arrive at a sufficient net gain in extracted oxygen in the capillary bed, the blood flow acceleration must be disproportionately high then. Initially, this sudden increase in blood flow prior to the capillary bed is not met by comparable transport acceleration in the venous drainage system. Thus, the downstream draining veins inflate like a balloon to cope with the excess in blood volume; hence the name “balloon model”. Shortly after the increase in blood flow, the inflated vein volume contains mostly the deoxygenated blood that was pushed out of the capillary bed. Later on, the excess oxygenated blood that could not be extracted in the capillary bed is accumulating in the venous balloon. Taken together, the balloon model predicts local, temporally variable changes of the deoxy/oxy-hemoglobin ratio at the site of increased energy demand and in downstream venous compartments. Thus, the ratio of deoxygenated to oxygenated hemoglobin in the brain constitutes a compelling link between local metabolism and magnetic properties of the tissue.
MRI can measure the local magnetization changes and thus detect the local fluctuations in (de)oxy-hemoglobin concentrations. This is mediated via the fundamental Larmor equation linking magnetic flux $B_0$ to the magnetic resonance frequency $\omega_0$ of the spins via their gyromagnetic ratio $\gamma$:

$$\omega_0 = \gamma \cdot B_0$$ (2.2)

Therefore, susceptibility changes $\Delta \chi$ and subsequent magnetization changes lead to an alteration in the magnetic resonance frequencies of the spins experiencing the main magnetic field. For example, proton spins in a typical main magnetic field of 3 Tesla, surrounded by fully (de)oxygenated red blood cells, can differ in their resonance frequency by up to

$$\Delta \omega = \omega_{\text{deoxy}} - \omega_{\text{oxy}} = \gamma \cdot B_{\text{deoxy}} - \gamma B_{\text{oxy}}$$

$$= \gamma \left( H + \chi_{\text{deoxy}} \cdot H \right) - \gamma \left( H + \chi_{\text{oxy}} \cdot H \right)$$

$$= \gamma \Delta \chi \cdot H = 4\pi \cdot 1.8 \cdot 10^{-7} \cdot 127.8 \text{ MHz} = 289 \text{ Hz.}$$ (2.3)

In a mesoscopic, semi-classical view, the precessing spins are imagined as rotating magnetic dipoles. The net magnetization within a volume element (voxel) is then formed as the volume integral of the dipole magnetization vectors. MRI measures the transverse component of this magnetization, perpendicular to the main magnetic field. This transverse magnetization in a voxel forms a 2D vector precessing at the Larmor frequency, and hence can be described via its magnitude and phase, i.e. as a complex number. Therefore, a typical MR image representing transverse magnetization from thousands of voxels, is complex-valued as well and can be decomposed into magnitude and phase images.

For fMRI, it is important to note that due to the non-uniform distribution of deoxygenated and oxygenated hemoglobin in the voxel, no single precession frequency exists. Rather, one can employ a mesoscopic stance again and conceptualize the magnetization vector within a voxel as the complex sum (i.e.
volume integral) of magnetization vectors in sub-compartments of that voxel, each rotating with their local resonance frequency.

Consequently, the local frequency distribution within the voxel induces two effects on its net magnetization. In principle, both mechanisms can serve as contrast for functional MRI. On the one hand, the phase of the voxel net magnetization is altered if the phases of the sub-compartments add up coherently, e.g. if the frequency distribution is very narrow and has a mean different from $\omega_0$. This effect is used in phase fMRI (Bianciardi et al., 2013). On the other hand, the magnitude of the voxel net magnetization is dependent on the local frequency distribution as well. If the variance of frequencies between sub-compartments is high, their phase coherence diminishes quickly. Therefore, the amplitude of their complex sum is reduced. This exponential decay in magnetization amplitude is described by the apparent spin-spin relaxation constant, $T_2^*$. For BOLD fMRI, since the paramagnetic deoxygenated blood typically creates a stronger frequency and phase dispersion in the voxel, $T_2^*$ decreases with a higher ratio of deoxy- to oxygenated hemoglobin (Ogawa et al., 1990). However, due to the overcompensation with inflowing oxygenated blood, $T_2^*$ increases in brain regions of elevated metabolic activity, leading to a higher magnetization amplitude, i.e. signal intensity, in the corresponding voxel.

Nowadays, for most applications, fMRI relies on magnitude images, because they are less susceptible to global field changes, since they reflect the spread of the local field distribution within or in the immediate vicinity to the voxel. In contrast to that, the voxel phase is affected by any non-local change in the magnetic field as well that might have sources far away from the voxel location.

In both cases, magnitude-based or phase fMRI, the BOLD effect size is rather small, amounting to maximally a few percent change compared to the mean signal (Bianciardi et al., 2013; Huettel et al., 2009; Kwong et al., 1992). Therefore, to increase the sensitivity of the measurement, experimental manipulations are repeated many
times, and the changes in voxel intensity are recorded in time series of MR images that contain several hundreds to thousands of images (Huettel et al., 2009). Herein, the governing principle of experimental design is to decouple any confounding noise mechanism from relevant signal. This allows for the coherent accumulation of effects of interest, while noise accrues incoherently and cancels out on the same time scale.
2.2 Modeling the BOLD Signal

We have seen how local changes in the (de)oxy-hemoglobin concentration of the blood can lead to image intensity (or phase) changes in $T_2^*$-sensitive MR images, which are summarized as BOLD signal. However, the reasons for MR images to fluctuate are manifold (see section 2.5) and ultimately limit the sensitivity of the fMRI measurement. Under simple additive assumptions, the BOLD fluctuations of interest are superposed with confounding fluctuations in the time series, constituting a “noise floor” (Figure 2.1 A). Thus, a model of the BOLD signal is required to disentangle the targeted fluctuations linked to brain metabolisms from noise, in order to perform inference on the hypothesized effects of interest.

Most commonly, the BOLD signal is modeled in a mass-univariate approach, the general linear model (GLM), considering each image voxel time series individually (Friston et al., 1994; Poline and Brett, 2012). Specifically, a voxel time series $\mathbf{y} = (y_1, ..., y_N)^T$ over $N$ imaging volumes is modeled as a linear combination of $M$ model time series $\mathbf{x}_1 = (x_{11}, ..., x_{1N})^T, ..., \mathbf{x}_M = (x_{M1}, ..., x_{MN})^T$, that represent hypothesized effects of interest or known confound mechanisms,

$$\mathbf{y} = \sum_{m=1}^{M} \beta_m \cdot \mathbf{x}_m + \mathbf{e} = X \cdot \mathbf{\beta} + \mathbf{e} \quad (2.4)$$

with the design matrix $X = (\mathbf{x}_1, ..., \mathbf{x}_M)$ containing the hypothesized effects as columns, the parameter or weighting vector $\mathbf{\beta} = (\beta_1, ..., \beta_M)^T$, and the noise floor, i.e. the unmodelled time series, $\mathbf{e} = (e_1, ..., e_N)^T$ (Figure 2.1 A).
The interplay of signal fluctuations and noise for BOLD sensitivity. (A) The BOLD fluctuations of interest (red) are superposed with confounding fluctuations constituting a “noise floor” (blue). If sensitivity is high, the measured signal (blue diamonds) is dominated by BOLD fluctuations, and the confidence of observing a true effect prevails. (B) If noise levels increase, the uncertainty about the measured fluctuation patterns (red shading) becomes too high to reliably detect an activation pattern correlated with brain activation.
The coefficient vector of the model, $\beta$, is then estimated using the Moore-Penrose pseudo-inverse of $X$,

$$\hat{\beta} = X^+ \cdot y = (X^T X)^{-1} X^T \cdot y \quad (2.5)$$

which is the least-squares solution to the GLM in eq. (2.4). This solution is optimal under the assumption that the noise floor $\varepsilon$ is sampled from a zero-mean Gaussian distribution. In fact, in the formulation of eq. (2.5), omitting the noise covariance matrix, noise samples have to be independent and of the same variance $\sigma_\varepsilon^2$ as well. This is typically ensured by pre-whitening the data and design matrix (Kiebel and Holmes, 2007).

The model estimates $\hat{\beta}$ only give a characterization of the signal of interest in the measured time series, irrespective of the noise present. They provide a relative quantification of how much the measured data (Figure 2.1 A, blue dots) resembles the time courses of each of the putative metabolic effects (represented by the $x_m$, Figure 2.1 A, red curve). The linearity in the model alludes to the assumption that different effects in the model do not interact, but superimpose to the local time course observed in fMRI (Poline and Brett, 2012).

However, the signal content in the data can be obscured in the presence of a dominating noise floor (Figure 2.1 B). This can either increase the uncertainty about the effect being present (Figure 2.1 A, red shading) or make it impossible to detect the effect at all (Figure 2.1 B). Thus, it is necessary to relate signal and noise content in the time series, which is accomplished by different measures of BOLD sensitivity and statistical significance.
2.3 Statistical Measures of Noise and BOLD Sensitivity

In general, the sensitivity of a measurement is characterized by its signal-to-noise ratio (SNR), i.e. the ratio of the signal power $P_s$ divided by the noise power $P_N$ in the measured data:

$$SNR = \frac{P_s}{P_N} \quad (2.6)$$

Herein, signal refers to the signal of interest, in our case BOLD contrast changes, whereas noise refers to any other, unmodelled or unknown component of the signal that occurs concurrently to the signal. The term “power“ is used in the sense of signal theory, i.e. as spectral power, and provides a summary measure of the information content. For a time series vector, power is computed as the sum of squared sample amplitudes, and thus the square of the norm.

In particular, for mean-free or mean-corrected entities, such as the Gaussian noise floor described in section 2.2 or the BOLD fluctuations about the mean voxel intensity, power is equivalent to the variance of the time-course considered, and thus, equation (2.6) can be written as

$$SNR = \frac{\sigma_S^2}{\sigma_N^2} \quad (2.7)$$

with the corresponding variances of the signal, $\sigma_S^2$, and noise, $\sigma_N^2$. Instead of power formulations, definitions referring to the amplitude ratios of signal and noise exist as well (Welvaert and Rosseel, 2013). This amplitude SNR, denoted by $SNR_A$ here to avoid confusion, is computed as the square root of equation (2.7):
What will be emphasized in the following is the strong link between statistical inference in fMRI and this conceptualization of SNR. Precisely, the tests assessing the GLM results in fMRI can be interpreted as scrutinizing SNR under specific Gaussian assumptions on the noise term to categorize the observed SNR as meaningful (Poline and Brett, 2012).

Two test statistics are commonly employed in fMRI to determine the significance of a modelled effect in the data, and both can be viewed as SNR measures, as will be shown here. An effect is represented by a contrast, i.e. a linear combination of the estimated contributions of each individual model time series \( x_m \) (cf. eq. (2.4)). Thus, a contrast is given by the product \( c^T \beta = \sum_{m=1}^{M} c_m \cdot \beta_m \), where the contrast vector \( c = (c_1, \ldots, c_m)^T \) contains zeros for modeled effects of no interest, and non-zero values for the effects that should be averaged or differentially contrasted.

The first statistical measure, the t-test, computes the t-value of a contrast in a GLM estimated on a voxel time series as (Kiebel and Holmes, 2007)

\[
t = \frac{c^T \beta}{\sigma_{c^T \beta}} = \frac{c^T \beta}{\sqrt{\hat{\sigma}_\varepsilon^2 c^T (X^T X)^{-1} c}}
\]  

(2.9)

with the design matrix \( X \) and the noise variance estimate \( \hat{\sigma}_\varepsilon^2 \), determined via the residuals of the GLM, i.e.

\[
\hat{\sigma}_\varepsilon^2 = \frac{1}{N-1} \hat{\varepsilon}^T \hat{\varepsilon}, \quad \hat{\varepsilon} = y - X \cdot \hat{\beta}.
\]  

(2.10)

For the case of a single, mean-corrected model time series in the GLM, i.e. \( X = x = (x_1, \ldots, x_N)^T \) and, subsequently, only one estimated \( \beta \), the identity between t-value (eq. (2.9)) and amplitude SNR (2.8) becomes obvious, setting \( c = 1 \):
2.3 Statistical Measures of Noise and BOLD Sensitivity

where the last equality holds if \( \mathbf{x} \) is mean-corrected and the residual \( \hat{\mathbf{e}} \) indeed contains noise only.

The second statistical measure in fMRI, the F-test, relates to the power formulation of SFNR. This is immediately seen in the definition of the F-value via the extra-sum-of-squares principle (Kiebel and Holmes, 2007; Poline and Brett, 2012): The F-value with respect to a given contrast is computed by conceptually splitting the design matrix \( \mathbf{X} \), i.e. the full model, into two parts \( \mathbf{X} = [\mathbf{X}_0 \, \mathbf{X}_1] \), such that \( \mathbf{X}_1 \) contains all \( M_1 \) model time series occurring in the contrast \( (c_n \neq 0) \). \( \mathbf{X}_0 \), on the other hand, is the reduced model that does contains the \( M_0 \) time series of no interest for the contrast.

Then the residual sum of squares (RSS) is computed for both of these models, i.e.

\[
\begin{align*}
\text{RSS}_\mathbf{X} &= (\mathbf{y} - \mathbf{X} \cdot \mathbf{\beta})^T \cdot (\mathbf{y} - \mathbf{X} \cdot \mathbf{\beta}) \\
\text{RSS}_{\mathbf{X}_0} &= (\mathbf{y} - \mathbf{X}_0 \cdot \mathbf{\beta}_{\mathbf{X}_0})^T \cdot (\mathbf{y} - \mathbf{X}_0 \cdot \mathbf{\beta}_{\mathbf{X}_0})
\end{align*}
\]

Their difference \( \text{RSS}_{\mathbf{X}_0} - \text{RSS}_\mathbf{X} \) is the “extra” sum-of-squares explained by \( \mathbf{X}_1 \), i.e. the contrasted effects.

The F-value itself now computes the ratio of this extra sum of squares to the residual sum of squares of the full model, i.e. the relative amount of additionally explained variance through \( \mathbf{X}_1 \):

\[
F = \frac{M_1}{N - M} \cdot \frac{\text{RSS}_{\mathbf{X}_0} - \text{RSS}_\mathbf{X}}{\text{RSS}_\mathbf{X}} = \frac{(\sigma_S^2 + \sigma_N^2) - \sigma_N^2}{\sigma_S^2 + \frac{\sigma_N^2}{\sigma_N^2}} = \frac{\sigma_S^2}{\sigma_N^2}
\]

Herein, the factor \( M_1/(N - M) \) accounts for the different degrees of freedom in the full and reduced model. Assuming that the contrast
contains all aspects of the BOLD signal, i.e. the signal power $\sigma_s^2$, and that the residual after fitting the full model is noise-induced only, one can substitute $RSS_{x_0} = \sigma_s^2 + \sigma_N^2$ and $RSS_x = \sigma_N^2$ in equation to recover the definition of SNR for the BOLD response:

$$F = \frac{N - M}{M_1} \cdot \frac{(\sigma_s^2 + \sigma_N^2) - \sigma_N^2}{\sigma_N^2} = \frac{N - M}{M_1} \cdot \frac{\sigma_s^2}{\sigma_N^2}$$

Statistical inference then assesses the significance of the determined t- and F-values by computing their probability under the null hypothesis. In other words, the inference process addresses the question: “How likely is it to observe the measured t-/F-value (or a higher value) under the statistical assumption that the true contrast value $c^T \beta$ (or signal amplitude $\sigma_s$) is zero?” If the observed t-/F-value is highly unlikely under this null hypothesis (e.g. < 5 %), the null hypothesis is refuted in favor of the alternative hypothesis that there is a significant, non-vanishing contrast value (and effect). F- and t-statistics have to be employed to compute this probability, since the noise variances used in the computation of the t- and F-value are estimated from the residuals, i.e. sample variances that do not equal the true variance of the assumed Gaussian distribution.

All sensitivity measures discussed thus far have built on the assumption that one can indeed model the signal of interest and thereby isolate the remaining fluctuations as noise to compute SNR. However, especially in methodological development, the opposite situation frequently arises. While fluctuations within a time series can be measured easily, no model of the signal is available. This is the case, e.g., in resting-state fMRI experiments that lack a well-defined task modulation over time. Also, since no task elicits activation in all brain regions, a sensitivity measure in non-activated regions is lacking.
Then, to provide a heuristic proxy for SNR, all fluctuations are categorized as noise, with an estimated standard deviation $\sigma_y$. The session mean $\bar{y}$, i.e. a constant time series, is hence considered to be the signal, arriving at the signal-to-fluctuation noise ratio (SFNR):

$$SFNR = \frac{\bar{y}}{\sigma_y} = \frac{\bar{y}}{\sqrt{\frac{1}{N-1}\sum_{n=1}^{N}(y_n - \bar{y})^2}}$$

(2.15)

A similar concept is the coefficient of variation (CoV), which is the inverse of SFNR, and pronounces the relative fluctuation compared to the mean. For the comparison of different measurements, ratios of standard deviations are occasionally employed, which is equivalent to a ratio of SFNRs under equal-mean assumptions.

However, if task-based evaluation is possible, GLM-based SNR-assessment is always preferable to pure SFNR-measurements. The fundamental disadvantage of SFNR is its conflating targeted fluctuations, i.e. BOLD, with unwanted fluctuations, into one same category of “noise”. An increase in standard deviation or decrease in SFNR is thus rendered ambiguous, and can in principle result from both an – unwanted – noise increase, as well as a – desired – higher sensitivity to BOLD fluctuations.

### 2.4 MR Image Encoding and Acquisition

The key to a mechanistic understanding of the sensitivity limits in fMRI lies in its underlying fundamental measurement principles. By revisiting image formation in MRI, the entry points and pathways of noise into the image time series can be revealed and comprehensively addressed.
Following excitation, the phase $\varphi$ of the local magnetization of an object evolves in the presence of the magnetic field (flux) $B$:

$$\varphi(r, t) = \gamma \int_0^t B(r, t') \cdot dt,$$  \hspace{1cm} (2.16)

with $\gamma$ being the gyromagnetic ratio of the excited spin nucleus, typically protons.

A single receiver coil can then detect the radiofrequency signal $s$ from the magnetization volume $V$

$$s(t) = \int_V m(r)e^{i\varphi(r, t)} \cdot dr + \eta(t),$$  \hspace{1cm} (2.17)

where $m$ represents the object magnetization at time zero, directly after excitation, and $\eta$ is the thermal noise in the receive coil (Johnson, 1928; Nyquist, 1928).

The principle of Fourier encoding now states that via a rapid phase modulation in time and space, the coil signal can carry enough information of the Fourier transform of $m$ to recover its spatial distribution. Typically, the rapid phase modulation is achieved via spatially linear magnetic field gradients $G$, i.e.

$$B(r, t) = B_0 + \mathbf{r} \cdot \mathbf{G}(t)$$

$$= B_0 + xG_x(t) + yG_y(t) + zG_z(t)$$ \hspace{1cm} (2.18)

These gradients reach bandwidths of up to several tens of kHz (S. Johanna Vannesjo et al., 2013; Signe J. Vannesjo et al., 2013), and induce a phase evolution, following eq. (2.16):

$$\varphi(r, t) = \gamma \int_0^t B_0 + \mathbf{r} \cdot \mathbf{G}(t') \cdot dt'$$

$$= \omega_0 t + \mathbf{r} \cdot \mathbf{G}(t') \cdot dt',$$ \hspace{1cm} (2.19)
where $B_0$ is the main magnetic field and $\omega_0$ the corresponding resonance frequency, which is typically used for demodulating the coil signal, and thus omitted in $\varphi$.

The Fourier relation between $m$ and $s$ becomes immediate after introducing the k-space formalism, where $k$ is the time integral of the gradient:

$$
k(t) = \begin{pmatrix} k_x(t) \\ k_y(t) \\ k_z(t) \end{pmatrix} := \gamma \int_0^t \begin{pmatrix} G_x(t) \\ G_y(t) \\ G_z(t) \end{pmatrix} \, dt' \tag{2.20}
$$

Now, by combining eq. (2.19) and (2.20) the MR image encoding equation (2.17) for linear gradient fields translates into a simple Fourier transform $FT$:

$$
s(t) = \int_V m(r)e^{ir \cdot k(t)} \cdot dr + \eta(t) \quad \Rightarrow \quad s(k) = FT\left(m(r)\right) + \eta(k(t)) \tag{2.21}
$$

Thus, the MR acquisition scheme is typically depicted as a trajectory through k-space (Figure 2.2), that collects information about the k-space (Fourier-conjugate) representation of the object (Ljunggren, 1983; Twieg, 1983). For fMRI, these trajectories have to be fast to allow for the acquisition of an image time series with sufficient temporal resolution. The typical trajectories used in fMRI, i.e. echo-planar imaging (EPI) and spiral trajectories, cover 2D k-space in less than 50 ms, and after a single excitation of the corresponding slice. From a more general perspective on image encoding than the k-space formulation, the phase term in eq. (2.17) can be expanded into higher spatial orders (Wilm et al., 2011), typically employing spherical harmonic basis functions (Roméo and Hoult, 1984).
It is important to note that even with higher order phase modulations or coil sensitivity encoding (Pruessmann et al., 1999), the image encoding process remains linear in terms of the magnetization $m$, because it essentially entails an integration. As the coil signal is digitally sampled and magnetization is represented in images with finite resolution, i.e. number of pixels, the image encoding equation (2.17) can be discretized spatially and temporally (s. also Figure 2.3):

**Figure 2.2** The $k$-space formalism explaining MR image encoding. MRI does not sample the object magnetization (left) directly, but its representation in terms of spatial frequencies (right). Both representations are linked via Fourier transformation. The MR acquisition process using time varying linear gradient fields can be visualized as a trajectory traveling through $k$-space (brown). Depicted is an echo-planar imaging (EPI) trajectory.
\[ s = E \cdot m + \eta \]  

with

\[ s = (s_1, \ldots, s_{\kappa}, \ldots, s_{N_{\kappa}})^T \]  

the sampled coil signal at \( N_{\kappa} \) time points \( t_1, \ldots, t_\kappa, \ldots, t_{N_{\kappa}} \),

\[ m = (m_1, \ldots, m_{\rho}, \ldots, m_{N_{\rho}})^T \]  

the magnetization image at \( N_{\rho} \) pixel positions \( r_1, \ldots, r_\rho, \ldots, r_{N_{\rho}} \),

\[ E_{\kappa\rho} = \exp(i\varphi(r_\rho, t_\kappa)) \]  

the entries of the encoding matrix \( E \),

\[ \eta = (\eta_1, \ldots, \eta_{N_{\kappa}})^T \]  

the sampled noise in \( s \).

Remarkably, in this form, the forward model of MR image encoding is equivalent to the general linear model (GLM) estimating BOLD voxel time series (cf. section 2.2, eq. (2.4)) – or vice versa.

Consequently, the problem of image reconstruction, i.e. finding an estimate of the object magnetization \( \hat{m} \), is solved by the Moore-Penrose pseudo-inverse again (cf. section 2.2, eq.(2.5)):

\[ \hat{m} = E^+ s \]  

with

\[ E^+ = (E^H \Psi^{-1} E)^{-1} E^H \Psi^{-1}, \]  

Here, conventionally, the noise covariance matrix \( \Psi = \overline{\eta} \cdot \overline{\eta}^T \) is retained in the definition of the pseudo-inverse to allow for generalization to the multi-channel case, where thermal noise between different coils may be correlated and of different amplitude.
Though conceptually equivalent to the GLM in fMRI analysis, the problem size of image reconstruction is considerably larger. Even in a single-coil case, the “design” or encoding matrix $E$ for an image with $N_p = 128 \times 128 = 16,384$ pixels (corresponding to about 1.5 mm resolution in a brain image) would consist of $N_p^2 > 268$ million entries, if the image shall be uniquely recoverable, i.e. $N_\kappa \geq N_p$.

Thus, $\hat{m}$ is typically computed iteratively by approximating the action of $E^+ s$ (eq. (2.23)) without ever explicitly computing $E^+$. To this end, the conjugate-gradient optimization method is frequently employed (Pruessmann et al., 2001; Shewchuk, 1994). In the case of pure gradient (spatially linear phase) encoding this method can be efficiently implemented by combining gridding and fast-Fourier transform between k-space and image space to speed up matrix-vector multiplications (Pruessmann et al., 2001; Beatty et al., 2005; Jackson et al., 1991).

Independent of the concrete estimation procedure, it becomes clear that $\hat{m}$, i.e. the magnetization image, depends on each component entering the encoding equation (cf. eqs. (2.22) and (2.23)), i.e. (1) the encoding matrix $E$, (2) object magnetization $m$ and (3) thermal noise $\eta$ (Figure 2.3, top). Therefore, if the forward model of image encoding deviates from the true encoding situation, model inversion in the reconstruction will introduce image artifacts or compromise image SNR.

In fMRI, since image time series are reconstructed, each of these three components can fluctuate over scans. The encoding equation becomes itself time-dependent. Consequently, the time series of (1) encoding matrices $E_n$, (2) magnetization $m_n$ and (3) thermal noise $\eta_n$ open up three distinct entry points for fluctuations to enter the reconstructed image time series (Figure 2.3, bottom).
2.5 The Noise Landscape Limiting BOLD Sensitivity

The MR image encoding equation (2.22) sets the grounds on which fluctuations can shape the noise landscape of BOLD fMRI. If fluctuations in the three components of encoding, i.e. magnetic fields, object magnetization and thermal noise, exist, they will propagate into the measured coil signal and, ultimately, the

\[
s = E \cdot m + \eta
\]

\[
s_1 = E_1 \cdot m_1 + \eta_1
\]

\[
s_2 = E_2 \cdot m_2 + \eta_2
\]

\[
\vdots
\]

\[
s_N = E_N \cdot m_N + \eta_N
\]

**Figure 2.3** MR image encoding for a single image (top) and a time series of images (bottom). This scheme depicts how fluctuations in the coil signal can arise from fluctuation in all parts of the encoding process over the course of a time series. These fluctuations may eventually compromise the images as noise contributions.
estimated image time series. What remains, is to evaluate in what form and to what extent each of these fluctuations arise in fMRI. This will be accompanied by a short overview of the corresponding correction methods and the approach to correction pursued in this work.

All fluctuations of encoding fields, magnetization and thermal noise originate predominantly from two sources: The MR imaging system and the imaged object (or subject). Different mechanisms direct the noise stemming from the object and imaging system to the three aforementioned entry points of noise (Figure 2.4).

Firstly, for the encoding magnetic fields, any system instability of the main field, the encoding linear gradient fields, or higher order shim fields produces “encoding noise” (Figure 2.4 A). Prominent examples are heating behavior in high-duty cycle sequences. The object, on the other hand, contributes to encoding noise primarily in-vivo, via displacement of magnetized material due to subject movement or breathing that alters the spatial field distribution from image acquisition to image acquisition.

The second noise entry, magnetization fluctuations, can be induced by the MR system, e.g. due to unstable RF excitation (i.e. the flip angle or its spatial homogeneity). The object itself, however, is often a much stronger source of magnetization fluctuation (Figure 2.4 B). Beyond bulk motion, which changes the coordinates of the magnetized object, many body parts experience non-rigid deformation on a (sub-)mm scale. The brain in particular experiences displacement following the cardiac cycle, since the blood volume in its vessels increases during systole, pushing CSF downwards through the aqueduct to the 4\textsuperscript{th} ventricle and the subarachnoid space close to the brainstem and spinal canal (Brooks et al., 2008; Soellinger, 2008). This movement is reversed during diastole, leading to a backflow of CSF in the third and lateral ventricles and subarachnoid space. Even without visible tissue deformations, the composition of tissue content changes on a micro-scale, e.g. due to CSF or blood flow, or as mentioned
before, the deoxy/oxy-hemoglobin ratio, thus altering magnetic properties, such as relaxation times and spin density locally, i.e. on the order of an imaged voxel. Ultimately, the BOLD effect itself falls in the category of magnetization fluctuations, though it is the only targeted one in fMRI while the rest are considered nuisance mechanisms (Krüger and Glover, 2001).

The third mechanism of noise injection refers to what has been “classically” considered as noise in MRI, namely the thermal noise in electric conductors (Figure 2.4 C). This form of noise was already described by Johnson and Nyquist in 1928 (Johnson, 1928; Nyquist, 1928). The term “thermal” arises, because this form of noise is proportional to the temperature in the conducting element. In MRI, thermal noise in the receiver coil channels stems, on the one hand, from the system itself, since the electrons in the receiver coils are subject to Brownian motion, and this movement creates a net random charge flux, i.e. current, in the coils, that is additive to the true signal. On the other hand, the measured object contributes to thermal noise via an inductive mechanism: The diffusive movement of ions dissolved in liquid compartments of the imaged object creates a net current, which, in the high static $B_0$ field of the MR system, following Faraday’s law, induces a detectable magnetic flux change in the receive coil, invoking an additional current. This noise has a Gaussian distribution and is white, i.e. exhibits constant power at all frequencies. It should be mentioned, however, that also non-thermal noise sources exist in the receive chain, e.g. due to variables gains or amplifier non-linearities, or discretization noise.

This list raises no claim to completeness, but illustrates the manifold of fluctuation mechanisms for fMRI that are channeled into the three entry points of encoding fields, magnetization, and thermal noise. Each of these fluctuations will transform into unexplained variance of the image time series, and hence, if not accounted for, a loss in BOLD sensitivity. Therefore, a lot of correction methods have been devised to prevent these
fluctuations arising or entering the noise floor of the fMRI time series.

First, however, with respect to field fluctuations, surprisingly few correction methods exist in the realm of fMRI. Presumably, this sparsity of corrections originates from the complexity of modeling field fluctuations and the unavailability of real-time measurement methods for magnetic fields. Field measurements during fMRI sessions have long been limited to navigators, i.e. short evaluations of the global field drift between scans of a session (Foerster et al., 2005; Pfeuffer et al., 2002). Frequently, corrections then either focused on dynamically updating the demodulation frequency of the coil signal, or were completely moved to the post-processing regime. For example, in typical EPI trajectories, a large portion of the field drift leads to voxel shifts in the phase encoding direction and can thus be dealt with through image realignment or high-pass filtering of the image time-series, as done in fMRI analysis packages ((Ashburner and Friston, 2007, p. 4; Kiebel and Holmes, 2007, p. 4). Furthermore, global field changes between scans can be estimated from phase images (Pfeuffer et al., 2002).

Second, with respect to magnetization fluctuations, nearly all correction efforts have focused on subject-induced magnetization fluctuations, which were coined “physiological noise” in this context (Krüger and Glover, 2001). The available correction methods can be broadly divided in two categories: Parametric techniques and data-driven approaches (Brooks et al., 2013). Parametric approaches try to model physiological fluctuations given peripheral measures of physiology, e.g. from cardiac monitoring via ECG or respiration monitoring via pneumatic breathing belts. The most widespread approaches focus on the periodicity, i.e. phase, of physiological fluctuations only, most prominently the retrospective image correction method, RETROICOR (Glover et al., 2000). In the meantime, these correction methods have been extended by more biophysical assumptions and incorporation of calibration data. For example, a respiratory response function was proposed (Birn et al., 2008) that
maps the peripheral breathing phase and amplitude measure onto fMRI time series fluctuations. An analogous approach was taken for the heart rate determining the cardiac response function (Chang et al., 2009). On the other end of the spectrum, purely data-driven approaches reside. In the simple form of temporal filters, they remove frequencies from the voxel time series that are implicated in physiology, e.g. 1 Hz for cardiac fluctuations and 0.2-0.3 Hz for respiratory noise (Brooks et al., 2013). However, since the sampling rate in BOLD fMRI is usually too slow to resolve these frequencies, aliases of the physiological frequencies will compromise the time-series. A more sophisticated data-driven approach is implemented by independent component analysis (ICA, (Beckmann and Smith, 2004). Here, the components are independent spatial maps of voxels that share a representative time course. By analyzing the spectra of these different time courses, one can select “noise components” manually and remove them from the data (implemented e.g. in MELODIC, part of the FMRIB software library (FSL)). ICA has been reported to be more robust towards temporal aliasing of the physiological frequencies than temporal filtering (Brooks et al., 2013, 2008), in particular in a recent combination with auto-classification of ICA components (Griffanti et al., 2014; Salimi-Khorshidi et al., 2014).

Third, thermal noise has been the target of many improvements, though not necessarily dedicated to fMRI, but MRI in general. On the hardware side, thermal noise in the receiver channels has been tackled directly by cryo-cools to reduce temperature in the conducting elements. Also, the relative influence of thermal noise compared to coil signal has been reduced by dedicated multi-channel head coils or even surface coils positioned closer to the sample. Also the trend towards MR systems with higher main magnetic field, $B_0$, is mostly motivated by this goal, since the available MR signal scales with external field strength. Furthermore, advancements in the MR acquisition strategy, i.e. the pulse sequence or trajectory design, usually follow the principle of thermal noise minimization. Specifically, higher acquisition efficiency is targeted, i.e. maximizing acquired signal per time,
such as in 3D EPI and multi-band acquisitions (Feinberg and Setsompop, 2013; Poser et al., 2010). On the post-processing side, statistical analysis in fMRI is typically preceded by spatial smoothing of the data (Carp, 2012), assuming that white thermal noise will average out and improve sensitivity for the BOLD signal of interest.

The above correction methods thus far have mostly been applied to one of the three entry points of noise in isolation. Therefore, little is known about their interaction nor unique contributions of encoding field fluctuations, magnetization fluctuations and thermal noise to the noise floor in fMRI and, hence, the relative efficacy of each of these corrections methods.

The remainder of this work will aim at closely examining these different noise entry points and quantifying their propagation into the image time series. The unique feature of this approach is to systematically consider the mechanisms of image generation in MRI. Consequently, within the next chapters, correction methods for fMRI will be developed that address each of the possible entry points for fluctuations. This means, we will take a mechanistic stance to correct noise in fMRI time series, and at the level of the encoding process where they occur (Figure 2.5), i.e. field fluctuations by measuring the encoding fields, magnetization fluctuations by modeling physiological noise per voxel, and thermal noise at the stage of an MR acquisition strategy. A vital factor to this end is the recurring use of concurrent magnetic field monitoring, which provides the comprehensive means to study and correct for encoding field fluctuations. Furthermore, field monitoring facilitates the robust implementation of system-demanding k-space trajectories developed in this work.

As a guideline, the following chapters can be categorized according to which noise entry point and correction mechanism they predominantly focus on (Figure 2.5).
2.5 The Noise Landscape Limiting BOLD Sensitivity

- Fluctuations in the encoding fields are measured, characterized and quantified in their influence on image noise in Chapters 6, 7 and 8. Specifically, the case of the most common 2D EPI acquisition for fMRI is considered on standard and high-field systems (7 T). Likewise, concurrent magnetic field monitoring is evaluated as a comprehensive correction method for field fluctuations, and is introduced beforehand in chapter 3.

- Magnetization fluctuations will be the topic of Chapter 8, especially in comparison to field fluctuations at high field (7 T). The physIO Toolbox employed to model and correct for physiological noise is introduced in Chapter 4.

- Thermal noise is addressed by matched-filter acquisition for BOLD fMRI in Chapter 5. The approach taken there combines acquisition strategy development with post-processing strategies. In order to achieve that, the mechanistic perspective on image encoding introduced in this chapter (section 2.4) is exploited.
FIGURE 2.4  Different mediating mechanisms for object- and MR-system-induced noise into (A) fluctuations of encoding magnetic fields, (B) magnetization fluctuations and (C) thermal noise compromising the receive chain.
The unifying theme of this thesis. Building on a mechanistic model of MR image encoding, different pathways of noise propagation in fMRI are identified, characterized and suitable correction methods proposed in the corresponding chapters.
3.1 NMR Field Probes

Concurrent Magnetic Field Monitoring using NMR field probes forms the basis of this work. It rests on the idea that a homogeneous excited NMR sample in itself constitutes a field sensor. If small enough, the phase of the magnetization within such a “field probe” can be summarized by one value, \( \phi_p(t) \). Thereby, the phase of the sample positioned at a point in space \( \mathbf{r}_p \) evolves as the time integral of the experienced external magnetic field \( B_z \)

\[
\phi_p(t) = \gamma_p \cdot \int_0^t B_z(\mathbf{r}_p, t') \cdot dt'
\]  

(3.1)

Historically, the idea to use this link between magnetization phase and magnetic field for measuring the field distribution itself has
been proposed early on, shortly after the discovery of nuclear magnetic resonance (Pound and Knight, 1950). However, the practical utility of this method critically depends on fulfilling the mentioned assumption to indeed detect phase from a point source. That means that (1) the sample has to be small compared to the spatial scale of the magnetic field changes. This requirement poses challenges for signal detection, because the NMR active volume has to be minute, i.e. on the order of the spatial resolution targeted by imaging. For example, to monitor the linear magnetic field gradient that accomplishes an image resolution of 0.4 mm, the probe extent in the gradient direction has to be at most 0.8 mm (Barmet et al., 2009). (2), with respect to measuring from a point source, the field also has to remain homogeneous in the presence of the material constituting the NMR probe. Any deviation from this homogeneity will lead to a phase dispersion within the sample and a faster apparent $T_2^*$ decay of the measured magnetization. Thus, the lifetime of the complex signal, from which the phase is extracted, will be greatly reduced. This effectively precludes from monitoring the relevant field dynamics of fMRI, since the encoding trajectories, e.g. EPIs or spirals, evolve over tens of milliseconds in fast single-shot readouts.

Only recently, these major challenges in probe design have been overcome by a combined effort targeting the physical, chemical and electronic properties of the field probe (Barmet et al., 2008; De Zanche et al., 2008). In particular, the probe head, that holds the NMR sample and the surrounding coil used for excitation and detection of the radio-frequency (RF) signal was optimized (Figure 3.1). One key aspect resolved with respect to (2) was to minimize phase dispersion by homogenizing the magnetic field within the sample by susceptibility-matching all components nearby (including the casing) to the same value. Furthermore, considering (1), i.e. signal detection, the available signal was maximized by choosing an NMR-active compound with high density of the targeted nucleus, and shortening the recovery time ($T_1'$) for re-excitation by an appropriate paramagnetic doping substance. Also, the sensitivity of RF signal detection was optimized by placing
copper wire windings right around the capillary holding the NMR sample, forming a maximally proximate solenoid coil. Additional care was taken in the design of the electronic processing of the RF signal, that consisted of the typical equipment of a dual-mode transmit and receive coil (tuning-matching-board, transmit/receive switches and pre-amplifiers for the receive-signal). In summary, this line of research and technological improvement has resulted in field probes with an effective NMR sample volume smaller than 1.5 mm$^3$, and the ability to measure field dynamics on a microsecond-scale for up to 100 ms, i.e. well above the typical resolution and duration of a 2D single-shot trajectory employed in fMRI.

One important additional requirement of field monitoring for fMRI is that it has to be performed simultaneously to the imaging process. On the one hand, this is required because in-vivo measurements suffer from irreproducible field modulations, e.g. through breathing. On the other hand, the long high-duty cycle measurements in fMRI induce magnet drifts due to heating that depend on the initial thermal state of the MR system. However, if performed concurrently, the two NMR experiments in the field probe and the imaged object can interfere with each other, if the same magnetic resonance frequencies are prevalent in the object and probe sample. Specifically, the power of the excitation pulse for the imaged object is several orders of magnitude higher than the power needed to excite the probe, and, if picked up by the field probe, will damage the sensitive electronics of the monitoring receive chain. Furthermore, the spin state of the NMR sample in the probe will be altered by this additional pulse, destroying the necessary phase coherence for monitoring. Vice versa, the excited magnetization sites in the field probes close to the imaged object are visible high-intensity spots for the imaging coils and will fold into the reconstructed image, if they are placed outside the field-of-view of the imaging sequence.

The most generic solution to this coupling between probe and object NMR lies in a spectral separation of the signal received from
field monitoring and the imaging experiment. Since imaging is typically performed on the proton (\(^1\)H) NMR signal, the field probe sample must utilize a different NMR-active nucleus. In this work, we rely on Fluorene (\(^{19}\)F) NMR signal for field monitoring, since compounds with a relatively high density of this nucleus exist. The gyromagnetic ratio of \(^{19}\)F is about 6% smaller than for protons, which translates into a resonance frequency of 120.2 MHz at 3 Tesla, compared to 127.8 MHz for \(^1\)H. This separation by a few MHz allows for mutually filtering the other frequency bands in the corresponding transmit/receive channels and enables a complete separation of the field monitoring and the imaging experiment. Additionally, both resonance frequencies are close enough to be processed by the same high-frequency spectrometer.

**FIGURE 3.1** Schematic and photographic depiction of a Fluorene-19 (\(^{19}\)F) NMR field probe (Barmet et al., 2009; De Zanche et al., 2008).
3.2 Field Estimation from Probe Phase Measurements

Registering the phase of a single NMR field probe only allows for a magnetic field estimate at the position of the probe. To study the encoding fields of MR imaging, however, one requires spatially resolved field dynamics, i.e. measures from multiple field probes (Figure 3.2). Even then, a model of the spatial field distribution between the probe positions is required. This leads to the concept of dynamic phase coefficient retrieval, described in the following (Figure 3.3).

**Figure 3.2** Conceptual depiction of a concurrent field monitoring setup for head imaging (courtesy of Skope Magnetic Resonance Technologies LLC). Probes are distributed around the head coil to allow for spatially resolved dynamic field monitoring from multiple positions outside the imaged brain.

Consider the complex signal of an array of $N_p$ probes positioned in the external magnetic field $B_z(r, t)$. After demodulation with the global resonance frequency, the phase of these probe coil signals is extracted and unwrapped along the temporal dimension, yielding a
phase time-course $\phi_p(t)$ for each probe $p$ over the lifetime of the signal. Since each probe is susceptibility-matched individually, they each exhibit a homogeneous, but not identical magnetization in the main magnetic field, even in the absence of any spatial variation of $B_z$. Thus, after an excitation, the probe phase will evolve linearly, according to this probe-specific magnetization difference, and consequently, frequency offset $\omega_{\text{ref},p}$. To extract the relevant field dynamics, this offset is typically determined by an initial free-induction decay (FID) experiment with constant $B_z$, and removed from the probe phase.

$$\tilde{\phi}_p(t) = \phi_p(t) - \omega_{\text{ref},p} \cdot t \quad (3.2)$$

To generalize from the measured phase evolution of the single probes to the dynamics of the spatial field distributions, the probe phases are typically expressed in a general linear model of spherical harmonic basis functions (Roméo and Hoult, 1984):

$$\tilde{\phi}_p(t) \approx \sum_{l=1}^{N_l} k_l(t) \cdot b_l(r_p), \quad (3.3)$$

with $N_l$ being the number of basis functions and $r_p = (x_p, y_p, z_p)^T$ the probe positions. There are theoretical arguments why the choice of spherical harmonics to express magnetic fields is advantageous to, e.g., a polynomial expansion. Spherical harmonic basis functions are orthogonal solutions of the Laplace equation that has to be fulfilled for the magnetic field inside the scanner bore, and, thus, their linear combinations are also solutions. Therefore, complex magnetic field distributions can be built from combining spherical harmonic fields. This leads to the practical motivation to use spherical harmonic basis functions for the phase expansion: All field-generating components of the MR system, including the gradient and shim system, are designed to create field distributions that are approximately spherical harmonics within the imaging volume.
3.2 Field Estimation from Probe Phase Measurements

Retrieval of Phase Coefficients $k(t)$

Because of their rotational symmetry, fewer basis functions than for a polynomial expansion suffice to express a second or third order spatial phase/field distribution (Table 3.1). However, with the typically employed number of field probes, i.e. 16, still only spatially slowly varying fields (up to $3^{rd}$ order) can be estimated. This emphasizes a conceptual limitation for magnetic field monitoring. The spatially highly localized field changes within the imaged object, e.g. the brain, cannot be monitored with only a few probes. Referring to the encoding equation (2.22) in chapter 2, this means that field monitoring is only sensitive to the encoding dynamics of gradients, shims and far-field object effects, but not to the object-intrinsic magnetization.
To estimate the phase coefficients, equation (3.3) can be vectorized to yield the classical form of a general linear model.
3.2 Field Estimation from Probe Phase Measurements

\[ \tilde{\phi}(t) = P \cdot k(t), \]
with
\[ \tilde{\phi}(t) = \left( \tilde{\phi}_1(t), ..., \tilde{\phi}_p(t), ..., \tilde{\phi}_{N_p}(t) \right)^T, \tag{3.4} \]
\[ P, \text{ the probing matrix, with entries } P_{p,l} = b_l(r_p), \]
\[ k(t) = \left( k_0(t), k_1(t), ..., k_{N_l-1} \right)^T, \]

This model is inverted using the Moore-Penrose pseudo-inverse of the probing matrix again, i.e.

\[ k(t) = P^+ \cdot \tilde{\phi}(t) = P^+ \left( \phi(t) - t \cdot \omega_{ref} \right) \]

with
\[ \phi(t) = \left( \phi_1(t), ..., \phi_p(t), ..., \phi_{N_p}(t) \right)^T, \tag{3.5} \]
\[ \omega_{ref} = \left( \omega_{ref,1}, ..., \omega_{ref,p}, ..., \omega_{ref,N_p} \right)^T \]

The sensitivity (or precision) of the individual phase coefficients directly depends on the conditioning of \( P^+ \). Precisely, the noise amplification from probe phase to phase coefficient is given by the norm of the rows of \( P^+ \) (Barmet et al., 2008), i.e.

\[ \sigma_l^2 \propto \sum_{p=1}^{N_p} b_l(r_p)^2 \tag{3.6} \]

To optimize monitoring sensitivity for certain phase coefficients, probe positioning thus remains the only degree of freedom, given the set of spherical harmonic basis functions, and assuming equal signal-to-noise ratio in all probes. Due to the rotational symmetry of the spherical harmonics, placing the probes maximally distant on the surface of a sphere is typically the optimal solution. However, practical limitations to probe positioning are given by the coil geometry and patient comfort, since the probes have to be
positioned alongside the rest of the measurement setup, usually on or around the head coil for brain imaging.

### 3.3 Concurrent Monitoring Setups

In the work presented here, we relied on two different concurrent magnetic field-monitoring setups for the 3 Tesla and 7 Tesla acquisitions, respectively (Barmet et al., 2010; Vannesjo et al., 2012). The common properties of the instrumental probes set used in both setups were determined by our targeted application to study the field dynamics for fMRI. This implies (1) the need for concurrent monitoring to capture non-reproducible field dynamics in-vivo, i.e. $^{19}$F-based compounds as NMR samples, (2) the ability to monitor typical single-shot readouts like EPIs or spirals, i.e. the longevity of the single probe excitation with a $T_2^*$ of about 50 ms, (3) the requirement to measure field dynamics for multiple slices and volumes, i.e. fast re-excitability of the probes via doping of the NMR compound for $T_1$-shortening and (4) fitting the monitoring to the imaging setup employed in fMRI, i.e. in the vicinity of the imaging coils and head.

Specifically, the 3 T setup relied on (1) 12-16 probes utilizing Hexafluorobenzene (HFB) as NMR-active substance, (2) a susceptibility-matched ellipsoidal epoxy casing holding a glass capillary of 0.7 mm diameter for HFB, (3) doping with 5.5 mM Gd(fod) and (4) glueing the probes permanently inside the spacious 8-channel head coil of the Philips 3T Achieva System.

The 7 T setup, on the other hand, utilized (1) 7 HFB probes and 9 probes filled with perfluoropinacol (PFC) exhibiting a higher $^{19}$F density, (2) a susceptibility-matched ellipsoidal epoxy casing holding glass capillaries of 0.8 mm diameter, (3) doping with Fe(III)acac yielding a $T_2$ of about 60 ms and (4) non-permanent mounting of the probes between the 16-Channel receive head coil.
and the quadrature volume resonator for transmission, employed at the 7T Philips Achieva system.

The design of transmit and receive chain for the probe signal followed the same rationale in both the 3 and 7 Tesla setup: while transmission relied on external devices, reception built on the standard spectrometer of the MR system, assigning probe signal to channels that were not used for imaging. More precisely, for probe excitation at the respective $^{19}$F Larmor frequencies (120.2 MHz at 3 Tesla, and 280.3 MHz at 7 Tesla), RF signal generators (Rohde&Schwarz) and RF amplifiers (Bruker Biospin) were combined in both setups. For probe signal reception, the probe signal at 3 Tesla was pre-amplified and then directly entered the spectrometer. The separate processing of $^{19}$F probe and $^1$H head coil signal was exclusively based on a software implementation within the Philips pulse programming environment (Barmet et al., 2010). In contrast to that, the implementation in the 7 T setup realized concurrent reception by a hardware implementation. Specifically, the received probe signals entered an RF mixing stage (ZX05-10L+, Mini-Circuits, NY, USA) shifting their modulation frequency to the same intermediate frequency as for the $^1$H signal. Then, all channels were treated equally, as if received at the same proton resonance frequency.

Probe positioning for both setups was inspired by earlier simulation results (Barmet et al., 2010). These simulations assumed a practical importance weighting of the different phase coefficients, emphasizing global and gradient fields more strongly than higher order coefficients. For the 16 probes typically available in both setups, a positioning on three rings of a cylinder (containing 4, 6 and 5 probes each) plus one probe at the top of the head coil provided optimal conditioning for phase coefficient estimation, with respect to equation (3.6). The accomplished condition number was close to the theoretical optimum yielded by spherical positioning of the probes. In practice, the concrete coil geometries allowed only for approximate positioning according to the simulation results. The exact probe positions were determined at
the beginning of each imaging session as part of several calibration measurements. Therein, the field probes were excited without magnetic field gradients first (FID measurement), and then under three constant gradients along the \( x, y, z \)-direction of the scanner coordinate system. The FID measurement identified the individual probe reference frequencies (cf. equation (3.2)). From the frequency shift of these probe frequencies under a gradient, the respective probe coordinate could be computes via the Larmor-relations, e.g. \( \Delta \omega / \gamma_p = x \cdot G_x \) for the \( x \)-gradient \( G_x \).

Furthermore, these calibrations measurements also served to determine the coupling coefficients between the probe channels. This became necessary, because the probes were unshielded and their RF signal could penetrate into the probe circuitry and cables of other channels. Specifically, a linear mixture model was employed for decoupling. The complex-valued coupling coefficients were determined for the above calibration measurements by identifying the contributions of the probe-specific frequency content to the spectra of other channels.
Figure 3.4 The actual concurrent field monitoring setups employed in this work. (A) Single 19F probe complete with resonance circuit board (120.2 MHz) (B) Probe positioning inside the head coil (3 T setup) The probes are positioned on three circles of a cylinder and centrally at the very back of the receive coil, thus optimizing sensitivity for global and linear phase coefficients. (C) 3 T setup with probes attached to the receive-only 8-channel head coil. (D) High-field 7 T setup with probes mounted between receive (inner coil) and transmit head coil (outer coil).
4.1 Physiological Noise in fMRI Data

Physiological Noise is a major limitation for BOLD sensitivity. Originally, it was defined in contrast to thermal noise as any “signal-proportional” fluctuation (Krüger and Glover, 2001). In our framework, physiological noise refers to true magnetization changes in the brain, which stem from physiological, non-BOLD sources. Specifically two main generators of physiological noise have been identified besides subject bulk motion: the cardiac and the respiratory cycle (Figure 4.1).

For the cardiac cycle, the noise generating mechanism arises from the antagonistic flow dynamics during systole and diastole within a
heartbeat. During systole, the pulse pressure wave of the blood reaches the brain, leading to an increase in blood volume and expansion of the transporting arteries (Soellinger, 2008). Since total cranial volume is invariant due to the skull boundaries, this brain expansion has to be compensated by an outflow of cerebrospinal fluid (CSF) via the fourth ventricle into the spinal canal. Conversely, during diastole, blood volume is reduced, leading to a slight shrinkage of the brain and a back-flow of the CSF into the ventricles and subarachnoid space from the spinal canal. Thus, three effects on magnetization follow from the cardiac cycle: pulsatile flow of the CSF through ventricles and aqueduct, alterations in brain voxel composition due to local blood volume changes, and tissue displacement at brain/CSF and brain/vessel boundaries. The tissue displacement is maximal in inferior brain regions, e.g. amounting to about 1-2 mm shift in head-foot direction for the brainstem (Soellinger, 2008).

The respiratory cycle, as second physiological noise generator, injects image fluctuations via encoding field changes on the one hand, and changes in tissue oxygenation on the other hand (Windischberger et al., 2002). Changes in the encoding magnetic fields are typically of low spatial order in the brain, since they originate from distant magnetization changes through tissue displacement surrounding the lungs. Consequently, if uncorrected during image reconstruction, respiratory field fluctuations induce rather global effects in the image, such as shifts or scaling for EPI acquisitions. The changes in oxygenation level, on the other hand, lead to more local effects, since they alter the voxel composition and susceptibility distribution through the relative oxygen content in the tissue. Note that this oxygen fluctuation is independent of the energy consumption effects investigated by BOLD fMRI, varying purely with the phase of the respiratory cycle. Furthermore, cardiac and respiratory noise generators also interact by the respiratory-sinus arrhythmia. Lung expansion during inhalation leads to an increase in heart rate, while heart rate decreases during exhalation (Hirsch and Bishop, 1981).
In summary, physiological noise is a major source of signal variability in voxel time series that accounts for up to 50% of the observed fluctuations (Bianciardi et al., 2009; Hutton et al., 2011) and occurs distributed at many sites all over the brain, including OFC, brainstem, and cortex adjacent to ventricles and subarachnoid space. Consequently, suitable correction methods for physiological noise are recommended for both task-based and resting-state fMRI studies, increasing the sensitivity for effects of interest and lowering the risk of spurious physiological correlations in functional connectivity analyses, respectively (Birn, 2012; Birn et al., 2006; Harvey et al., 2008; Hutton et al., 2011).

**Figure 4.1** Mechanisms of physiological noise generation in the brain. *(Top)* Source of physiological noise. *(Center)* Specific localization or property where physiological noise manifests. *(Bottom)* Entry point of noise into the MR image encoding (cf. Chapter 2, Figure 2.5). The schematic depicts an image-based perspective where uncorrected field fluctuations lead to changes in the estimated, i.e. apparent magnetization.


The PhysIO Toolbox for Localized Physiological Noise Correction

4.2 Image-based Physiological Noise Correction

To identify and correct for physiological noise in image time series, exploratory techniques, such as independent component analysis (ICA (Beckmann and Smith, 2004; Perlberg et al., 2007), as well as voxel-wise noise modeling have been suggested (Glover et al., 2000). Both approaches focus on isolating the typical periodicity of the cardiac and breathing cycle (Figure 4.2).

ICA methods, since they do not employ concurrent measures of physiology, have to rely on prior assumptions about the structure of physiological noise. For example, spatial ICA (sICA, (Thomas et al., 2002) classifies components post-hoc as physiological noise, if their representative time series is dominated by the characteristic breathing and heart rate, i.e. 0.2-0.3 Hz and about 1 Hz, respectively. An alternative approach, termed CORSICA (CORrection of Structured noise using spatial Independent Component Analysis (Perlberg et al., 2007), instead utilizes the spatial characteristics of physiological noise to identify components. Specifically, the larger blood vessels (basilar artery, circle of Willis) are major sites of pulsatile displacement, while CSF reservoirs (ventricles, subarachnoid space) experience flow effects, and cortex/CSF boundaries are sensitive to global displacements.

Voxel-wise physiological noise modeling, on the other hand, relies on peripheral physiological time series, acquired from e.g. pneumatic breathing belts, electrocardiograms (ECG) or pulse oximetry units (attached to the finger/wrist). Different ways to utilize the information in this peripheral data have been proposed, most prevalently its frequency content via RETROICOR (RETROspective Image CORrection (Glover et al., 2000)). This approach is similar to sICA in that it focuses on the periodicity of the physiological noise as captured by the cardiac and respiratory phase (Figure 4.3). Herein, the cardiac phase at time $t$ is expressed
as the time passed since the last heartbeat relative to the duration of the current cycle, i.e.

\[
\varphi_{\text{card}}(t) = 2\pi \frac{t - t_1}{t_2 - t_1} \tag{4.1}
\]

with \(t_1\) being the time of the last heartbeat, and \(t_2\) the time of the next one (Figure 4.3 A).

The respiratory phase, \(\varphi_{\text{resp}}\), on the other hand, is computed using an equalized-histogram transfer function, accounting for the differing breathing amplitudes in each cycle:

\[
\varphi_{\text{resp}}(t) = \pm \pi \frac{\int_{R_{\text{min}}}^{R(t)} H(R) dR}{\int_{R_{\text{min}}}^{R_{\text{max}}} H(R) dR} \tag{4.2}
\]

Herein, \(R(t)\) is the amplitude of the respiratory signal and \(H\) is the histogram capturing the frequency of each breathing amplitude over the course of the time series (Figure 4.3 BC). The use of the histogram-equalization ensures maximum sensitivity of the phase for the most frequently occurring amplitudes. Furthermore, a full breathing cycle is attained only if inhalation and exhalation are both complete. The sign of \(\varphi_{\text{resp}}\) is determined by the temporal derivative of \(R\), i.e. positive for inhalation \((dR/dt > 0)\), and negative for exhalation \((dR/dt < 0)\).

In RETROICOR, the periodic physiological noise time series is then modelled as a Fourier expansion of both cardiac and respiratory phase.

\[
x_{\text{card,resp}}(t) = \sum_{m=1}^{N_m} A_m \cdot \cos(m\varphi_{\text{card,resp}}) + B_m \\
\quad \cdot \sin(m\varphi_{\text{card,resp}}), \tag{4.3}
\]
where $N_m$ is the order of the expansion, and $A_m, B_m$ are the Fourier coefficients that have to be estimated for each voxel time series individually. Considering higher harmonics ($N_m > 1$) of the estimated physiological frequencies is a consequence of the low sampling rate of fMRI, typically 0.3-0.5 Hz (TR 2-3 seconds). Thus, aliasing occurs such that the under-sampled breathing and cardiac signals (0.25 Hz and 1 Hz) fold back into the spectrum of the sampled time series at different frequencies. To account for interaction effects between respiratory and cardiac cycle, e.g. via the respiratory-sinus arrhythmia, extensions to RETROICOR incorporating multiplicative Fourier terms have been proposed (Brooks et al., 2008; Harvey et al., 2008).

$$x_{\text{card} \times \text{resp}}(t) = \sum_{m=1}^{N_m} A_m \cdot \cos(m\phi_{\text{card}}) \cdot \cos(m\phi_{\text{resp}}) + B_m \cdot \sin(m\phi_{\text{card}}) \cdot \cos(m\phi_{\text{resp}}) + C_m \cdot \cos(m\phi_{\text{card}}) \cdot \sin(m\phi_{\text{resp}}) + D_m \cdot \sin(m\phi_{\text{card}}) \cdot \sin(m\phi_{\text{resp}}).$$  \hspace{1cm} (4.4)

Beyond frequency content, other aspects of the physiological signal have been considered as independent noise sources, such as heart rate variability or respiratory volume per time (Birn et al., 2006; Chang et al., 2009). This follows the rationale that the arterial CO$_2$ level governs vasodilation and constriction, thus altering blood flow (Shmueli et al., 2007), and is in itself modulated by heart rate and respiratory volume. Modeling their impact on the image voxel time series follows an approach analogous to BOLD modeling in the GLM (Chapter 2.2). Instead of a hemodynamic response function, which translates hypothesized neural activation into BOLD changes, cardiac and respiratory response functions were proposed to map heart rate and respiratory volume per time onto physiological noise of the fMRI time series. Assuming a linear, time-invariant (LTI) system, the noise model time series can then be retrieved as a convolution between the respective response
function and the physiological input time series. The concrete form of these response functions was determined from experimental calibration data.

Specifically, for the respiratory response function $RRF(t)$, the LTI was probed by single impulses, i.e. observing the BOLD response to single deep breaths (Birn et al., 2006). As functional form for the $RRF$, the difference of two gamma variate functions was proposed, which are typically used to describe bolus experiment dynamics, and the fit to the experimental data yielded:

$$RRF(t) = 0.6t^{2.1}e^{-t^{1.6}} - 0.0023t^{3.54}e^{-t^{4.25}} \quad (4.5)$$

This function is convolved with the estimated respiratory volume per time (RVT), i.e. the local integral of breathing belt amplitude, to yield the physiological noise time series.

To determine the cardiac response function $CRF(t)$, a free-form Gaussian-process deconvolution of BOLD data was performed with respect to the estimated current heart rate (Chang et al., 2009). Post-hoc, the resulting $CRF$ was fitted to a combination of a gamma variate and Gaussian function, yielding

$$CRF(t) = 0.6t^{2.7}e^{-t^{1.6}} - \frac{1}{\sqrt{18\pi}}e^{-\frac{(t-12)^2}{4.5}} \quad (4.6)$$

As for the $RRF$, the resulting physiological noise time series can be retrieved by convolving the $CRF$ with the running estimate of the heart rate (typically via a sliding-window average over 6 seconds).

Finally, the overall impact of physiological noise on the voxel time series is then modelled as a linear superposition of all the above-mentioned different Fourier and/or convolution terms, i.e. assuming that there is no further interaction between the different aspects of physiology. For actual noise correction, the weighting parameters (e.g. $A_m, B_m$) of the different noise time series have to be fitted to the voxel time series and projected out of the data.
Conveniently, for the mass-univariate analysis approach prevalent in fMRI (Chapter 2.2), this amounts merely to an inclusion of these different noise mode time series into the design matrix of the GLM (Josephs et al., 1997). Thus, physiological noise time series, sampled at the volume acquisition times, become confound regressors, analogous to movement parameters or session means of the BOLD time series. Finally, this inclusion into the fMRI analysis enables to evaluate the significance of physiological noise removal via F-tests on the estimated weighting parameters (Chapter 2.3). Furthermore, since the F-test reports the extra-sum-of-squares explained by the physiological noise regressors, this also provides a quantitative measure of the efficacy of physiological noise removal.
4.2 Image-based Physiological Noise Correction

**Figure 4.2** Different image-based physiological noise correction methods. Individual methods are given in boxes with reference of first occurrence. White boxes indicate specific input data or priors of each method.
**Figure 4.3** Cardiac and Respiratory Phase Estimation in RETROICOR. (A) For the cardiac phase, the R-peaks of the ECG-wave are detected and the phase at slice acquisition time is estimated by the relative position within the current heartbeat duration. (B) For the respiratory phase, the amplitude of the breathing signal $R$ is transformed into a positive phase (inhalation) or negative phase (exhalation). The peak absolute phase of $\pi$ is only reached for maximum amplitude over the whole time-course. (C) The mapping from respiratory volume to respiratory phase is non-linear, realized by a histogram-equalized transfer function that allocates sensitivity for the most frequently occurring respiration amplitudes.
4.3 Implementation of Noise Correction in the PhysIO Toolbox

4.3.1 Overview

The physIO Toolbox was developed within this work to provide state-of-the-art model-based physiological noise correction for fMRI using peripheral measurements. The toolbox models voxel-wise physiological noise components via RETROICOR (Glover et al., 2000; Harvey et al., 2008) as well as cardiac and respiratory response functions (Birn et al., 2006; Chang et al., 2009). A particular focus of the implementation of this software was robustness and ease-of-use for large-scale studies. Hence, considerable effort went into standardizing and automatizing the processing stream for various kinds of MR systems and peripheral measurement devices. The physIO toolbox is aimed at both researchers and clinicians, and provides seamless integration with existing packages used in the neuroscientific community, in particular Statistical Parametric Mapping (SPM, www.fil.ion.ucl.ac.uk/spm/). Furthermore, it was implemented platform-independent in Matlab and as part of the software suite TAPAS (TNU Algorithms for Psychiatry-Advancing Science, http://www.translationalneuromodeling.org/tapas/) of the Translational Neuromodeling Unit (TNU), that offers long-term support and development. The software is open-source, published under the GP 3.0 license.

The workflow of the toolbox consists of five major modules that are explained in more detail in the following sections (Figure 4.4): (1) read-in of (vendor-specific) physiological log-files, (2) preprocessing of noisy peripheral physiological data, (3) physiological noise modeling using RETROICOR and cardiac/respiratory response functions, (4) physiological noise correction by providing confound regressors for the mass-univariate GLM analysis and (5) assessment of noise correction efficacy using automated F-contrast generation in SPM.
The overall workflow is executed by running the main function `tapas_physio_main_create_regressors`. This function takes one input argument, the `physIO-structure`, which holds all parameter and processing choices for the workflow. PhysIO is created by the constructor-function `tapas_physio_new`.

The generation and modification of the `physIO-structure`, as well as the execution of the toolbox functions, can be inspected for various example datasets in the `examples/`-folder provided with the toolbox. For example, the standard use case using ECG and a pneumatic breathing belt is illustrated in `examples/Philips/ECG3T/main_ECG3T.m`.

In the following, we will dissect the workflow of the physIO toolbox along by a commented step-wise walk-through of `tapas_physio_main_create_regressors`. 
4.3 Implementation of Noise Correction in the PhysIO Toolbox

**Figure 4.4** The Workflow of the PhysIO Toolbox. **(Left)** Modules of the PhysIO Toolbox. **(Center)** Typical graphical output in respective modules. **(Right)** Most relevant functions within module (function name prefixed with `tapas_physio_`).
4.3.2 Read-in of Physiological Log files

Currently, physiological log-files from Philips and General Electric (GE) MR systems are natively supported by the physIO Toolbox. For both vendors, measurements of electrocardiograms (ECG), pulse plethysmograph/oximetry units (PPU) and pneumatic respiration belts are accepted inputs. This first module of the physIO Toolbox reads in the physiological log files and synchronizes the scan timing to the physiological measurements.

To specify the input files for read-in, the physIO-structure has to be initialized first by a call of the constructor:

\[
\text{physIO} = \text{tapas\_physio\_new();}
\]

Then, the following parameters in the physIO.log\_files and physio.thresh sub-structures have to be set:

- `thresh.cardiac.modality`: ‘PPU’ or ‘ECG’
- `log_files.vendor`: ‘Philips’, ‘Siemens’ or ‘GE’
- `log_files.cardiac`: ‘SCANPHYSLOG*.log’ or ‘ECGData_epiRT*’
- `log_files.respiration`: ‘SCANPHYSLOG*.log’ or ‘RespData_epiRT*’
- `log_files.sampling_interval`: in seconds, e.g. 2e-3, 40e-3

Note that for Philips, both cardiac and respiratory information are saved in the same log file, SCANPHYSLOG <timestamp>.log, and the sampling interval of the physiological log file is fixed (2 ms, 500 Hz sampling rate).

In the main function of the toolbox, tapas\_physio\_main\_create\_regressors, this input information is used to generate the raw vectors of sampling time.
4.3 Implementation of Noise Correction in the PhysIO Toolbox

and physiological information (PPU or ECG time course, breathing belt amplitude signal) by calling

```matlab
[ons_secs.c, ons_secs.r, ons_secs.t, ons_secs.cpulse] = ...
    tapas_physio_read_physlogfiles(log_files,
    thresh.cardiac.modality);
```

where the output is saved in the `physIO.ons_secs` substructure (“onsets in seconds”).

- `ons_secs.c`: [nSamples, 1] vector of cardiac signal time course (ECG/PPU)
- `ons_secs.r`: [nSamples, 1] vector of respiratory amplitude signal
- `ons_secs.t`: [nSamples, 1] Vector of sampling times (in seconds)
- `ons_secs.cpulse`: [nBeats, 1] vector of heartbeat onsets (in seconds) – if provided by the log file

For other vendors, the physIO toolbox can be used as well, if `physIO.ons_secs` is created manually with the aforementioned fields. The `tapas_physio_main_create_regressors` function has to be slightly adapted then by replacing the `tapas_physio_read_logfiles` with a custom-made read-in function.

The second important functionality of this module is the synchronization of the physiological data with the scan timing, which is crucial for the correction of the fMRI voxel time series later on. The nominal scan timing is defined in the `physIO.sqpar-substructure` (“sequence parameters”), holding the following parameters:
The PhysIO Toolbox for Localized Physiological Noise Correction

sqpar.Nslices  number of slice per volume
sqpar.NslicesPerBeat  default: Nslices; for triggered sequences: number of slices per heartbeat
sqpar.TR  repetition time (seconds)
sqpar.Ndummies  number of dummy volumes before first scan
sqpar.Nscans  number of scans (volumes) in session
sqpar.Nprep  number of preparation scans; leave [] or set to integer value
sqpar.TimeSliceToSlice  time between acquisition of subsequent slices; if [], TR/Nslices is assumed, enter a duration for non-equidistant slice spacing
sqpar.onset_slice  default: Nslices/2; reference slice for timing within a volume

From these inputs, the physIO toolbox generates the nominal scan timing of each slice and volume acquisition (LOCS, VOLLOCS given in sample indices) during the run via the function

[VOLLOCS, LOCS] = tapas_physio_create_nominal_scan_timing(ons_secs.t, sqpar);

with

VOLLOCS  [nPrep+nDummies+nScans,1] vector of volume scan onsets (in sample indices of
If `sqpar.Nprep` is empty `[]`, the toolbox assumes that the physiological log files end exactly when the last slice of the last volume of the fMRI run has been acquired and counts slices and volumes from the end of the files. Conversely, if `Nprep` has an integer value $\geq 0$, the toolbox ignores the start of the log file up to time $(Nprep+Ndummies) \times TR$, and then creates slice and scans timestamps in a forward direction.

For Philips SCANPHYSLOG-files, given appropriate software keys, a more accurate way to determine the exact scan timing relative to the physiological time courses is available. Specifically, the gradient time course during the scan is also logged in the SCANPHYSLOG-file. The PhysIO toolbox provides functions to extract the onset of every slice and volume acquisition that is accurate up to 10 ms, i.e. on the order of one slice. To activate this functionality, the `physio.thresh.scan_timing` substructure, that is empty per default, has to be defined with the following fields:

- `scan_timing.grad_direction` ‘x’, ‘y’ or ‘z’; specifies which physical gradient time course shall be used
- `scan_timing.zero` e.g. 1500; amplitudes below this value are not considered for slice detection
- `scan_timing.slice` e.g. 1700; minimum peak height of a slice-encoding gradient (arbitrary units)
- `vol` e.g. 1800; minimum peak height of a preparation gradient at the start of a volume
vol_spacing e.g. 20e-3 (in seconds); instead of the vol amplitude threshold, vol_spacing can be specified as the time gap between the last slice and first slice of the next volume

Then, the slice and volume acquisition time-stamps are retrieved by the following call:

\[
\text{[VOLLOCS, LOCS]} = \\
\text{tapas_physio_create_scan_timing_from_gradients_philips( log_files,} \\
\text{thresh.scan_timing, sqpar, verbose);}
\]

The values of the thresholds have to be determined for each fMRI sequence individually (but can be kept between different subjects and sessions). By setting verbose \( \geq 2 \), the physIO toolbox provides informative plots about the gradient time course and the current thresholds, thus enabling their effective adjustment to the sequence, in order to detect all slice/volume acquisitions.

Finally, for the workflow realized in \text{tapas Physio Main Create Regressors}, the complete scan timing is converted into seconds and inserted into \text{physIO.ons_secs} via

\[
\text{[ons_secs.svolpulse, ons_secs.spulse,} \\
\text{ons_secs.spulse_per_vol, verbose] = } \\
\text{tapas_physio_get_onsets_from_locs(} \\
\text{ons_secs.t, VOLLOCS, LOCS, sqpar, verbose);}
\]
4.3 Implementation of Noise Correction in the PhysIO Toolbox

4.3.3 Pre-Processing of Peripheral Physiological Data

After read-in of the raw physiological data, both the respiratory and cardiac signal time courses have to be pre-processed to improve SNR for subsequent noise modeling.

Typically, the respiratory amplitude signal recovered from pneumatic breathing belts is rather robust, if the belt was properly attached to the subject. Hence, simple band-pass filtering and outlier removal suffice for respiratory pre-processing. In the physIO toolbox, a 2nd order Butterworth bandpass filter (0.1-5 Hz) is implemented that accounts for long-term drifts (e.g. through loosening of the belt) and high-frequency noise (micro-movement, digitization noise). Furthermore, extreme apparent breathing amplitudes, e.g. through subject movement, exceeding more than 3 amplitude standard deviations are removed as outliers. Both, filtering and outlier removal are performed via a call to

```matlab
ons_secs.fr =
    tapas_physio_filter_respiratory(ons_secs.r, log_files.sampling_interval);
```

where `physIO.ons_secs.fr` holds the filtered respiratory signal.

The cardiac signal, on the other hand, requires more pre-processing for both ECG and PPU data, since the amplitude signal of these devices has to be transformed into the phase information of the cardiac cycle. Specifically, cardiac pulses, i.e. the R-wave peaks of the ECG signal or maxima of the pressure wave of the PPU have to be detected. However, especially at high field or with badly attached electrodes, the ECG signal acquired in the MR environment is typically very noisy due to magneto-hydrodynamic effects. Similarly, hand movement affects pulse oximetry units attached to the finger. Thus, the default prospective R-wave or plethysmograph peak detection of the MR system, which is used for cardiac triggering, frequently fails in this situation, and cardiac pulse time stamps in the log-files are incomplete.
To enable reliable cardiac pulse detection, the physIO toolbox pursues a two-step procedure for retrospective detection of the cardiac pulse onsets. The options for this pulse detection are set in `physio.thresh.cardiac`. In the first pass, pulses can be either loaded from the prospective algorithm logged by the MR-system or re-estimated via autocorrelation with a representative time-course during a single heartbeat. For ECG-data at and below 3 Tesla, the prospective detection by the system is usually sufficient, and data can be adopted from the Philips SCANPHYSLOG-file by setting:

\[
\begin{align*}
\text{thresh.cardiac.modality} & : \text{'ECG'} \\
\text{thresh.cardiac.initial_cpulse_select.method} & : \text{'load_from_logfile'}. \\
\end{align*}
\]

However, at high field (7 Tesla and above), it is recommended to determine the R-peaks of the ECG by auto-correlating it with a single representative QRS-wave for the subject. This is accomplished by setting:

\[
\begin{align*}
\text{thresh.cardiac.modality} & : \text{'ECG'} \\
\text{thresh.cardiac.initial_cpulse_select.method} & : \text{'auto'} \\
\text{thresh.cardiac.initial_cpulse_select.file} & : \text{<filenameECGWave>} \\
\end{align*}
\]

which selects an algorithm by Steffen Bollmann (Children's Hospital Zurich) that automatically determines this representative QRS-wave in an iterative, self-calibrating way. This method has been optimized for very noisy peripheral pulse oximetry data in a patient population (children with ADHD). Alternatively, a manual selection of the representative QRS-wave is possible (setting `cpulse_select.method = 'manual'`). The first-pass peak detection itself is then performed via a call to:

\[
\begin{align*}
\text{[ons_secs.cpulse, verbose]} & = \\
\text{tapas_physio_get_cardiac_pulses}(
\end{align*}
\]
4.3 Implementation of Noise Correction in the PhysIO Toolbox

```matlab
ons_secs.t, ons_secs.c,
thresh.cardiac.initial_cpulse_select,
thresh.cardiac.modality, [], verbose);
```

The determined QRS-wave is stored in `<filenameECGWave>`, and repeated runs (e.g. for other sessions) of the cardiac pulse detection can afterwards be performed by setting

```matlab
thresh.cardiac.modality 'ECG'
thresh.cardiac.initial_cpulse_select.method 'load'
thresh.cardiac.initial_cpulse_select.file '<filenameECGWave>'
```

The second pass for peak determination is an optional manual R-wave/pulse oximetry peak selection implemented by Jakob Heinzle (Translational Neuromodeling Unit, University of Zurich and ETH Zurich). Herein, a graphical user interface is presented in Matlab that shows the cardiac time course with the detected pulses and asks for manual addition and removal of pulses via mouse clicks. This functionality is activated by setting

```matlab
thresh.cardiac.posthoc_cpulse_select.method 'manual'
thresh.cardiac.posthoc_cpulse_select.file '<filenameManualPulses>'
```

before calling

```matlab
[onssecs, outliersHigh, outliersLow] =
tapas_physio_correct_cardiac_pulses_manually(ons_secs, thresh.cardiac.posthoc_cpulse_select);
```

The close-up region chosen for display and manual pulse selection/removal can be modified by adjusting the outlier detection parameters in `cardiac.posthoc_cpulse_select`:
The PhysIO Toolbox for Localized Physiological Noise Correction

As for the QRS-wave, the manually detected and removed pulses are stored in `<filenameManualPulses>` and can be loaded by setting `posthoc_cpulse_select.method='load'`. If no post-hoc manual pulse selection is desired, set `cardiac.posthoc_cpulse_select.method='off'`.

Finally, preprocessing of the physiological time courses, i.e. the filtered respiratory time course `ons_secs.fr` and the vector of cardiac pulse occurrences, `ons_secs.cpulse`, is concluded by cropping them to the time interval relevant for scanning, i.e. from the start of the first scan (after dummy scans) until the end of the last scan of the session:

```matlab
[ons_secs, sqpar] =
    tapas_physio_crop_scanphysevents_to_acq_window(ons_secs, sqpar);
```

The uncropped time series are preserved in a substructure `ons_secs.raw`.

### 4.3.4 Physiological Noise Modeling

Given the cropped physiological time series of filtered breathing belt amplitude and onset times of heartbeats, the modeling of the physiological noise time series can take place.
4.3 Implementation of Noise Correction in the PhysIO Toolbox

The physIO Toolbox offers to model Fourier expansions of cardiac and respiratory phase according to RETROICOR (Glover et al., 2000; Harvey et al., 2008), as well as noise modeling of heart rate variability (HRV) and respiratory volume per time (RVT) utilizing the cardiac and respiratory response function, respectively (Birn et al., 2008; Chang et al., 2009).

Modeling options for the physiological noise can be set in the physio.model-substructure:

- `model.type`: 'RETROICOR', 'HRV', 'RVT' or any combination of them, e.g. 'RETROICOR_HRV', 'RETROICOR_HRV_RVT', 'HRV_RVT'
- `model.order.c`: e.g. 3; order of cardiac phase Fourier expansion
- `model.order.r`: e.g. 4; order of respiratory phase Fourier expansion
- `model.order.cr`: e.g. 1; order of sum/difference of cardiac/respiratory phase expansion (phase interaction)

For both the cardiac and respiratory RETROICOR regressors, the regressor generation consists of three steps: (1) phase estimation, (2) downsampling to the acquisition time-points (at a reference slice of each scan volume defined by sqpar.onset_slice) and (3) generation of different noise time series via Fourier expansion. Finally, an interaction between cardiac and respiratory phases can be modelled via an expansion of their phase sum and differences (Brooks et al., 2008; Harvey et al., 2008).

These three steps are comprised in one function for cardiac, respiratory and interaction terms

```plaintext
[cardiac_sess, respire_sess, mult_sess, ons_secs] =
    tapas_physio_create_retroicor_regressors(
```
ons_secs, sqpar, model.order, verbose);

with the following output parameters:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>cardiac_sess</td>
<td>[nScans, 2*model.c] Fourier expansion (cosine/sine columns) of cardiac phase at reference slice for each scan</td>
</tr>
<tr>
<td>respire_sess</td>
<td>[nScans, 2*model.r] Fourier expansion of respiratory phase for each scan</td>
</tr>
<tr>
<td>mult_sess</td>
<td>[nScans, 4*model.cr] Fourier expansion of sum and difference of cardiac and respiratory phase for each scan</td>
</tr>
<tr>
<td>ons_secs.</td>
<td>[nScans, 1] cardiac phase sampled at reference slice for each scan</td>
</tr>
<tr>
<td>c_sample_phase</td>
<td>sampled at reference slice for each scan</td>
</tr>
<tr>
<td>ons_secs.</td>
<td>[nScans, 1] respiratory phase</td>
</tr>
<tr>
<td>c_sample_phase</td>
<td>sampled at reference slice for each scan</td>
</tr>
</tbody>
</table>

Within `tapas_physio_create_retroicor_regressors`, step (1), the phase estimations, are performed via

```plaintext
c_phase =
tapas_physio_get_cardiac_phase(ons_secs.cpulse, sqpar.spulse);
r_phase =
tapas_physio_get_respiratory_phase(ons_secs.fr, log_files.sampling_interval);
```

for cardiac and respiratory data, respectively. These functions implement equations (4.1) and (4.2) (cf. Figure 4.3), following the original RETROICOR publication (Glover et al., 2000). Step (2), the downsampling to one reference time-point per scan, is accomplished by two functions:
4.3 Implementation of Noise Correction in the PhysIO Toolbox

```matlab
sample_points =
    tapas_physio_get_sample_points(ons_secs, sqpar);
c_sample_phase =
    tapas_physio_downsample_phase(spulse, c_phase, sample_points, log_files.sampling_interval);
r_sample_phase =
    tapas_physio_downsample_phase(spulse, r_phase, sample_points, log_files.sampling_interval);
```

Finally, step (3), the Fourier expansion, is performed via `tapas_physio_get_fourier_expansion` for cardiac, respiratory and interaction regressors:

```matlab
cardiac_sess =
    tapas_physio_get_fourier_expansion(c_sample_phase,order.c);
respire_sess =
    tapas_physio_get_fourier_expansion(r_sample_phase,order.r);
crplus_sess =
    tapas_physio_get_fourier_expansion(c_sample_phase+r_sample_phase,order.cr);
crdiff_sess =
    tapas_physio_get_fourier_expansion(c_sample_phase-r_sample_phase,order.cr);
mult_sess = [crplus_sess crdiff_sess];
```

For the impulse-response function based noise models, the confound regressors are generated in three different steps by (1) estimation of the time series of the respective physiological signal component, i.e. heart rate and respiratory volume per time, (2) convolution with the corresponding response functions at a high temporal resolution (slice TR) and (3) extraction of the reference time-points within each scan volume.
These three steps are summarized in one function for each heart rate variability (HRV) and respiratory volume per time (RVT) regressors:

```matlab
[convHRV, ons_secs.hr, verbose] =
    tapas_physio_create_hrv_regressor(ons_secs,
                                    sqpar, verbose);
[convRVT, ons_secs.rvt, verbose] =
    tapas_physio_create_rvt_regressor(ons_secs,
                                       sqpar, verbose);
```

The relevant output parameters of these functions are:

- **convHRV**: \([nScans, 1]\) heart-rate variability regressor; convolved with cardiac response function
- **convRVT**: \([nScans, 1]\) respiratory volume per time regressor; convolved with respiratory response function
- **ons_secs.hr**: \([nScans, 1]\) estimated heart rate at reference slice during each scan
- **ons_secs.rvt**: \([nScans, 1]\) estimated respiratory volume per time at reference slice during each scan

**Within** `tapas_physio_create_hrv_regressor`, the heart rate is (1) computed from the cardiac pulse data for all slices by calling

```matlab
hr = tapas_physio_hr(ons_secs.cpulse,
                     sample_points);
```
This vector $hr$ is (2) convolved with the cardiac response function $\text{tapas\_physio\_crf}$ realizing equation (4.6) before (3) being reduced to the values at the reference slice.

Similarly, $\text{tapas\_physio\_create\_rvt\_regressor}$ computes (1) the respiratory volume per time for all slices via

$$\text{rvt} = \text{tapas\_physio\_rvt}(\text{ons\_secs.fr}, \text{ons\_secs.t}, \text{sample\_points});$$

and then (2) convolves the sampled $\text{rvt}$ with the respiratory response function $\text{tapas\_physio\_rrf}$, which implements equation (2.1). The resulting vector is (3) reduced to the final $\text{convRVT}$ by extracting the values at the reference slice time for all scans.

### 4.3.5 Physiological Noise Correction

The estimated noise time series are summarized as a design matrix of nuisance or confound regressors by the physIO Toolbox. Specifically, RETROICOR, HRV and RVT regressors are concatenated – if existing – as subsequent columns to yield

$$\text{physIO.model.R} = [\text{cardiac\_sess}, \text{resp\_sess}, \text{mult\_sess}, \text{convHRV}, \text{convRVT}];$$

This design matrix can be appended to the specified design matrix of a mass-univariate GLM employed in fMRI analysis.

Optionally, some of the physiological regressors can be orthogonalized to each other by specifying

$$\text{model.order.orthogonalise} \ 'none', 'cardiac', 'resp', 'mult', 'all'$$

We have found this to be beneficial for fMRI sessions acquired with cardiac triggering, since cardiac regressors tend to be nearly
constant there due to recurring cardiac phases for the same slice over scans (Kasper et al., 2009).

Furthermore, other confound regressors, e.g. motion parameters, can be appended to `model.R` by specifying the name of an ASCII-file with the same `[nScans, nRegressors]` matrix structure:

```
model.input_other_multiple e.g. ‘rp_fMRI_001.txt’_regressors
```

The final nuisance matrix will be saved to the file specified in
model.output_multiple_regressors filename, e.g. 'multiple_regressors.txt'

If the filename contains an extension other than .mat (e.g. .txt), the matrix is saved as ASCII-file, in which each column represents one physiological regressor, and the rows contain regressor entries for each scan in ascending order. For SPM in particular, the output file can also be specified as .mat-file, holding a variable R. In both cases, this output file can serve as “multiple regressors” entry for the first level GLM specification in SPM. Thus, the physIO Toolbox provides a direct interface of noise correction using the established GLM framework (Josephs et al., 1997). The voxel-wise estimation of the physiological noise component itself is performed by the fMRI analysis software of choice, e.g. SPM, independent of the physIO Toolbox.

**4.3.6 Assessment of Noise Correction Efficacy**

The efficacy of voxel-wise physiological noise correction can be assessed using F-contrasts, as mentioned in section 4.2. Therefore, the physIO Toolbox provides scripts to automatically create the relevant contrasts for physiological regressors in SPM and subsequently report the statistical maps of physiological noise distribution in a PostScript-file. Specifically, family-wise error corrected contrasts are displayed on a structural overlay, centered on the global maximum F-value, for each subject and all existing sets of physiological noise regressors, including movement parameters.

The script to run this automated assessment of noise efficacy is `tapas_physio_check_efficacy.m`. Herein, all paths at the beginning of the script (flagged by #MOD) have to be modified to match the actual study/subject/GLM/physIO-code folders. All relevant auxiliary functions to this script are also prepended with `tapas_physio_check_` and include SPM-jobs for contrast creation and results reporting, as well as functions to extract regressor names and columns from the SPM.mat-file itself.
A typical output page of the script can be found in Figure 4.5.

**FIGURE 4.5** Typical output page of PostScript-file created by `tapas_physio_check_efficacy-script` using SPM12b.
4.4 Applications of the PhysIO Toolbox

To date, the PhysIO Toolbox has been successfully used in a number of fMRI studies covering sensory-reward-learning paradigms (Iglesias et al., 2013), social learning experiments (Diaconescu et al., 2014b), real-time feedback fMRI (Sulzer et al., 2013) and high-field fMRI (Kasper et al., 2009). Furthermore, its complementary value for noise reduction in combination with magnetic field monitoring was demonstrated utilizing basic visuo-motor tasks and resting-state fMRI (Kasper et al., 2014b). In fact, for any kind of fMRI experiment, physiological noise correction is highly recommended. Benefits of model-based physiological noise correction have been reported for both task-based (Hutton et al., 2011) and resting-state fMRI (Birn, 2012; Birn et al., 2006).

In particular for the classical mass-univariate GLM analysis, as e.g. implemented in SPM, a three-fold improvement due to physiological noise correction is anticipated on the single-subject level. First and foremost, the reduction in unexplained variance, i.e. residual noise, directly enhances the sensitivity for relevant task effects in statistical parametric maps. Both t- and F-values contain an expression of residual noise in the denominator (cf. Chapter 2.3). Thus, t- and F-based statistics will improve through proper physiological noise correction, since unexplained variance decreases. Secondly, physiological noise modeling will reduce the risk of false positives and negatives for the contrasts of interest. Specifically, false positives are avoided, because task regressors that are partially correlated with physiology contain shared variance with physIO regressors and thus lower parameter estimates after noise correction. False negatives, on the other hand, are mitigated by reducing effects of partial anticorrelation between task and physiological regressors. Thirdly, physiological noise modeling removes the long-lasting autocorrelation in fMRI voxel time series due to the approximate periodicity of cardiac and respiratory fluctuations. Hence, the AR(1)-assumptions of the hyperparameter estimations are better fulfilled for the empirical Bayesian model.
inversion procedure of the GLM in SPM, presumably providing more accurate parameter and contrast estimates (Kiebel and Holmes, 2007).

In principle, all these improvements of first-level analyses through the physIO Toolbox propagate to the second-level, i.e. group effects, directly, if a full random-effects analysis is performed (Penny and Holmes, 2007). However, practically, the summary statistics approach is typically employed in second-level analysis (Holmes and Friston, 1998). Herein, only contrast estimates (i.e. numerators of t-contrasts) are taken to the second level to perform a t-test, assuming an equal noise distribution between subjects; Thus, the above-mentioned first improvement of first-level statistics through residual error reduction does not translate into improved second-level sensitivity. Instead, the more accurate parameter estimation for regressors correlated with physiology as well as AR(1) hyperparameters will improve second-level statistics by reducing inter-subject variability.

Beyond mass-univariate GLM analyses, physiological noise correction using the physIO toolbox can both impact on functional connectivity analysis of resting-state data (Beckmann and Smith, 2004; Biswal et al., 1995) and DCM-based effective connectivity measures (K. Friston, 2007). For functional connectivity analyses, it is essential to remove physiological noise, because it is often correlated over brain regions, and can thus be misinterpreted as the neuronally-induced BOLD coupling targeted in resting-state fMRI (Birn, 2012; Cole et al., 2010). For effective connectivity analyses, on the other hand, the modelled time series extracted from brain regions of interest can be adjusted for the physIO contrasts. Thereby, unexplained variance of the time series due to physiological fluctuations is reduced and the estimates of relevant connectivity parameters become more robust.

The aforementioned conceptual benefits of applying the physIO toolbox have been validated on empirical data, as well as the robustness of the employed noise modeling approach. To illustrate
the effect of physIO-based noise correction, we conclude with some examples from a recent cognitive neuroscience fMRI study focusing on social learning (Diaconescu et al., 2014b). In this experiment, participants had to make decisions based on the advice of another agent. Hence, they had to learn the advice reliability to perform optimally. In the study, the observable learning signals in the fMRI data were hypothesized to be hierarchical prediction errors that contrasted the predicted advice reliability with the actual advice validity on every single trial.

With regard to the robustness and reproducibility of the noise correction, we find the same spatial noise distribution patterns for physIO regressors in every subject (Figure 4.6 A). Fluctuations correlated to the cardiac cycle manifest around major vessels (basilar artery, anterior communicating arteries, internal carotid arteries, sagittal sinus) and in pulsatile CSF regions (especially surrounding the brainstem), but also more distributed in gray matter cortical areas. The breathing cycle, on the other hand, particularly induces fluctuations close to tissue and brain boundaries as well as inferior brainstem areas (pons). Interactions between cardiac and respiratory cycle generate additional noise foci in the aqueduct, temporal horn of the lateral ventricle, and the inferior part of the pons, close to the basilar artery.

These fluctuations, if unaccounted for, increase the voxel variance by up to 70 % (Figure 4.6 A). Consequently, on the single-subject level, we found that the application of the physIO-based noise correction lead to widespread variance reduction in the brain, significant after whole-brain multiple comparison correction in every subject (family-wise error rate p=0.05). The spatial extent of the clusters affected by physiological noise varied between subjects, but not the qualitative localization mentioned in the last paragraph (Figure 4.6 B).

Furthermore, we found that physiological noise correction does not only improve BOLD sensitivity for physiology-related tasks, but also in subtle cognitive paradigms, like learning from social
information and reward. We observed that, for the relevant learning-related contrasts, a higher sensitivity at the group level could be accomplished through physiological noise correction (Figure 4.7). Specifically, predictions of advice reliability could be localized in the bilateral fusiform-face area (FFA), the right posterior superior temporal sulcus (STS), anterior temporal-parietal junction (TPJ), and dorsomedial prefrontal cortex (dmPFC) in GLMs including physIO regressors. These areas have been implicated in social learning and learning from facial expressions in previous studies (Diaconescu et al., 2014b). In contrast to that, without physiological noise correction, only the left FFA was robustly recovered. Similarly, social prediction error signals could be captured in the bilateral superior occipital cortex (SOC) and right dmPFC after physiological noise correction, but only in the SOC without noise modeling. Interestingly, false positives were also reduced through the physIO-based noise correction for the prediction error contrast. Part of the substantia nigra (SN) that seemed to correlate with prediction error in the absence of physiological noise modeling, did not exhibit significant activation after applying the physIO correction. This emphasizes the need for a rigorous physiological noise correction, since a priori the SN is both a region connected to prediction error learning and a site of particularly high fluctuations.

In summary, the correction for physiological fluctuations in fMRI data is an essential component of fMRI analysis, regardless of the experimental paradigm (resting or task-based), research area (e.g. cognitive or sensory-motor processes) or analysis approach (GLM, functional/effective connectivity). Explicit physiological noise modeling, as offered by the physIO Toolbox, improves the robustness of statistical findings, enables the detection of subtle cognitive effects, and prevents from interpreting false positives arising from non-BOLD physiology.
**Figure 4.6** Robust Noise Reduction through physIO Regressors (A) Average additional noise variance explained by physIO regressors (relative to residual after correction) over subjects (N=35); F-value corrected for degrees of freedom (B) Subject count for significant physiological noise detected in each voxel (whole brain FWE-corrected p=0.05)
The PhysIO Toolbox for Localized Physiological Noise Correction

A. Advice Reliability Prediction

with PhysIO

without PhysIO

B. Social Prediction Error

with PhysIO

without PhysIO

C. Prevention of False Positives (Social PE)
**Figure 4.7** Improvement in Sensitivity through Physiological Noise Correction in a Cognitive Paradigm. (A) Group statistics for t-contrast modeling the prediction of advice reliability. Only by using PhysIO noise correction, bilateral FFA, TPJ and dmPFC can be identified as task-relevant regions. (B) Group statistics for t-contrast modeling the prediction error learning signal. Involvement of dmPFC is implicated only after physiological noise correction. (C) Prevention of false positives through physIO noise correction. The correlation of midbrain (substantia nigra) activity with prediction error can be explained away by shared variance with physiological fluctuations, preventing false conclusions of the involvement of the midbrain in this task.


5.1 Introduction

Spatial smoothing of imaging volumes is ubiquitous in fMRI (Carp, 2012; Poldrack et al., 2008). Its routine use before statistical analysis aims at improving the sensitivity and interpretability of blood-oxygen level dependent (BOLD) contrast in three ways, i.e., from the perspective of (1) signal processing, (2) statistical inference at the single-subject level and (3) group level inference (K. J. Friston, 2007).
Firstly, with respect to the signal processing perspective, smoothing the data with a filter that resembles the spatially extended hemodynamic response is considered optimal to detect activation of this particular shape and scale, according to the *matched filter theorem* (K. J. Worsley et al., 1996). Secondly, regarding single-subject inference, image smoothing facilitates the application of multiple comparison correction using random field theory (K J Worsley et al., 1996) since it ensures spatial smoothness of the residual error distribution. Thirdly, at the group level, spatial smoothing helps to absorb anatomical variability between subjects.

Image smoothing is commonly performed with a filtering operation in k-space that attenuates signal content at high spatial frequencies. In doing so it alters the effective point spread function (PSF) such as to broaden its main peak and suppress far-range contamination. However, importantly, variable k-space attenuation not only affects the PSF but also the propagation of noise from raw data into smoothed images. The noise content of the raw data undergoes the same k-space weighting such that the relative impact of noise increases towards the center of k-space. As a consequence, to maximize the SNR of the smoothed data, the raw data should be acquired with variable sensitivity by corresponding k-space weighting at the acquisition level. As will be detailed in the theory part, optimal net SNR is achieved by acquisition weighting that exactly matches the eventual smoothing filter. The underlying mathematics correspond closely to the matched-filter rationale (North, 1963) of the smoothing operation. It is important, however, to distinguish the different filter-matching rationales. Aiming to match the hemodynamic response by smoothing is common practice today and serves for the purposes summarized initially. The utility of also matching data acquisition is a consequence of the smoothing strategy and serves exclusively for SNR optimization given a chosen smoothing kernel.

Acquisition weighting has previously been used to improve the sensitivity of MR spectroscopic imaging and non-proton MRI, summarized under the theme of density-weighted phase encoding.
5.1 Introduction

(Adalsteinsson et al., 1999; Greiser and von Kienlin, 2003; Greiser et al., 2005; Stobbe and Beaulieu, 2008). In this work, we introduce matched-filter acquisition for fMRI with single-shot echo-planar readouts, which is challenging in that it cannot be accomplished merely by altered phase encoding but requires 2D trajectory design with complex modulation of k-space velocity. Such trajectories are particularly susceptible to common imperfections of gradient systems such as bandwidth limitations and eddy currents. To gauge and address this issue, we incorporate concurrent magnetic field monitoring (Barmet et al., 2010, 2009, 2008) with NMR probes (Barmet et al., 2010; De Zanche et al., 2008), which permits accounting for imperfections in magnetic field evolution at the image reconstruction stage.

The SNR benefit expected from filter matching relies on the incoherence of noise. In particular, the exact form of the matched-filter acquisition rule proposed here refers to the assumption of independent and identically distributed white noise. Thermal noise, which is prevalent in MR, exhibits this property (Johnson, 1928; Nyquist, 1928). For this noise regime, we show analytically that the distribution of acquisition time should indeed exhibit the same weighting in k-space as the target PSF, to achieve maximum SNR. However, BOLD fMRI is also subject to noise related to physiological processes with non-white statistics (Bianciardi et al., 2009; Krüger and Glover, 2001), including inherent neurophysiological fluctuations as well as respiration and cardiovascular dynamics (Birn et al., 2008; Chang et al., 2009; Dagli et al., 1999; Glover et al., 2000; Shmueli et al., 2007). Therefore, the experimental validation of matched-filter fMRI comprises signal-to-fluctuation-noise ratio (SFNR) measurements of phantom and in vivo time series, in which we vary the degree of signal-mediated fluctuations and evaluate their influence on the observed SFNR gain. Finally, we perform a proof-of-principle experiment showing the feasibility of matched-filter acquisition also for task-based fMRI. Using a visual paradigm in a preliminary group of four subjects, robust t-value increases are reported over standard EPI acquisition.
5.2 Theory and Methods

5.2.1 Theory: Matched-density acquisition for image post-processing filters

In the following section, we establish the relationship between variable acquisition speed in k-space, the point-spread function (PSF) and signal-to-noise-ratio (SNR) within an MR image. This is contrasted to shaping the PSF by retrospective smoothing only.

To estimate SNR, we consider the different propagation of signal and noise in both stages, focusing on the total thermal noise contribution similar to (Pipe and Duerk, 1995; Stobbe and Beaulieu, 2008), but treating all quantities in a continuous fashion, which then leads to a variational optimization of SNR.

Accrual of signal and noise in a given k-space region depends on how much acquisition time is spent in that region. If local acquisition time is distributed non-uniformly, it becomes dependent on the k-space position vector $k = (k_x, k_y, k_z)$. Hence, we denote the resulting distribution of acquisition time as acquisition density $d_{acq}(k)$. Upon gridding reconstruction, $d_{acq}$ becomes effectively smooth on the scale of the Nyquist sampling interval and represents the local density of trajectory segments and their velocity.

Signal accrues coherently over time and thus linearly with $d_{acq}(k)$. Thermal noise, on the other hand, accrues incoherently because it is uncorrelated due to being identically, independently normally distributed (Johnson, 1928; Nyquist, 1928). Hence, the variance of the thermal noise increases linearly with local acquisition density:

$$\sigma_{acq}^2(k) \propto d_{acq}(k)$$  \hspace{1cm} (5.1)
Let us now consider smoothing during post-processing which is performed to achieve a target PSF. As the combined action of smoothing and acquisition weighting in k-space should yield the target density, we obtain a defining equation for the smoothing filter:

$$d_{\text{smooth}}(\mathbf{k}) := \frac{d_{\text{target}}(\mathbf{k})}{d_{\text{acq}}(\mathbf{k})}$$  \hspace{1cm} (5.2)

with $d_{\text{target}}$ and $d_{\text{smooth}}$ being the Fourier transform of the PSF and smoothing kernel, respectively.

We now investigate the action of this post-processing filter on the acquired k-space data, which is already a superposition of signal and noise. The application of $d_{\text{smooth}}(\mathbf{k})$ is a mere re-weighting of these data. Thus, the signal scales linearly with this density as in the case of acquisition weighting. The noise amplitude, however, is now also proportionally scaled with this density, inducing a quadratic dependency of the noise variance on $d_{\text{smooth}}$ in the final, post-processed data,

$$\sigma_{\text{final}}^2(\mathbf{k}) = d_{\text{smooth}}^2(\mathbf{k}) \cdot \sigma_{\text{acq}}^2(\mathbf{k})$$
$$\propto d_{\text{smooth}}^2(\mathbf{k}) \cdot d_{\text{acq}}(\mathbf{k})$$
$$= \frac{d_{\text{target}}^2(\mathbf{k})}{d_{\text{acq}}(\mathbf{k})},$$  \hspace{1cm} (5.3)

where equality and proportionality arise from Eq. (5.2) and (2.1), respectively.

This equation illustrates that the acquisition density is an additional degree of freedom for an MR experiment with a given target PSF, because the target PSF can always be achieved retrospectively by smoothing with an appropriate image filter $K_{\text{smooth}}$. The choice of the acquisition density, on the other hand, then determines the noise landscape in k-space, $\sigma_{\text{final}}^2$ for the final, reconstructed image, as described in Eq. (5.3).
Given a specific target PSF, an immediate application of Eq. (5.3) is to find the acquisition density that maximizes SNR in the image. As long as Nyquist sampling is ensured, the signal level is independent of $d_{\text{acq}}$, because it is determined by the target PSF (which is the same for all acquisition densities). Thus, to maximize SNR, it suffices to minimize the noise variance in each image voxel. As we reconstruct an image from the acquired k-space data of an individual coil through Fourier transformation and the thermal noise accrued in k-space is uncorrelated, the noise landscape in the conjugate image space will be flat according to the Wiener-Khinchin theorem (Weisstein, 2006a), rendering all voxel noise variances in the image equal. Minimizing the noise variance per voxel is therefore equivalent to minimizing the total noise power in the image which, in turn, is equivalent to the noise power in k-space due to Parseval's theorem (Weisstein, 2006b).

Hence, maximizing the SNR per voxel amounts to a constrained minimization of the noise power in the covered k-space volume $V_k$ which we define as

$$|\sigma_{\text{final}}|^2 := \int_{V_k} \sigma_{\text{final}}^2(k) \, dk$$

(5.4)

The optimization constraint is given by a constant total acquisition time $T_{\text{acq}}$, such that the full optimization problem incorporating relation (5.4) reads

$$|\sigma_{\text{final}}|^2 = \int_{V_k} \frac{d_{\text{target}}(k)}{d_{\text{acq}}(k)} \, dk$$

$$\Rightarrow \min \text{ with } \int_{V_k} d_{\text{acq}}(k) \, dk = T_{\text{acq}}.$$ 

(5.5)

The solution to this optimization uses a Lagrange multiplier $\lambda$ and fulfills
\[
\frac{\partial \left( |\sigma_{\text{final}}|^2 \right)}{\partial \left( d_{\text{acq}}(k) \right)} = \lambda \frac{\partial \int d_{\text{acq}}(k) \, dk}{\partial \left( d_{\text{acq}}(k) \right)}
\]

\[
\Rightarrow - \frac{d_{\text{target}}^2(k)}{d_{\text{acq}}^2(k)} = \lambda \cdot \text{const.}
\]

\[
\Rightarrow d_{\text{acq}}(k) \propto d_{\text{target}}(k)
\]

Therefore, for optimal SNR, target density and acquisition density should be equal in k-space (up to a proportionality factor), in analogy to the \textit{matched filter} theorem (Figure 5.1 (North, 1963)). Specifically, in the common case where the target PSF is a Dirac function that maps the object onto image pixels identically, uniform sampling is optimal (Pipe and Duerk, 1995).

The SNR ratio between a matched acquisition and the standard uniform sampling can be expressed via the ratio of final noise variances, i.e.,

\[
\frac{\text{SNR}_{\text{final}}^{\text{matched}}}{\text{SNR}_{\text{final}}^{\text{uni}}} = \sqrt{\frac{|\sigma_{\text{uni}}|^2}{|\sigma_{\text{final}}|^2}}
\]  \ 

(5.7)

We now simplify the numerator and denominator of the right hand side term separately using Eq. (5.5). For the square of the numerator, the acquisition density fulfills \( \int_{V_k} d_{\text{acq}}(k) \, dk = T_{\text{acq}} \), while the uniform sampling density reads \( d_{\text{uni}}(k) = T_{\text{acq}} / V_k = \text{const.} \), yielding

\[
|\sigma_{\text{final}}|_2^2 = \int_{V_k} \frac{\frac{d_{\text{target}}^2(k)}{T_{\text{acq}}}}{\frac{T_{\text{acq}}}{V_k}} \, dk
\]

\[
= \frac{V_k}{T_{\text{acq}}} \int_{V_k} d_{\text{target}}^2(k) \, dk.
\]  \ 

(5.8)
We normalize the matched acquisition density to \(d_{\text{matched}}(k) = C^{-1} \cdot T_{\text{acq}} \cdot d_{\text{target}}(k)\) with \(C := \int_{V_k} d_{\text{target}}(k) \, dk\), and, hence, can rewrite the square of the denominator of Eq. (5.7):

\[
|\sigma_{\text{final}}^{\text{matched}}|^2 = \int_{V_k} \frac{d_{\text{target}}^2(k)}{C^{-1} \cdot T_{\text{acq}} \cdot d_{\text{target}}(k)} \, dk
\]

\[
= \frac{1}{C^{-1} \cdot T_{\text{acq}}} \int_{V_k} d_{\text{target}}(k) \, dk
\]

(5.9)

The SNR ratio between matched and uniform acquisition then evaluates to

\[
\frac{SNR_{\text{final}}^{\text{matched}}}{SNR_{\text{final}}^{\text{uni}}} = \sqrt{\frac{|\sigma_{\text{final}}^{\text{uni}}|^2}{|\sigma_{\text{final}}^{\text{matched}}|^2}}
\]

\[
= \frac{\sqrt{V_k}}{T_{\text{acq}}} \frac{\int_{V_k} d_{\text{target}}^2(k) \, dk}{C^2 \cdot \frac{C^2}{T_{\text{acq}}}}
\]

\[
= \sqrt{\frac{V_k}{C^2}} \cdot \int_{V_k} d_{\text{target}}^2(k) \, dk
\]

(5.10)

and is therefore proportional to the 2-norm of the target density.

For the fMRI application under consideration, the SNR gain can be explicitly calculated given the ratio between the nominal resolution before smoothing and the FWHM of the Gaussian target PSF, as derived formally in Appendix A. The result is an intrinsic SNR gain capturing the situation of ideal density-weighting, which, in practice, is limited by the fidelity of the gradient system. Typical choices of the Gaussian FWHM deliver an intrinsic SNR gain of 2D matched-filter compared to uniform acquisition between 6% and
200 % (s. Table 5.1) that depends approximately linearly on the FWHM of the Gaussian kernel.

Intuitively, this linear dependence of SNR gain on FWHM can be understood as follows: Acquisition time is spent inefficiently by uniform sampling in areas of k-space where the target density weighting is low, because noise is accumulated, but the signal information is hardly used. This area shrinks quadratically with the FWHM of the target k-space density and therefore increases quadratically with the FWHM of the target PSF. Thus, the additional standard deviation in the final image increases linearly with this FWHM of the target PSF due to uniform sampling.

<table>
<thead>
<tr>
<th>FWHM of target PSF in nominal pixels</th>
<th>1</th>
<th>1.5</th>
<th>2</th>
<th>2.5</th>
<th>3</th>
<th>3.5</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNR gain (2D)</td>
<td>6 %</td>
<td>23 %</td>
<td>53 %</td>
<td>88 %</td>
<td>126 %</td>
<td>163 %</td>
<td>201 %</td>
</tr>
<tr>
<td>Intrinsic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SNR gain (2D)</td>
<td>3 %</td>
<td>12 %</td>
<td>25 %</td>
<td>40 %</td>
<td>55 %</td>
<td>72 %</td>
<td>92 %</td>
</tr>
<tr>
<td>Reference Experiment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 5.1** Theoretical SNR gains expected for a matched-filter 2D acquisition of a Gaussian target PSF for different values of its full-width at half maximum (FWHM). The intrinsic SNR gain refers to a perfect realization of a Gaussian acquisition density, while the reference experiment values are calculated for the designed matched-filter EPI trajectory constrained by typical gradient amplitude and slew-rate system limits.
As a k-space trajectory is needed for MR image encoding, we now show how to transform the target acquisition density obtained in the last section into a continuous trajectory subject to gradient system limitations. Specifically, we design a single-shot Gaussian acquisition density $d_{acq}$ is equivalent to the Fourier transform of the target post-processing filter.

**Figure 5.1** The concept of matched-filter acquisition: After identifying the target post-processing filter $K_{smooth}$ of a statistical analysis, a corresponding k-space trajectory is designed for image acquisition. Following the matched filter theorem, this trajectory delivers SNR-optimal images, if its variable k-space acquisition density $d_{acq}$ is equivalent to the Fourier transform of the target post-processing filter.

**5.2.2 Theory: EPI-Trajectory Design for a Matched-filter Gaussian Density**

As a k-space trajectory is needed for MR image encoding, we now show how to transform the target acquisition density obtained in the last section into a continuous trajectory subject to gradient system limitations. Specifically, we design a single-shot Gaussian acquisition density 2D-EPI trajectory to enable a direct comparison
with the most prominent fMRI acquisition technique, i.e., a 2D EPI with uniform acquisition density.

In principle, the k-space acquisition density can be altered by two aspects of trajectory specification: Firstly, the shape of the trajectory can be modified by variable spacing of different trajectory segments, such as EPI traverses or spiral revolutions (Greiser and von Kienlin, 2003; Greiser et al., 2005; Kim et al., 2003; Spielman et al., 1995). Secondly, the velocity along the trajectory can be modulated, thus distributing acquisition time variably in k-space.

For EPI, modifying the trajectory shape could be readily implemented by only modulating the density of traverses. A variable time allocation would be accomplished, as more acquisition time is allocated to regions with relatively more traverses. On the downside, more traverses would accrue more traverse turns locally, such that too much acquisition time is deployed compared to the Nyquist sampling density needed. To minimize the number of such turns, the general objective of an effective trajectory design is to pay as few separate visits to the same k-space region as possible. Consequently, as reducing the number of turns would violate Nyquist sampling, it is best to perform density weighting for single-shot EPIs via velocity modulation exclusively.

The Gaussian kernel is separable, therefore the density weighting in \( k_x \) and \( k_y \) can be designed independently. First, we will determine the acquisition weighting within a single EPI traverse, i.e. along \( k_x \): Because gradient strength is proportional to k-space speed, it is inversely proportional to the time spent in this particular part of k-space and therefore to the acquisition density (cf. Eq. (2.1)). The ideal k-space (and gradient) evolution \( k(t) \) \( (G(t)) \) then solves the following differential equation (\( \gamma \) being the gyromagnetic ratio for protons):
\[ \text{d}_{\text{acq}}(k) \propto \frac{1}{|k|} = \frac{1}{\gamma \cdot |G(t)|} \quad (5.11) \]

If the acquisition density is Gaussian, a closed form solution exists for this equation, whose derivation can be found in Appendix B. With the nominal resolution \( \Delta x \) determining \( \kappa_{\text{max}} = \frac{\pi}{\Delta x} \) and the FWHM of the smoothing kernel defining \( \sigma_r = \text{FWHM} / \sqrt{8 \ln 2} \), one obtains:

\[
G(t) = C_1 \cdot \exp \left( \operatorname{erf}^{-1} \left( C_2 \cdot \left( 2 \cdot \frac{t}{T_{\text{traverse}}} - 1 \right) \right)^2 \right) \quad (5.12)
\]

With \( C_1 = \frac{\sqrt{2\pi} \cdot \operatorname{erf}(\frac{\sigma_r k_{\text{max}}}{\sqrt{2}})}{\gamma T_{\text{traverse}} \sigma_r} \), and \( C_2 = \operatorname{erf}\left(\frac{\sigma_r k_{\text{max}}}{\sqrt{2}}\right) \)

In practice, due to gradient amplitude and slew-rate limitations, this time-course cannot be realized at the traverse turns, which require the fastest possible gradient switching.

To achieve a Gaussian density weighting along the phase encoding direction, \( k_y \), we vary the acquisition time spent on different traverses, \( T_{\text{traverse}} \): While the gradient shape follows Eq. (5.12) for all traverses, the scaling factor \( C_1 \) of the gradient amplitude depends on the \( k_y \)-coordinate of the specific traverse, according to Eq. (5.6) and (5.12):

\[
C_1 \propto \frac{1}{T_{\text{traverse}}(k_y)} \propto \frac{1}{\text{d}_{\text{target}}(k_y)} \propto \exp \left( \frac{k_y^2 \sigma_r^2}{2} \right) \quad (5.13)
\]

For traverses where \( C_1 \) exceeds the maximum gradient amplitude, the Gaussian acquisition density is replaced by a baseline uniform density ensuring Nyquist sampling.

This method for designing a Gaussian density 2D EPI-trajectory may be applied to arbitrary fields of view, resolutions and readout acquisition times. Furthermore, parallel imaging acceleration in
phase encoding direction can be implemented simply by increasing the constant spacing between EPI traverses. The matched-filter considerations, including the expected SNR gain, equally apply to the parallel imaging case since parallel imaging reconstruction is highly local in k-space and the Gaussian acquisition density is smooth, i.e. approximately constant locally.

Due to the finite acquisition time and gradient system limitations, the matched-filter EPI trajectory implemented as such does not lead to a perfect Gaussian acquisition density. Strictly speaking, a standard EPI trajectory does not implement a uniform acquisition density either due to the traverse turns mentioned above which over-emphasize high spatial frequencies.

Therefore, the expected reference SNR gain must be calculated specifically for the matched-filter and uniform EPI trajectory implemented by inserting their actual acquisition densities into Eq. (5.5) and (5.7). For the imaging parameters and gradient specifications reported in the subsequent section, the reference SNR gain reaches approximately half of the intrinsic SNR gain referring to ideal density-weighting (Table 5.1), i.e. about 40 % for a typically chosen Gaussian FWHM of 2.5 voxels.

\footnote{According to a recent meta-study on 300 fMRI studies (Carp, 2012), 88 % of all studies reported using (presumably Gaussian) smoothing, and nearly more than half of them with a FWHM of 8 mm and larger, which corresponds to more than 2.5 pixels for voxel sizes of 3 mm and below.}
5.2.3 Image Acquisition, Concurrent Field Monitoring and Image Reconstruction

For all our experiments, data were acquired on a Philips 3T Achieva (Best, The Netherlands) system equipped with an 8-channel head coil (Philips, Best, The Netherlands) and gradient specifications of 31 mT/m maximum amplitude and 200 T/m/s maximum slew-rate. We compared a matched-filter EPI to a uniform EPI trajectory that shared the following acquisition parameters: TR 3 s (phantom data: 6.25 s), TE 35 ms, readout duration 41 ms, receiver bandwidth 375 kHz, FOV 227 mm, SENSE reduction factor 3, voxel size 1.8 x 1.8 x 3 mm$^3$, 5 slices with 3 mm between-slice gap. The target filter was a 2D Gaussian with a FWHM of 4.5 mm (or 2.5 voxels).

We deliberately designed the uniform EPI to have the same readout duration as the matched-filter EPI (41 ms), although the gradient specifications would have allowed for a faster uniform readout (29 ms), and hence, more volumes per time. This prolonged readout enabled a fair SFNR comparison to the matched-filter trajectory, because the increase in temporal SNR when decreasing slice $TR \approx TE + T_{acq}/2$ from 56 to 50 ms is outweighed by the SNR loss per image when decreasing image acquisition time from 41 to 29 ms.

Separate $B_0$ and coil receive sensitivity maps were acquired in each session ($TR$ 800 ms, $TE_1$ 1 ms, $\Delta TE = 2.3$ ms, spin-warped images with a resolution of 1 x 1 x 3 mm$^3$).

Our implementation of the matched-filter Gaussian EPI trajectory using variable gradient strengths is particularly susceptible to any kind of gradient imperfections. There are two reasons for this sensitivity: On the one hand, the gradient system is operated close to its limits to enable a large range of velocity modulation. On the other hand, the non-periodic gradient time-course precludes standard correction methods for gradient inaccuracies, such as EPI phase correction. Therefore, we utilized concurrent magnetic field monitoring as introduced by Barmet et al. (Barmet et al., 2011, 2010,
2009, 2008, p. 20) to (1) investigate the feasibility and accuracy of the demanding gradient evolutions of the proposed matched-filter EPIs on a clinical MR system, (2) study deviations in k-trajectories and k-space densities from the ideal matched-filter EPI and (3) enable image reconstructions informed by the actual, measured k-space trajectory. In the hetero-nuclear monitoring setup 16 transmit/receive $^{19}$F NMR field probes were attached to the head coil (Barmet et al., 2010; De Zanche et al., 2008; Wilm et al., 2011). The acquired probe phase evolutions were expanded into real-valued spherical harmonics (Barmet et al., 2008; Signe J. Vannesjo et al., 2013; Wilm et al., 2011), yielding phase coefficients for the global phase, $k_0(t)$, the linear k-space, $k_x(t)$, $k_y(t)$ and $k_z(t)$ and second order phase coefficients $k_{5-9}(t)$ over the entire readout.

All image reconstructions, for both matched-filter and uniform EPI, were performed using concurrent field monitoring data from the probe phase fits. Global ($k_0$) phase information was used for demodulation of the raw coil data of the 8-channel head coil. Afterwards, the images were reconstructed from the demodulated data in combination with 1st order k-space trajectory information ($k_x$, $k_y$, $k_z$) in an iterative, gridding-based, conjugate-gradient SENSE algorithm (Pruessmann et al., 2001; Beatty et al., 2005; Jackson et al., 1991), using an in-house Matlab implementation (The MathWorks, Natick, MA). This algorithm was augmented with multi-frequency interpolation (MFI) for static $B_0$-field correction (Man et al., 1997; Sutton et al., 2003). The application of this reconstruction algorithm ensured an SNR-optimal image reconstruction where the target PSF was achieved post-hoc via smoothing, which is equivalent to direct reconstruction with the target PSF (Pruessmann and Tsao, 2008). In particular, the objective function of the reconstruction required a Dirac target PSF, thus performing an implicit density correction for the variable acquisition density of the matched-filter trajectory. Consequently, both matched-filter and uniform EPI scans exhibited the same image resolution and smoothness before entering statistical pre-processing.
5.2.4 Experiment 1: Assessment of SFNR gain for EPI Time Series in Different Noise Regimes

The first experiment assessed the validity of the matched-filter acquisition argument for different noise regimes with different levels of signal fluctuations. Phantom data was acquired from a water-filled sphere. In vivo data was acquired from 4 healthy volunteers (1 male) after written informed consent and with approval of the local ethics committee. Subjects were asked to lie still in the scanner with their eyes closed (i.e., a “resting-state” condition).

For both uniform and matched-filter EPI, we acquired 9 sessions with different excitation flip angles (0, 5, 15, 25, 40, 50, 60, 75 and 90 degrees) to vary the signal content and therefore the contribution of signal-dependent noise. Each session contained 95 scans for the phantom data, and 48 scans for in-vivo sessions, plus 5 void scans to minimize saturation effects. Realignment and smoothing with the matched target kernel was performed on all images using SPM8 (http://www.fil.ion.ucl.ac.uk/spm/).

We considered SFNR ROI-wise by first determining the mean of the magnitude signal within the ROI for each image. Then, the SFNR was computed as the ratio of the temporal mean of this ROI-mean and its temporal standard deviation. The ROI in the phantom was a centered disc in each slice extending to 2/3 of the object diameter to avoid edge effects. For the in-vivo case, subject-specific grey matter, white matter and CSF regions – that suffer from different levels of physiological noise (Krüger and Glover, 2001; Triantafyllou et al., 2006) – were included as separate ROIs in the analysis. These regions were extracted using $B_1\text{ bias field correction}$ (Salvado et al., 2006) and a k-means clustering algorithm on the spin-warp $TE_1$ image.
5.2.5 Experiment 2: fMRI Paradigm and Analysis

In the second experiment, the benefits of matched-filter EPI acquisition were assessed in a visual fMRI paradigm using t-contrast values as a summary statistic of activation detection.

The fMRI paradigm was designed to stimulate the quarter-fields of the visual cortex: 16 seconds of flickering, color-changing wedges were interleaved with 5 seconds of fixation; 8 blocks of upper-left/lower-right (ULLR) and upper-right/lower-left (URLL) wedges were presented over 120 scans (TR 3 s). The visual presentation was performed using a projector (resolution 800x600) and a mirror mounted on the head coil. Subjects’ attention was maintained using a simple button response task to any contrast alteration of the fixation point.

The data was acquired in the same subjects and – apart from subject 4 – on the same measurement day as for experiment 1. Two sessions of each uniform EPI and matched-filter EPI acquisition were measured to compare within-modality variance to between-modality variance of the statistical results. The order of matched and uniform acquisitions was counterbalanced between subjects, and independently for the 1st and 2nd repetition of these sessions. The slice geometry was equivalent to experiment 1. Specifically, slice orientation was oblique transverse, parallel to the calcarine sulcus to cover visual cortex. Peripheral physiological measures characterizing cardiac pulsation and the respiratory cycle were recorded simultaneously with fMRI using an Electrocardiogram (ECG) and breathing belt, respectively.

Spatial preprocessing and statistical analysis of the fMRI data were performed in SPM8. Preprocessing included realignment and spatial smoothing with the target Gaussian PSF. The General Linear Model (GLM) for the statistical analysis included a canonical hemodynamic response function (HRF) and temporal/dispersion derivative regressors of the ULLR and URLL-blocks. Furthermore, we included 2 types of nuisance regressors into the GLM: movement parameters from realignment and
physiological noise modeling using RETROICOR (Glover et al., 2000). Our specific implementation of RETROICOR, the physIO Toolbox, ((Kasper et al., 2009); open source code available as part of the TAPAS software collection: http://www.translationalneuromodeling.org/tapas/) uses Fourier expansions of different order for the estimated phases of cardiac pulsation (3rd order), respiration (4th order) and cardio-respiratory interactions (1st order) following (Harvey et al., 2008).

The statistical results were assessed on t-maps contrasting ULLR-URLL (contrast 1) and URLL-ULLR (contrast 2). Both peak t-value and total cluster sizes were compared between matched and uniform acquisition sessions. All results were p=0.05 FWE-peak level corrected for the whole acquisition volume. Finally, for a more quantitative handle on BOLD sensitivity, we performed a total least squares regression (TLS, modified Matlab implementation, (Hall, 2011) of all corresponding brain voxels for the t-value change of one session compared to a reference session. TLS reports an average t-value change over all voxels, and thus a more robust summary measure than peak t-values or activation extent.
5.3 Results

5.3.1 Monitoring: Trajectories and k-Space Densities

For the implemented matched-filter EPI, the concurrently monitored encoding magnetic fields, phase coefficients and corresponding k-space densities are shown in Figures 5.2-5.4, respectively. We present the measured matched-filter readout for the representative 5th scan of the 1st fMRI session of subject 3, but the asserted statements hold for all observed readouts.

In general, the demanding non-trapezoidal readout gradient waveform is reproduced quite accurately by the gradient system, exhibiting only the common bandwidth limitation of the gradients, smoothing of switching events and small gradient delays (Figure 5.2, red curve, compared to black curve of nominal gradient evolution). Note that the amplitude of the measured phase encoding gradient blip is also greatly reduced due to this low-pass filter property of the gradient chain (Figure 5.2 B), but its area is preserved due to commensurate broadening of the blip (cf. the EPI traverse spacing in Figure 5.4 A).

Figure 5.3 shows the phase evolutions induced by this gradient waveform expanded in 0th to 2nd spatial order spherical harmonics: For the monitored global phase $k_0$, a roughly linear increase during the readout is evident that carries the distinct sinusoidal modulation of the EPI traverses (about 300 Hz). This modulation presumably stems from slight $B_0$ eddy currents induced by the readout gradient. Similarly, the reduced slope of the linear component of $k_0$ during the central part of the readout might result from the lower frequency of phase encoding gradients and their concomitant $B_0$ eddy currents for the inner, density-weighted traverses.

The linear phase coefficients (Figure 5.3, middle panel), i.e. the k-space representation of the trajectory, exhibit two main deviations
from the nominal matched-filter EPI, which are best visible in the classical 2D representation of the trajectory (Figure 5.4): Firstly, we found a compression of about 25 rad/m of the trajectory in frequency encoding direction, resulting in a slightly reduced actual image resolution, which has also been reported for uniform EPI trajectories (Signe J. Vannesjo et al., 2013). Secondly, the actual sampling points within the traverse did not coincide exactly with the nominal positions but deviated by up to one Nyquist sampling interval in frequency encoding direction (Figure 5.4 zoomed panels).

In turn, the distribution of these actual sampling points determines the realized acquisition density $d_{acq}$, whose resemblance to a Gaussian is crucial for the expected SNR gains derived in the theory section of this paper. Visually, the 2D sampling point distribution (Figure 5.4) indicates a density weighting with rotational symmetry which was assessed quantitatively using a gridding-based estimation of the acquisition density from the sampling points (Jackson et al., 1991). Indeed, the acquisition density is Gaussian (Figure 5.4 B), but, compared to the nominal density, exhibits a slight reduction (root mean square error, RMSE, 3 %) in k-space centre, i.e. for $|k| < 60 \% k_{max}$, and considerable overshoot (RMSE 20 %) at its periphery, i.e. the EPI turns (Figure 5.4 C).

In summary, even though the individual positions of the k-space samples vary between nominal and actual trajectory, the induced densities exhibit high similarity and render the matched filter prerequisites on the expected SNR gains valid.
FIGURE 5.2  Gradient design and concurrent field monitoring results of a 2D-Gaussian density-weighted “matched-filter” EPI. (A) Intra-traverse weighting via gradient Modulation in readout-direction (black = nominal; red = measured) (B) Inter-traverse weighting via variable traverse duration in phase-encoding direction.
5.3 Results

**Figure 5.3** Measured phase evolution during a Matched-filter EPI readout of 40 ms (TE 35 ms). Shown are the spherical harmonics coefficients $k$ of different spatial order retrieved by concurrent magnetic field monitoring. (A) $0^{th}$ order phase coefficient: A linear component (frequency offset) is modulated by the EPI traverse frequency as well as the density weighting close to the echo time. (B) $1^{st}$ order phase coefficients in readout ($k_x$, red line) and phase direction ($k_y$, green line). The nominal $k$-space evolution is plotted for comparison (black and black-dotted line): The only apparent difference is the reduced $k_{\text{max}}$ of the measured compared to the prescribed $k_x$. (C) $2^{nd}$ order phase coefficients: maximum phase in a spherical acquisition volume of 20 cm diameter. The concomitant field in $k_4 \propto 2z^2 - (x^2 + y^2)$ exhibits the strongest deviation to the spatial non-linearity of the phase evolution.
Matched-Filter Acquisition for BOLD fMRI

A

B

Measured K-space density

C

Difference to nominal density
5.3 Results

**Figure 5.4** Measured 2D sampling scheme and k-space acquisition densities of the matched-filter EPI trajectory. (A) 2D visualization of the measured (red) and nominal (black) trajectory. Dots indicate every 10th k-space sample. The general shape of the nominal and measured trajectory, including the more densely sampled k-space centre, coincide. However, the individual position of samples as well as the EPI turns differ between nominal and measured trajectory (zoomed insets). (B) k-Space acquisition density calculated from the measured 2D trajectory. The shape approximates a Gaussian distribution. (C) Difference between k-space acquisition density of measured and nominal k-space trajectory. While the realized density in k-space centre is slightly lower than prescribed (RMSE 3 %), the actual EPI turns provide an increased density in k-space periphery (RMSE 20 %).

5.3.2 Monitoring: Image reconstruction

Figure 5.5 shows the unsmoothed reconstructed images of the undersampled, single-shot variable density EPI acquisition in comparison to the spin-warp image acquired for coil sensitivity estimation. The matched-filter EPI (Figure 5.5 A) exhibits a low level of artifacts and high geometric congruency to the spin-warp image used as anatomical reference (Figure 5.5 C). Specifically, the edges of the brain, CSF and gray/white matter boundaries coincide in the matched-filter EPI and the anatomical reference (Figure 5.5 B, edges of spin-warp image overlayed on matched-filter EPI).

We investigated the particular impact of concurrent field monitoring on image quality in a series of alternative reconstructions, where we either used the nominal trajectory, the fully monitored 1st order trajectory including the global phase \( k_0 \), or a hybrid reconstruction with measured global phase, but nominal \( k_x \) and \( k_y \), as input to the gridding-based iterative reconstruction (Figure 5.6). The resulting images show the necessity of a reconstruction utilizing full knowledge about the actual trajectory and global phase. While this image reconstruction is virtually artifact-free, a reconstruction on the sole nominal trajectory exhibits both ghosting and blurring artifacts (Figure 5.6 BDGI). The reconstruction incorporating the measured global phase to the
nominal trajectory sheds light on the different artifact mechanisms (Figs. 5.6 CEHJ): The ghosting edges parallel to phase encoding direction $k_y$ are greatly reduced for this reconstruction, hence they mainly stem from a mismatch in $k_0$ during the readout. However, the blurred, rippled edges along frequency encoding direction remain and, thus, are presumably related to the gradient impulse response-induced compression of the matched-filter trajectory along $k_x$. 
Figure 5.5  Image quality and geometric accuracy of a single-shot matched-filter
EPI slice reconstructed with concurrent field monitoring data, SENSE (2.5) & $B_0$-
map based conjugate-phase correction. (A) Matched-filter EPI reconstruction,
virtually artifact-free. (B) Geometric accuracy: An edge contour map of the
geometric reference (C) overlaid onto (A). (C) Spin-warp image used as geometric
reference and as first TE image for the $B_0$-correction.
Matched-Filter Acquisition for BOLD fMRI

Uniform EPI

Full Monitoring Information
Nominal Trajectory
Nominal Traj. & Monitored $k_0$

Matched-filter EPI

Difference

20 %
10 %
0 %
-10 %
-20 %
5.3 Results

Figure 5.6 Image reconstructions of matched-filter EPIs using nominal and concurrently monitored field evolutions. (A-E) Uniform EPI, (F-J) Matched-filter EPI. (A,F) Coil data reconstructed with the concurrently monitored $k_0$-phase and linear $k$-space trajectory (B,G) Reconstruction with nominal $k$-space trajectory (C,H) Hybrid reconstruction with nominal $k$-space trajectory, but incorporating the measured $k_0$-phase. (D) Difference image of (B) and (A): The mismatch to the actual trajectory creates prominent SENSE-ghosting in phase encoding direction as well strong intensity modulations. Artifact levels reach up to $\pm 20\%$ voxel intensity. (E) Difference image of (C) and (A). Correcting for the measured $k_0$-phase, but reconstructing on the nominal trajectory greatly reduces intensity modulations, but does not fully eliminate image artifacts due to SENSE-ghosting. (I) Difference image of (G) and (F): The mismatch to the actual trajectory creates prominent SENSE-ghosting in phase encoding direction as well as Gibbs-like ringing artifacts close to tissue edges in readout direction. Artifact levels reach up to $\pm 20\%$ voxel intensity. (J) Difference image of (H) and (F). Correcting for the measured $k_0$-phase, but reconstructing on the nominal trajectory greatly reduces image artifacts due to SENSE-ghosting, while the edge-ringing and blurring artifacts remain unaltered.

5.3.3 SFNR Analysis

We evaluated local SFNR for each EPI session as a function of signal strength, which is proportional to the sine of the excitation flip angle (Figure 5.7). First, we captured the statistics of pure thermal noise by measuring a session with $0^\circ$ excitation flip angle, both in the phantom and in vivo (Figure 5.7, horizontal dashed lines). Before reconstruction, each of these measured noise instances was added to the coil data of one fixed scan of the $90^\circ$ session to evaluate pure thermal noise influence on SFNR. In this limiting case, the local SFNR gain of matched-filter compared to uniform EPI reached $45\%$, in good congruence with the theoretical expectation of $41\%$.

Secondly, in the phantom, the SFNR increased with signal level for both, matched-filter and uniform EPI, but with a steeper slope for matched-filter EPI, thus preserving an SFNR advantage compared to uniform EPI. However, the observed SFNR gain decreased for higher signal level (Figure 5.7 A, blue-shaded area). This indicates
MR signal fluctuations in addition to thermal noise, which could occur at any stage of the excitation, encoding and reception process. Nevertheless, even for the practically relevant case of high signal level, the SFNR gain in the phantom remained well above 30 % for matched-filter compared to uniform EPI.

Finally, for the in vivo measurements, we found regional differences in the SFNR dependence on signal-level, most likely due to varying contributions of physiological noise in the areas considered: For white matter ROIs, the SFNR curves resembled those in the phantom, but exhibiting a lower minimal SFNR gain at high signal levels of about 20 % for matched-filter compared to uniform EPI (Figure 5.7 B). In areas containing cerebro-spinal fluid (CSF), on the other hand, SFNR increased at low, but decreased at high signal level, presumably due to the strong pulsatile physiological noise (Figure 5.7 D, (Krüger and Glover, 2001)). However, we could still observe a relative gain in SFNR of about 15 % for matched-filter compared to uniform EPI. For fMRI-relevant gray matter ROIs, an SFNR gain of up to 20 % was found at high signal levels. The individual matched and uniform SFNR curves resembled those in white matter qualitatively, while the SFNR ratio exhibited decay with flip angle as in CSF, presumably reflecting the intermediate contribution of physiological noise in gray matter regions compared to white matter and CSF (Figure 5.7 C).
5.3 Results

A  SFNR: Uniform EPI
- Flip Angle 5°
- 25°
- 50°
- 90°

B  SFNR: Matched-filter EPI
- 5°
- 25°
- 50°
- 90°

C  Phantom
- uniform
- matched

D  White Matter
- uniform
- matched

E  Gray Matter
- uniform
- matched

F  CSF
- uniform
- matched
**Figure 5.7** Dependence of matched-filter signal-to-noise fluctuation (SFNR) advantage on signal level (sine of excitation flip-angle). (A) In-vivo resting-state SFNR maps for uniform EPI scans after smoothing. For low signal levels (5°, 25°), the SFNR distribution is governed by the SENSE-geometry factor and mean signal level. For medium and high signal levels (50°, 90°), the contrast is increasingly dominated by physiological noise prevalence. (B) In-vivo resting-state SFNR maps for matched-filer EPI scans after smoothing. For all signal levels, SFNR is increased compared to the uniform EPI SFNR maps in (A). The delineation of regions with different physiological noise prevalence is even more pronounced than in uniform EPI (cf. white matter in 90° SFNR map). (C) Phantom data: Approximately linear SFNR increase for uniform and matched-filter EPI (black curves; standard error of the mean smaller than dot size). The ratio of SFNR (blue shade) between matched-filter and uniform EPI drops below the SFNR gain bound determined by pure thermal noise (dotted horizontal line) for high signal levels. (D) In-vivo resting-state SFNR for a brain region containing white matter. The SFNR dependence on signal level resembles the phantom data in (C). (E) In-vivo resting-state SFNR for a gray matter brain region. Compared to white matter (D), the SFNR gains for high signal levels become more variable. (F) In-vivo resting-state SFNR for a brain region containing cerebro-spinal fluid (CSF): Contrary to white and gray matter, SFNR drops in CSF for high signal levels. Still, a considerable SFNR gain advantage of matched-filter compared to uniform EPI acquisition remains.
5.3.4 fMRI Analysis: t-Maps and Total Least Squares

In the individual SPM analysis of each acquired session, all contrast maps showed the expected activations patterns, representing the quarter-fields in the visual cortex by contrasting the two stimulation blocks either as ULLR-URLL (contrast 1, Figure 5.8, red voxels) or URLL-ULLR (contrast 2, Figure 5.8, green voxels). The activation patterns are visualized as overlays on an EPI scan of the corresponding session and show nice alignment with gray matter structures in the individual subject. Comparing the t-maps in terms of peak t-values and cluster sizes of significant voxels, the sessions with matched-filter acquisitions outperformed uniform EPI acquisitions consistently within subjects (across sessions) and between subjects (Figure 5.8). In particular, for both the first and second repetition (effect of session) of each acquisition in all subjects, matched-filter EPI provided superior activation patterns (according to the aforementioned criteria) than uniform EPI, whereas the activation patterns within an acquisition modality resembled each other closely in the 1st and 2nd repetition.

For a more quantitative and comprehensive view on this improved BOLD contrast sensitivity, especially its robustness and test/retest reliability, we generated a scatter plot depicting each individual voxel of a subject (Figure 5.9). The t-value change in the session of interest was plotted against the original t-value of the corresponding voxel in the reference session. Significant voxels were colored with the colors of the corresponding contrasts. As contrast 2 was just the negative of contrast 1, the voxels with highly negative t-values for contrast 1 (t < -4.73, corresponding to a peak-level family-wise error correction at p = 0.05) were significant voxels in contrast 2.

This data representation was evaluated using a total least squares (TLS) estimation of the mean slope \( \Delta t/t \), which indicates the relative increase in contrast (and therefore BOLD) sensitivity for the session of interest compared to the reference session, averaged over all voxels significant in both sessions (Table 5.2). TLS is an
extension of ordinary least squares regression for cases where both dependent and independent variables contain observation noise, as in our case. Pairing corresponding matched-filter and uniform EPI sessions, the TLS analysis yielded a positive slope indicating a t-value increase of $35 \% \pm 2 \%$ (95% confidence limits using bootstrapping) in session 1 (Figure 5.9 A) and $41 \% \pm 2 \%$ in session 2 (Figure 5.9 B) for the matched-filter acquisition in a single subject. On the other hand, pairing matched-filter acquisitions of session 1 and 2 as well as uniform acquisitions of session 1 and 2 in the TLS-analysis, the resulting slope assessed test-retest reliability, where a horizontal line indicates identical replication. Within the chosen subject, we saw good test-retest reliability with session differences of only $2 \% \pm 1 \%$ and $7 \% \pm 2 \%$ for the matched-filter and uniform acquisition, respectively. These findings were reproduced qualitatively in all subjects (Table 5.2), in particular the BOLD sensitivity increase of about 20 to 40 % for matched-filter compared to uniform EPI acquisitions. Two outliers with unusually high sensitivity gains of $83 \% \pm 3 \%$ and $146 \% \pm 19 \%$ occurred in subjects that also exhibited poor test-retest reliability within each acquisition scheme between session 1 and 2.
5.3 Results

**Table 5.2** The BOLD sensitivity increase in task-based fMRI using matched-filter acquisition. The mean t-value increase (including 95% confidence limits) is reported, as computed by the TLS analysis for the relevant contrasts, comparing all pairs of sessions (columns) for all subjects (rows). A graphical representation of the corresponding data for subject 4 is depicted in Fig. 9.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Mean Percent t-Value Change and 95% Confidence Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Session 1 Matched vs Uniform</td>
</tr>
<tr>
<td>1</td>
<td>39.7 (7.4)</td>
</tr>
<tr>
<td>2</td>
<td>23.7 (1.3)</td>
</tr>
<tr>
<td>3</td>
<td>83.1 (2.4)</td>
</tr>
<tr>
<td>4</td>
<td>34.8 (1.3)</td>
</tr>
</tbody>
</table>
EPI Acquisition

Matched  Uniform

Session 1  Reproducibility  Session 2

Contrasts
(p=0.05 (FWE))
Figure 5.8  Single subject activation patterns for task fMRI sessions utilizing a visual quarter-field stimulation. Depicted are the T-maps (FWE-corrected p=0.05 peak level) for the differential contrast of condition 1 vs 2 (red colormap) and 2 vs 1 (green colormap), overlayed on the mean EPI image of the corresponding sessions. The topological organization of the early visual areas is clearly recovered by the activation patterns. For the 1st as well as the 2nd repetition of the fMRI sessions, cluster extent and peak level T-value were significantly increased in both contrasts for the matched-filter EPI compared to the uniform acquisition. (A) Matched-filter EPI, 1st session (B) Uniform EPI, 1st session (C) Matched-filter EPI, 2nd session (D) Uniform EPI, 2nd session.
5.4 Discussion and Conclusion

The results presented have shown the feasibility of a matched-filter acquisition for fMRI in four stages: First, we verified that a single-shot EPI trajectory with Gaussian acquisition density and typical resolution and readout duration can be accomplished within the limits of a commercial MR gradient system. The concurrent field monitoring results confirmed that the experimentally realized acquisition density was indeed Gaussian, as is optimal for the Gaussian filter post-processing, with a root mean squared error.
(compared to the prescribed Gaussian density) of 3% in k-space center and 20% at the EPI turns.

Secondly, virtually artifact-free image reconstructions could be retrieved from these matched-filter k-space trajectories. To this end, it was crucial to perform image reconstructions using both static Bo-field correction as well as concurrent dynamic field monitoring for highest image quality. Concurrent field monitoring proved to be a robust and reliable method for correcting eddy-current and gradient imperfections. In this study, effects on 0\textsuperscript{th} and 1\textsuperscript{st} order phase coefficients entered our image reconstruction (although extensions to incorporate concurrently monitored higher-order phase information exist (Wilm et al., 2012, 2011)). Alternatively, reproducible deviations from the nominal k-space trajectory could be corrected using a calibration-based image reconstruction method (Graedel et al., 2013) that relies on the characterization of the gradient impulse response function in an independent, field monitoring-based experiment (S. Johanna Vannesjo et al., 2013; Signe J. Vannesjo et al., 2013).

Thirdly, we have seen that the experimentally obtained SFNR improvements in the phantom and \textit{in vivo} match the theoretically derived SFNR gains of 40% very well in the regime of thermal noise. Furthermore, even in the regime of high signal-induced noise contributions, a substantial SFNR increase of about 20% could be retained. Last, and most importantly, these SFNR increases translated into improved sensitivity for task-based fMRI contrasts, as demonstrated by a comparison of voxel-wise t-statistics under matched-filter and uniform EPI acquisition. A total least squares analysis for t-values of corresponding voxels confirmed that t-statistics of significant voxels were replicably higher for matched-filter fMRI by 20 to 40%. On top of that, again using TLS, we confirmed that in most subjects this difference was considerably higher than the within-modality t-value fluctuations of matched-filter and uniform EPI acquisition sessions, though the small number of subjects precludes a generalization of these preliminary findings.
In summary, it is remarkable that despite the multiple potential image artifact mechanisms and limited scope of our theoretical noise considerations, a considerable portion of the theoretical SNR advantage of matched-filter fMRI could be preserved through these four stages. Still, the quantitative progression of the realized SFNR gains within and through these stages deserves further discussion here, most prominently (1) the decrease of the \textit{in vivo} SFNR gain from 40 to 20\% for high signal levels, and (2) the subsequent rise of contrast-to-noise ratio (CNR) advantage in task-based fMRI to 20–40\% compared to the aforementioned 20\% SFNR increase in resting-state. Both observations arise from the intricate noise situation for \textit{in vivo} time series, which violates the white Gaussian noise assumption exploited in our theoretical treatment of matched-filter acquisitions. These deviations from a flat noise spectrum are induced by fluctuations in the measured MR signal and can be categorized into two classes: system-dependent and object-dependent fluctuations.

Typically, object-dependent fluctuations are the dominant non-white noise source in MRI, particularly at high main field strength (Krüger and Glover, 2001; Triantafyllou et al., 2006). They arise from the measured physiological systems themselves, which frequently exhibit a tendency towards low frequency noise, i.e. a “pink” noise spectrum, e.g. through breathing and cardiac pulsation (Birn et al., 2008; Chang et al., 2009; Dagli et al., 1999; Glover et al., 2000; Shmueli et al., 2007). System-dependent MR signal fluctuations, on the other hand, were particularly small in our measurements, since the concurrent field-monitoring approach corrected for instabilities in the encoding main and gradient fields, as well as any clock jitter of the spectrometer. Still, non-white noise components might have been introduced in the transmission and reception chain of the system, i.e. the excitation B, field and receiver gain, respectively.

A general quantification of these system- and object-dependent noise spectra is challenging, but may in principle serve two applications. Firstly, the prediction of \textit{in vivo} matched-filter SFNR
gains could become more accurate when deduced from a pink noise spectrum. Specifically, the upper bound on SFNR gain computed in the theory section for white noise would become tighter, because acquisition weighting unfolds its full strength if noise adds up incoherently, i.e. for white noise. In principle, these pink noise assumptions could then predict the aforementioned deviation between low and high signal level SFNR gain in our resting-state experiments.

Secondly, one could envisage a pink noise spectrum dictating different acquisition strategies to achieve the maximum SFNR gain. However, pink noise shares spectral characteristics with the BOLD signal of interest, thus accruing with similar coherence over time. Consequently, both pink noise and BOLD signal might be suppressed by an acquisition matched in this way, causing information loss. For pink noise, it therefore seems preferable to rely not only on noise statistics, but rather the exact knowledge of the occurring noise instances. Actual instances of physiological noise, for example, can be readily modeled from peripheral measures, such as ECG and breathing belts, and used as confound regressors to de-noise voxel time series, e.g. using RETROICOR (Glover et al., 2000; Hutton et al., 2011; Kasper et al., 2009). The second quantitative deviation in our experiments (up to 40% CNR-increase for task-based fMRI compared to only 20% SFNR increase in “resting-state” fMRI) may be understood as a special case of this pink noise correction: While spontaneous BOLD fluctuations in resting-state were considered “noise”, thus lowering the SFNR, the contrast-related BOLD responses in significant voxels were identified as signal of interest and therefore did not contribute to the residual error, i.e. noise amplitude, for the task-based fMRI sessions. Consequently, also resting-state connectivity analysis (Biswal et al., 1995), in contrast to pure SFNR measurements, should benefit from matched-filter acquisition on the same order as task-based fMRI, because correlations in (BOLD) signal fluctuations become a signal of interest here. Hence, the confounding noise in correlation detection has a noise spectrum
more similar to white noise and the matched-filter theory assumptions.

In this work, we exemplified the principle of matched-filter acquisition, showing how a variable density 2D EPI readout can be used in fMRI to achieve SNR-optimality for a Gaussian target PSF. The general framework of matched-filter acquisition, however, is not restricted to any of the four design decisions made here; neither the EPI readout, nor the Gaussian target PSF, not the fMRI application and not even the criterion of SNR optimality. In the following, we will conclude with an outlook to possible extensions of matched-filter acquisitions regarding these four aspects, in order of increasing generality:

Choosing a 2D EPI trajectory to implement a variable density acquisition was motivated by demonstrating the matched-filter principle for the currently most robust and commonly used readout in fMRI. However, as shown in Eq. (5.10), the SFNR gain scales with the square root of covered k-space volume, which promises an even greater advantage for 3D matched-filter acquisitions, such as concentric shell trajectories (Zahneisen et al., 2012) or the 3D EPIs recently adopted for fMRI (Lutti et al., 2013; Poser et al., 2010). More generally, the choice of the EPI trajectory itself for a Gaussian smoothing kernel is suboptimal. Inevitably, the EPI turns at traverse ends waste acquisition time in the de-emphasized high-frequency regime of the target PSF. Spiral readouts (Ahn et al., 1986; Glover and Lai, 1998) might be natural alternatives to implement a Gaussian acquisition density, since they are rotationally symmetric, and have been successfully utilized for variable-density acquisitions before (Chang and Glover, 2011). Moreover, they feature only a few sharp turns in the k-space center, thus allowing for more efficiency in realizing the prescribed acquisition density. However, their sensitivity to static B0-inhomogeneity poses a considerable challenge (Börnert et al., 1999).
The next design consideration refers to the selection of a Gaussian target PSF itself: While smoothing with a Gaussian kernel is prevalent, other filters for image post-processing in fMRI applications have been proposed, such as prolate spheroidal functions or wavelets (Lindquist and Wager, 2008; Yang et al., 2002; Van De Ville et al., 2006). The rationale for matched-filter acquisition holds unaltered for any target PSF, as do the global SNR gains derived in Eq. (5.10), as long as the target PSF is shift-invariant. For more specialized applications, e.g. cortical surface mapping or adaptive smoothing (Andrade et al., 2001; Harrison et al., 2008; Tabelow et al., 2006), taking into account regional anatomical variability for kernel adaptation, a matched-filter acquisition strategy will achieve SNR optimality for one pre-selected kernel, i.e. only locally in the image.

Beyond fMRI, fast single-shot readouts using matched-filter acquisitions may have applications in other notoriously low-SNR measurements such as echo-planar spectroscopic imaging (EPSI), diffusion- or perfusion-weighted imaging. Here, other target PSFs, such as Hamming filters for ringing suppression, might be desirable (Greiser et al., 2005; Kasper et al., 2012; Stobbe and Beaulieu, 2008). However, enforcing density-weighting via gradient modulation for an arbitrary target PSF requires a more general method to design the gradient waveform than the one presented here for the Gaussian PSF. To this end, a promising algorithm for time-optimal gradient waveform design was presented by (Lustig et al., 2008), which could be extended to allow for variable k-space densities through arc-length parameterized gradient limits along the trajectory, hence implementing Eq. (5.11).

One limitation of our approach to achieve acquisition density weighting with a variable velocity in k-space is the requirement of sufficient flexibility for gradient modulation. Therefore, readouts that require maximum gradient amplitude or slew-rate at all times cannot be augmented by a matched-filter acquisition. Objectives like robustness to T2* and off-resonance effects, ultra-high spatial
resolution or large slice coverage demand these maximally fast readouts.

However, acknowledging recent advances in gradient performance that allow for maximum gradient strengths of 100-300 mT/m and slew-rates above 200 T/m/s (Kimmlingen et al., 2012; Van Essen et al., 2012), this constraint might be diminished in the near future to open up versatility and application range for matched-filter acquisition methods even further.

On a final, conceptual note, SNR-optimality is only one, albeit important, criterion for coordinating acquisition and reconstruction to shape signal and noise behavior. According to our Eq. (5.3), acquisition weighting can be recruited to design any noise variance landscape in k-space for a given target PSF, as the final noise variance in k-space is simply the ratio of the squared target PSF and acquisition density at each k-space position. For example, setting the acquisition density to a multiple of the squared target PSF, the dependence on $k$ between numerator and denominator in Eq. (5.3) cancels out. Hence, the final noise variance in k-space is constant, i.e. flat, and, by the Fourier autocorrelation theorem, the noise variances in image space are uncorrelated. Taken together, this means that we can achieve voxel-wise noise decorrelation in an MR image by making the acquisition density proportional to the square of the target PSF. In this way, acquisition density matching could broaden its scope to areas where the delineation of unique signal contributions per voxel is crucial, such as high-resolution, layer-specific fMRI (Goense et al., 2012; Koopmans et al., 2010) and multivariate statistical analyses of fMRI data (Haynes and Rees, 2006), or applications that rely on voxel correlation measures, e.g. “resting-state” functional connectivity (Biswal et al., 1995; Buckner et al., 2013; Cole et al., 2010).
6.1 Introduction

In functional MRI (fMRI), image time series are acquired to analyze brain activity-related signal fluctuations in each voxel over many scans. The targeted changes in image intensity over the course of
the experiment are induced by blood oxygen level dependent (BOLD) or perfusion signal fluctuations. However, fluctuations in the magnetic fields encoding the images induce signal fluctuations in the image time series as well. These encoding field fluctuations can be caused by a wide range of object-independent effects, such as instabilities in the gradient system, eddy current alterations in the cryostat, the main magnet and the shim coils, atmospheric pressure variations, changes in the cryogen level and heating. These unwanted signal fluctuations lead to confounds and sensitivity loss in the image time series analysis.

So far, reproducible deviations from ideal encoding fields within one readout have been addressed thoroughly and many correction methods have been proposed (Addy et al., 2012; Börnert et al., 1999; Duyn et al., 1998; Signe J. Vannesjo et al., 2013). However, fluctuations in the encoding fields, which we define here as the variability of the encoding fields from readout to readout or image to image, remain largely unknown. One prominent exception are navigators, which partially address the question of dynamic corrections by globally assessing field fluctuations using point-wise measurements between scans (Foerster et al., 2005; Pfeuffer et al., 2002). Since these point-wise measurements are not taken during the actual encoding, the capability of correcting fluctuations in the encoding fields is limited to frequency shifts in the main magnetic field. Furthermore, additional measurements are required which alter the MR sequence and the timing of the data acquisition.

Recently, magnetic field monitoring using NMR field probes was introduced as a means to comprehensively measure and correct for spatio-temporal magnetic field fluctuations (Barmet et al., 2009, 2008; De Zanche et al., 2008). Specifically, magnetic field monitoring enables to study the complete evolution of the encoding fields concurrently (Barmet et al., 2010) with the imaging process, and without any alterations to the imaging sequence itself. This opens up the opportunity to follow encoding field fluctuations over different time scales and quantify their contribution to image
fluctuations. Furthermore, it also enables a general correction method for measured field fluctuations in the image reconstruction (Wilm et al., 2011).

In this work, we use concurrent magnetic field monitoring to study and correct for fluctuations in the encoding fields of a typical echo-planar imaging (EPI) trajectory common to fMRI experiments. In particular, we compare fluctuations over different time scales, i.e. between different scans of a session, between different sessions within a day, and between different days. We focus on phantom experiments exclusively, to isolate the effects of the imaging system. First, we measure field fluctuations both in the global phase evolution as well as the imaging trajectory itself. Second, we quantify the effects of these field fluctuations on image reconstruction by comparing reconstructed images which are corrected for field fluctuations with images where observed fluctuations are assumed to be unknown, as is the case in standard imaging on commercial MR systems. Third, we apply principal component analysis (PCA) as a data-driven approach to explore characteristic fluctuations in the encoding fields and the characteristic image fluctuations they induce.
6.2 Methods

6.2.1 MR Image Encoding and Field Fluctuations

Spatial encoding in MRI relies on the spatio-temporal variation of magnetic field amplitude $B(r, t')$ leading to a phase $\varphi(r, t)$ of excited transverse magnetization at readout time $t$ with $r = (x, y, z)^T$:

$$\varphi(r, t) = \gamma \int_0^t B(r, t') \, dt'.$$

(6.1)

The signal $s(t)$ obtained by a receiver coil from an imaging volume $V$ within the object $m(r)$ then reads

$$s(t) = \int_V m(r) \cdot \exp(i \varphi(r, t)) \, dr + \eta(t).$$

(6.2)

where $\eta(t)$ is the thermal noise arising from the sample and the receive chain.

Commonly, the magnetization phase is expanded linearly in space to arrive at the well-known k-space formulation of 2D-image encoding:

$$s(t) \approx \int_V m(r) \cdot \exp(i k_0(t) + k_{xy}(t) \cdot r_{xy}) \, dr,$$

$$= \exp(i k_0(t)) \cdot \left[ \int_V m(r) \cdot \exp(i k_{xy}(t) \cdot r_{xy}) \, dr \right]_{B_0 \text{ modulation}} \left[ \text{Fourier Encoding} \right],$$

(6.3)

where $k_0(t)$ represents the global phase evolution, $k_{xy}(t)$ the trajectory with $k_{xy}(t) = (k_x(t), k_y(t))$, $r_{xy}(t) = (r_x(t), r_y(t))$ equivalently, and
Methods

\(\cdot\) denotes the dot product. But see, e.g. ref. (Wilm et al., 2011), where the inclusion of higher order phase terms is described.

The aim of the image reconstruction process is to invert this signal model, assuming a certain global phase evolution \(k_0(t)\) and trajectory \(k_{xy}(t)\), to retrieve an estimate of the magnetization image that is minimally sensitive to the measurement noise \(\eta(t)\). An incongruity between assumed and actual field evolution can induce various artifacts. For example, in EPI encoding a linear global phase \(k_0(t)\) creates a pixel shift in the object (Zeng and Constable, 2002). A mismatch between the odd and even lines in \(k_{xy}(t)\) creates the typical \(N/2\)-ghosting artifact (Haacke et al., 1999). In practice, one usually cannot create pure gradient fields and those created are not always exact. However, for image time series used in fMRI analysis, always the same field evolution is assumed for the image reconstruction. Hence, fluctuations in the estimated images can also result from fluctuations in the encoding fields, due to a mismatch between the assumed and actual field evolution. Given the coil signal \(s(t)\) only, the origin of image fluctuations between different readouts remains ambiguous; both, the effects of encoding field fluctuations and true changes in the object magnetization are mapped onto the resulting image time series. This compromises the sensitivity for the time course of interest, i.e. BOLD. In this work, we measure the encoding fields, and characterize and quantify typical fluctuations in the encoding fields of an EPI time series. To investigate the influence of encoding field fluctuations on image reconstruction, we apply various reconstruction schemes based on different degrees of knowledge about the encoding fields (cf. Table 6.1).
6.2.2 Concurrent Magnetic Field Monitoring

**Table 6.1**  Reconstruction schemes. Different reconstruction schemes were used to study fluctuations in the encoding fields and their correction.

<table>
<thead>
<tr>
<th>Reconstruction Schemes</th>
<th>k₀ time series used</th>
<th>kₓᵧ time series used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concurrent Monitoring (Reference)</td>
<td>k₀(t)</td>
<td>kₓᵧ(t)</td>
</tr>
<tr>
<td>Effect of k₀ Session Calibration</td>
<td>k₀(t)</td>
<td>kₓᵧ(t)</td>
</tr>
<tr>
<td>Effect of kₓᵧ Session Calibration</td>
<td>k₀(t)</td>
<td>kₓᵧ(t)</td>
</tr>
<tr>
<td>Effect of k₀ Fluctuations</td>
<td>k₀(t)</td>
<td>kₓᵧ(t)</td>
</tr>
<tr>
<td>Effect of kₓᵧ Fluctuations</td>
<td>k₀(t)</td>
<td>kₓᵧ(t)</td>
</tr>
<tr>
<td>Standard</td>
<td>0</td>
<td>Nominal kₓᵧ(t)</td>
</tr>
</tbody>
</table>

**Phase coefficients**

We determine the phase coefficients k₀(t), kₓ(t) and kᵧ(t), which characterize the encoding fields, using concurrent magnetic field monitoring (Barmet et al., 2010, 2009, 2008; Wilm et al., 2011). Herein, N_p magnetic field sensors, or NMR probes (De Zanche et al., 2008), are distributed spatially at positions r_p, and each probe accrues a phase depending on the local magnetic field during image readout as described in equation (5.2). The retrieved phases Φ_p(t) are then expanded in terms of spherical harmonic basis functions (Barmet et al., 2008):


\[ \Phi_p(t) = \frac{\gamma_p}{\gamma} \sum_{l=1}^{N_l} k_l(t) \cdot h_l(r_p) + \eta(t), \quad (6.4) \]

where \( k_l(t) \) are the sought phase coefficients, \( h_l(r_p) \) are the basis functions evaluated at the probe positions, and \( \eta(t) \) the thermal noise arising in the receive chain of the probes. To allow for magnetic field monitoring concurrently with image acquisition, \(^{19}\text{F}\) probes were used. Due to the spectral separation of \(^{19}\text{F}\) and \(^1\text{H}\), the monitoring becomes independent from image acquisition and the probe excitation trigger could be set just before the acquisition start (Barmet et al., 2010). This necessitated a correction factor in the probe phase computation taking into account the different gyromagnetic ratios of \(^1\text{H} \,(\gamma)\) and \(^{19}\text{F} \,(\gamma_p)\).

Collecting the phase of all probes into a single vector \( \Phi \), equation (6.4) reads:

\[ \Phi(t) = \frac{\gamma_p}{\gamma} \cdot P \cdot k(t), \quad \text{where} \]

\[ P_{pl} = h_l(r_p), \]

\[ k(t) = \left( k_0(t), k_1(t), ..., k_{N_l-1}(t) \right)^T \quad \text{with} \]

\[ k_1(t) = k_x(t) \quad \text{and} \quad k_2(t) = k_y(t), \]

\[ \Phi(t) = \left( \Phi_1(t), ..., \Phi_{N_p}(t) \right)^T. \]

The phase coefficients \( k_0(t), k_x(t) \) and \( k_y(t) \) used in the image reconstruction can then be retrieved from the probe phase evolution via the Moore-Penrose pseudo-inverse \( P^+ \) of \( P \) (Barmet et al., 2008):

\[ \hat{k}(t) = \frac{\gamma}{\gamma_p} P^+ \Phi(t), \quad (6.6) \]
where "\( \hat{\cdot} \)" denotes an estimated entity. The phase coefficient \( k_0(t) \) characterizes the global phase evolution, whereas \( k_x(t) \) and \( k_y(t) \) constitute linear phase coefficients that represent the 2D k-space trajectory \( \mathbf{k}_{xy}(t) \).

In summary, the phase coefficients \( k_0(t) \), \( k_x(t) \) and \( k_y(t) \) are retrieved concurrently with the image acquisition and in every scan individually. They can then be used in the image reconstruction to enhance the inversion of the signal model. For convenience, we will introduce the labels \( k_o \) for global phase evolution and \( k_{xy} \) for the trajectory.

**Field Measurement Sensitivity**

To characterize the field measurement sensitivity, we investigated the probe phase noise \( \phi_{\text{noise},p} \) and its propagation into the noise statistics of the phase coefficients \( k_0(t) \) and \( \mathbf{k}_{xy}(t) \), which in turn enter image reconstruction. The precision of \( \hat{\mathbf{k}}(t) \) is determined by the conditioning of \( \mathbf{P}^+ \) on the one hand, and the noise distribution governing the measurement of the probe signal \( \Phi(t) \) on the other hand (Barmet et al., 2008). With respect to the conditioning of \( \mathbf{P}^+ \), we fitted \( N_p = 12 \) probe phases on \( N_l = 9 \) basis functions, and chose \( r_p \) approximately equidistant on a cylindrical surface to minimize correlations between the rows of \( \mathbf{P}^+ \), i.e. spherical harmonics basis functions.

The noise statistics of the individual probes can be retrieved from a separate experiment consisting of \( N_{\text{FID}} \) free induction decays (FID). Assuming a constant field for each individual FID, the probe phase noise \( \phi_{\text{noise},p} \) is isolated by removal of the linear phase \( (\omega_p \cdot t) \) for each probe \( p \) and FID \( \tau \) individually from the measured probe phase \( \phi_p \):

\[
\phi_{\text{noise},p}(\tau,t) = \phi_p(\tau,t) - \omega_p(\tau) \cdot t. \tag{6.7}
\]
We compute the noise covariance matrices $\sigma_{p,p'}^2(t)$ of phase noise between probes at each sampling point $t$ during the readout:

$$\sigma_{p,p}^2(t) = \frac{1}{N_{\text{FID}} - 1} \sum_{\tau} \left( \phi_{\text{noise},p}(t, \tau) - \bar{\phi}_{\text{noise},p}(t) \right) \left( \phi_{\text{noise},p'}(t, \tau) - \bar{\phi}_{\text{noise},p'}(t) \right),$$

where "$\bar{\phi}(t)$" denotes the mean phase at time point $t$ over $N_{\text{FID}}$ FIDs.

Assuming a Gaussian noise distribution for each probe, the joint noise distribution of all probes can then be described via a zero-mean multivariate Gaussian at each readout sampling point:

$$\mathcal{N} \left( 0, \sigma_{p,p'}^2(t) \right).$$

This probe phase noise is propagated into image reconstruction via $P^+$ (cf. (6.6)).

### 6.2.3 Data Acquisition

**Measurements**

Phantom data were acquired from a CuSO$_4$-doped water sphere (15 cm diameter) on a Philips Achieva 3 T system with an 8-channel head coil and a concurrent magnetic field monitoring setup (12-channel T/R $^{19}$F NMR probes). All scans utilized a 2D EPI sequence with the following acquisition parameters: TR 3 s, TE 35 ms, EPI readout duration 41.6 ms, receiver bandwidth 375 kHz, voxel size 2.6 x 2.6 x 2.5 mm$^3$, FOV 220 x 220 x 47.5 mm, 10 slices with 2.5 mm inter-slice gap.

To emulate a typical fMRI acquisition protocol, we acquired a total of 9 sets of EPI data on 3 different days with three imaging sessions...
on each day (Table 6.2). Each set contained 400 scans, leading to a total duration of 20 minutes per set. Every set was followed by an equally long break (20 min) to mimic rest and preparation periods or the arrival of a new volunteer. Additionally, we acquired 120 FIDs to estimate the probe phase noise (cf. setup sensitivity).

<table>
<thead>
<tr>
<th>Session</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>set 1</td>
<td>set 4</td>
<td>set 7</td>
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<tr>
<td>break</td>
<td>break</td>
<td>break</td>
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</tr>
<tr>
<td>set 2</td>
<td>set 5</td>
<td>set 8</td>
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<tr>
<td>break</td>
<td>break</td>
<td>break</td>
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</tr>
<tr>
<td>set 3</td>
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<td></td>
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<tr>
<td>20 min</td>
<td>20 min</td>
<td>20 min</td>
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</tr>
</tbody>
</table>

**Figure 6.1** Reconstruction Framework. The coil signal is demodulated with phase coefficient $k_0$. This demodulated signal and the measured $k$-space trajectory $k_{xy}$ then enter a conjugate gradient – gridding based iterative reconstruction algorithm.
6.2 Methods

Simulations

We generated additional synthetic coil data to eliminate any effects of fluctuations in the transmit/receive chain or in the object, which can also induce image fluctuations. In this way, we isolated pure field-induced image fluctuations. Specifically, we used a numerical phantom and the measured phase coefficients $k_0$ and $k_{xy}$ to encode single coil data for all scans of all sets following (Eq. (6.11)):

$$s_\kappa = \sum_{\rho=1}^{N_\rho} m_\rho \cdot \exp(i k_{0,\kappa}) \cdot E_{\kappa,\rho},$$

(6.10)

with the entries of the Fourier encoding matrix $E_{\kappa,\rho} = \exp(i k_\kappa \cdot r_\rho)$.

The numerical phantom $m(r)$ was retrieved using the mean image of the concurrently monitored time series of set 1 (Figure 6.2), with the background set to zero to remove any remaining artifacts. We then applied the same reconstruction schemes as for the measured coil data (Table 6.1).

![Mean Image](image1.png) ![Mean k-Space Trajectory](image2.png)

**Figure 6.2** (Left) Mean of the reconstructed images using the concurrently monitored phase coefficients for reconstruction (set 1, slice 9). (Right) Mean k-space trajectory (set 1, slice 9).
Additionally, to investigate the setup sensitivity and the influence of probe phase noise on the images, we first synthesized single coil data readout using the numerical phantom and a reference encoding field evolution given by the mean phase coefficient \( \overline{k_0}(t) \) and \( \overline{k_{xy}}(t) \) computed from the mean probe phase of set 1. Then, we emulated measurement noise by adding 400 instantiations of probe phase noise time courses onto this mean probe phase. The noise statistics herein follows the multivariate Gaussian distribution \((6.9)\), i.e. is readout-time dependent. Finally, we determined the phase coefficients \( k_0 \) and \( k_{xy} \) from these noisy probe phases and used them for reconstructing 2x400 images from the single coil data readout, evaluating effects in \( k_0 \) and \( k_{xy} \) separately. Altogether, we emulated probe phase noise entering the image reconstruction while the encoding fields and the object were kept constant.

### 6.2.4 Image Reconstruction

We reconstructed a vectorized image matrix \( \mathbf{m} = (m_1, ..., m_\rho, ..., m_\rho^N) \) from the sampled coil data \( \mathbf{s} = (s_1, ..., s_\kappa, ..., s_\kappa^N) \), which is encoded by a discrete version of the signal equation \((6.2)\):

\[
    s_\kappa = \sum_{\rho=1}^{N_\rho} m_\rho \cdot \exp(ik_{0,\kappa}) \cdot E_{\kappa,\rho}, \tag{6.11}
\]

with the entries of the Fourier encoding matrix \( E_{\kappa,\rho} = \exp(ik_{\kappa} \cdot r_\rho) \).

First, this coil signal was demodulated with the phase coefficient \( k_{0,\kappa} \) describing the global phase evolution:

\[
    s_{\kappa, demod} = s_\kappa \cdot \exp(-ik_{0,\kappa}). \tag{6.12}
\]
The SNR-optimal image estimate \( \hat{m} \) was then computed via the Moore-Penrose Pseudo-Inverse of the encoding matrix \( E \) (Pruessmann et al., 2001):

\[
\hat{m} = (E^H \Psi^{-1} E)^{-1} E^H \Psi^{-1} s_{\text{demod}},
\]

where \( \Psi \) is the noise covariance matrix of the signal samples.

This inversion operation to retrieve \( \hat{m} \) was carried out using a conjugate gradient – gridding based iterative reconstruction combining fast matrix-vector multiplication for non-uniform FFT and density compensation (Pruessmann et al., 2001; Beatty et al., 2005; Jackson et al., 1991), depicted in Figure 6.1. The eight coil images were reconstructed separately and combined to the final image using sum-of-squares.

### 6.2.5 Reconstruction Schemes

Given the coil data from all scans and sets, we implemented different reconstruction schemes (Table 6.1) to investigate the effects of encoding field fluctuations on the reconstructed image time series (as outlined schematically in Figure 6.1). As a reference reconstruction, we chose the concurrent monitoring scheme: reconstructing all coil data using the corresponding concurrently monitored \( k_0 \) and \( k_{xy} \) data. In general, we separated the effects of the different spatial field orders \( k_0 \) and \( k_{xy} \). To investigate the effect of fluctuations in \( k_0 \), we reconstructed the coil data with only limited information about \( k_0 \) while retaining the full concurrent monitoring information in \( k_{xy} \). Specifically, we demodulated each scan by using the mean \( \overline{k_0}(t) \) of the 400 evolutions measured in set 1. In this way, we isolated the effects of \( k_0 \) fluctuations on the reconstructed images: While \( k_0 \) fluctuations were present during encoding, none of this information about \( k_0 \) fluctuations entered the reconstruction process. The mean \( \overline{k_0}(t) \) was chosen to avoid a selection bias concerning any specific scan and to remove any probe phase noise. This selection of a single representative field evolution for image reconstruction of all sets emulates the typical
reconstruction situation on a commercial scan system. While incorporating static corrections (gradient delays, eddy current correction), dynamic corrections are usually omitted (with the exception of navigators). To investigate the effect of fluctuations in $k_{xy}$, an analogous strategy was employed. This time, we used the mean $\overline{k_{xy}}(t)$ of the 400 evolutions measured in set 1, but the concurrently measured data for $k_o$ during for image reconstruction.

We also investigated the possibility of a session calibration that assumes reproducibility of the fluctuations in each fMRI set of 400 scans. Under this assumption, it suffices to measure the phase coefficients of a single set (calibration) and use them to reconstruct other sets acquired with the same imaging sequence. Therefore, to investigate the session calibration approach for the fluctuations in $k_o$, we used the 400 time courses acquired in set 1 to reconstruct the remaining eight sets, too. Specifically, for the $n$-th scan in any set, we applied the corresponding $n$-th $k_o$-time course of set 1 during the demodulation step. The used trajectory data was the concurrently measured $k_{xy}$ data for each set. The same approach was used to study the possibility of a session calibration for the fluctuations in $k_{xy}$.

### 6.2.6 Statistical Analysis of Image Fluctuations

We assessed the fluctuations within an EPI image time series using standard deviation (SD) and root mean squared error (RMSE). The SD characterizes the fluctuations over the image time series within each voxel. The SD image depicts the spatial fluctuation pattern and allows the localization of areas with strong fluctuations. On the other hand, the RMSE quantifies the artifact level over the whole image compared to a reference for each scan individually. It provides a temporal fluctuation pattern and allows the identification of points in time with strong deviations. The reference image for the estimation of the RMSE was the mean image of the corresponding set reconstructed using the concurrently measured phase coefficients. For the simulated coil data, the numerical phantom served as a reference.
Actually, the SD can be seen as a measure for the precision in the image time series, which in turn is crucial for BOLD sensitivity. The RMSE, on the other hand, can be interpreted as a measure for image accuracy, which plays an important role in effect localization. Strictly speaking, accuracy is defined as the deviation from the ground truth, which is only known using the coil data simulations. However, the mean of the reconstructed images using the concurrently monitored phase coefficients is a reasonable estimate of this ground truth.

### 6.2.7 Data-Driven Time Series Analysis: Principal Component Analysis

To characterize key contributions to the observed encoding field fluctuations, we performed a Principal Component Analysis (PCA) (Pearson, 1901) of the phase coefficients. PCA determines a new representation of the data that captures maximum data variability in a minimum set of orthogonal components. Thus, it is a natural choice for studying fluctuation patterns. Additionally, PCA quantifies the relative importance of each component via the amount of explained variance. In particular, if variance is concentrated along few dimensions (principal components), PCA helps identifying important sources of fluctuation, and the reproducibility of these fluctuations (Shlens, 2009).

Mathematically, the aim of PCA is to find a new set of basis vectors, the so-called principal components (PCs), along dimensions of high variance in the data. Thus, each principal component represents a characteristic fluctuation of the readout time course of each phase coefficient. These principal components are computed via an eigen-decomposition of the covariance matrix $\text{COV}^{\text{I}}_{\kappa, \kappa'}$ of the data for each phase coefficient $k_o$, $k_x$ and $k_y$ individually.
\[
COV_{\kappa,\kappa'}^l = \frac{1}{N_\tau - 1} \sum_{\tau=1}^{N_\tau} \left( k_l(t_{\kappa'}, \tau) - \overline{k}_l(t_{\kappa}) \right) \cdot \left( k_l(t_{\kappa'}, \tau) - \overline{k}_l(t_{\kappa'}) \right),
\] (6.14)

where \( \tau \) is the scan number and \( \overline{k}_l(t) \) denotes the mean phase over \( N_\tau = 9 \times 400 \) scans.

The principal components are ordered according to the amount of variance they explain. The first principal component explains most of the variance in the data, the second principal component the second most variance, and so on. In a second step, the temporal evolution of these characteristic readout time courses over all \( N_\tau \) scans is assessed by the projection of the phase coefficient data onto each principal component:

\[
projection_{\rho,l}(\tau) = PC_{\rho,l}(\tau)^T \cdot k_l(\tau),
\] (6.15)

with \( \rho \) being the number of the respective principal component and \( l = 0, x, y \).

This projection visualizes how the contribution of a certain principal component changes over scans, and thus provides a picture of the fluctuation patterns over time. To characterize typical image fluctuations induced by field fluctuations, we performed a PCA on the images without correcting for fluctuations in \( k_0 \) or \( k_{xy} \). This yielded principal components in the image domain and their corresponding projections, which depict the evolution of image fluctuations over time.
6.3 Results

The results section starts by looking at the effects of fluctuations in $k_0$ and $k_{xy}$ on the image time series. This will emphasize the characteristic fluctuations in EPI time series introduced by an incomplete knowledge of encoding field fluctuations – as is the typical case for standard image reconstruction on commercial MR imaging systems.

6.3.1 Image Accuracy and Precision Losses Induced by Field Fluctuations

First, we considered the effect of $k_0$ fluctuations (Table 6.1) on the image time series using the measured coil data (Figure 6.3) (max. SD: 31.3 %, mean SD: 1.0 %). The SD values were scaled to the maximum intensity value of the mean image reconstructed using the concurrently monitored phase coefficients. The SD image, characterizing the spatial fluctuation pattern, depicted fluctuations in the image, which were especially high at the edges of the object (max. SD: 31.3 %, mean SD: 1.0 %). The RMSE, depicting the temporal fluctuation pattern, showed a characteristic temporal evolution with a large dynamic range (max. RMSE: 10.8 %, mean RMSE: 4.7 %) (Figure 6.3, top right). The minimum is located in the central part of set 1, where the actual global phase evolution during image acquisition, corresponds to the mean $k_0$ used for image reconstruction (Figure 6.5). Hence, the image deviations were very small. However, scans occurring much earlier or later than this instance exhibited strong image deviations. In contrast, the RMSE of the image time series reconstructed using the concurrently monitored phase coefficients is very low and shows a minimal dynamic range (Figure 6.4, top right) (max. RMSE: 0.6 %, mean RMSE: 0.3 %). Equivalently, the fluctuations are reduced, verified by the low SD (max SD: 1.2 %, mean SD: 0.3 %) (Figure 6.9, top left).
Effect of $k_0$ Fluctuations

**Standard Deviation**

**RMSE**

- Measured Coil Data
- Simulated Coil Data
- Measurement Noise
6.3 Results

**Figure 6.3** Effect of $k_0$ Fluctuations. (Top) Standard deviation image depicting the effects of $k_0$ fluctuations (set 1, slice 9). RMSE of the image time series affected by $k_0$ fluctuations in black (slice 9). RMSE of the reference image time series reconstructed using the concurrently monitored phase coefficients in magenta. (Center) Standard deviation image using simulated coil data and an identical reconstruction scheme as above. RMSE of the image time series affected by $k_0$ fluctuations using simulated coil. (Bottom) Standard deviation image and RMSE characterizing the influence of probe phase noise in $k_0$ on the image time series.

Second, we evaluated the effect of $k_{xy}$ fluctuations on the image time series. We observed ghosting artifacts, which strongly compromise the image precision locally (max SD: 2.0 %, mean SD: 0.4%) (Figure 6.4, top left). The RMSE showed a very similar temporal evolution on day one and two in all sets. The data sets of day three don’t show such a correspondence, only a general decrease of the RMSE can be observed (Figure 6.4, Top Right) (max. RMSE: 1.5 %, mean RMSE: 0.6 %).

For $k_0$ as well as $k_{xy}$, the observed image time series fluctuations from the measured coil data could be reproduced, in terms of both their quantity and quality, on simulated coil data (Figure 6.3 and Figure 6.4, center). This means that the characteristic fluctuation patterns can indeed be attributed to fluctuations in the encoding fields, for T/R chain and object fluctuations are eliminated in the simulations.

Also the field monitoring measurement itself constitutes no relevant source of image fluctuations. Both, the SD (precision) and RMSE (accuracy) of the image time series disturbed solely by probe phase noise were one order of magnitude higher than observed effects due to fluctuations in $k_0$ and $k_{xy}$ (Figure 6.3 and Figure 6.4). Furthermore, the observed fluctuation patterns in the images were qualitatively different from image fluctuations due to encoding field fluctuations.
6.3 Results

**Figure 6.4**  Effect of $k_{xy}$ Fluctuations. *(Top)* Standard deviation image depicting the effects of $k_{xy}$ fluctuations (set 1, slice 9). RMSE of the image time series affected by $k_{xy}$ fluctuations in black (slice 9). RMSE of the reference image time series reconstructed using the concurrently monitored phase coefficients in magenta. *(Center)* Standard deviation image using simulated coil data and an identical reconstruction scheme as above. RMSE of the image time series affected by $k_{xy}$ fluctuations using simulated coil. *(Bottom)* Standard deviation image and RMSE characterizing the influence of probe phase noise in $k_{xy}$ on the image time series.

In summary, we have seen in phantom experiments that accuracy and precision in image time series suffer considerably from field fluctuations, resulting in SD values up to 31.3 % in $k_0$ and 2.0 % in $k_{xy}$.

### 6.3.2 Fluctuations of Global Phase and Trajectory

Depicting the measured phase coefficients for all scans of set 1 (slice 9), we found fluctuations in the encoding fields at different orders of magnitude for distinct phase coefficients (Figure 6.5 and Figure 6.6). Specifically, for $k_0$ (Figure 6.5), the main fluctuations over scans are an increasing slope of the linear component (top). This becomes even more obvious after subtracting the mean of the time series (bottom). Furthermore, by indicating the SD of the probe noise determined in a separate experiment (cf. setup sensitivity), the high sensitivity of the measurement setup is illustrated: actual $k_0$ fluctuations between subsequent readouts are higher than the probe phase noise. For $k_x$ and $k_y$ (Figure 6.6), the observed fluctuations are small compared to the dynamic range of the EPI trajectory (0.5 ‰ and 2 ‰, respectively). However, a complex fluctuation scheme is present in $k_y$ (readout direction), exhibiting a dominant high-frequency modulation at approximately the EPI traverse frequency, which can be detected clearly with the given setup sensitivity. The complex temporal structure of the observed field fluctuations necessitated dimensionality reduction using principal component analysis (PCA).
Measured $k_0$

**Phase Coefficient**

![Phase Coefficient graph](image)

**Difference to Mean**

![Difference to Mean graph](image)
6.3 Results

**Figure 6.5** Measured $k_o$. (Top) Evolution of phase coefficient $k_o$ during single-shot EPI readouts (set 1, slice 9). The color coding indicates the scan index within one session (blue = 1, red = 400). (Center) Zoom depicting the mean of phase coefficient $k_o$ in black ± the standard deviation of the setup noise in dotted black. (Bottom) Difference of the measured phase coefficient $k_o$ and its mean. The ± standard deviation of the setup noise is given in black.

The PCA characterized the phase coefficient fluctuations on different time scales: While the principal components itself represent fluctuations within a readout, their corresponding projections enable to follow fluctuation dynamics between readouts, i.e. within session, between sessions, and between days. We observed only few effects driving the variability between all scans in all sets (Figure 6.8). In all three-phase coefficients, the first principal component explained more than 80% of the variance.

For $k_o$, the first principal component (explaining 99.98% of the variance) constituted a linear phase increase within each readout. The corresponding projections, i.e. slopes of the linear term, reflect a drift in the static $B_0$-field over readouts, since a constant offset in the $B_0$-frequency induces a linear phase in $k_o$, (5.2). Specifically, the projections showed temporal characteristics of a heating process: A smooth non-linear increase approaching, but never reaching a steady state. The dynamic range within one set was about 30 Hz. The same pattern emerged on each day, though variable offsets occurred between session and days (Figure 6.8).
Measured $k_{xy}$

Phase Coefficient

Zoom 1

Zoom 2

Difference to Mean

Phase Coefficient

Zoom 1

Zoom 2

Difference to Mean
FIGURE 6.6   Measured $k_{xy}$ (Top) Evolution of phase coefficient $k_x$ (phase encoding, left) and phase coefficient $k_y$ (frequency encoding, right) during single-shot EPI readouts (set 1, slice 9). The color-coding indicates the scan index within one session (blue = 1, red = 400). (Center) Zoom depicting the mean of phase coefficient $k_x$ (left) and $k_y$ (right) in black ± the standard deviation of the setup noise in dotted black. (Bottom) Difference of the measured phase coefficient $k_x$ (left) and $k_y$ (right) and their mean, respectively ± standard deviation of the setup noise is given in black.

The PCA of $k_x$ yielded a first principal component (84.6% of explained variance) containing a superposition of linear increase and a modulation around the EPI traverse frequency. Interestingly, although the component itself had distinct features, the projection was relatively noisy and did not show a reproducible temporal pattern across sets. The first component of $k_y$ (85% of explained variance) exhibited a similar linear increase and modulation as $k_x$. The corresponding projection showed a linear decrease over time and considerable fluctuations on the time scale of seconds. These fluctuations do not origin from probe phase noise. We evaluated the variance in the PCA projections originating from probe phase noise using propagation of uncertainty; the standard deviation in the first projection in $k_y$ is more than one order of magnitude smaller than the observed fluctuations in the projection over seconds.

For $k_y$, the second principal component also explained a significant proportion of the total variance (12.1%). Furthermore, it showed a distinct structure both in the principal component itself and its projection: Again, an oscillation approximately at the EPI frequency was the dominating pattern within the principal component, which was modulated by a low frequency amplifying the central part of the readout. The evolution of the projection showed heating characteristics similar to $k_o$, which were fairly reproducible in every set.
Monitoring, Analysis and Correction of Magnetic Field Fluctuations in EPI Time Series

PCA of Field Fluctuations

**Principal Component 1**

\[ \sigma^2_{exp} = 99.98\% \]

**Projection of PC 1**

**Principal Component 1**

\[ \sigma^2_{exp} = 84.6\% \]

**Projection of PC 1**

**Principal Component 1**

\[ \sigma^2_{exp} = 85.0\% \]

**Projection of PC 1**

**Principal Component 2**

\[ \sigma^2_{exp} = 12.1\% \]

**Projection of PC 2**
Figure 6.7

PCA of Field Fluctuations. (Top) Principal component 1 and the corresponding projection of phase coefficient $k_0$. (Center) Principal component 1 and the corresponding projection of phase coefficient $k_0$. (Bottom) Principal component 1 and 2 and the corresponding projections of phase coefficient $k_y$.

6.3.3 Analysis of Image Fluctuations using Image PCA

We used PCA to characterize image fluctuations induced by $k_0$ and $k_{xy}$ fluctuations for each day separately (Figure 6.8). Fluctuations in the encoding fields induce few very strong effects (64% - 81% explained variance) and the principal components are very stable over different days. Fluctuations in $k_0$ induced a downwards shift of about one pixel in one session (Figure 6.8, top). The projection is smooth and reproducible on each day. Fluctuations in $k_{xy}$ induce mainly a ghosting artifact and a horizontal line due to the $\text{N}/2$ ghost edges at the FOV border. Again, the projection has the same time course on each day and is slightly noisier compared to $k_0$ (Figure 6.8, bottom).
PCA of Image Fluctuations

\( k_0 \)

Principal Component 1, \( \sigma_{expl}^2 : 81 \% \pm 1 \%

Projection of PC 1

\( k_{xy} \)

Principal Component 1, \( \sigma_{expl}^2 : 64 \% \pm 5 \%

Projection of PC 1
Figure 6.8 PCA of Image Fluctuations. (Top) Principal component 1 and the corresponding projections of the image time series affected by $k_o$ fluctuations, separated for each day. The Principal Components were scaled to the same dynamic range as the mean image. (Bottom) Principal component 1 and the corresponding projections of the image time series affected by $k_{xy}$ fluctuations, separated for each day.

6.3.4 Reproducibility of Field Fluctuations for Calibration

Based on the results of the phase coefficient PCA, where we found the same characteristic fluctuations in each set and projections with a similar dynamic, we investigated the feasibility of a session calibration approach (Table 6.1) to reduce image fluctuations induced by field fluctuations (Figure 6.9). Image fluctuations due to non-reproducible effects remain, e.g. history-dependent and random phase coefficient fluctuations, which can only be corrected for via concurrent magnetic field monitoring. In $k_o$, the SD compared to the reference is increased, especially at the edges in the object (max SD: 9.1 %, mean SD: 0.4 %). Between sessions of the same day, the RMSE is increasing approaching nearly ten times as high values as in the concurrent monitoring case (max. RMSE: 8.6 %, mean RMSE: 4.4 %). Between days, the RMSE is lowest in corresponding sessions and has a reduced dynamic. However, an offset of up to 2 % remains. Compared to the BOLD effect with signal fluctuations in the low percent range, both precision and accuracy are too low following this calibration approach.

In contrast, the SD images in $k_{xy}$ are comparable to the concurrent monitoring case (max SD: 1.2 %, mean SD: 0.3 %). However, the RMSE increased over days indicating an accuracy loss with its maximum in set 7 with triple the amount of RMSE (max. RMSE: 1.0 %, mean RMSE: 0.6 %).
In this study, we have measured and characterized encoding field fluctuations in EPI time series, in the global phase $k_0$ as well as the trajectory $k_{xy}$, which induced substantial image fluctuations in the range of the BOLD effect: Fluctuations in $k_0$ led to severe precision (SD up to 31%) and accuracy losses (RMSE up to 11%) due to...
variable pixel shifts. Fluctuations in $k_{xy}$ induced strong ghosting artifacts with SD values up to 2% and RMSE values up to 1.5%. Concurrent magnetic field monitoring substantially reduced the fluctuations in the EPI image time series (SD up to 1.2%, RMSE up to 0.6%) and removed temporally correlated image fluctuations. Hence, we expect that resting-state fMRI will strongly benefit from concurrent magnetic field monitoring since spurious correlation patterns are removed, which might otherwise conceal the neuronally induced coupling of brain regions. Likewise, for task-based fMRI, the increased sensitivity and accuracy due to magnetic field monitoring will likely improve effect detection and localization.

As seen, concurrent magnetic field monitoring provides a comprehensive means to correct for field fluctuations in image time series. This also indicates that the reported field changes indeed affect the imaged object and are not mere artifacts of the measurement setup. Furthermore, the high congruency between measured and simulated coil data showed that the image time series fluctuations observed in the experiment were predominantly caused by fluctuations in the encoding fields. Consequently, fluctuations in the measured object magnetization due to instabilities in the transmit/receive chains or coil sensitivities contributed less to image fluctuations. A further reduction in the remaining fluctuations can be expected by the incorporation of measured higher-order field terms in the reconstruction (Vannesjo et al., 2012).

We characterized the effects of a typical EPI time series schedule on system-related encoding field fluctuations via principal component analysis. Herein, we observed only a few strong effects driving field variability. The fluctuations in $k_o$ were nearly exclusively explained by a linear phase increment in the first principal component, expressing a change in the global $B_0$ field. The projection of this component showed slow drift dynamics over scans of a session approaching saturation, with an overall range of 30 Hz, in line with literature describing heating effects on magnet,
gradients and shims (Foerster et al., 2005). However, since the
dynamic $f_0$ correction and the helium pump were turned off for our
experiments, the magnitude of these field drifts may vary in
practice, depending on vendor-specific correction methods. The
fluctuations in $k_x$, i.e. the phase encoding, were small, on the order
of the sensitivity of our monitoring setup (0.1 rad/m). They
exhibited two prominent features in their principal components: a
linear phase increment and an oscillation at and around the EPI
readout frequency. The evolution of this fluctuation followed no
clear trend over scans and appeared to be noisy. Thus, the physical
causes of these fluctuation patterns remain speculative. The
fluctuations in $k_y$, the frequency encoding, were dominated by two
principal components with features already observed in $k_x$: a linear
phase increment in the first principal component, and an
oscillation at and around the EPI readout frequency in both
components. The linear phase increment of the first principal
component in $k_y$ reflects an offset in the gradient field. The
modulation with the EPI frequency in both relevant principal
components in $k_y$ might reflect a delay as well as a slight shift in
the EPI frequency. For the first component, the projection again
seemed to be noisy on the order of seconds. These seemingly
random fluctuations could not be attributed to measurement
noise, which was verified by propagation of uncertainty (Ku, 1966)
using the independently measured probe phase noise statistics.
Over the course of a full session, the projection exhibited an overall
slow linear decrease. Also the projection of the second principal
component exhibited slow dynamics over a session, which are
similar to the temporal characteristics of the projections in $k_o$, thus
pointing to a heating effect. The co-occurrence with the EPI
frequency makes mechanic resonances of the gradient system at
about 1 kHz, as observed in (Signe J. Vannesjo et al., 2013), a likely
cause of this heating process. In turn, heating would slightly
downshift the corresponding resonance frequencies of the
mechanic oscillations, explaining variability of the readout gradient
waveform and leading to the observed beat in the second principal
component of $k_y$. Given these hypotheses, generated through the
dimensionality reduction via PCA, a more mechanistic characterization of the fluctuations in $k_0$, $k_x$ and $k_y$ becomes possible. For example, one could use a linear model of mechanistically motivated basis functions to explain the magnetic field fluctuations. These basis functions could represent all of the above-mentioned effects, such as field offsets, gradient delays or frequency shifts in mechanic resonances. To verify and explore the nature of the temperature dependence of these effects, one would have to employ heat sensor measurements in parallel to field monitoring.

Given the impact of the observed field fluctuations, the question of effective correction arises. Simpler correction or even calibration methods to counteract field fluctuations might be conceivable given the limited amount of principal components in the fluctuations we observed and their apparently predictable projection behavior over session. With respect to using field monitoring itself as a calibration method, we found the sole field dynamics of one session insufficient to calibrate field fluctuations in other sessions. Specifically, while the fluctuation patterns were qualitatively reproducible, several of their parameters varied between sessions. In particular, the global $B_0$ offset differed at the start of each session, depending on the heating history of the system. Consequently, strong image fluctuations (mean SD: 0.4 %, max SD: 9.1 %) remained despite calibration with the $k_0$ dynamics of another session. For $k_{xy}$, the variation between sets predominantly manifested in the offset and dynamic range of the projections. Therefore, the image accuracy decreased from day to day using session calibration. One could envisage that calibration methods might succeed if the reproducible behavior determined by magnetic field monitoring would be complemented by a simpler measure for the variable parameters, such as navigators for the determination of the $f_0$ frequency offset or temperature measurements informing a model of the slow saturation dynamics that the projections of $k_0$ and $k_y$ comprise.
With respect to the generalizability of these results to other imaging sequences, such as spirals (Ahn et al., 1986; Glover and Lai, 1998) we expect that high-duty cycle single-shot sequences will induce comparable system-related field fluctuations. This prognosis is based on the observed few readout fluctuation patterns and their recurrent dynamics in each session and on each day, which indicate system-immanent properties. The concrete manifestation of these fluctuations in the images, however, will depend on the acquisition parameters and the k-space trajectory itself. We observed a correspondence in the projections of field and image fluctuations. Based on this, we infer that the majority of image time series fluctuations (64-81%) can be attributed to specific types of field fluctuations. However, there is no straightforward one-to-one mapping. We observed a correspondence of the projection of the second principal component of phase coefficient \( k_y \) (Figure 6.7) and the projection of the first principal component of the reconstructed images influenced by fluctuations in \( k_{xy} \) (Figure 6.8). Despite the first principal component of phase coefficient \( k_y \) captures the vast majority of the variance, the projections of the second principal component in \( k_y \) matches better with the projection of the first principal component of the reconstructed images. Hence, we conclude that also the characteristics of the fluctuations in k-space play a central role.

In this work, we considered field fluctuations in phantom experiments and simulations to isolate the system-related field effects and establish their non-negligible impact on image fluctuations. A natural extension would be to compare the observed effects to the in-vivo case and to assess the influence of physiological fields on EPI image time series. Besides characterizing physiological field fluctuations, this would allow for a comparison to the system-related fluctuations described here and the investigation of their interactions.
7.1 Introduction

Functional MRI (fMRI) targets fluctuations in MR image time series that are correlated with hypothesized time courses of metabolic changes. These changes are linked to brain activity, e.g. via the blood oxygen level dependent (BOLD) contrast. However, this BOLD effect is typically small, amounting to fluctuations on the order of few percent of the mean signal intensity. Hence, to improve the sensitivity of BOLD fMRI, i.e. the detection of
functionally meaningful fluctuations, other confounding fluctuations in the time series have to be minimized.

The main sources of these undesired fluctuations are the imaged object on the one hand, and the MR system on the other hand. Both, the object and the MR system, propagate their fluctuations into the measured signal at three entry points, following the principles of MR Fourier encoding: thermal noise in the receiver channels, magnetization fluctuations, and fluctuations in the encoding magnetic fields.

While the role of thermal noise and physiological noise, a ubiquitous form of magnetization fluctuations, has been studied extensively for fMRI (Birn, 2012; Birn et al., 2008, 2006; Chang and Glover, 2009; Chang et al., 2009; Glover et al., 2000; Hutton et al., 2011; Krüger and Glover, 2001; Triantafyllou et al., 2011), studies of fluctuations in the encoding magnetic fields mainly focused on drifts in the global $B_0$ field. Likewise, the existing correction methods target drifts as well, e.g. using navigators (Foerster et al., 2005; Pfeuffer et al., 2002). Navigators provide point-wise frequency shift measurements between scans and, hence, are blind to any field changes during a scan. Furthermore, they entail changes to the imaging sequence itself, thus increasing acquisition time and altering the prepared magnetization state.

Overall, to this day, the noise landscape formed by encoding magnetic field fluctuations, including global $B_0$ as well as linear gradient fields, remains uncharted territory. In particular, it is unclear how strongly the encoding fields fluctuate during typical fMRI sessions, and how much they increase the noise power in the image time series subsequently. Thus, the prospect of BOLD sensitivity improvements by a suitable correction for field fluctuations also remains elusive.

With the recent advent of concurrent magnetic field monitoring using NMR field probes (Barmet et al., 2010, 2009, 2008; De Zanche et al., 2008), a comprehensive assessment of encoding field
fluctuations became available, simultaneously to image acquisition, and without any changes to the imaging sequence or magnetization state of the object. In a previous phantom study (Kasper, Bollmann et al., 2014, Chapter 6), we used concurrent magnetic field monitoring to investigate system-related encoding field fluctuations. For EPI time series on the relevant time scales for fMRI, i.e. within and between sessions, we found considerable dynamic field changes, such as $B_0$ drifts and trajectory instabilities over several hundred images. These field fluctuations introduced image intensity fluctuations in the percent range, i.e. on the order of the BOLD effect. In particular, field-induced image fluctuations largely outweighed both thermal noise and magnetization preparation fluctuations. Furthermore, concurrent monitoring provided the field information to adequately correct these fluctuations during image reconstruction. The elucidation of system-related field fluctuation effects in this phantom study forms a necessary prerequisite to study the more intricate noise situations for fMRI: In vivo, physiological fields, e.g. due to breathing, may inject additional encoding noise (Foerster et al., 2005; Pfeuffer et al., 2002).

In this work, we assess the effects of encoding field fluctuations for fMRI in a realistic in vivo setting. We set out by measuring the field fluctuations during 2D EPI time series using concurrent magnetic field monitoring. Second, we identify the characteristic fluctuations of both global field and EPI trajectories, and their temporal evolution during fMRI sessions using principal component analysis (PCA). Third, we disentangle subject-induced, i.e. physiological field fluctuations from system-related field fluctuations via their spectral characteristics. Fourth, we systematically study the impact of these field fluctuations of different spatial orders and origins on the image time series. We assess the relative contribution of field-mediated noise to image fluctuations in the measured data, compared to the remaining fluctuations of magnetization or thermal noise. Complementary simulations, isolating the field fluctuations, provide further insight into the structure of field-mediated image fluctuations. Finally, by a detailed ROI analysis
within and between subjects, we address the question how much benefit for BOLD sensitivity is to be expected from field monitoring on a routine basis in fMRI.

7.2 Methods

7.2.1 MR Image Encoding and Field Fluctuations

Spatial encoding in MRI relies on the spatio-temporal variation of magnetic field amplitude $B(r, t')$, leading to a phase $\varphi(r, t)$ of excited transverse magnetization at readout time $t$ with $r = (x, y, z)^T$:

$$\varphi(r, t) = \gamma \int_0^t B(r, t')dt'.$$

(7.1)

The signal $s(t)$ obtained by a receiver coil from an imaging volume $V$ within the object $m(r)$ then reads

$$s(t) = \int_V m(r) \cdot \exp(i\varphi(r, t)) \, dr + \eta(t).$$

(7.2)

where $\eta(t)$ is the thermal noise arising in the receive chain.

Commonly, the magnetization phase is expanded linearly in space to arrive at the well-known k-space formulation of 2D-image encoding:

$$s(t) \approx \int_V m(r) \cdot \exp\left(i\left(k_0(t) + k_{mp}(t) \cdot r_{mp}\right)\right) \, dr,$$

(7.3)

$$= \exp(i k_0(t)) \cdot \int_V m(r) \cdot \exp\left(i k_{mp}(t) \cdot r_{mp}\right) \, dr,$$

\[\text{\underline{B_0 modulation}} \quad \text{\underline{Fourier Encoding}}\]
where \(k_0(t)\) represents the global phase evolution, \(k_{mp}\) the trajectory with \(k_{mp}(t) = (k_m(t), k_p(t))\), and \(r_{mp}\) the coordinate vector within the imaged slice, consisting of a measurement (frequency) and phase encoding direction, i.e. \(r_{mp}(t) = (r_m(t), r_p(t))\). A complete description of the image encoding process would include higher order phase terms in eq. (7.3) as well (Wilm et al., 2011).

The aim of image reconstruction is to invert this signal model, assuming a certain global phase evolution \(k_0(t)\) and trajectory \(k_{mp}(t)\), to retrieve an estimate of the magnetization image that is minimally sensitive to the measurement noise \(\eta(t)\). An incongruity between assumed and actual field evolution can induce various artifacts. Given the coil signal \(s(t)\) only, the origin of image fluctuations between different readouts remains ambiguous; both, i.e., the effects of encoding field fluctuations and true changes in the object magnetization, are mapped onto the resulting image time series. This compromises the sensitivity for the time course of interest, i.e. BOLD.

### 7.2.2 Concurrent Magnetic Field Monitoring

We determine the phase coefficients \(k_0(t), k_x(t)\) and \(k_y(t)\), which characterize the encoding fields, using concurrent magnetic field monitoring (Barmet et al., 2010, 2009, 2008; Wilm et al., 2011). Herein, \(N_p\) magnetic field sensors, or NMR probes (De Zanche et al., 2008), are distributed spatially at positions \(r_p\), and each probe accrues a phase depending on the local magnetic field during image readout as described by equation (5.2). The retrieved phases \(\Phi_p(t)\) are then expanded in terms of spherical harmonic basis functions (Barmet et al., 2008; Roméo and Hoult, 1984):

\[
\Phi_p(t) = \frac{\gamma_p}{\gamma} \sum_{l=1}^{N_l} k_l(t) \cdot h_l(r_p) + \eta(t),
\]  

(7.4)
where $k_l(t)$ are the sought phase coefficients, $h_l(r_p)$ are the basis functions evaluated at the probe positions, and $\eta(t)$ the thermal noise arising in the receive chain of the probes. To allow for magnetic field monitoring concurrently with image acquisition, $^{19}$F probes were used. Due to the spectral separation of $^{19}$F and $^1$H, the monitoring becomes independent from image acquisition and the probe excitation trigger could be set just before the acquisition start (Barmet et al., 2010). This necessitates the correction factor in the probe phase computation taking into account the different gyromagnetic ratios of $^1$H ($\gamma$) and $^{19}$F ($\gamma_p$).

Collecting the phase of all probes into a single vector $\Phi$, equation (7.4) reads:

$$\Phi(t) = \frac{\gamma_p}{\gamma} \cdot P \cdot k(t), \quad \text{where}$$

$$P_{pl} = h_l(r_p),$$

$$k(t) = \left(k_0(t), k_1(t), ..., k_{N_l-1}(t)\right)^T \quad \text{with}$$

$$k_1(t) = k_x(t), \quad k_2(t) = k_y(t), \quad \text{and} \quad k_3(t) = k_z(t),$$

$$\Phi(t) = \left(\Phi_1(t), ..., \Phi_{N_p}(t)\right)^T.$$

The phase coefficients $k_0(t), k_x(t), k_y(t)$ and $k_z(t)$ used in the image reconstruction can then be retrieved from the probe phase evolution via the Moore-Penrose pseudo-inverse $P^+$ of $P$ (Barmet et al., 2008):

$$\hat{k}(t) = \frac{\gamma}{\gamma_p} P^+ \Phi(t), \quad \text{equation (7.6)}$$
where "" denotes an estimated entity. The phase coefficient $k_0(t)$ characterizes the global phase evolution, whereas $k_x(t), k_y(t)$ and $k_z(t)$ constitute linear phase coefficients that can be transformed into the 2D $k$-space trajectory $k_{mp}(t)$ via a simple rotation and translation operation mapping the scanner coordinate system onto the slice geometry.

In summary, the phase coefficients $k_0(t), k_m(t)$ and $k_p(t)$ are retrieved concurrently with the image acquisition and in every scan individually. They can then be used in the image reconstruction to enhance the inversion of the signal model. For convenience, we will introduce the labels $k_0$ for global phase evolution and $k_{mp}$ for the 2D trajectory in the slice plane.

### 7.2.3 Data Acquisition

**Setup and Subjects**

All data was acquired on a Philips Achieva 3 T system equipped with a vendor 8-channel head coil and a custom-built concurrent magnetic field monitoring setup (12-channel T/R $^{19}$F NMR probes). Four healthy subjects (two female, normal weight) participated in this study after written informed consent and under approval of the local ethics committee. One of the subjects (subject 1) underwent the identical measurement protocol repeatedly on three different days to examine within-subject reproducibility. Peripheral Measures of cardiac and respiratory physiology were performed in all measurements using an ECG and breathing belt, respectively.

**Measurement Protocol and Imaging Sequence**

To emulate a typical fMRI acquisition protocol, we acquired three fMRI sessions for each subject per day. Each session contained 400 scans, leading to a total duration of 20 minutes per session. The imaging sessions were interleaved with equally long physiological monitoring sessions (20 min), where concurrent field monitoring continued, while no imaging was performed. On the one hand, this
enables the study of physiological fields in the absence of image encoding fields and system-related fluctuations. On the other hand, this period without EPI measurements mimics breaks between sessions or the arrival of a new subject.

All fMRI sessions utilized a 2D EPI sequence with the following acquisition parameters: TR 3 s, TE 35 ms, EPI readout duration 41.6 ms, receiver bandwidth 375 kHz, voxel size 2.6 x 2.6 x 2.5 mm³, FOV 220 x 220 x 47.5 mm, 10 slices with 2.5 mm inter-slice gap, oblique-transverse orientation with RL-tilt of -20°.

Additionally, a T1-weighted anatomical scan (3D turbo field echo, 1 mm resolution, TR/TE 7.4/3.4 ms) was acquired for each subject.

**Experimental Paradigm: The Social Learning Experiment**

In every fMRI session, subjects performed a variant of the social learning experiment, introduced by (Diaconescu et al., 2014a). Herein, participants had to predict the outcome of a binary lottery for which the probabilities were shown. In the fMRI implementation of the experiment (Diaconescu et al., 2014b), participants received social advice on which option to choose via video-playback of pre-recorded, ecologically valid advice situations, and needed to evaluate the trustworthiness of the adviser when forming their decisions.

The main goal of utilizing this paradigm was to emulate a realistic cognitive neuroscience study and to keep the subject engaged and in a controlled experimental state during the measurements. For the physiological monitoring sessions, on the other hand, no paradigm was performed, and subjects were instructed to remain still and relaxed.
7.2.4 Analysis of Field Fluctuations

Principal Component Analysis of Phase Coefficients

To characterize key contributions to the observed encoding field fluctuations, we performed a Principal Component Analysis (PCA) (Pearson, 1901) of the phase coefficients. Details of this procedure have been described in a previous study (Kasper et al., 2014a). Here, we focus on the key motivation for PCA and the interpretation of the principal components and their projections for the analysis of field fluctuations.

PCA determines a new representation of the data that captures maximum data variability in a minimum set of orthogonal components. Thus, it is a natural choice for studying fluctuation patterns. Additionally, PCA quantifies the relative importance of each component via the amount of explained variance. Furthermore, the projections of the principal components on the data characterize the temporal evolution of these fluctuations. Thereby, PCA helps identifying important sources of fluctuation, and assesses the reproducibility of these fluctuations (Shlens, 2009).

Each principal component (PC) represents a characteristic fluctuation of the readout time course of each phase coefficient. The principal components are eigen-vectors of the covariance matrix $\text{COV}_{k,k'}^l$ of the data, and were computed for each phase coefficient $k_o$, $k_m$ and $k_p$ individually:

$$\text{COV}_{k,k'}^l = \frac{1}{N_t - 1} \sum_{t=1}^{N_t} \left( k_l(t_k, \tau) - \bar{k}_l(t_k) \right) \cdot \left( k_l(t_{k'}, \tau) - \bar{k}_l(t_{k'}) \right),$$

where $n$ is the scan number and $\bar{k}_l(t)$ denotes the mean phase over $N = 3600 = 9 \times 400$ scans for subject 1 and $N = 1200 = 3 \times 400$ scans for the other subjects, with $l \in \{0, m, p\}$. 
The temporal evolution of these characteristic readout time courses over all \( n = 1 \ldots N \) scans is assessed by the projection of the phase coefficient data onto each principal component:

\[
projection_{c,l}(n) = \sum_t PC_{c,l}(t)^T \cdot k_l^{(n)}(t) \tag{7.8}
\]

with \( c \) being the number of the respective principal component.

The corresponding projection visualizes how the contribution of a principal component changes over scans, and thus depicts field fluctuation patterns over time.

**Spectral Separation of Physiological and System-related Field Fluctuations**

The separation of system and physiological field fluctuations is based on the frequency content of their PCA projections, in comparison to a simultaneous peripheral measure of physiology, e.g. via ECG and breathing belt (see Figure 7.2).

First, we estimated the periodogram of the individual PCA projections adopting Bartlett’s method (Bartlett, 1948). We computed the discrete Fourier transform of the projections per session and averaged their amplitude spectra, reducing overall variance. Given the spectral analysis of each projection and the peripheral measures of physiology, we categorized any projection content between 0.15 Hz and 1.2 Hz as physiological fluctuations. Hence, we designed a corresponding Butterworth bandpass filter to retrieve these physiological projection contents, denoted by \( proj_{phys} \) using the Signal Processing Toolbox in Matlab (The MathWorks, Natick, MA), damping frequencies below 0.1 Hz and above 1.4 Hz by at least 15 dB.

The system-related content in each projection, \( proj_{system} \), was computed as the difference between the original projection and the physiological projection content. Consequently, a new set of phase coefficients was computed, which contained system-related
fluctuations exclusively, by multiplying the physiological projections with the corresponding principal components and subtracting these from the raw phase coefficients:

\[ k_{l,\text{System}}^{(n)}(t) = k_{l}^{(n)}(t) - \sum_{c=1}^{N_c} \left( \text{proj}_{c,\text{phys}}^{(n)} \cdot PC_c(t) \right) \]  

(7.9)

The number of components, \( N_c \), was chosen such that the included PCs together explained at least 99% of the variance in the phase coefficients.

Similarly, a new set of phase coefficients containing only the physiological field fluctuations was constructed by subtracting only system-related fluctuations from the raw phase coefficients:

\[ k_{l,\text{Phys}}^{(n)}(t) = k_{l}^{(n)}(t) - \sum_{c=1}^{N_c} \left( \left( \text{proj}_{c,l,\text{Orig}}^{(n)} - \text{proj}_{c,l,\text{Phys}}^{(n)} \right) \cdot PC_c(t) \right) \]  

(7.10)

### 7.2.5 Image Reconstruction

We reconstructed a vectorized image matrix \( m = (m_1, \ldots, m_{\rho}, \ldots, m_{N_\rho}) \) from the sampled coil data \( s = (s_1, \ldots, s_{\kappa}, \ldots s_{N_\kappa}) \), which is encoded by a discrete version of the signal equation (7.2):

\[ s_{\kappa} = \sum_{\rho=1}^{N_\rho} m_{\rho} \cdot \exp(ik_{0,\kappa}) \cdot E_{\kappa,\rho}, \]  

(7.11)

with the entries of the Fourier encoding matrix \( E_{\kappa,\rho} = \exp(ik_{\kappa} \cdot r_{\rho}) \).
First, this coil signal was demodulated with the phase coefficient $k_{0,\kappa}$ describing the global phase evolution:

$$s_{\kappa, \text{demod}} = s_\kappa \cdot \exp(-i k_{0,\kappa}).$$ (7.12)

The SNR-optimal image estimate $\hat{\mathbf{m}}$ was then computed via the Moore-Penrose Pseudo-Inverse of the encoding matrix $E$ (Pruessmann et al., 2001):

$$\hat{\mathbf{m}} = (E^H \Psi^{-1} E)^{-1} E^H \Psi^{-1} s_{\text{demod}},$$ (7.13)

where $\Psi$ is the noise covariance matrix of the signal samples.

This inversion operation to retrieve $\hat{\mathbf{m}}$ was carried out using a conjugate gradient gridding-based iterative reconstruction combining fast matrix-vector multiplication for non-uniform FFT and density compensation (Pruessmann et al., 2001; Beatty et al., 2005; Jackson et al., 1991). The eight coil images were reconstructed separately and combined to the final image using sum-of-squares.

### 7.2.6 Reconstruction Schemes

We reconstructed all images with different reconstruction schemes varying the amount of field monitoring information entering image reconstruction. Thereby, we delineated the influence of field fluctuations on image fluctuations for different spatial orders, $k_0$ and $k_{mp}$, and of different origin, i.e. physiological and system-related field fluctuations (Table 7.1).

As a reference reconstruction, we chose the concurrent monitoring scheme: i.e., reconstructing all coil data using the corresponding concurrently monitored $k_0$ and $k_{mp}$ data for all scans and sessions in all subjects i.e., correcting for all measured field fluctuations in $k_0$ and $k_{mp}$.

The other reconstruction schemes then followed a 2x2 factorial design with respect to $k_0/k_{mp}$ and physiological/system-related field fluctuations. For example, to investigate system fluctuations
in $k_o$, the concurrently monitored phase coefficients of $k_{mp}$ were used to reconstruct the corresponding coil data of each set and scan, while demodulation was performed using $k_{o,\text{Phys}}$ only, i.e. the physiological part of $k_o$ fluctuations. In this way, the effects of uncorrected system-related fluctuations of $k_o$ could be studied in the image time series: While system-related fluctuations were clearly present during signal encoding, we deliberately omitted this information during reconstruction to allow for the propagation of the encoding noise into the image time series – which is the typical situation when reconstructing images on commercial MR systems.

The remaining reconstruction schemes were created in an analogous manner. A complete set of the resulting phase coefficient configurations is listed in Table 7.1.
TABLE 7.1  Reconstruction Schemes. For a definition of $k_o$, $k_{mp}$ see section 7.2.2. For a definition of $k_{System/Phys}$ see eq. (7.10) and (7.11).

<table>
<thead>
<tr>
<th>Reconstruction Schemes</th>
<th>Phase Coefficients used for Reconstruction</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>$k_o$</td>
</tr>
<tr>
<td>CoMo</td>
<td>$k_{0}^{(n)}(t)$</td>
</tr>
<tr>
<td>System Fluctuations $k_o$</td>
<td>$k_{0,Phys}^{(n)}(t)$</td>
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<tr>
<td>System Fluctuations $k_{mp}$</td>
<td>$k_{0}^{(n)}(t)$</td>
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<tr>
<td>Physiological Fluctuations $k_o$</td>
<td>$k_{0,System}^{(n)}(t)$</td>
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<tr>
<td>Physiological Fluctuations $k_{mp}$</td>
<td>$k_{0}^{(n)}(t)$</td>
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7.2.7 Coil Data Simulations

We generated additional synthetic coil data to eliminate any effects of fluctuations in the transmit/receive chain or in the object on the signal. In this way, we isolated pure field-induced image fluctuations. Specifically, we used a numerical phantom and the measured phase coefficients $k_o$ and $k_{mp}$ to encode single coil data for all scans of all nine sessions of subject 1, utilizing the discretized MR signal encoding equation (Eq. (7.11)). Herein, the mean image of session 1, as reconstructed with the reference reconstruction and after removing background noise and non-brain tissue, served as a numerical phantom for the magnetization to be encoded. Image reconstruction using these simulated coil signals then followed the reconstruction schemes described earlier (cf. Table 7.1), incorporating varying degrees of phase coefficient information.
7.2 Methods

### 7.2.8 Statistical Analysis of Image Fluctuations

We assessed quantitatively, how much BOLD sensitivity is compromised by different types of field fluctuations and, vice versa, how much improvement of BOLD sensitivity could be expected by suitable correction methods for field fluctuations, such as concurrent field monitoring.

Different measures for BOLD sensitivity exist (Welvaert and Rosseel, 2013), aiming at characterizing the magnitude of confounding image fluctuations, i.e. noise power, either in absolute terms or relative to the signal of interest. Here, we chose to analyse the signal-to-fluctuation noise ratio (SFNR) per voxel, defined as

\[
SFNR_{\text{voxel}} = \frac{\text{mean}_N(m_{\text{voxel}})}{SD_N(m_{\text{voxel}})},
\]

where both mean and standard deviation (SD) of the voxel magnetization are taken over the \( N \) scans of a session. SFNR makes no assumptions on the particular BOLD signal fluctuation of interest. By relating image fluctuations to the mean intensity, SFNR therefore provides a simple heuristic to estimate the impact of confounding fluctuations on BOLD fMRI, since BOLD fluctuations are typically in the range of a few percent of the mean signal. Furthermore, as we used the same coil data for all reconstruction schemes, SFNR differences purely reflect effects of field fluctuations on the image time series, or the correction thereof.

We computed the mean SFNR in gray matter compartments of the brain, which are the target regions for BOLD fMRI. As a control condition, we chose to compute SFNR in white matter compartments as well, which exhibit a different signal and physiological noise content compared to gray matter. To extract gray and white matter brain regions, we coregistered the anatomical T1 image to the mean functional image of session 1 for each subject using Statistical Parametric Mapping (SPM version 12b), and retrieved white matter and gray matter tissue probability...
Assessment of Magnetic Field Monitoring for EPI Time Series in-vivo maps (TPMs) via the segmentation utility of SPM 12b. The regions of interest (ROI) masks for gray and white matter were created by thresholding the TPMs (probability > 90 %) and eroding the margin pixel of the resulting binary mask. SFNR was then averaged within these ROIs for each subject and fMRI session, as well as for each reconstruction scheme. Finally, the relative SFNR loss compared to the reference reconstruction (concurrent monitoring) was computed.
7.3 Results

7.3.1 Characterization of Field Fluctuations

Regarding the field fluctuations, we present the results of subject 1, who performed the experiment repeatedly on three different days. These data are therefore best suited to examine the reproducibility of the observed field fluctuations. In general, the results were qualitatively and quantitatively reproducible in the other three subjects.

The PCA revealed that most of the field fluctuations (> 99 %) in all phase coefficients could be explained by either one or two principal components (Figure 7.1, left column). Specifically, for $k_o$, the first principal component (PC 1) explained 99.996 % of the variance over all 9 sessions. Similarly, for $k_p$, PC 1 explained 99.7 %. For $k_m$, the readout gradient direction, the first and second principal component explained significant amounts of variance of 94.2 % and 4.6 %, respectively.
Assessment of Magnetic Field Monitoring for EPI Time Series in-vivo
The principal components, i.e. the typical fluctuations patterns within a 2D EPI readout, exhibited a subset of three distinct features for all phase coefficients: The first feature is a linear phase increment over the course of the readout, which can be found in PC 1 of \(k_0\), \(k_m\) and \(k_p\). This corresponds to an offset or shift in the underlying fields, since the phase coefficient expresses the integral of the field (cf. eq. (5.2)). Hence, field offsets occur both in the global field, i.e. in relation to \(k_0\), as well as the spatially linear gradient fields within the slice plane (\(k_m\) and \(k_p\)). Since the PCs are scaled to a dynamic range of 1 rad for \(k_0\) or 1 rad/m for \(k_m,p\) and have a duration of 41.1 ms, a slope (or projection) change of 1 in this linear feature translates into a field offset of \(2\pi/41.1\) ms (/m) \(\approx 4\) Hz (/m).

The second feature of the principal components is a high-frequency modulation at about the EPI readout frequency of 1 kHz, which manifests itself in all PCs of \(k_m\) and \(k_p\), i.e. in the linear gradient fields. A third feature of the principal components can be found in the PCs of \(k_m\), namely a low-frequency modulation of approximately one cycle, i.e. 25 Hz, over the image readout. This low-frequency modulation is present in both relevant PCs of \(k_m\), though with opposite phase. Interestingly, all three features of the principal components occurred in the PCA of the previous phantom study as well (Kasper et al., 2014a), and with the same assignment to principal components and phase coefficients. Since

**FIGURE 7.1**  Principal Component Analysis of field fluctuations over 9 sessions on 3 different days. *(Left)* First Principal Components (PC) for global \(k_0\), phase-encoding \(k_p\) and frequency-encoding \(k_m\) phase coefficients. Most PCs exhibit a linear drift \((k_0, k_m, k_p)\) and modulations with the EPI frequency \((k_p, k_m)\). *(Middle)* Corresponding projections to the principal components, depicting their slow dynamics over sessions and days. A projection change of 1 reflects a field change of 4 Hz for \(k_0\) or 4 Hz/m for \(k_m\) and \(k_p\). *(Right)* PCA projections, zoom into one session. A low periodic modulation (0.2-0.3 Hz) is visible in all projections, presumably due to breathing. Its amplitude corresponds to field changes of about 0.8 Hz in \(k_0\), 8 Hz/m in \(k_p\) and 4 Hz/m in \(k_m\) (PC 1).
no other features occurred in either phantom or in-vivo study, the principal components exhibit no distinct influence of physiological compared to system-related field fluctuations. Thus, the field fluctuation patterns within an image-readout are not affected by physiological noise sources.

The projections of the PCs show the evolution of these typical fluctuation patterns over sessions and days (Figure 7.1, central column). Qualitatively, the within-sessions dynamics are fairly reproducible between sessions and days for most PCs, apart from an arbitrary offset between sessions. The projections cover a dynamic range of up to 10 for $k_o$ and $k_p$, but only 4 for the PCs of $k_m$. Since PC 1 exhibits a linear drift in all phase coefficients, the corresponding projections express slopes, and thus translate into field changes of $10 \cdot 4 \text{ Hz} = 40 \text{ Hz in } k_o$, $40 \text{ Hz/m in } k_p$ and $16 \text{ Hz/m in } k_m$, respectively.

Moreover, the projections exhibit three distinct features for their within-session dynamics: Firstly, a linear drift can be observed in the projection of PC 1 of $k_o$ and $k_m$. For the first two sessions of each day, this drift behavior continues over sessions, but a random offset is introduced for the third session of the day. Most likely, this offset arose from the 20 min break between session 2 and 3, in which subjects left the scanner. Afterwards, they had to be repositioned and re-shimmed, including a re-estimation of the demodulation frequency $f_0$.

The second feature of the projections is a nonlinear decay, that dominates the projections of PC 1 for $k_p$ and PC 2 for $k_m$. Starting rapidly at the beginning of each session, this decay settles into a slow drift towards the end of each session. Especially for $k_p$, the different behavior in session 3 on each day is observed again, altering offsets, phase and decay constants of the session dynamics. The third feature is a modulation of about $0.25 \text{ Hz}$ present in all projections of $k_o$, $k_m$ and $k_p$. On a global scale (Figure 7.1, central column), this feature appears to be noise in the projections. However, after zooming into the session dynamics (Figure 7.1, right
column), the regularity of this modulation becomes evident: The frequency is the same for all projections of $k_0$, $k_m$ and $k_p$, while amplitude and phase vary between phase coefficients and components. Specifically, the projections of PC 1 for $k_0$, PC 1 for $k_p$ and PC 2 for $k_m$ are all in-phase at this frequency, while PC 1 for $k_m$ carries the opposite phase. Relative to the other two global features of the projections, i.e. linear drift and decay, the amplitude of this periodic modulation varies. For PC 1 of $k_m$ and $k_p$, the amplitudes reach about 13 % and 8 % of the dynamic range of the projections within the sessions. For the projections of PC 1 of $k_0$ and PC 2 of $k_m$, on the other hand, the relative amplitudes of this periodic modulation are a lot smaller, peaking at about 1 % and 3 % of the respective dynamic range of the projections within-session.

Compared to the phantom study, similar global features of drift and decay were present there as well, and they related to the same phase coefficients and PCs. Thus, drift and decay in the projections seem to be system-related. The third feature of the projections, however, was absent in the phantom experiment. Hence, the observed low-frequency modulation of all fluctuation patterns at 0.25 Hz appears to be of physiological origin.

Examining the spectral characteristics of the projections (Figure 7.2, left column) further, we found that the frequency content of this periodic modulation in the projections coincides with the main spectral component of the breathing belt measure, at 0.25 Hz. This indicates that the projections are indeed modulated by breathing. Also one higher harmonic of the breathing frequency can be discovered in the spectrum of the projections. In contrast to that, no trace of the second physiological measure, i.e. the ECG, could be found in any of the PCA projections, and thus, no relation between cardiac cycle and field fluctuations could be established.
Assessment of Magnetic Field Monitoring for EPI Time Series in-vivo
7.3 Results

**Figure 7.2** Disentangling physiological and system-related field fluctuations in the PCA projections. *(Left)* Amplitude spectrum of projections of PC 1 compared to peripheral measures of respiratory and cardiac cycle. The breathing frequency can be identified clearly in the 1st projection of $k_o$, $k_m$ and $k_p$. *(Right)* Projections after filtering out the breathing frequencies, reflecting the dynamics of system fluctuations (in gray: unfiltered projections).

After filtering the projections with the proposed bandpass and subtracting these physiology-related periodic modulations, the residual, i.e. system-related, projections reflect the slow drift and decay dynamics described as the first and second feature of the projections (Figure 7.2, right column).

### 7.3.2 Reference Reconstruction: Concurrent Monitoring

Using the full concurrent magnetic field monitoring information, ghosting-free EPIs could be reconstructed, despite the long readout duration of 41 ms (Figure 7.3). However, especially in inferior slices (slice 1,2), dropouts and distortions, i.e. stretching in phase encoding direction (AP) occurred. Overall, the image quality was high, despite that no SENSE acceleration or static Bo correction was applied, apart from some minor checkerboard artifacts in the center of the image.

The standard deviation (SD) images, taken over all 400 scans of one session, revealed similar fluctuations levels in all slices of up to 2.5% of the maximum signal intensity. Location with high concentrations of cerebro-spinal fluid (CSF) exhibited an elevated SD level, namely the ventricles, the borders of the brainstem and the subarachnoid space surrounding the cortex. Additionally, the inferior slices had higher SD frontally, i.e. in the vicinity of strong susceptibility gradients at air/tissue interfaces.

Since SD levels and their spatial distribution were comparable between slices, we focussed on one central slice (slice 5) for further presentation of the image fluctuations in different reconstruction schemes.
FIGURE 7.3  Mean EPI of session 1, day 1 for all acquired slices of subject 1.
FIGURE 7.4  Standard deviation (SD) over session 1, day 1, for all slices of subject 1. Apart from the most inferior slice 1, all slices exhibit a similar SD range, reaching a maximum of 2.5 % signal intensity in the cerebrospinal fluid (CSF).
7.3.3 Characterization of Field-mediated Image Fluctuations

We compared standard deviation (SD) images of the reference reconstruction (Figure 7.4, Figure 7.5 A) to SD images of reconstructions with limited field monitoring information according to the reconstruction schemes (Table 7.1).

For image time series affected by physiological field fluctuations, no discernible difference to the reference SD image is visible in the measured data. Thus, the SD images appear to be dominated by magnetization fluctuations in the object both for $k_o$ and $k_{mp}$ (Figure 7.5 BC). Indeed, when removing magnetization fluctuations in the simulations (Figure 7.6), physiological field fluctuations induce rather small image fluctuations of maximally 0.3 % ($k_o$) or 0.1 % ($k_{mp}$). Fluctuations in $k_o$ manifest themselves at brain and tissue boundaries (Figure 7.6 B), while fluctuations in $k_{mp}$ are concentrated at the brain periphery in phase encoding direction (Figure 7.6 C).

For image time series affected by system-related field fluctuations (Figure 7.5 DE), a strong increase of fluctuations compared to the reference SD image is evident in the measured data for $k_o$ fluctuations (Figure 7.5 D), as well as a moderate increase due to $k_{mp}$ fluctuations (Figure 7.5 E). The complementary coil simulations reveal that SD levels of up to 7 % are introduced by $k_o$ fluctuations, which is a three-fold increase compared to the reference SD image, which mostly contains magnetization fluctuations. These increases are predominantly found at brain and tissue boundaries (Figure 7.6 C). For system-related fluctuations in $k_{mp}$, the image SD reaches 0.7 % in the simulations, which equates to a 25-30 % increase compared to the reference SD image, most prominently in the form of a more strongly varying N/2 ghost (Figure 7.6 D).
7.3 Results

7.3.4 BOLD Sensitivity Losses due to Field Fluctuations

For subject 1, we compared the SFNR losses due to field fluctuations between sessions and days. Both in gray and white matter, we found consistently that field fluctuation led to SFNR losses, or, vice versa, SFNR increased when correcting for field fluctuations using concurrent magnetic field monitoring. In general, SFNR losses due to field fluctuations were higher in gray matter than white matter. However, also the variability of SFNR losses was much higher in gray matter between sessions and days. Overall, we found similar variability between sessions of the same day and between days.

System-related field fluctuations induced much larger SFNR losses, compared to physiological field fluctuations. Specifically, system-related fluctuations in $k_0$ caused SFNR losses of about 40% in gray and 20-30% in white matter (Figure 7.7 C). Fluctuations in $k_{mp}$ induced moderate SFNR losses of 1-3% in gray matter and about 1% in white matter (Figure 7.7 D). These $k_{mp}$-related SFNR losses appeared to be more variable than the losses related to $k_0$. 
Assessment of Magnetic Field Monitoring for EPI Time Series in-vivo

Reference SD Image

$A$

$\kappa_0$

physiological fluctuations

$B$

$C$

$\kappa_{mp}$

system fluctuations

$D$

$E$
Figure 7.5 Standard Deviation (SD) of a measured EPI time series resulting from different reconstruction schemes (equal scaling). (A) The reconstruction using full monitoring information in $k_o$ and $k_{mp}$ serves as a reference. The SD image of slice 5 reflects magnetization fluctuations in the object, most prominently due to CSF pulsatility. (B, C) Physiological field fluctuations in $k_o$ (B) and $k_{mp}$ (C) do not induce discernible alterations of the SD distribution compared to the reference reconstructions. (D) System-attributed field fluctuations in $k_o$ increase SD in most parts of the image significantly, in particular at tissue and brain borders, indicating a varying pixel shift in phase encoding direction. (E) System-attributed field fluctuations in $k_{mp}$, i.e. the EPI trajectory, lead to a more pronounced N/2-ghost structure in the SD images.
Assessment of Magnetic Field Monitoring for EPI Time Series in-vivo

physiological fluctuations

system fluctuations

$k_0$

$k_{mp}$
Physiological field fluctuations, on the other hand, contributed much less to SFNR losses. For $k_0$, physiological field fluctuations comprised small SFNR losses of about 0.5 % in gray and 0.1-0.2 % in white matter (Figure 7.7 A). For $k_{mp}$, the SFNR losses were even smaller, i.e. 0.1-0.2 % in gray matter and less than 0.02 % in white matter (Figure 7.7 B).

The between-subjects analysis of SFNR losses confirmed most of the findings in subject 1 (Figure 7.8). In all four subjects, field fluctuations of different order and origin induced SFNR losses – with the single exception of system-fluctuations in $k_0$ for subject 4, where SFNR decreased in the reference concurrent monitoring data. The variability of SFNR losses between sessions was on the same order as the variability between subjects. Again, SFNR losses were a lot higher in gray matter than white matter regions. Also the ranking of the impact of different field fluctuation on SFNR loss stayed the same as in the within-subject analysis: System-related fluctuations in $k_0$ compromised BOLD sensitivity the most, by reducing SFNR on average by 40 % in gray matter and 25 % in white matter (Figure 7.8 C). System-related field fluctuations in $k_{mp}$ were the second-most important source of SFNR loss, amounting to 1 % the gray matter, and about 0.5 % in white matter areas (Figure 7.8 D). Once more, physiological field fluctuations contributed little to SFNR loss, i.e. 0.2 % due to $k_0$ and 0.02 % due
to $k_{mp}$, although with high variability between sessions and subjects (Figure 7.8 AB).

**Figure 7.7** Reproducibility of SFNR losses in subject 1 over days due to field fluctuations. All SFNR losses are reported relative to the SFNR of the reference reconstruction with full field monitoring information. (A) Physiological fluctuations in $k_o$ consistently induce moderate to small SFNR losses of about 0.5 % in gray and 0.1-0.2 % in white matter. (B) Physiological Fluctuations in $k_{mp}$ induce small SFNR losses in gray matter (0.1-0.2 %) and negligible losses in white matter (< 0.02 %). (C) System-related fluctuations in $k_o$ cause large SFNR losses of about 40 % in gray and 20-30 % in white matter. (D) System-related fluctuations in $k_{mp}$ induce moderate SFNR losses of 1-3 % in gray matter and about 1 % in white matter. These fluctuations appear to be more variable over sessions and days than the other field fluctuation-induced SFNR losses.
7.3 Results

Figure 7.8  SFNR losses per session for all four subjects (S1...S4) due to field fluctuations. All SFNR losses are reported relative to the SFNR of the reference reconstruction with full field monitoring information. (A) Physiological fluctuations in $k_0$ cause small SFNR losses of about 0.1-0.2% in gray and 0.1-0.2% in white matter. (B) Physiological fluctuations in $k_{mp}$ induce low (< 0.1%) or no SFNR losses. (C) System-related fluctuations in $k_0$ cause large SFNR losses consistently in all subjects, amounting to about 30-50% in gray and 20-30% in white matter. (D) System-related fluctuations in $k_{mp}$ induce moderate SFNR losses of 1-3% in gray matter and about 1% in white matter for most subjects. However, high variability between sessions occurs, with subject 4 even showing artifactual SFNR increase in two sessions.
7.4 Discussion

Characterizing field fluctuations for EPI time series in-vivo, we found that only a few fluctuation patterns, i.e. principal components, explained the largest share of variability in the fields (> 99%). In particular, the EPI readout exhibited only 3 different features of variability in zeroth and first spatial order: the field offset during the readout, a high-frequency modulation around the EPI frequency, and a slow modulation of about one cycle over the 40 ms readout.

Interestingly, these features match exactly the fluctuation patterns observed in the previous phantom study. Given that phantom and in-vivo study were conducted on the same system approximately one year apart, this speaks to a high qualitative reproducibility of these fluctuation patterns over extended periods of time. It also implies that the fluctuation patterns are properties of the system and chosen trajectory. Maybe surprisingly, subject physiology, as introduced in this in-vivo study, did not alter the fluctuation patterns within the EPI readout.

Considering the sources of these field fluctuation patterns, we reiterate our speculation from the phantom study that they probably arise from thermal effects. Long, repeated EPI sessions maintain a high gradient duty cycle of the system, leading to heating of the gradient and cryostat, and thus subsequent geometric deformations and field changes. The variable field offset could be explained like this, but also the interaction of a high- and low-frequency fluctuation component. As suggested in the phantom study before, this interaction might reflect a beating of nearby frequencies around the EPI readout frequency that arise from a slight shift (~1-2 %) of mechanic resonances in the MR system with temperature (S. Johanna Vannesjo et al., 2013; Signe J. Vannesjo et al., 2013).
In contrast to previous findings (Foerster et al., 2005; Pfeuffer et al., 2002), these results emphasize that the encoding field evolution during the image readout is changed from scan to scan, not just its static component between scans.

With respect to the temporal evolution of field fluctuation patterns between scans, we found that the PCA projections exhibited global dynamics of linear drift and transient decay over the course of a session. These slow dynamics were reproducible between sessions, apart from their initial values. The dynamic range of field changes reached $40 \text{ Hz}$ for the global field ($k_0$), $40 \text{ Hz/m}$ in the phase encoding gradient ($k_p$), and $20 \text{ Hz/m}$ in the frequency encoding gradient ($k_m$). Both the quality and magnitude of these slow drift-and decay dynamics had been observed in the phantom study. Therefore, they can be assigned to system-related sources as well. The temporal evolution of the decay feature in particular reminds of an exponential heating curve approaching a steady state.

Furthermore, the temporal evolution of field fluctuations over scans exhibited one new feature that was related to subject physiology. We could discern a periodic modulation of the projections of all fluctuation patterns with the breathing frequency that was absent in the previous phantom study. Effect sizes were moderate, amounting to $0.8 \text{ Hz}$ in $k_0$, $8 \text{ Hz/m}$ in $k_p$ and $4 \text{ Hz/m}$ in $k_m$. Other effects linked to subject physiology, e.g. related to the cardiac cycle, could not be detected in the evolution of the field fluctuations.

Overall, the concerted action of these encoding field fluctuations led to a strong increase in fluctuation levels for the uncorrected image time series (up to 50%). Conversely, using the full monitoring information in image reconstruction proved to be a comprehensive correction method to account for the effects of field fluctuations. For all sessions and subjects, SFNR in gray and white matter was consistently maximized when reconstructing the image time series by concurrent monitoring of all reconstruction schemes.
The impact of field fluctuations on image fluctuations differed largely between field fluctuations of different order and origin: As for the field fluctuations themselves, system-related field fluctuations also dominated image fluctuations compared to physiological field fluctuations. System-related fluctuations in $k_o$ were most detrimental, reducing SFNR on average by up to 40% in gray matter regions. Thus, they were of the same order as magnetization fluctuations, i.e. physiological noise, observed in the reference reconstruction using full monitoring information. System-related fluctuations in $k_{mp}$ introduced moderate SFNR losses of up to 3%, which, however, are still on the order of the BOLD effect. Physiological field fluctuations, on average, contributed much less to image fluctuations, i.e. SFNR losses of well below 0.2% for $k_o$ and less than 0.02% for $k_{mp}$ in gray matter regions. However, the spatial distribution of these image fluctuations was highly inhomogeneous, with peak standard deviations of up to 0.3% for $k_o$ and 0.1% for $k_{mp}$.

Nevertheless, compared to previously reported impacts of physiological fields (Pfeuffer et al., 2002), we found rather subtle effects. This discrepancy could be explained by the normal weight and shape of our subjects. Specific subject populations, e.g. obese patients, might induce much stronger effects. The same is true for non-compliant subjects, e.g. psychiatric patients, with irregular, deep-breathing patterns. Furthermore, the magnitude of physiological fields scales with field strength. Thus, correcting of physiological fields will be of particular importance in ultra-high field applications.

The simulations gave further insight into the localization of the observed SFNR losses. $k_o$ fluctuations, both of system and physiological origin, manifested themselves in increased voxel standard deviation (SD) at brain and tissue boundaries. $k_{mp}$ fluctuations, on the other hand, led to a more strongly varying N/2 ghost affecting extended image regions both inside and outside the brain. Therefore, our estimates of mean SFNR loss due to field fluctuations might be conservative, since the most affected gray
matter areas close to tissue boundaries were eroded from the mask for ROI analysis. On the other hand, realignment procedures will partially compensate for bulk shifts of the imaging volume due to a pure $B_0$ drift between scans.

In general, the assessment of voxel-wise SFNR is a suboptimal measure in itself, since partial volume effects of neighbouring voxels will lead to apparent SFNR losses and gains in neighbouring voxels that partially average out effects within the whole region of interest. Conceptually, SFNR will also conflate all magnetization fluctuations, i.e. physiological noise and the BOLD effect. Thus, the definite measure of BOLD sensitivity is the assessment of activation patterns for task-based fMRI, which will be part of our future analysis work.

7.5 Conclusion

In this work, we provided an in-depth analysis of the impact of magnetic field fluctuations on EPI-based fMRI. Employing concurrent magnetic field monitoring using NMR field probes, we measured field fluctuations both in the main field ($k_0$) and k-space trajectory ($k_{mp}$). We found that these field fluctuations propagated into considerable SFNR losses in the in-vivo image time series that reached up to 40 % for $k_0$ and 3 % for $k_{mp}$. Since these effects exceed or equal typical BOLD fluctuations, our results suggest that field fluctuations are a relevant factor compromising BOLD sensitivity. Furthermore, we showed that concurrent magnetic field monitoring provides comprehensive means to correct for the effects of field fluctuations on fMRI time series. By augmenting image reconstruction with the full extent of collected field information, SFNR could be maximized, with highest improvements in gray matter areas. Thus, we believe that concurrent magnetic field monitoring will improve the sensitivity of both task-based and resting-state fMRI, especially in detecting
subtle BOLD effects in small regions of interest underlying learning mechanisms captured with more complex cognitive tasks.
8.1 Introduction

Ultra-high field promises unprecedented insight for functional MRI due to the expected increase in BOLD sensitivity (Huettel et al., 2009) and the feasibility of new functional contrast mechanisms, such as phase fMRI or susceptibility-weighted fMRI (Bianciardi et al., 2013).
However, physiological noise becomes a key limitation to the net contrast-to-noise gain beyond field strengths of 3 Tesla in both task-based (Hutton et al., 2011) and resting-state fMRI (Bianciardi et al., 2009). The category of physiological noise comprises any fluctuations of the voxel time series assessed in BOLD fMRI that do not arise from neuronal metabolism, but have their origin in subject physiology. The main sources of physiological noise are known – movement, cardiac pulsation and respiration (Bianciardi et al., 2009; Brooks et al., 2013) – but for comprehensive noise removal, we lack validated mechanistic models of how the imaging process and the imaged brain itself are affected by these noise sources. Specifically, subject physiology can both alter the encoded magnetization in the brain, as well as the dynamically changing magnetic fields that spatially encode the MR image of that magnetization (Glover et al., 2000; Pfeuffer et al., 2002).

Since the correction for field-mediated physiological effects requires the measurement of the encoding magnetic fields, the proposed correction methods for physiological noise mostly focus on the more accessible fluctuations in encoded magnetization. Purely data-driven approaches (e.g. ICA (Beckmann et al., 2005)) have dwelled alongside voxel-wise noise models derived from peripheral measures of physiology (Birn et al., 2006; Glover et al., 2000). While the data-driven methods focus on typical frequency contents of physiological signal (e.g. heart or breathing rate) or its spatial prevalence (Griffanti et al., 2014; Salimi-Khorshidi et al., 2014) the model-based techniques recruit additional calibration or concurrent measurements to characterize the individual physiology and its translation into magnetization changes. For example, measures of the respiratory and cardiac cycle were used to model periodic changes in voxel time series. Such models were augmented by incorporating magnitude effects, e.g. breathing volume via the respiration response function (Birn et al., 2008) or heart rate via the cardiac response function (Chang et al., 2009). These models typically rest on a solid understanding of the influence of physiology on the BOLD signal, e.g. breathing volume.
and blood oxygenation (Windischberger et al., 2002) or cardiac cycle and pulsatile movement.

In contrast to that, the role of fluctuations in the encoding magnetic fields due to subject physiology has not enjoyed the same level of attention in fMRI, though acknowledged early on (Glover et al., 2000; Noll and Schneider, 1994). Theoretically, the forward signal model of the MR imaging process is well defined and suggests field fluctuations to be a non-negligible source of coil signal fluctuations. These signal fluctuations, in turn, will translate into image fluctuations, if not accounted for during image reconstruction. However, the practical limitations to measuring the crucial, fast-varying magnetic fields simultaneously to image acquisition precluded a comprehensive correction for these field fluctuations thus far. Instead, existing field-related approaches to physiological noise correction mainly targeted snapshots of the main magnetic field dynamics, i.e. $f_0$ changes, due to breathing. They have been assessed using navigator measurements or retrospective phase estimations (Pfeuffer et al., 2002), and corrected for retrospectively or via a feedback-control of the field-homogenizing shim system (Gelderen et al., 2007). Other fluctuations, e.g. modulations of the main field during the encoding of the imaging volume, or alterations of the k-space trajectory, have not been investigated or corrected with these methods.

Recently, concurrent magnetic field monitoring using NMR field probes was introduced as a comprehensive means to measure the magnetic field dynamically and simultaneously with MR image encoding (Barmet et al., 2010, 2008; De Zanche et al., 2008). This technology enables both to study and correct for any field fluctuation of low spatial order that is prevalent in fMRI, including physiological fields. The correction is performed during image reconstruction by augmenting the MR signal model with the additional information of the actual magnetic fields that encoded each image. Initial evidence of the versatility of this method was given in a previous phantom as well as an in-vivo study at 3 T
Physiological Noise in High-Field fMRI: Disentangling Field from Brain (Kasper, Bollmann et al., 2014, Chapter 6, Chapter 7). There, we have seen that both instrumental (MR-system-related) and physiological field fluctuations induce considerable fluctuations in EPI time series. These fluctuations amount to several percent signal change, i.e. are on the order of the BOLD effect itself. Furthermore, for high-field structural imaging, compelling improvements due to field monitoring have been reported (Vannesjo et al., 2012, 2011).

In this work, for the first time, we perform direct measurements of the physiology-induced magnetic fields outside the head during resting-state and task-based fMRI experiments at 7 Tesla. We investigate the effects of both global field and EPI trajectory fluctuations on BOLD image time series. Additionally, we explore the prospects of field monitoring for phase fMRI (Bianciardi et al., 2013), which is more sensitive to long-range external field instabilities, such as physiological fields or shim-field instabilities. We compare signal changes arising from physiological field fluctuations to a voxel-based physiological noise model using peripheral physiological data (Glover et al., 2000; Kasper et al., 2009). Thereby, we can disentangle physiological noise within the brain from the effect of field fluctuations onto the image time series.

In summary, the combination of image-based noise modeling with concurrent magnetic field monitoring provides a comprehensive mechanistic insight into how different noise sources enter the image encoding process, and what their respective contributions are. Finally, by incorporating field information into image reconstruction, our study exemplifies how concurrent magnetic field monitoring serves as a generic correction method for physiological noise in fMRI data at 7 Tesla.
8.2 Methods

8.2.1 MR Image Encoding and Field Fluctuations

Spatial encoding in MRI relies on the spatio-temporal variation of magnetic field amplitude \( B(\mathbf{r}, t') \), leading to a phase \( \varphi(\mathbf{r}, t) \) of excited transverse magnetization at readout time \( t \) with \( \mathbf{r} = (x, y, z)^T \):

\[
\varphi(\mathbf{r}, t) = \gamma \int_0^t B(\mathbf{r}, t') dt'.
\] (8.1)

The signal \( s(t) \) obtained by a receiver coil from an imaging volume \( V \) within the object \( m(\mathbf{r}) \) then reads

\[
s(t) = \int_V m(\mathbf{r}) \cdot \exp(i\varphi(\mathbf{r}, t)) \, d\mathbf{r} + \eta(t).
\] (8.2)

where \( \eta(t) \) is the thermal noise arising in the receive chain.

Commonly, the encoding magnetic field is considered up to the linear gradient fields with time-varying amplitudes \( G_x, G_y, G_z \), and includes the global field drift \( B_0(t) \), i.e.

\[
B(\mathbf{r}, t) \approx B_0(t) + x \cdot G_x(t) + y \cdot G_y(t) + z \cdot G_z(t).
\] (8.3)

Hence, the phase as field integral can be expressed using temporally varying phase coefficients \( k \):

\[
\varphi(\mathbf{r}, t) \approx \gamma \int_0^t B_0(t') dt' + x \cdot \gamma \int_0^t G_x(t') dt' +
\]

\[
\underbrace{y \cdot \gamma \int_0^t G_y(t') dt'}_{k_y(t)} + z \cdot \gamma \int_0^t G_z(t') dt' \cdot
\] (8.4)
where $k_0(t)$ represents the global phase evolution and $k(t) = (k_x(t), k_y(t), k_z(t))$ is the k-space trajectory.

This leads to the well-known k-space formulation of MR-image encoding, using eq. (8.4) with (7.2):

$$s(t) \approx \int_V m(r) \cdot \exp \left( i(k_0(t) + r \cdot k(t)) \right) \, dr$$

$$+ \eta(t),$$

$$= \exp(ik_0(t)) \cdot B_0 \text{ modulation} \cdot \int_V m(r) \cdot \exp(i r \cdot k(t)) \, dr + \eta(t).$$

A complete description of the image encoding process would include higher order phase terms in eq. (7.3) as well (Wilm et al., 2011).

The aim of image reconstruction is to invert this signal model, assuming a certain global phase evolution $k_0(t)$ and trajectory $k(t)$, to retrieve an estimate of the magnetization image that is minimally sensitive to the measurement noise $\eta(t)$. An incongruity between assumed and actual field evolution can induce various artifacts. Given the coil signal $s(t)$ only, the origin of image fluctuations between different readouts remains ambiguous; both the effects of encoding field fluctuations and true changes in the object magnetization are mapped onto the resulting image time series. This compromises the sensitivity for the time course of interest, i.e. BOLD.

### 8.2.2 Concurrent Magnetic Field Monitoring

We determine the phase coefficients $k_0(t)$, $k_x(t)$, $k_y(t)$ and $k_z(t)$, which characterize the encoding fields, using concurrent magnetic field monitoring (Barmet et al., 2010, 2009, 2008; Wilm et al., 2011). Herein, $N_p$ magnetic field sensors, or NMR probes (De Zanche et al., 2008), are distributed spatially at positions $r_p$, and each probe accrues a phase depending on the local magnetic field during
image readout as described by equation (5.2). The retrieved phases $\Phi_p(t)$ are then expanded in terms of spherical harmonic basis functions (Barmet et al., 2008; Roméo and Hoult, 1984):

$$\Phi_p(t) = \frac{\gamma_p}{\gamma} \sum_{l=1}^{N_l} k_l(t) \cdot h_l(r_p) + \eta(t), \quad (8.6)$$

where $k_l(t)$ are the sought phase coefficients, $h_l(r_p)$ are the basis functions evaluated at the probe positions, and $\eta(t)$ the thermal noise arising in the receive chain of the probes. To allow for magnetic field monitoring concurrently with image acquisition, $^{19}$F probes were used. Due to the spectral separation of $^{19}$F and $^1$H, the monitoring becomes independent from image acquisition and the probe excitation trigger could be set just before the acquisition start (Barmet et al., 2010). This necessitates the correction factor in the probe phase computation taking into account the different gyromagnetic ratios of $^1$H ($\gamma$) and $^{19}$F ($\gamma_p$).

Collecting the phase of all probes into a single vector $\Phi$, equation (7.4) reads:

$$\Phi(t) = \frac{\gamma_p}{\gamma} \cdot P \cdot k(t), \text{ where} \quad (8.7)$$

$$P_{pl} = h_l(r_p),$$

$$k(t) = \left(k_0(t), k_1(t), ..., k_{N_l-1}(t)\right)^T \text{ with}$$

$$k_1(t) = k_x(t), k_2(t) = k_y(t), \text{ and } k_3(t) = k_z(t),$$

$$\Phi(t) = \left(\Phi_1(t), ..., \Phi_{N_p}(t)\right)^T.$$
Physiological Noise in High-Field fMRI: Disentangling Field from Brain evolution via the Moore-Penrose pseudo-inverse $P^+$ of $P$ (Barmet et al., 2008):

$$\hat{k}(t) = \frac{\gamma}{\gamma_p} P^+ \Phi(t), \quad (8.8)$$

where "̂" denotes an estimated entity. The phase coefficient $k_0(t)$ characterizes the global phase evolution, whereas $k_x(t), k_y(t)$ and $k_z(t)$ constitute linear phase coefficients, i.e. the k-space trajectory.

In summary, the phase coefficients $k_0, k_x, k_y$ and $k_z$ are retrieved concurrently with the image acquisition and in every scan individually. They can enter image reconstruction to enhance the inversion of the signal model.

### 8.2.3 Data Acquisition

**Setup and Subjects**

All data was acquired on a Philips Achieva 7 T system equipped with a vendor 16-channel head coil and a custom-built concurrent magnetic field monitoring setup (12-channel transmit/receive $^{19}$F perfluoropinacol NMR probes, Vannesjo et al. 2011). The employed 12 NMR probes were unshielded and doped with Fe(III)acac to yield a T2 of about 60 ms. With an inner diameter of the probe capillaries of 0.8 mm, k-space trajectories up to an image resolution of 0.4 mm can be fully monitored (Barmet et al., 2008). While probe excitation was realized at the $^{19}$F Larmor frequency via a separate signal generator and RF amplifier, probe signal reception utilized vacant channels of the scanner spectrometer. To this end, the probe signal first entered a custom RF mixing stage (ZX05-10L+, Mini-Circuits, NY, USA) shifting it to the same intermediate frequency as for the $^1$H signal.

Five healthy subjects (two female, mean age $28 \pm 2$ y, BMI $21.6 \pm 1.8$) participated in this study after written informed
8.2 Methods

consent and under approval of the local ethics committee. Peripheral Measures of cardiac and respiratory physiology were performed in all measurements using an ECG and breathing belt, respectively. Visual stimulation was delivered using MR-compatible LCD-goggles (VisuaStim, Resonance Technology Inc.)

**Measurement Protocol and Imaging Sequence**

To emulate a typical fMRI acquisition protocol, we acquired several fMRI sessions for each subject. Every session consisted of 92 scans with a volume TR of 3 s, amounting to a total duration of just under 5 minutes.

All five subjects participated in three resting state sessions. They were asked to remain still and with their eyes closed. In two of the sessions (Rest 1, Rest 2), subjects were further instructed to breathe normally. In the third session (Rest Deep), subjects were engaged in deep-chest breathing.

Four of the five subjects additionally underwent two task-based fMRI sessions (Task 1, Task 2). Herein, participants performed a simple visual paradigm, observing flickering wedges. These wedges occurred for blocks of 16 seconds either in the upper left and lower right (ULLR) part of the screen or in the upper right and lower left (URLL) part of the screen. Thus, retinotopic quarter-fields in the visual cortex were stimulated alternatingly. Meanwhile, subjects were asked to fixate on a central bright dot. To sustain alertness, they had to respond to slight contrast changes of this fixation dot via button presses.

Two of the four subjects performing the task, repeated the paradigm in a third session (Task Move). This time, they were instructed to accompany every button press with a movement of the whole left arm. Specifically, the button box was positioned on the abdomen, while the left arm remained in a rest position beside the body, only moving to the box for button presses. This behavior should emulate task-correlated limb movement.
The order of all sessions (fMRI 1, fMRI 2, Rest 1, Rest 2, Rest Deep, fMRI Move) was kept identical between subjects to investigate the effect of long-term field changes.

All fMRI sessions utilized a 2D EPI sequence with the following acquisition parameters: TR 3 s, TE 19 ms, EPI readout duration 28.9 ms, SENSE 4, receiver bandwidth 400 kHz, voxel size 1.5 x 1.5 x 1.5 mm³, FOV 192 x 192 x 63 mm, 36 transverse slices with 0.25 mm inter-slice gap. For the chosen slice geometry, $k_x$ corresponds to the phase encoding direction, $k_y$ to the frequency encoding direction, and $k_z$ to the slice encoding direction.

Additionally, a T1-weighted anatomical scan (inversion-recovery, 3D turbo field echo, 1 mm resolution) was acquired for each subject, as well as a Bo and coil receive sensitivity maps ($TR$ 1800 ms, $TE_1$ 3.9 ms, $\Delta TE$ = 1 ms, spin-warp images with a resolution of 2 x 2 x 1.5 mm³).

8.2.4 Analysis of Field Fluctuations using Principal Component Analysis

To characterize key contributions to the observed encoding field fluctuations, we performed a Principal Component Analysis (PCA) (Pearson, 1901) of the phase coefficients. Details of this procedure have been described in a previous study (Kasper, Bollmann et al., 2013, cf. Chapter 6). Here, we focus on the key motivation for PCA and the interpretation of the principal components as well as their projections for the analysis of field fluctuations.

PCA determines a new representation of the data that captures maximum data variability in a minimum set of orthogonal components. Thus, it is a natural choice for studying fluctuation patterns. Additionally, PCA quantifies the relative importance of each component via the amount of explained variance. Furthermore, the projections of the principal components on the data characterize the temporal evolution of these fluctuations. Thereby, PCA helps identifying important sources of fluctuation,
8.2 Methods

and assesses the reproducibility of these fluctuations (Shlens, 2009).

Each principal component (PC) represents a characteristic fluctuation of the readout time course of each phase coefficient. The principal components are eigen-vectors of the covariance matrix $\text{COV}_{k,k'}^l$ of the data, and were computed for each phase coefficient $k_0, k_x, k_y$ and $k_z$ individually:

$$\text{COV}_{k,k'}^l = \frac{1}{N_t - 1} \sum_{\tau=1}^{N_t} \left( k_l(t_k, \tau) - \bar{k}_l(t_k) \right) \cdot \left( k_l(t_{k'}, \tau) - \bar{k}_l(t_{k'}) \right), l \in \{0, x, y, z\}$$

where $n$ is the scan/slice number and $\bar{k}_l(t)$ denotes the mean phase over maximally $N = 19,872 = 6$ sessions x 92 scans x 36 slices.

The temporal evolution of these characteristic readout time courses over all $n = 1 ... N$ scans·slices is assessed by the projection of the phase coefficient data onto each principal component:

$$\text{projection}_{c,l}(n) = \sum_t \text{PC}_{c,l}(t)^T \cdot k_l^{(n)}(t),$$

with $c$ being the number of the respective principal component.

The corresponding projection visualizes how the contribution of a principal component changes over scans, and thus depicts field fluctuation patterns over time.

8.2.5 Image Reconstruction and Pre-Processing

Reconstruction Schemes

We reconstructed all images twice with 2 different reconstruction schemes varying the amount of field monitoring information
entering image reconstruction. Thereby, we delineated the influence of field fluctuations on image fluctuations.

First, as a reference reconstruction, we chose the concurrent monitoring scheme. Herein, all coil data was reconstructed using the corresponding concurrently monitored $k_0$ and $k_{x,y,z}$ information for all scans and sessions in all subjects, thus comprehensively correcting for all measured field fluctuations of zeroth and first order. Global ($k_0$) phase information was used for demodulation of the raw coil data of the 16-channel head coil. The demodulated coil data was then combined with 1st order k-space trajectory information ($k_x, k_y, k_z$) in an iterative, gridding-based, conjugate-gradient SENSE algorithm (Pruessmann et al., 2001; Beatty et al., 2005; Jackson et al., 1991), using an in-house Matlab implementation (The MathWorks, Natick, MA). This algorithm was augmented with multi-frequency interpolation (MFI) for static $B_0$-field correction (Man et al., 1997; Sutton et al., 2003) to yield the final, reconstructed images.

Beside this reference reconstruction scheme, a second “standard” reconstruction was performed on each coil dataset that reflects the typical situation when reconstructing images on commercial MR systems. In this “standard” reconstruction scheme, mean phase coefficients entered both demodulation and gridding-cg stage of the reconstruction. Precisely, the coil data of every scan was reconstructed with the mean phase coefficients $k_0(t), k_x(t), k_y(t), k_z(t)$ taken over all scans of a session, but computed individually for each slice. This reconstruction approach, omitting dynamic updates, resembles common image reconstruction on vendor systems that incorporate reproducible field imperfections, e.g. eddy currents, via EPI phase correction.

Image Pre-processing

The outputs of both reconstruction schemes were complex-valued images, from which magnitude and phase images were computed. The phase images were unwrapped in 3D using PRELUDE (FMRIB
Software Library, FSL), followed by a 1D unwrapping of the voxel phase time series in Matlab.

All sessions of all reconstruction schemes were then realigned to an overall mean using the two-pass procedure of SPM 12b (http://www.fil.ion.ucl.ac.uk/spm/). Specifically, the magnitude images entered the realignment, and the resulting realignment parameters were afterwards applied to the phase images as well. Finally, data was smoothed with a Gaussian kernel (FWHM 4.5 mm).

For subsequent statistical analysis, anatomical masks of gray matter (GM), white matter (WM) and cerebro-spinal fluid (CSF) regions in the brain were created. To this end, the mean magnitude image resulting from realignment was segmented in SPM 12b using unified segmentation and six tissue probability map priors.

8.2.6 Statistical Analysis of Image Fluctuations

SFNR Analysis

We wanted to assess how BOLD sensitivity is compromised by signal fluctuations arising from field fluctuations. To this end, we compared the overall image fluctuations for sessions reconstructed with and without field monitoring information.

We evaluated the magnitude and phase EPI time-series voxel-wise on the realigned, but unsmoothed data. For magnitude data, we quantified the signal-to-fluctuation-noise ratio (SFNR), while for the phase data, we computed the standard deviation (SD) of each voxel time course.

Here, the choice of SFNR to characterize BOLD sensitivity was motivated by having a whole-brain measure, independent of task, since SFNR can be defined for every voxel in the brain as:
Physiological Noise in High-Field fMRI: Disentangling Field from Brain

\[
SFNR_{\text{voxel}} = \frac{\text{mean}_N(m_{\text{voxel}})}{SD_N(m_{\text{voxel}})},
\]

(8.11)

where both mean and standard deviation (SD) of the voxel magnetization are taken over the \( N \) scans of a session. By relating image fluctuations to the mean intensity, SFNR therefore provides a simple heuristic to estimate the impact of confounding fluctuations on BOLD fMRI, since BOLD fluctuations are typically in the range of a few percent of the mean signal.

However, for the phase data, SFNR is not an informative measure, since the mean phase of a voxel can be negative and vary greatly over voxels due to external fields, independent of tissue category. Here, the fluctuations themselves are the signal of interest. Thus, we assessed the denominator of equation (8.11) only, i.e. the standard deviation of the voxel phase over the time course.

For the comparison between concurrent monitoring and standard, non-monitoring reconstruction, we report the SFNR and SD differences as \( \Delta = \text{Monitoring} - \text{Standard} \). Thus, for magnitude data, positive \( \Delta SFNR \) indicates BOLD sensitivity improvement through monitoring, while for phase data, negative \( \Delta SD \) expresses a sensitivity improvement for monitoring. Note that because standard and monitoring-informed reconstructions were performed on the same coil data, the differences in SFNR or SD between both reconstruction schemes purely reflect downstream consequences of field fluctuations.

**Model-based Evaluation of Signal/Noise Components**

Since SFNR does not incorporate any model of the BOLD signal change, it conflates the targeted with the confounding fluctuations into a single SD value, thus providing a somewhat ambiguous measure of BOLD sensitivity. Hence, for a more principled and quantitative evaluation of signal and noise components in fMRI data, the time series of BOLD and physiological fluctuations have to be modelled explicitly.
Therefore, to assess and discriminate different magnetization fluctuations, we analyzed the voxel-wise time series of the smoothed magnitude data in a general linear model (Friston et al., 1994) using SPM 12b. The GLM included 6 rigid-body movement parameters of SPM realignment and 18 regressors generated by the physIO toolbox (part of the TAPAS software suite, http://www.translationalneuromodeling.org/tapas/). These physiological regressors incorporated a $3^{rd}$ order Fourier expansion of the cardiac phase, a $4^{th}$ order expansion of the respiratory phase and a $1^{st}$ order expansion of the interaction (Brooks et al., 2008; Glover et al., 2000). For the task-based fMRI sessions, the two block conditions of ULLR-URLL and URLL-ULLR were modeled using three regressors for the respective convolutions with canonical hemodynamic response function, as well as its temporal and dispersion derivative.

T-contrasts of the task effects and F-contrasts of the physiological regressors were computed and compared between field-monitoring and standard reconstruction. Since the F-contrast is a ratio of extra-sum-of-squares to residual noise variance (Poline et al., 2007), it provides a direct measure of how much variance of the time series is explained by physiological effects. Hence, differences in F-value $ΔF$ between standard and monitored reconstruction were used to elucidate how much variance related to physiology can be reduced by field monitoring.

8.3 Results

8.3.1 Fluctuations in Encoding Fields

The PCA of the individual phase coefficients over slices, scans and sessions provided very consistent results between subjects. In general, most of the phase (or field) fluctuations (i.e. more than 99% of the total variance) could be explained by only a few principal components for each phase coefficient. Predominantly, one or two components sufficed, and only for the frequency
encoding direction \( k_y \), three or four components were necessary. Thus, for the sake of clarity, we will limit our presentation of the field fluctuation results to PC 1, which in all cases explained more than 80% of the total phase coefficient variance, and in 17 out of 20 cases (5 subjects, 4 phase coefficients) more than 95% of the measured variance (Figure 8.1-Figure 8.4).

For the global phase coefficient \( k_0 \), the first principal component strongly dominated all fluctuations, explaining more than 99% of the total variance in \( k_0 \) for all subjects (Figure 8.1). Consistently in all subjects, this first principal component exhibited two distinct features comprising the dominant fluctuation patterns during the EPI readout. Firstly, the phase increased linearly over the course of the imaging readout. PC 1 was normalized, such that the slope of this increase, i.e. the global field offset, corresponded to \( 1 \text{ rad}/29 \text{ ms} \approx 5.5 \text{ Hz} \). Secondly, PC 1 was modulated at or about the EPI readout frequency. However, the relative amplitude of this modulation compared to the linear increase varied across subjects, and maximally reached about 10% of the dynamic range of the linear increase. For the projection of PC 1, which characterizes the temporal evolution of the fluctuation patterns over slices, scans and sessions, two dominating features were discernible as well. Firstly, a low-frequency drift was present in the projections, that was continuous even over sessions, as long as there were no breaks in between them. The dynamic range of this drift covered two projection units, i.e. 11 Hz. Secondly, a high-frequency modulation (compared to the time scale of sessions) superposed the slow drift. This modulation, on first glance, resembled a noisy projection behavior, but became apparent to be periodic at the breathing frequency in a close-up view (Figure 8.6). Furthermore, its dynamic range was greatly increased in the deep breathing session, indicating a causal relation to the respiratory cycle. For all other sessions, this breathing modulation amounted to 0.2-0.3 projection units, i.e. 1.5 Hz or 10% of the slow drift contribution. In contrast to that, for sessions acquired during deep breathing, the breathing modulation increased to 0.4-0.6 projection units, i.e. 4 Hz.
Interestingly, the amplitude of the breathing modulation seemed to be larger for male (S2,S3,S5) than female (S1,S4) subjects. Other than this distinct modulation pattern in the deep breathing session, $k_0$ fluctuations appeared to be the same in rest and task sessions. In particular, the hand movement in the “Task Move” session could not be recovered in either the principal component or its projection.

For the phase-encoding phase coefficient $k_x$, between 95.6 % and 99.8 % of the variance were explained by PC 1 (Figure 8.2). Again, this principal component contained a linear feature, which was normalized to yield a slope of 1 rad/m / 29 ms, i.e. 5.5 Hz/m. Also a high-frequency modulation of the principal component could be discerned, that was somewhat more irregular and not exactly periodic at the EPI frequency. Furthermore, PC 1 showed a small initial dip close to the beginning of the EPI readout. With respect to the projection of PC 1, slow drift and fast breathing modulation were the only clear properties again. The drift, however, was not consistent in all sessions, but could span up to 5 projection units (27.5 Hz/m). The breathing modulation, on the other hand, had a relatively higher contribution than for $k_0$, (20 %, i.e. 1 projection unit or 5.5 Hz/m). For deep breathing, this contribution grew to 1.5-4 projection units, i.e. 22 Hz/m.

$k_y$, the phase coefficient in EPI frequency-encoding direction, showed more variability in fluctuation patterns than the other phase coefficients (Figure 8.3). Specifically, while the first principal component explained more than 98 % of the variance in subject 1,3 and 4, this value dropped to less than 85 % for subject 2 and 5. Furthermore, also the features of the principal component were altered in these two subjects. The high-frequency modulation around the EPI frequency had much higher amplitude and was comparable to the linear phase increase. Furthermore, a slow-frequency modulation occurred for PC 1 in these two subjects, that included 2 cycles per readout, i.e. about 70 Hz. Concerning the projections of $k_y$, once more a slow drift behavior as well as a breathing modulation dominated the fluctuation dynamics over
sessions. The offset of the slow drift changed after re-
determination of $f_0$ (e.g. S1, between session fMRI 1 and fMRI 2) or
after longer breaks between sessions. The range of the drift varied
from 4 projection units (22 Hz/m, S2,S5) to 10 projection units
(S1,3,4). The breathing modulation amounted to 10 % or 25 % of the
drift range, respectively, i.e. about 2 Hz/m. Interestingly, the deep
breathing session did not exhibit a stronger amplitude of the
projection for $k_y$ compared to normal breathing.

For the phase coefficient in slice-encoding direction, $k_z$, the
explained variance by PC 1 reached between 94.8 % and 99 %
(Figure 8.4). Also the features of PC 1, i.e. a linear phase increase
and a modulation at the EPI frequency, resembled the
 corresponding components in $k_0$ and $k_x$. The temporal evolution
of PC 1 over sessions incorporated the same characteristics already
encountered in $k_0$ and $k_x$. However, the slow drift behavior over
sessions seemed somewhat less linear, and was also absent in some
sessions altogether. The dynamic range of the drift was about 5
projection units (27.5 Hz/m) within sessions, but offsets between
sessions could imply an overall range of up to 20 projection units,
i.e. 110 Hz/m. The relative contribution of the breathing
modulation to the projection dynamics was in general high, but
very variable. For the deep breathing session, the modulation
amplitude could reach from 25 % (S1), over 50 % (S4) up to 100 %
(S5) of the drift range.

In summary, comparing all principal components and projections
over the different phase coefficients, we found very similar features
in the fluctuations patterns and in their temporal characteristics
over sessions (Figure 8.5). It is important to note that few
fluctuation patterns (i.e. PCs) explained the vast majority of field
fluctuations (>99 % with 1-2 components; max 4). The first
principal components, i.e. the fluctuation patterns within the EPI
readout, typically constituted a superposition of a linear phase
increase and a modulation at or around the EPI frequency. The
linear phase increase corresponds to a magnetic field offset ($k_0$)
that apparently occurred in the global field, as well as all gradient
fields \((k_x, k_y, k_z)\). The modulation around the EPI frequency might reflect variable eddy current effects due to temperature changes in the MR-system that alter the gradient impulse response function (S. Johanna Vannesjo et al., 2013; Signe J. Vannesjo et al., 2013). The projections of all principal components, reflecting the temporal evolution of the field fluctuations over scans, also comprised two features: a slow drift behavior with variable offset between sessions, and a modulation with the breathing frequency. The slow drift could amount to 3 Hz within a session and 11 Hz over all sessions for \(k_0\), and would reach 11-22 Hz/m within a session and up to 110 Hz/m over all sessions for the linear phase coefficients \(k_x, k_y\) and \(k_z\) constituting the k-space trajectory. The second feature, the modulation of the projections with the breathing frequency, was generally less pronounced than the slow drift, amounting to 1.5 Hz for \(k_0\) and up to 5.5 Hz/m for the linear phase coefficients. For the deep breathing sessions, however, this modulation experienced a two- to fourfold amplitude increase, leading to field changes of up to 4 Hz in main field and 22 Hz/m for the gradient fields (Figure 8.6). The relative ranges of the projections between sessions were comparable over the different phase coefficients, with the prominent exception of the deep breathing session for \(k_y\). Here, the phase coefficient fluctuations, which covered the EPI frequency encoding direction, were hardly altered by deep compared to normal breathing patterns (Figure 8.6).
Physiological Noise in High-Field fMRI: Disentangling Field from Brain

**Subject**

**Principal Component 1**

### Projections of PC 1 over Sessions

- **S1**
  - Phase (rad)
  - $\sigma^2 = 99.7\%$
  - 5 ms to 25 ms

- **S2**
  - Phase (rad)
  - $\sigma^2 = 99.1\%$
  - 5 ms to 25 ms

- **S3**
  - Phase (rad)
  - $\sigma^2 = 99.5\%$
  - 5 ms to 25 ms

- **S4**
  - Phase (rad)
  - $\sigma^2 = 99.9\%$
  - 5 ms to 25 ms

- **S5**
  - Phase (rad)
  - $\sigma^2 = 99.8\%$
  - 5 ms to 25 ms
**FIGURE 8.1** Dominant encoding field fluctuations for $k_o$ in resting state and task-based fMRI sessions. Each row corresponds to one subject (S1-S5). **(Left)** First principal component (PC1) explaining most of the fluctuations of $k_o$ during the image readout. **(Right)** Projection of $k_o$ onto PC1, yielding the temporal evolution over sessions. A projection change of 1 corresponds to a field drift of 5.5 Hz (1 rad/29 ms), given the normalization of the slope of PC1.
262 Physiological Noise in High-Field fMRI: Disentangling Field from Brain

Subj Principal Component 1

$\sigma^2 = 95.6\%$

$\sigma^2 = 99.8\%$

$\sigma^2 = 98.2\%$

$\sigma^2 = 99.2\%$

$\sigma^2 = 99.3\%$

Projections of PC 1 over Sessions

$k_x$

Task 1 Task 2 Rest 1 Rest 2 Rest Deep Task Move

Task 1 Task 2 Rest 1 Rest 2 Rest Deep Task Move

Task 1 Task 2 Rest 1 Rest 2 Rest Deep Task Move

Task 1 Task 2 Rest 1 Rest 2 Rest Deep Task Move

Task 1 Task 2 Rest 1 Rest 2 Rest Deep Task Move
FIGURE 8.2  Dominant encoding field fluctuations for $k_x$ (phase encoding direction) in resting state and task-based fMRI sessions. Each row corresponds to one subject (S1-S5). (Left) First principal component (PC 1) of $k_x$ fluctuations during image readout. (Right) Projection of $k_x$ onto PC 1 over sessions. A projection change of 1 corresponds to a field offset of 5.5 Hz/m.
Physiological Noise in High-Field fMRI: Disentangling Field from Brain.

**Subj**  | **Principal Component 1**  | **Projections of PC 1 over Sessions**
---|---|---
S1  | ![Graph of phase vs time for S1](image1.png) \(\sigma^2=98.7\%\)  | ![Graph of projections for S1](image2.png)
S2  | ![Graph of phase vs time for S2](image3.png) \(\sigma^2=81.7\%\)  | ![Graph of projections for S2](image4.png)
S3  | ![Graph of phase vs time for S3](image5.png) \(\sigma^2=98.4\%\)  | ![Graph of projections for S3](image6.png)
S4  | ![Graph of phase vs time for S4](image7.png) \(\sigma^2=98.1\%\)  | ![Graph of projections for S4](image8.png)
S5  | ![Graph of phase vs time for S5](image9.png) \(\sigma^2=83.1\%\)  | ![Graph of projections for S5](image10.png)
Figure 8.3  Dominant encoding field fluctuations for $k_y$ (frequency encoding direction) in resting state and task-based fMRI sessions. Each row corresponds to one subject (S1-S5). (Left) First principal component (PC 1) of $k_y$ fluctuations during image readout. (Right) Projection of $k_y$ onto PC 1 over sessions. A projection change of 1 corresponds to a field offset of 5.5 Hz/m.
Physiological Noise in High-Field fMRI: Disentangling Field from Brain
8.3 Results

**Figure 8.4** Dominant encoding field fluctuations for $k_2$ (slice encoding direction) in resting state and task-based fMRI sessions. Each row corresponds to one subject (S1-S5). *(Left)* First principal component (PC 1) of $k_2$ fluctuations during image readout. *(Right)* Projection of $k_2$ onto PC 1 over sessions. A projection change of 1 corresponds to a field offset of 5.5 Hz/m.

**Figure 8.5** Dominant encoding field fluctuations of different spatial order for a representative subject (S4) in resting state and task-based fMRI sessions. The highlighted time-courses are magnified in Figure 8.6.
**Figure 8.6** Zoom into projections of Figure 8.5. A projection change of 1 corresponds to a field change of 5.5 Hz ($k_0$) or 5.5 Hz/m ($k_{x,y,z}$), respectively. The periodic breathing cycle is clearly discernible in all projections of all orders, and exhibits a 2-4-fold higher magnitude for deep breathing (colored curves) compared to normal breathing (gray curves).
8.3 Results

8.3.2 Impact of Field Fluctuations on fMRI Time Series

Localization of Field-Induced Image Fluctuations

To investigate where in the brain field fluctuations induce fluctuations in voxel time series, we computed session-wise statistics of the images reconstructed either with field monitoring correction or without. Specifically, we evaluated mean and standard deviation over single sessions, but separately for magnitude and phase images (Figure 8.7).

For the magnitude time series, the mean and standard deviation (SD) images themselves did not reveal any discernible alteration of artifact or noise levels due to field fluctuations. The fluctuations levels (SD) reached about 3% of maximum signal intensity, and were highest in CSF and brain borders (sub-arachnoid space), in particular for the frontal brain regions. In the difference images, consistent artifacts could be found comparing the means that mainly comprised edge enhancement and checkerboard patterns. The edge enhancement reflects a slight shift between monitored and unmonitored sessions, and the checkerboard artifact speak to a slight mismatch in assumed k-space coverage. However, both effects were small, amounting to less than 0.1% of maximum mean signal level. The difference in SD images was also small (< 0.1%), and showed a diffuse distribution over the brain, with slightly higher effects were SD was maximal as well, i.e. at the brain borders, CSF and remaining SENSE ghosts.

For the phase time series, no artifact was visible in the mean images itself, but the SD image showed some more pronounced fluctuations in orbitofrontal areas when no field-monitoring correction was employed. Noise levels reached up to 5% of the dynamic range of the phase. The difference image for the mean again contained edge enhancement hinting at a shift in phase encoding direction. In the difference of the SD images, the phase noise reduction through field monitoring became clearly visible
and amounted to about 1% of the dynamic range of the mean phase.

**Figure 8.7** Manifestation of field fluctuations in in-vivo EPI time series for a representative session (Rest 1) of a single subject (S4). (Top) Mean and standard deviation (SD) of phase and magnitude data using a standard image reconstruction (Center) Same data as (Top), but employing the field-monitoring information during image reconstruction, i.e. removing field fluctuations. (Bottom) Difference between (Top) and (Center), reflecting pure field-fluctuation-induced changes to the image statistics of the session.
8.3 Results

Quantification of Field-Induced Image Fluctuations

We summarized and quantified the encountered image fluctuations by an ROI analysis of segmented gray matter in the brain. Specifically, for the magnitude data, SFNR was computed per voxel and averaged over all gray matter voxels in a slice. Then, the SFNR difference between field-monitoring and standard reconstruction was computed to assess SFNR gain through field fluctuation corrections.

The magnitude data SFNR distribution over slices (Figure 8.8) comprised an increase in SFNR with ascending slice order in all sessions, presumably reflecting coil array sensitivity with proximity to cortex containing gray matter. For different conditions (task, rest) and sessions, SFNR varied, but not consistently over subjects.

We found consistent, but moderate increases in SFNR (1-2 %) for all subjects, when field-induced fluctuations were corrected through monitoring. For the deep breathing sessions, the SFNR increase through field-monitoring doubled to tripled (2-4 %). This indicates the potential order of magnitude of field-mediated physiological noise in the magnitude data. The hand movement, in contrast to that, did not alter the noise statistics.

For a few individual slices, also decreases in SFNR could be observed, presumably due to misalignment of voxels between standard and field-corrected sessions. In subject one, the unusually high SFNR gain through monitoring in the Rest 2 and Rest Deep sessions seems to be of the same origin and artifactual, due to failed realignment.

In the phase images we considered standard deviation (SD) images, since SFNR does not constitute a suitable measure of fluctuations. The mean phase varies vastly over the brain due to external field sources, but independent of tissue category.
SFNR per slice in Gray Matter

<table>
<thead>
<tr>
<th>Subj</th>
<th>SFNR per session</th>
<th>ΔSFNR (with – without Field Monitoring)</th>
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<tr>
<td>S1</td>
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<td>S5</td>
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Without Field Monitoring

With Field Monitoring
8.3 Results

**Figure 8.8**  Quantification of field-induced image fluctuations in the magnitude data (Abs). One subject per row (S1-S5) (Left) Signal-to-Fluctuation-Noise Ratio (SFNR) in Gray Matter (GM) for all sessions and slices (ascending 1-36). All sessions were reconstructed by using the concurrent field-monitoring information (green) and the session mean of the field monitoring data (black). (Right) SFNR difference between monitored and standard image reconstruction for all sessions and slices.

The phase SD distribution over slices showed similar behavior to the magnitude data, in that fluctuations were maximal in lower slices. This might relate to coil sensitivity again, but could also speak to the stronger presence of physiological fields in inferior slices due to the proximity to the magnetized tissue displacement in the thorax.

For different conditions (rest, task), no consistent variations of SD could be found. However, the deep breathing introduced a two- to threefold increase in phase SD, which was more pronounced in inferior than superior slices, hinting again at the stronger field effects of physiological noise closer to the lungs through breathing.

For all subjects, we found consistent and considerable phase SD reduction through field monitoring in a majority of sessions. These improvements reached typically 10-20% in resting and task-based sessions, and where strongest in the deep breathing session. Where field monitoring could reduce the SD by up to 50%, compared to standard reconstruction.

Occasionally, one session (subject S3, S4) or once even two sessions (S5) showed increased SD through field fluctuation correction, possibly indicating limited robustness of the phase estimates through monitoring, or higher order field effects that were erroneously projected onto lower field orders. In subject 1, the Rest 2 and Rest Deep sessions again seemed to reflect the realignment problem, since no valid gray matter voxels could be found in the standard reconstruction scheme for some slices.
Phase SD per slice in Gray Matter

Subj | SD per session | ΔSD (with – without Field Monitoring)

S1

Phase SD

S2

Phase SD

S3

Phase SD

S4

Phase SD

S5

Phase SD

SD per session:
- Task 1
- Task 2
- Rest 1
- Rest 2
- Rest Deep
- Task Move

ΔSD (%):
- Without Field Monitoring
- With Field Monitoring
8.3 Results

**FIGURE 8.9** Quantification of field-induced image fluctuations in the phase data. One subject per row (S1-S5). *(Left)* Standard deviation (SD) of the voxel phase in Gray Matter (GM) for all sessions and slices (ascending 1-36). All sessions were reconstructed by using the concurrent field-monitoring information (green) and the session mean of the field monitoring data (black). *(Right)* SD difference between monitored and standard image reconstruction for all sessions and slices.

In general, SFNR and SD can only serve as a proxy for BOLD sensitivity and subsequent improvement for fMRI, because the signal of interest, i.e. BOLD, is also a fluctuation, and thus conflated with untargeted noise sources. A model-based statistical analysis gives a more principled means to study these different fluctuation aspects.

### 8.3.3 Localization of Physiological Effects: Magnetization vs Field

We assessed the statistical parametric maps of contrasts modeling BOLD response and physiology-correlated noise for both field-monitoring and standard reconstruction. Thereby, the influence of field-monitoring correction on statistical fMRI analyses can be studied, as well as the disentanglement of everything termed “physiological noise” into a field-mediated and purely magnetization fluctuation component.
Physiological Noise in High-Field fMRI: Disentangling Field from Brain
8.3 Results

**Figure 8.10** BOLD contrasts of interest and sites of physiological noise for one representative subject (S4). Statistical maps of all sessions are overlayed. (Top) Statistical Results computed on standard-reconstruction imaging data. T-maps of the difference contrasts between both conditions of visual stimulation (left); F-maps of respiratory (blue-green) and cardiac (red-yellow) phase regressors (right). (Center) Same contrasts as above, but computed on field-corrected data. (Bottom) Difference between T/F-maps of standard (top) and field-corrected data (center), illustrating the influence of field monitoring on statistical analysis results.

For the t-contrasts comprising the task effects of visual stimulation (ULLR-URLL and URLL-ULLR, see Figure 8.10), we found the expected stimulation of the visual quarter-fields for the respective conditions, that was robust in all subjects (p < 0.05 whole-brain family-wise error correction (FWE)). Both standard reconstruction and field-monitoring corrected reconstruction delivered the same activation patterns, with only subtle differences in t-values (< 5%). No clear trend of sensitivity improvement could be found for standard or field-monitoring reconstruction. Two subjects showed a slight overall increase with monitoring, while the other two revealed an equally small reduction in t-values that did not survive multiple comparison correction.

For the F-contrasts assessing physiological regressors, we found the typical sites of elevated explained variance in both standard and field-monitoring reconstruction, for all subjects (p < 0.05 FWE, F>10). Fluctuations correlated with the cardiac cycle close to the circle of Willis, anterior communicating arteries and the CSF surrounding the brainstem (Figure 8.10, right, red-yellow overlay). Fluctuations correlated with the respiratory cycle predominantly at the tissue borders and brain boundary in all slices. The difference in F-values between standard reconstruction and field-monitoring correction indicates a strong noise reduction effect of field monitoring, that was consistently observed in 4 of 5 subjects (Figure 8.11). Subject 1 seems to be an outlier again with changing physiological noise patterns due to field monitoring all over the brain.
Physiological Noise

Subject  \( \Delta F \) (Without Field Monitoring – With Field Monitoring)

S1

S2

S3

S4

S5

\( \Delta F \)

1

Respiration

1

Cardiac

5

5
This noise reduction through field monitoring was mostly observed for the breathing-related regressors and amounted to 10-20% of their explained variance. The location of maximum noise reduction coincided with the sites of highest explained variance, i.e. mostly at brain and tissue borders. Note that this noise reduction was purely the effect of a correction for field fluctuations. Therefore, a considerable amount of the commonly found variance correlated to breathing presumably stems from field-mediated effects, such as trajectory scaling or slice shifts.

On the other hand, for the cardiac regressors, only localized changes of the F-contrast could be observed in the lower brainstem and aquaeduct. Typically, these are also sites of interaction effects between cardiac and respiratory cycle (Brooks et al., 2008). Removing the field-mediated breathing component mights shift the fluctuation to a pure correlation with the cardiac cycle. Independent of this, the vast majority of cardiac-related physiological noise seems to manifest in the magnetization directly, and not the mediated through encoding fields.

8.4 Discussion

In this work, for the first time, we successfully demonstrated the application of concurrent magnetic field monitoring in ultra-high-field fMRI. Measuring field and image time series during different task and rest conditions, we provided a comprehensive overview of the type and strength of field fluctuations that occur in global field and 2D EPI trajectories within and between scans and in typical imaging situations. We observed that the main alterations (> 99%
explained variance) of the encoding magnetic fields at $0^{th}$ and $1^{st}$ spatial order could be summarized by as few as two features. On the one hand, field offsets of global and gradient field occur, which remain constant during the individual readout. On the other hand, global and gradient field fluctuate at about the EPI readout frequency during the readout. Between slices and volumes, these magnetic field fluctuations experience a slow drift and a quicker modulation with the breathing frequency. The drifts can accumulate to field shifts of 11 Hz and gradient deviations of up to 110 Hz/m. The field modulation with respiratory cycle reaches up to 1.5 Hz (5.5 Hz/m for the gradients) for normal breathing and 4 Hz (22 Hz/m) for deep breathing, with no influence of task.

The second major insight of this study lies in the impact of magnetic field fluctuations on image fluctuations in EPI time series. Herein, we confirmed that field fluctuations at high field introduce SFNR losses up to a few percent in the magnitude time series, i.e. in the range of the BOLD effect. This is in good congruence to previous findings at lower main fields (Kasper et al., 2014a). Furthermore, we evaluated the sensitivity of phase images to field fluctuations, and showed that external field fluctuations up to first order contribute up to 50 % to the overall phase fluctuations in a voxel time series.

In both cases, i.e. for magnitude and phase fMRI time series, we demonstrated how concurrent magnetic field monitoring could serve as a general correction method for field-induced image fluctuations. In particular, the inclusion of field fluctuations in the image reconstruction process removed unexplained encoding variance in the signal model that led to a net increase of magnitude SFNR by up to 5 % or a considerable reduction in phase SD by up to the aforementioned 50 %. Thus, in particular for phase fMRI, field monitoring may become an enabling technology. Note that, because all analyses were performed on the realigned image time series, field monitoring provides an additional benefit for noise removal. The typical image pre-processing strategies, including drift removal, did not correct for these intricate effects of field
fluctuations, since they do not possess a mechanistic, measurement-informed model of the underlying noise-generating processes.

Thirdly, we presented the first successful combination of field-monitoring with voxel-based physiological noise modeling in this study. We utilized the physIO toolbox to derive physiological fluctuations of the magnetization from peripheral measures and compared their contributions to image time series reconstructed with and without field monitoring. This way, we were able to disentangle field-mediated and magnetization-residing physiological noise. We could confirm that a significant amount of respiratory noise is indeed field-mediated (> 10%), i.e. does reflect a fluctuation in the encoding fields rather than a localized change in magnetization, e.g. through oxygenation levels in the blood. Cardiac noise, on the other hand, as modelled by RETROICOR (Glover et al., 2000), remained largely unaffected by field fluctuations, with the possible exception of cardio-respiratory interactions. Thus, cardiac noise predominantly arises from local magnetization fluctuations, e.g. through pulsatile flow or blood volume changes. Overall, concurrent field monitoring and voxel-based physiological noise modeling provided complementary benefits for BOLD sensitivity.

To further improve and investigate the noise situation for BOLD fMRI at high field, some extensions to the current study can be foreseen. Firstly, the experiments could be replicated in a larger subject pool with a wider range of anatomic variability. This would also justify a more detailed quantitative analysis of the fluctuations than the SFNR/SD assessment presented here. Specifically, the relative contribution of BOLD signal power compared to physiological noise and field noise power could be evaluated by a GLM analysis of the task-based sessions. For example, F-value differences of task/RETROICOR contrasts could be evaluated in an ROI analysis for both anatomically and functionally defined regions. Similarly, for resting state applications functional connectivity analyses could be performed on sessions
reconstructed with and without field monitoring. Thereby, one could exclude widespread voxel time series correlations due to encoding field fluctuations that are not related to neuronally induced, i.e. functional, connectivity. Along the same lines, the field-monitored phase time series could be analyzed with the full pre-processing framework proposed for phase fMRI (Bianciardi et al., 2013), combining noise reduction at the generative and post-processing stage of the phase image time series.

The decisive question to answer with our work is whether field-mediated image fluctuations are a considerable factor for BOLD sensitivity, that justify the extra measurement and reconstruction effort brought in by monitoring. We believe that the results presented here already provide first evidence to a favorable answer towards monitoring, since the observed fluctuations corrected by our approach were in the range of the BOLD effect. These results will be further corroborated by simulation studies that employ the field fluctuations measured here. By generating image time series with true encoding field, but only artificial magnetization fluctuations, we will be able to quantify the unique contribution of field monitoring up to the level of statistical parametric maps.

However, we also believe that the effect sizes reported here constitute a rather conservative estimate of the impact of field fluctuations on BOLD fMRI. For example, compared to other studies (Pfeuffer et al., 2002; Versluis et al., 2010), we saw smaller physiological field fluctuations of only 1.5-4 Hz. On the other hand, these findings correspond well to a linear scaling of the effects we observed at 3 Tesla before (0.8 Hz breathing amplitude in $k_0$, cf. Chapter 7) and reported effect sizes for anatomical imaging (Vannesjo et al., 2011). One possible explanation for this unusually small amplitude of the breathing-field may be the low BMI of our subjects (BMI<22). Furthermore, the magnetic fields induced by breathing have been reported to contain higher, i.e. 2$^{nd}$ and 3$^{rd}$ spatial order components, that were not corrected for in our field-monitoring reconstruction (Gelderen et al., 2007). The extension of the reconstruction to include higher-order field information has
been established before (Vannesjo et al., 2012; Wilm et al., 2012, 2011) and can be performed on the already existing data, since we acquired full 2nd order field information with the 12 employed NMR field probes. With respect to system-related field fluctuations, we have also seen unexpectedly low effects of main field or gradient drifts. Specifically, the overall dynamic range of drifts in the global field amounted to only 11 Hz within an hour, whereas in previous studies at 3 Tesla, we observed drifts up to 30-40 Hz for a different EPI sequence (Kasper et al., 2014a). Thus, in the current study, by the choice of resolution and SENSE-factor, we presumably chose a favorable EPI readout frequency and duty cycle. Consequently, we probably avoided a mechanical resonance of the system and minimized heating effects of the system.

In summary, the ability to study field fluctuations for fMRI concurrently to image acquisition using NMR field probes opens up at least three different worthwhile opportunities: First, the main contributing field effects can be characterized and their impact on time series fluctuations can be estimated. Second, and at the same time, the comprehensive correction of these field fluctuations becomes available during image reconstruction. Third, field monitoring can be employed at an earlier stage to inform fMRI acquisition design, e.g. with respect to geometry parameters or the trajectory choice. Herein, on the one hand, measuring the field dynamics over sessions helps identifying robust sequences that are only affected by physiological fields, but minimally sensitive to system instabilities, as seen in this study. On the other hand, by utilizing field monitoring, even sequences with a high impact on system fluctuations can be realized without SFNR penalty (Kasper et al., 2014a). Hence, concurrent magnetic field monitoring facilitates the design and practical application of system-demanding sequences that are optimal for fMRI acquisition in terms of measurement efficiency (Kasper et al., 2010).
9.1 Conclusion

This work employed a mechanistic stance on MR image encoding in the pursuit of noise reduction for fMRI. The key concept of this perspective is that noise enters fMRI via three distinct paths defined by the fundamental MR image encoding equation: the encoded object, the encoding fields and the signal detector. While each pathway received undivided attention in the different chapters of this thesis and required unique correction methods, one overarching technology has been instrumental to the comprehensive perspective on noise presented here: concurrent magnetic field monitoring.

Monitoring the encoding fields simultaneously to MR image acquisition provides both the means to quantify and correct for diverse encoding field fluctuations, as well as to expand the space of efficient acquisition schemes by lifting fidelity and reproducibility constraints on the encoding fields. Hence, it can
directly target the two respective entry points of noise for fMRI, i.e. encoding field fluctuations and thermal noise (via acquisition efficiency).

This work has given a first tentative demonstration of the potential of field monitoring for fMRI in both respects, focusing on the prevalent acquisition scheme in fMRI, 2D echo-planar imaging (EPI). Specifically, on the one hand, for the correction of undesired encoding field modulations, the unique impact of system- and physiology-induced field fluctuations on resting-state and task fMRI has been studied employing EPI encoding at 3 Tesla and 7 Tesla. With respect to the implementation of demanding, optimized field modulations, on the other hand, matched-filter 2D EPI was introduced and validated as an acquisition-efficient extension to EPI with a complex gradient waveform in need of field monitoring.

First, with respect to field fluctuations in EPI, a correction built on concurrent magnetic field monitoring could so much as double the signal-to-fluctuation noise ratio (SFNR) in fMRI time series (Chapter 6, 7). Herein, system-inherent field fluctuations were the dominant noise source, and mainly arose from heating-induced field fluctuations in the main magnetic field. If uncorrected, these main-field fluctuations deteriorated SFNR by up to 50% (Chapter 6). Fluctuations of the encoding EPI trajectory itself contributed to a lesser degree, i.e. several percent SFNR loss. Both effects critically depended on timing parameters of the acquisition sequence, and could be mitigated by avoiding mechanic resonance frequencies of the MR system in the choice of the EPI readout (Chapter 6/7 vs 8). The second considerable source of field fluctuations arose from subject physiology, in particular breathing (Chapter 7, 8). These effects scaled with the main magnet strength amounting to just under 1% SFNR loss at 3 Tesla (Chapter 7), and 2% at 7 Tesla (Chapter 8). More than main field strength, subject behavior, e.g. breathing depth, altered the noise impact of physiological fields, and could triple the SFNR loss, reaching up to 5% at 7 Tesla (Chapter 8). Importantly, the observed field fluctuations were
9.1 Conclusion

highly unpredictable and could only be corrected for by real-time concurrent assessments, such as concurrent magnetic field monitoring. Moreover, field monitoring gave insight into the generating mechanisms of the fluctuations and their temporal evolution.

With respect to the second realm of monitoring benefits, the implementation of efficient, but system-demanding acquisition schemes, standard EPI was developed into a matched-filter acquisition within this work (Chapter 5). Therein, the inevitable thermal noise entry through signal detection, i.e. the receiver coil, was counteracted by an SNR-optimal trajectory to realize an overall 30% SFNR yield. Furthermore, the SFNR gain translated into comparable increases in BOLD sensitivity of up to 30% for task-based fMRI. This sensitivity increase was accomplished by adapting the MR acquisition to a priori knowledge about the subsequent fMRI analysis pipeline. Specifically, image smoothing during post-processing was accommodated by 2D Gaussian density-weighted EPI. Field monitoring proved to be essential for the practical implementation of this trajectory, since the demanding velocity modulation of the gradient waveform was not realized as nominally specified. Hence, only image reconstructions employing concurrent field monitoring provided artifact-free image time series viable for practical use in fMRI.

For the third entry point of noise, non-BOLD magnetization fluctuations, field monitoring facilitated noise correction by removing field-mediated apparent magnetization fluctuations (Chapter 8). Up to 25% of image fluctuations correlating with respiration were in fact field-mediated and could be corrected by field monitoring-based image reconstruction. However, the origins of magnetization fluctuations go beyond image encoding itself, and require to incorporate models of the physiological mechanisms intrinsic to the brain. To this end, the physIO Toolbox was developed within this work to model physiological noise from peripheral measures of cardiac and respiratory cycle (Chapter 4, 8). This approach could remove up to 70% of the residual variance in
voxel time series, in particular related to the cardiac cycle. In summary, the physIO Toolbox provided complementary noise correction to concurrent magnetic field monitoring, in that it addressed effects of field fluctuations originating inside the head as well as fluctuations of magnetization that were uncorrelated to field changes.

### 9.2 Outlook

The combination of concurrent magnetic field monitoring with fMRI in this work emphasized the methodological aspects of the technique, while relying on established resting-state or basic sensory-motor paradigms. Now, monitoring could be employed to answer state-of-the-art neuroscientific questions by exploiting its ability to avoid SFNR losses related to field fluctuations. The accomplished BOLD sensitivity gains might benefit the detection of subtle task effects in cognitive paradigms (Diaconescu et al., 2014b; Iglesias et al., 2013). Similarly, field monitoring bears great potential as an enabling technology for the recently introduced phase fMRI contrast (Bianciardi et al., 2013), since it considerably reduced variance in phase images at high field (Chapter 8). Furthermore, even model-based noise correction could profit directly from field monitoring. Given calibration data that links peripheral physiology to field fluctuations, the MR image-encoding model could provide voxel-wise estimates of time series arising from field fluctuations. These time series could be integrated into the physIO Toolbox and in turn enable image-based noise correction for physiological, but field-mediated noise. To this end, an even more precise characterization of the magnetic field fluctuations might be desirable, incorporating field terms of higher spatial order in both measurement and image reconstruction.

Conceptually, an important insight of this work concerns the relative robustness of 2D EPI against both physiological noise and system-related fluctuations of this trajectory during typical
imaging sessions. This might not come as a surprise, since 2D EPI has remained the method of choice for fMRI applications over the last two decades. However, as seen in the comparison of field drifts for EPI at 3 Tesla and 7 Tesla (Chapter 6/7 vs 8), the robustness of EPI critically depends on specific parameter choices for the acquisitions. For example, if the combination of field of view and resolution results in an EPI readout frequency close to a mechanic resonance of the MR system, heating effects on the main field could attain a multiple of the field drift observed otherwise (50 Hz at 3 Tesla with 1100 Hz readout frequency compared to only 11 Hz at 7 Tesla with 500 Hz readout frequency). Obviously, this information about the system response has to be available up-front, e.g. via suitable calibration measurements, to avoid unfortunate parameter choices. In fact, monitoring has been successfully used to this end, determining the impulse response function of gradient and shim systems using a magnetic field camera (S. Johanna Vannesjo et al., 2013; Signe J. Vannesjo et al., 2013). With the resulting information on mechanic resonances, acquisition schemes exhibiting a high predisposition for field fluctuations can be avoided. Concurrent magnetic field monitoring, on the other hand, adds a new degree of freedom to fMRI sequence design and selection. Instead of excluding unstable trajectories, candidates with superior acquisition properties can be chosen regardless of their sensitivity to field imperfections or fluctuations. The down-stream consequences of SFNR loss in the time series can be prevented by incorporating concurrent field monitoring information into image reconstruction. Conversely, concurrent magnetic field monitoring will only unfold its full potential for sequences that are sensitive to field fluctuations in the first place.

In particular, two existing fMRI acquisition schemes appear to be perfectly suited for the combination with concurrent magnetic field monitoring: spiral trajectories (Ahn et al., 1986; Glover and Lai, 1998; Law and Glover, 2009) and 3D EPI (Poser et al., 2010). In principle, both trajectories exhibit higher acquisition efficiency than 2D EPI, but suffer more strongly from field fluctuations.
Firstly, for spiral fMRI, the demanding, sinusoidal gradient waveforms required to parameterize the trajectory are likely to produce larger inaccuracies compared to the trapezoidal EPI waveforms that are in the core specification of every gradient system. Furthermore, the resulting high-frequency field modulation may coincide with mechanic resonances of the system, and lead to pronounced heating and field drift, as seen for 2D EPI in this work (Chapter 6, 7). Correction for physiological fields is critical for spiral fMRI, too, since off-resonances alter the point-spread function of spiral readouts globally, i.e. translate into blurring everywhere in the brain, as opposed to the dominant shift in phase encoding direction prevalent in EPI. Thus, applying field monitoring to spiral fMRI seems highly desirable to address this sensitivity to field fluctuations. On top, due to the rotational symmetry and inherent density weighting of spirals, the design of a matched-filter spiral acquisition (following the principles of Chapter 5) appears to be a natural combination of both the design and corrective aspects of field monitoring, embracing matched-filter acquisition ideas (Jauslin, 2012). Secondly, 3D EPI, especially at high resolution and main field strength, holds enormous potential for superior acquisition efficiency (Poser et al., 2010). However, physiological field fluctuations become a within-volume confound for 3D EPI, because TR is on the order of seconds (instead tens of milliseconds for 2D EPI). Thus, the full amplitude range of a cardiac and respiratory cycle disturbs a single volume acquisition, deteriorating SNR directly instead of SFNR only (Lutti et al., 2013). Since such physiological fields can be readily monitored and corrected for by the methods introduced in this work, they will provide a considerable SNR yield for 3D EPI.

The framework of concurrent magnetic field monitoring presented here has the inherent character of a retrospective correction method. Precisely, the capability of recovering artifact-free images is based on collecting knowledge about the encoding fields during the acquisition and utilizing it off-line for the inversion of the signal model. However, field fluctuations can mutilate signal generation so severely that the remaining information in the data
becomes insufficient to retrieve a good image estimate at all. In this case, prospective correction methods are required that rectify field deviations at the time of occurrence. Fortunately, field monitoring exhibits great potential in this domain as well, particularly in the form of real-time shim feedback and prospective motion correction using NMR field probes. First, real-time shim feedback can measure and correct magnetic fields up to third spatial order with shim updates in less than 100 ms, i.e. covering typical physiological frequencies as well as system-related drifts. Successful feedback applications for spectroscopy (Wilm et al., 2013) and high-field $T_2^*$-weighted anatomical images (Duerst et al., 2013) have recently been reported, and initial feasibility for resting-state fMRI utilizing 2D EPI was demonstrated, too (Wilm et al., 2014). Second, prospective motion correction can be realized using NMR field probes attached to the head. In an implementation directly applicable to fMRI, high-frequency content of the EPI trajectory is used as a signature for position tracking. The amplitudes of phase modulations in the respective frequency bands provide estimates of the current probe positions with an accuracy of about 30 μm (Haeberlin et al., 2014). Subsequently, the head position is computed and updated in the MR system, such that slice excitation and the geometry of the encoding gradients are adapted to target the displaced acquisition plane. Both probe-based shim-feedback and motion correction can be used complementary to concurrent magnetic field monitoring, thus providing a combined SFNR and BOLD sensitivity gain.

Ultimately, understanding and mastering the noise landscape of fMRI by the combination of field monitoring, trajectory design and image-based physiological noise modeling is likely to generate a multi-fold signal-to-noise improvement for fMRI. Invested into ultra-high resolution applications, this sensitivity gain could broaden the scope of fMRI, e.g. into the emerging field of translational neuromodeling. Translational neuromodeling strives for a mechanistic understanding of brain function in order to propose new, model-based treatments of psychiatric disorders. To this end, investigating the role of neurotransmitter systems is
pivotal, since they can be targeted by psychopharmacological therapy. Two key regions are of particular interest in this approach – and have thus far evaded a robust fMRI measurement on the single-subject level: the brainstem and the cortical layers (Koopmans et al., 2010). The brainstem constitutes the most important hub for neurotransmitter networks in the brain. Distinct functional units, the nuclei embedded in the brainstem, are major production sites of the main neurotransmitters and project to all cortical areas. The nuclei themselves have a spatial extent of only a few mm, requiring high-resolution acquisition. The six layers of cortex, on the other hand, with a thickness of about half a mm each, form important nodes of the neurotransmitter network, since its projections within and between (sub-)cortical areas target specific cortical layers. Even within a brain region, distinct cortical layers may recruit different neurotransmitters for message passing. Therefore, sub-mm fMRI is required to resolve the spatial specificity of the connectivity between layers and their response to particular neurotransmitter modulation. Moreover, accomplishing layer-specific fMRI enables to test important hypotheses for translational neuromodeling concerning synaptic plasticity, such as predictive coding or corollary discharge – a popular theory for psychotic symptoms in schizophrenia.

Both regions, the brainstem and the cortical layers, are particularly susceptible to the noise sources addressed in this work. The brainstem is located in the inferior part of the brain where the strongest SFNR losses from physiological field fluctuations occurred (Chapter 8). Similarly, cortical layers reside close to the brain boundaries that exhibited the strongest image variance increases from breathing-induced field fluctuations. By utilizing concurrent magnetic field monitoring, the impact of these field fluctuations can be effectively reduced. Furthermore, both regions also suffer from pronounced magnetization fluctuations due to the proximity of pulsatile media. Specifically, the brainstem is embedded in CSF surrounding the fourth ventricle, and tangential to the basilar artery. Superficial cortical layers are close to the subarachnoid space (containing CSF) and major veins, e.g. the sagittal sinus.
9.2 Outlook

Model-based physiological noise correction as implemented in the physIO Toolbox has already demonstrated maximum efficacy for SNR improvement in precisely these regions due to the removal of image fluctuations generated by the cardiac and respiratory cycle (Chapter 4, 8).

In summary, the methods developed in this work – concurrent magnetic field monitoring for fMRI, the physIO Toolbox, and matched-filter acquisition – are apt to considerably improve BOLD sensitivity, thereby enhancing and facilitating the application of high-resolution fMRI for translational neuromodeling. Beyond that, one unifying belief inspires the approach to fMRI noise reduction presented here as well as translational neuromodeling in general – it is the belief that a mechanistic understanding of both the measurement technique and its physiological observables will be essential to bring about change to the treatment of psychiatric disorders, and yield the much sought after clinical relevance for fMRI.
A Theoretical SNR Gain of Matched-Filter fMRI for Gaussian Smoothing

We calculate the expected SNR gain for a Gaussian smoothing kernel with a FWHM defining a k-space target density:

\[ d_{target}(k) = \begin{cases} C \cdot \exp\left(-\frac{k^2 \sigma_r^2}{2}\right) & \text{for } |k| \leq k_{max} \\ 0 & \text{otherwise} \end{cases} \quad (A.1) \]

with \( k_{max} = \frac{\pi}{\Delta x} \) and \( \sigma_r = \text{FWHM} / \sqrt{8 \ln 2} \) and \( C = \text{const.} \), such that \( \int_{V_k} d_{target}(k) \, dk = 1 \).

As the Gaussian kernel is separable, we can calculate the SNR gain for each acquisition dimension individually utilizing Eq. (5.10), where \( V_k = 2 \cdot k_{max} \), and yield, for a \( d \)-dimensional scan:

\[
\frac{SNR_{matched}}{SNR_{uni}} = \left( 2 \cdot k_{max} \cdot \int_{-k_{max}}^{k_{max}} d_{target}(k) \, dk \right)^{\frac{d}{2}} \quad (A.2)
\]
The integral on the right hand side can be expressed using the error function \( \text{erf}(x) = \frac{1}{\sqrt{\pi}} \int_{-x}^{x} e^{-k^2} \, dk \) via variable substitution \( k \to k \sigma_r \) yielding

\[
\frac{\text{SNR}_{\text{matched}}}{\text{SNR}_{\text{uni}}} = \left( 2 \cdot k_{\text{max}} \cdot C \cdot \frac{\sqrt{\pi} \cdot \text{erf}(k_{\text{max}} \sigma_r)}{\sigma_r} \right)^{\frac{d}{2}} \quad (A.3)
\]

Because of \( \int_{-k_{\text{max}}}^{k_{\text{max}}} \! dt_{\text{target}}(k) \, dk = 1 \), \( C \) itself can be expressed via the error function as \( C^{-1} = \frac{\sqrt{2 \pi} \cdot \text{erf}(k_{\text{max}} \sigma_r / \sqrt{2})}{\sigma_r} \) to arrive at the final expression for the SNR gain using a matched-filter compared to a uniform acquisition:

\[
\frac{\text{SNR}_{\text{matched}}}{\text{SNR}_{\text{uni}}} = \left( 2 \cdot k_{\text{max}} \cdot \frac{\sigma_r}{\sqrt{2 \pi} \cdot \text{erf}(k_{\text{max}} \sigma_r / \sqrt{2})} \cdot \frac{\sqrt{\pi} \cdot \text{erf}(k_{\text{max}} \sigma_r)}{\sigma_r} \right)^{\frac{d}{2}}
\]

\[
= \left( \sqrt{2} \cdot k_{\text{max}} \cdot \frac{\text{erf}(k_{\text{max}} \sigma_r)}{\text{erf}(k_{\text{max}} \sigma_r / \sqrt{2})} \right)^{\frac{d}{2}} \quad (A.4)
\]
B Analytic Expression for a Gradient Waveform with Gaussian Acquisition Weighting

We derive the readout gradient time-course \( G(t) \) realizing a Gaussian acquisition density \( d_{acq}(k) \) on a k-space traverse from \(-k_{\text{max}}\) to \( k_{\text{max}}\) as follows: By inserting the Gaussian target density of Eq. (A.1) into the differential Eq. (5.11), we first yield a concrete differential equation for the one-dimensional readout trajectory time-course \( k(t) := k_x(t) \):

\[
|\dot{k}| = \frac{1}{d_{acq}(k)} = \tilde{C} \cdot \exp \left( + \frac{k^2 \sigma_r^2}{2} \right) \tag{B.1}
\]

where tilded \( C \) refers to a constant of no interest.

As \( k \) should increase monotonously during a traverse, \( \dot{k} \geq 0 \) and we can neglect the absolute value in Eq. (B.1). Following a logarithmic transform and differentiation, Eq. (B.1) appears in the normal form of a second order nonlinear ordinary differential equation

\[
\ln \dot{k} - \sigma_r^2 k^2 = \tilde{C} \quad \frac{d}{dt} \frac{\dot{k}}{k} - \sigma_r^2 \dot{k} = 0 \tag{B.2}
\]

\[\Rightarrow \ddot{k} - \sigma_r^2 k^2 \cdot k = 0\]

The general solution for this differential equation reads

\[
k(t) = \frac{\sqrt{2}}{\sigma_r} \cdot \text{erf}^{-1} \left( \sqrt{\frac{2}{\pi}} c_1 \sigma_r (t + c_2) \right) \tag{B.3}
\]

with \( \text{erf}^{-1} \) being the inverse error function and \( c_{1,2} \) constants to be determined via side-conditions.
The side conditions arise as the interval $-k_{\text{max}}$ to $k_{\text{max}}$ has to be covered within a traverse duration $T_{\text{traverse}}$, i.e.

\[
k(0) = -k_{\text{max}} \Rightarrow -\sqrt{\frac{\pi}{2}} \cdot \frac{1}{\sigma_r} \cdot \text{erf}\left(\frac{\sigma_r k_{\text{max}}}{\sqrt{2}}\right) = c_1 c_2 \tag{B.4}\]

\[
k(T_{\text{traverse}}) = -k_{\text{max}} \Rightarrow \sqrt{\frac{\pi}{2}} \cdot \frac{1}{\sigma_r} \cdot \text{erf}\left(\frac{\sigma_r k_{\text{max}}}{\sqrt{2}}\right) = c_1 (T_{\text{traverse}} + c_2) \tag{B.5}\]

Dividing Eq. (B.5) through Eq. (B.4) and back-substitution into Eq. (B.4) provides the values for $c_{1,2}$ as

\[
-1 = \frac{T_{\text{traverse}} + c_2}{c_2} \Rightarrow c_2 = -\frac{T_{\text{traverse}}}{2} \tag{B.6}\]

\[
c_1 = \frac{\sqrt{2\pi}}{T_{\text{traverse}} \sigma_r} \cdot \text{erf}\left(\frac{\sigma_r k_{\text{max}}}{\sqrt{2}}\right). \tag{B.7}\]

From that, we yield the final form for the $k$-space trajectory evolution as

\[
k(t) = \frac{\sqrt{2}}{\sigma_r} \cdot \text{erf}^{-1}\left(\frac{\sigma_r k_{\text{max}}}{\sqrt{2}}\right) \cdot \left(2 \frac{t}{T_{\text{traverse}}} - 1\right) \tag{B.8}\]

Taking the temporal derivative of Eq. (B.8), we yield the gradient waveform as specified in Eq. 5.12:
\[ G(t) = \frac{\dot{k}(t)}{\gamma} \]

\[ = \frac{\sqrt{2\pi} \cdot \text{erf} \left( \frac{\sigma_r k_{\text{max}}}{\sqrt{2}} \right)}{\gamma T_{\text{traverse}} \sigma_r c_1} \exp \left( \text{erf}^{-1} \left( \frac{\text{erf} \left( \frac{\sigma_r k_{\text{max}}}{\sqrt{2}} \right)}{c_2} \right)^2 \right) \cdot \left( 2 \frac{t}{T_{\text{traverse}}} - 1 \right) \]

(B.9)


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Cover art based on a CAD rendering of the 7T “clip-on camera” concurrent monitoring setup, courtesy of Skope Magnetic Resonance Technologies LLC. Modified with permission.