High frequency oscillations in healthy brain functions

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Abstract

Neural high frequency activity above 30 Hz has been linked to various brain functions, including sensory processing as well as higher-order functions like attention and memory. However, the origin, role, and function of this gamma band activity is still unclear and popular theories on high frequency activity are highly debated.

This dissertation addresses two major aspects of gamma research: in the first part (Studies 1 and 2), it examines high frequency activity in the visual system, highlighting the interplay of retina and cortex. In the second part (Studies 3 and 4), it addresses the problem that gamma activity constitutes a rather weak signal by examining which recording conditions are ideal and whether the analysis of high frequency activity can benefit from state-of-the-art analysis methods.

Study 1  Several studies imply that the processing of dark stimuli benefits from greater neural resources compared to the processing of light stimuli and is thus faster. Exactly which portions of the visual pathway could be involved in such differences is not yet resolved, and furthermore, related evidence from the human visual system is scant. This study examines the interplay of retina and cortex in the processing of darks and lights by simultaneously recording retinal and cortical responses with electroretinogram (ERG) and magnetoencephalography (MEG) to light offsets and onsets in ten participants. High frequency activity in response to light offset occurred faster than light onset in cerebral cortex, but not in the retina. Furthermore, the bandwidth of the onset and offset responses differed: while light onset elicited a broadband response, light offset was accompanied by narrowband gamma activity. The findings of this study suggest that retinal high frequency activity is transmitted to visual cortex, and that this transmission is presumably faster for light offset activity. These differences in propagation speed point to
the importance of considering retinocortical interactions when interpreting cortical visual activity. Furthermore, this study contributes to the ongoing discussion about the origin and function of visual narrowband oscillations.

Study 2 The retina clearly transfers massive amounts of information to visual cortex, but it is not conclusively resolved whether any information flows in the opposite direction in humans, from the cortex to the retina. This pilot study combines transcranial magnetic stimulation of visual cortex with the simultaneous recording of retinal activity to investigate whether the stimulation of cortical visual areas can affect the retina. In both subjects, retinal activity resembling flash-evoked activity was observed following transcranial stimulation of primary visual cortex, showing a slow potential as well as high frequency activity. Most of the suspected artifacts could be ruled out by sham stimulations and a phantom head investigation. The findings of this study are consistent with the existence of a corticofugal pathway and furthermore provide important indications for an improved design of the forthcoming full study.

Study 3 The application of single-trial and decoding analyses can reveal meaningful brain activity that is obscured in the trial average. In the case of high frequency activity, however, the low signal-to-noise ratio complicates single-trial analyses. In this study, the applicability of a single-trial classification approach to decode stimulus modality from gamma activity was explored. The results show a successful classification of trials with auditory versus visual presentation of words across subjects. High frequency activity in both visual and auditory areas contributed to the classification model. Especially in visual cortex, this gamma activity had a broad bandwidth. The findings of this study show the feasibility of single-trial approaches to weak signals like high frequency activity and furthermore support the view that broadband and narrowband gamma activity may indeed have different roles and should be distinguished.
**Study 4**  Source reconstruction with the beamforming technique is a widely used approach to localize brain activity and increase signal-to-noise ratio. Whether this approach profits from the growing number of channels in state-of-the-art recording systems, e.g. magnetoencephalographic systems, remains unclear. This study investigates how beamformer performance is impacted by sensor count in tandem with key properties of the input data, including signal strength. Counterintuitively, beamformer performance decreases with higher sensor count for strong input signals. With weak signals like high frequency activity, however, source reconstruction with beamformers improves with more sensors.

Integrating these studies, the present thesis sheds light on the origin of high frequency activity in the visual system and highlights the importance of retinocortical interactions to the interpretation of visual cortical activity. It further provides new findings on the role of narrowband and broadband gamma activity and adds to the discussion how high frequency activity in the human brain may represent functional mechanisms. This work furthermore describes the impact of sensor count on beamformer performance, demonstrating that the reconstruction of weak signals like gamma activity profits from having more sensors. Finally, it demonstrates that decoding approaches, combined with beamforming, can successfully classify single-trial high frequency activity, with significant implications for cognitive applications and brain-computer interfaces.
Zusammenfassung

Hochfrequente Hirnaktivität über 30 Hz wird mit verschiedensten Hirnfunktionen in Verbindung gebracht, unter anderem mit sensorischer Verarbeitung oder auch höheren kognitiven Funktionen wie Aufmerksamkeit oder Gedächtnis. Ursprung, Aufgabe und Funktion dieser Gammaband-Aktivität sind jedoch ungeklärt, und gängige Theorien über hochfrequente Aktivität sind umstritten.

Die vorliegende Doktorarbeit befasst sich mit zwei bedeutenden Aspekten der Gamma-Forschung: Im ersten Teil (Studie 1 und 2) wird hochfrequente Aktivität im visuellen System unter besonderer Beachtung der Interaktion zwischen Retina und Kortex untersucht. Der zweite Teil (Studie 3 und 4) befasst sich mit der Problematik, dass Gammaaktivität ein schwaches Signal darstellt. Es wird untersucht, welche Bedingungen bei der Datenerhebung ideal sind, und ob die Analyse hochfrequenter Aktivität von modernen Auswertungsmethoden profitieren kann.


Studie 3 Die Analyse einzelner, nicht gemittelter Zeitreihen oder die Anwendung von Decoding-Ansätzen kann bedeutsame Hirnaktivität offenlegen, welche verborgen bleibt, wenn über die einzelnen Epochen gemittelt wird. Im Falle von hochfrequenter Aktivität wird die erfolgreiche Anwendung solcher Methoden jedoch durch


Bei einer zusammenfassenden Betrachtung dieser Studien gibt die vorliegende Dissertation Aufschluss über den Ursprung hochfrequenter Aktivität im visuellen System und hebt die Bedeutung retinokortikaler Interaktionen für die Interpretation kortikaler visueller Aktivität hervor. Weiterhin werden neue Erkenntnisse
Acknowledgments

First, I would like to express my gratitude to my supervisor, Prof. Sarang Dalal. He introduced me to the topics of high frequency activity and source reconstruction with beamformers, let me engage in the fascinating field of retinocortical interactions, and encouraged me in developing my own research ideas. Thank you, Sarang, for sharing your enthusiasm about science and your extensive knowledge, for all the great opportunities you gave me, and for your support and guidance. I am excited to be your first PhD student and about the forthcoming scientific work in Aarhus!

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Abbreviations

AAL  Automated Anatomical Labeling
BOLD  blood oxygen level-dependent
cTMS  cortical transcranial magnetic stimulation
dACC  dorsal anterior cingulate cortex
DFT  discrete fourier transform
DTL  Dawson-Trick-Litzkow fiber electrode
EEG  electroencephalography
EOG  electrooculogram
ERG  electroretinography
FDR  false discovery rate
FIR  finite impulse response
FlyTri  Flying Triangulation, 3D face sensor
fMRI  functional magnetic resonance imaging
GABA  gamma-aminobutyric acid
GLM  general linear model
HEOG  horizontal electrooculogram
HPI  head position indicator coils
ICA  independent component analysis
iEEG  intracranial electroencephalography
IFG  inferior frontal gyrus
ITC  intertrial coherence
Abbreviations

LCMV  linearly constrained minimum variance beamformer
LFP  local field potential
LGN  lateral geniculate nucleus
MEEG  magneto-/electroencephalography
MEG  magnetoencephalography
MNE  minimum norm estimation
MOBS  modified binary search procedure
MRI  magnetic resonance imaging
MRS  magnetic resonance spectroscopy
MUA  multi-unit activity
PET  positron emission tomography
r.m.s.  root mean square
SAM  synthetic aperture magnetometry beamformer
SFG  superior frontal gyrus
SNR  signal-to-noise ratio
TMS  transcranial magnetic stimulation
V1  primary visual cortex
V2  secondary visual cortex
VEOG  vertical electrooculogram
Chapter 1

Introduction

When Berger reported the first electroencephalography (EEG) measurements from the human brain in 1929, he showed brain waves of different frequencies, among them the famous eyes-closed alpha rhythm, but also oscillations of higher frequencies (around 28 Hz). He argued that these higher frequencies could reflect intellectual work and wondered whether it was possible to prove a link between this intellectual work and the human EEG. Over the following decades, evoked responses came to dominate EEG research and later its magnetic counterpart, magnetoencephalography (MEG). This approach, which involved averaging over many stimulus repetitions, was introduced by Davis et al. (1939) and became ubiquitous by the 1960s with the advent of averaging devices and eventually computing technology. However, in this framework, oscillatory brain activity was regarded as nuisance “background activity” (Singh, 2012) and averaged out. Yet, the interest in brain rhythms returned (Pfurtscheller and Aranibar, 1977), and since then, decreases and increases in oscillatory power have been shown to be important correlates of brain functions (Singh, 2012). Remarkably, some researchers today consider evoked responses to be a mere manifestation of oscillatory activity rather than a distinct feature of the magneto-/electroencephalographic (MEEG) signal (Makeig et al., 2002; Klimesch et al., 2004; Mazaheri and Jensen, 2010).
Research on oscillatory activity first concentrated on rhythms below 30 Hz, especially the theta to beta range (theta: 4–8 Hz, alpha: 8–12 Hz, beta: 12–30 Hz), but with advances in both recording and analysis techniques, higher frequency activity attracted increasing attention (Dalal et al., 2011b). Since the first reports of activity above 30 Hz in the visual system of cats (Gray and Singer, 1989; Gray et al., 1989), such high frequency activity – also termed gamma activity – has been related to different sensory modalities, e.g., auditory (Crone et al., 2001; Brosch et al., 2002) or somatosensory perception (Schoffelen et al., 2005; Bauer et al., 2006; Gross et al., 2007). In line with Berger’s early observations, high frequency activity was also linked to higher order functions such as memory (Osipova et al., 2006; van Vugt et al., 2010; Roux et al., 2012) or cognitive engagement and processing (Jensen and Colgin, 2007; Womelsdorf and Fries, 2007; Jerbi et al., 2009). However, whether gamma plays a functional role in any of those processes remains unclear.

The present dissertation investigates gamma-band activity in the human nervous system along two major themes. The first theme investigates the key facets of high frequency activity in the visual system, with particular focus on how the retina and cerebral cortex interact. The second theme addresses the inherently low amplitude of gamma activity, examining different analysis methods to approach weak signals, namely, beamformer source reconstruction and decoding algorithms. In sum, the studies described here contribute to the ongoing debates about the significance of high frequency neural signals by introducing both key physiological evidence regarding their functional role, as well as improved techniques for resolving such activity noninvasively in humans.
The following sections will give an overview of the field of research into the gamma band, discussing different theories on the origin, mechanism and function of high frequency activity, before introducing the research line of this dissertation in more detail.

\section{High frequency activity: Background}

The first challenge in the field of high frequency activity research is the question: what is high frequency activity? One obvious answer could be: oscillatory activity in the gamma range as measured with MEG or EEG – and this is where the problems start. While there is a reasonable consensus regarding the boundaries of other frequency bands, for example alpha or beta activity, the term “gamma” is rather general and can describe any activity above 25–30 Hz (cf. Dalal et al., 2011b). To mention some examples: gamma (sometimes termed low gamma) has been defined as activity between 30 and 100 Hz (Fries et al., 2008), 30 and 60 Hz (Jerbi et al., 2009; Uhlhaas et al., 2011) or 40 and 80 Hz (Fries, 2009; Hermes et al., 2015). These characterizations are often complemented by the term “high gamma” for any activity above this defined range. Sometimes, even further bands are specified, for example the ultrafast gamma band above 200 Hz, ripples, and high ripples (Uhlhaas et al., 2011).\footnote{This work will use the terms “gamma activity” and “high frequency activity” interchangeably. In the presented studies, the exact frequency bands will be stated instead of defining additional frequency bands (“high gamma”).}

A further distinction is often made between narrowband and broadband gamma activity. Narrowband gamma activity is determined by a distinct peak in the power spectrum (Miller et al., 2009a) and often considered true oscillatory activity. Broadband high frequency activity on the other hand spans a wider range of frequencies and is often linked to a non-specific increase in neural activity, which is supposedly not related to synchronous oscillatory activity of neural assemblies (Miller,
2010; Ray and Maunsell, 2015). This discrepancy delineates that the definition of
“gamma” is not merely a problem of labels, but that different designations might
refer to distinct neural mechanisms or functions.

In the following, some well-established theories on the nature, function, and
origin of gamma activity will be described and discussed. The first section will focus
on narrowband activity, the second section on broadband gamma, and the third
section will explore if those high frequency activity variations can be linked to each
other. Subsequently, the aims and topics of this dissertation will be introduced.

1.1.1 Narrowband oscillatory activity

After the initial descriptions of high frequency activity in the central nervous
system – e.g., the oscillatory potential in the retina (Fröhlich, 1914) or high fre-
quency oscillations in the olfactory bulb (Adrian, 1950) – the first cortical gamma
band response was described in cat visual cortex (Gray and Singer, 1989; Gray
et al., 1989). This high frequency activity was elicited by moving light bars and
characterized by an approximately 20 Hz wide oscillation centered at 40–50 Hz.
The localization of the response was restricted to a small area in visual cortex
and dependent on stimulus orientation, suggesting a functional role (Gray and
Singer, 1989). In the human brain, comparable induced gamma band activity
was recorded in response to visual stimuli with EEG (Lutzenberger et al., 1995;
Tallon-Baudry et al., 1996; Tallon-Baudry et al., 1997). However, Yuval-Greenberg
et al. (2008) later showed that depending on the referencing scheme, putative
gamma responses in the EEG can be generated by saccadic eye movements and thus
do not reflect oscillatory brain activity. More recently, narrowband gamma activity
was observed in the MEG (e.g., Adjamian et al., 2004b; Hoogenboom et al., 2006;
Swettenham et al., 2009; Muthukumaraswamy et al., 2010; van Pelt and Fries,
2013), a recording technique which does not exhibit such reference problems. All of
those MEG studies used high-contrast visual stimuli (stripe patterns or gratings) and consistently showed narrowband responses below 100 Hz, with a bandwidth around 20 Hz.

**The role of inhibitory interneurons** In their seminal paper on visual high frequency oscillations, Gray and Singer (1989) considered neural networks with both excitatory and intermittent inhibitory activity as generators for the observed high frequency responses, building on physiological work and theoretical models (Finette et al., 1978; Martin and Whitteridge, 1984; Von Seelen et al., 1987). The inhibitory activity in the networks was later linked to inhibitory gamma-aminobutyric acid (GABA)-ergic interneurons (Llinás, 1992; Whittington et al., 1995; Wang and Buzsáki, 1996). By imposing rhythmic inhibition to the network, GABAergic interneurons entrain the synchronous firing of both inhibitory and excitatory cells in the gamma-rhythm (Buzsáki and Chrobak, 1995; Bartos et al., 2007; Fries, 2009). According to Fries and colleagues (2007; 2009), this mechanism renders excitatory input most effective when it arrives at time windows without inhibitory activity. Neurons with higher excitatory drive are able to overcome subsiding inhibition first, thereby converting their excitatory levels into a temporal code within the gamma cycle.

The role of GABAergic interneurons in high frequency oscillations has been further examined by investigating the relationship between MEG gamma activity and GABA concentration measured with magnetic resonance spectroscopy (MRS) in the visual cortex. Muthukumaraswamy et al. (2009) reported that an increased concentration of the inhibitory GABA neurotransmitter at rest was associated with an increased gamma activity following a visual stimulus. This relation was replicated in the visual and motor cortex (Edden et al., 2009; Gaetz et al., 2011) and related to memory processes and schizophrenia (Chen et al., 2014). However, several studies failed to find similar results (Hall et al., 2010; Muthukumaraswamy et al., 2013;
Shaw et al., (2013) and Cousijn et al. (2014) reasoned that neither GABA nor glutamate measured with MRS have a consistent relationship to gamma oscillations. More recently, Kujala et al. (2015) measured the density of GABA\textsubscript{A} receptors in primary visual cortex (V1) with the more sensitive positron emission tomography (PET). They showed a positive correlation of receptor density with gamma peak frequency following visual stimulation; the density additionally correlated negatively with the amplitude of the gamma signal. Furthermore, there was no such relationship between GABA\textsubscript{A} receptor density and alpha or beta activity. In summary, this suggests a link between narrowband high frequency oscillations and GABAergic interneurons.

**Binding by synchronization and communication through coherence** Several theories have been formulated to explain a potential functional gain of this synchronized oscillatory high frequency activity. Gray et al. (1989) reported the synchronization of gamma oscillations in spatially distributed areas of visual cortex when presenting two moving light bars. The authors related this finding to the *binding by synchronization* hypothesis, which suggests that higher order stimulus properties are represented by different neural assemblies which are “bound” together through oscillatory synchronization, creating a transient relation between different features of a visual scene or pattern (Malsburg and Schneider, 1986; Eckhorn et al., 1988; Gray et al., 1989; Singer and Gray, 1995; Singer, 1999).

Fries (2005) expanded the role of gamma oscillations beyond perceptual binding: in his *communication through coherence* framework, the shunting inhibition generated by interneurons establishes “windows of communication”, and thereby only neural assemblies oscillating coherently are able to efficiently share information.
1.1.2 Broadband high frequency activity

The theories on the functional relevance of gamma activity introduced above, binding by synchronization and communication through coherence, both presume a narrowband oscillation for effective synchronization among neural assemblies. With the first intracranial electroencephalogram (iEEG) recordings of high frequency activity, however, a different activity pattern emerged. Surprisingly, those studies found broader and higher frequency responses than the original studies on visual gamma activity (e.g., Crone et al., 1998; Lachaux et al., 2000). Such broadband gamma responses (ranging from 40 to 150 Hz and beyond) were reported in many iEEG studies and for different sensory modalities or tasks (for review see Lachaux et al., 2005; Jerbi et al., 2009; Crone et al., 2011; Lachaux et al., 2012). Corresponding results were also revealed in MEG and EEG studies (e.g., Vidal et al., 2006; Dalal et al., 2008; Ray et al., 2008; Ossandón et al., 2012; Popov et al., 2017).

These broadband increases were shown to correspond with multi-unit activity (MUA) spike rates, i.e., extracellularly recorded spiking activity of neural cells: numerous studies described a correlation of MUA and high frequency activity in the surface EEG or in local field potential (LFP) recordings of extracellular electrophysiological activity in rats and monkeys (Csicsvari et al., 2003; Rasch et al., 2008; Whittingstall and Logothetis, 2009; Ray and Maunsell, 2011), and also in the human auditory cortex (Nir et al., 2007). Belitski et al. (2008) showed this link between spiking activity and LFPs exclusively for the gamma band; activity below 40 Hz did not correlate with MUA, and neither did narrowband gamma responses elicited by grating stimuli (Jia et al., 2011; Ray and Maunsell, 2011). The association between spiking activity and broadband gamma power suggests that this type of high frequency response could represent an unspecific marker of neural activity (Buzsáki et al., 2012; Burke et al., 2015; Ray and Maunsell, 2015). Consequently, broadband gamma would not reflect a specific functional mechanism, e.g., signal flow control, but could still be indicative of task-related neural activation. However,
it has also been suggested that broadband gamma activity merely reflects random noise in synaptic membrane potentials (Miller, 2010). Following this hypothesis, any broadband increase in activity echoes an augmentation across a broad range of frequencies, corresponding to a slope change in the 1/f power spectrum, and does not emphasize a specific frequency range (Miller et al., 2007; Miller et al., 2009a; Miller, 2010; Voytek and Knight, 2015).

### 1.1.3 Linking narrowband and broadband responses

**Narrowband gamma oscillations: Rule or exception?** A study by Hermes et al. (2014) investigated the occurrence of narrowband and broadband gamma activity in response to visual stimuli and found that narrowband oscillations were only reliably induced by grating stimuli but absent in response to natural or noise stimuli. This study – which was highly discussed (Brunet et al., 2014; Mazaheri and Van Diepen, 2014; Hermes et al., 2015) – thus questions the role of narrowband gamma oscillations as being necessary in visual processing: possibly, they are the exception and not the rule.

Furthermore, several studies reported different gamma frequency peaks across visual cortex in response to one stimulus (Lima et al., 2010; Ray and Maunsell, 2010) and varying gamma periods from cycle to cycle (Henrie and Shapley, 2005; Burns et al., 2011). Whether the proposed functional mechanisms of binding or communication are robust to such variability remains unclear (Ray and Maunsell, 2010; Ray and Maunsell, 2015).

Gamma rhythmic optogenetic stimulation of inhibitory interneurons or excitatory neurons yielded mixed results: while some studies show a functional or behavioral impact, other studies report no effect (Cardin et al., 2009; Sohal et al., 2009; Histed and Maunsell, 2014; Siegle et al., 2014; Cho et al., 2015; Kim et al., 2016).
Narrowband and broadband gamma: Two distinct mechanisms? A further open question is, whether narrowband and broadband high frequency activity reflect a common phenomenon. Crone and Hao (2002) suggested that adjacent cell assemblies could generate narrowband gamma oscillations at different frequencies, for example while processing different stimulus properties in the visual system. Such an effect could be beyond the spatial resolution of MEG, iEEG or LFP measurements, and therefore resemble a broadband gamma increase in the recorded data.

Lundqvist et al. (2016) recently showed systematic trial-to-trial variations in gamma frequency during a working memory task in monkey prefrontal cortex. Interestingly, the trial-averaged data resembled a sustained, rather broadband gamma response. Thus, even if single trials contain narrowband gamma oscillations at different peak frequencies, the average across trials could still present broadband power (cf. Stokes and Spaak, 2016). However, whether oscillatory activity with highly variable peak frequencies across cell assemblies or trials can provide a functional mechanism remains controversial (Ray and Maunsell, 2010; Ray and Maunsell, 2015).

Interestingly, both narrowband and broadband gamma responses show a correspondence to the blood oxygen level-dependent (BOLD) effect measured with functional magnetic resonance imaging (fMRI). A spatial co-localization of broadband gamma power and the BOLD response was shown in several tasks (Mukamel et al., 2005; Niessing et al., 2005; Lachaux et al., 2007; Nir et al., 2007; Ojemann et al., 2010). Similarly, a co-localization was described for visual narrowband gamma activity elicited by high-contrast stimuli (Brookes et al., 2005; Hoogenboom et al., 2006). Consequently, both broadband and narrowband high frequency activity correlated with BOLD in the same manner. However, the BOLD
response is known to be a fairly non-specific marker of neural activation (Lachaux et al., 2012), thus, narrowband and broadband gamma activity could still represent different mechanisms, both echoed in the global BOLD effect.

**Gamma in a cross-frequency framework**  A discussion on gamma band responses might not be complete without the investigation of its relation with other frequencies. Numerous studies suggest a nesting of gamma band activity within slower frequencies (e.g., Bragin et al., 1995; Lakatos et al., 2005; Canolty et al., 2006; Osipova et al., 2008; Popov et al., 2012; Spaak et al., 2012; Jensen et al., 2014). Recently, gamma activity was proposed to reflect a feedforward mechanism, complemented by alpha oscillations as a feedback process (Van Kerkoerle et al., 2014; Dougherty et al., 2015; Michalareas et al., 2016; Popov et al., 2017). This hypothesis is consonant with the *gating by inhibition* framework (Jensen and Mazaheri, 2010), where alpha activity reflects an inhibitory mechanism that blocks and prioritizes cortical processing, which is echoed by gamma activity. Recently, these concepts were combined with the *communication through coherence* hypothesis (Bonnefond et al., 2017): herein, the alpha activity enables communication between cortical areas, following the principle of “windows of communication”. Interestingly, this unified framework does not rely on narrowband gamma oscillations, since alpha oscillations serve as the carrier frequency.

### 1.1.4 Open questions

To summarize, MEEG activity above 25–30 Hz is associated with numerous brain functions, but whether it represents a functional mechanism, an unspecific increase in neural activity or even just neural noise remains unclear (Miller et al., 2009a; Buzsáki et al., 2012; Ray and Maunsell, 2015). This underscores the fact that much of the origin, mechanism, and potential function of high frequency activity in the human brain is still unknown, since these open questions remain highly debated.
This work approaches high frequency activity in healthy brain functions from different perspectives: Chapter 2 (with Study 1 and Study 2) focuses on retinocortical interactions and the origin and potential function of high frequency activity in the visual system, while Chapter 3 (with Study 3 and Study 4) concentrates on the methodological aspects of low signal-to-noise ratio (SNR) signals like high frequency activity. The following two sections will introduce the background and significance of those two research lines and briefly outline the conducted studies.

1.2 High frequency activity in the visual system

As described above, cortical gamma activity was first observed in the visual system (Gray and Singer, 1989; Lutzenberger et al., 1995; Tallon-Baudry et al., 1996). Despite persistent interest in high frequency activity in the visual domain, there are still many open questions. Aside from the narrowband versus broadband debate reviewed above, it is for example not fully understood yet, where the high frequency activity observed in the visual cortex originates. While some reports suggest that cortical high frequency activity is generated locally (Doty and Kimura, 1963; Molotchnikoff et al., 1975; Heinrich and Bach, 2004), other studies view gamma activity as a feedforward mechanism (Van Kerkoerle et al., 2014; Michalareas et al., 2016; Popov et al., 2017) and several studies suggest that visual gamma in the cortex could be transmitted from the retina (Lopez and Sannita, 1997; Castelo-Branco et al., 1998; Sannita et al., 1999; Heinrich and Bach, 2001; Neuenschwander et al., 2002; Todorov et al., 2016). Recently, Saleem et al. (2017) proposed the idea that narrowband gamma oscillations are inherited from thalamus (and supposedly the retina), whereas broadband high frequency activity reflects corticocortical processing.
Brain research and the retina Although the retina is part of the central nervous system, it has essentially been overlooked in human neuroscience research to date: studies that simultaneously record retinal and cortical activity in humans are rare. The complex wiring and massive number of different retinal cell types (Masland, 2001) suggest that the retina could be more than a plain light detector, which is confirmed by recent research: the retina is involved in motion processing and other higher-order processing (for a review, see Gollisch and Meister, 2010). While the timing of activity in visual cortex is often considered to reflect cortical computation times (e.g., when interpreting peak time differences between tasks or subject groups), it could very well be that differences in timing are already introduced at the retinal processing stage and transmitted to visual cortex. This motivates the investigation of retinocortical interactions in the human brain, enabled by the simultaneous recording of retinal and cortical activity.

The electroretinogram The first recording of retinal activity in humans was done by Dewar in 1877, preceding the first EEG measurement by several decades. Retinal evoked responses have been used in clinical routines for some decades (Marmor et al., 1989; Marmor et al., 2009), recorded with the electroretinogram (ERG). In this work, the ERG was measured with Dawson-Trick-Litzkow (DTL) fiber electrodes (Figure 1.1). These disposable electrodes are placed on the lower eye lid and generally well-tolerated, especially for participants with experience in wearing contact lenses.

Figure 1.1: DTL fiber electrode. The picture shows the DTL fiber electrode which was used to measure retinal activity in this work.
The recorded retinal activity in response to a light flash resembles cortical evoked potentials (cf. Figure 1.2A): the first potential is referred to as the $a$-wave, a negative deflection originating from the photoreceptors (Perlman, 2001; Frishman, 2013). It is followed by the positive $b$-wave, which is generated by the ON bipolar cells (Sieving et al., 1994; Frishman, 2013; Vukmanic et al., 2014). If the duration of the light flash is long enough, the light offset response is visible in the ERG as well: a positive deflection called $d$-wave, which originates from the OFF bipolar cells (Sieving et al., 1994; Perlman, 2001; Frishman, 2013). Fröhlich (1914) discovered that retinal cells produce a high frequency burst centered at 120 Hz (Munk and Neuenschwander, 2000), called the oscillatory potential (Figure 1.2B). The underlying mechanisms of this millisecond precise high frequency activity are still unknown, presumably ganglion, amacrine, and bipolar cells are involved (Doty and Kimura, 1963; Perlman, 2001; Kenyon et al., 2003; Frishman, 2013). There is evidence that the oscillatory potential could be directly transmitted to visual cortex (Lopez and Sannita, 1997; Castelo-Branco et al., 1998; Sannita et al., 1999; Heinrich and Bach, 2001; Neuenschwander et al., 2002; Todorov et al., 2016; but see Doty and Kimura, 1963; Molotchnikoff et al., 1975; Heinrich and Bach, 2004). Therefore, this high frequency activity can potentially serve as an instrument to examine retinocortical interactions.

Chapter 2 of this work comprises two studies investigating the interaction between retina and visual cortex and associated high frequency activity. The research questions and significance of these studies will shortly be highlighted in the following paragraphs.
1.2.1 Retinocortical interactions in response to darks and lights

The visual system processes lights and darks in two different pathways, the ON and OFF pathway (Werblin and Dowling, 1969). While it was assumed for a long time that these pathways are parallel, later studies showed that these two channels exhibit numerous asymmetries. More precisely, there is support for the notion that darks are processed faster than lights (e.g., Chubb and Nam, 2000; Nichols et al., 2013; Komban et al., 2014) and that the visual system provides more resources for the processing of darks (e.g., Ahmad et al., 2003; Jin et al., 2008; Yeh et al., 2009). However, studies on the human visual system, especially on retinocortical interactions, are rare in this context. Study 1 compares the retinocortical interactions in response to darks and lights, focusing on the high frequency activity related to light onsets and offsets. Retinal responses were hereby recorded with the ERG, while the cortical activity was recorded with MEG (Cohen, 1968), a method which records the magnetic fields generated in the brain mainly...
by postsynaptic currents (Lopes da Silva, 2010). The simultaneous recording of retinal and cortical activity enables a close examination of the interplay of retina and cortex.

1.2.2 Information flow in the corticoretinal system

Various species possess a corticoretinal pathway, transmitting information from the cortex to the retina (for review, see Repérant et al., 2006; Ortiz et al., 2016). In humans, the existence and potential function of such a corticofugal pathway is still debated (Marg, 1953; Mangun et al., 1986; Repérant and Gallego, 1976; Wasserman et al., 2010). **Study 2** combined transcranial magnetic stimulation (TMS) with ERG to investigate whether cortical stimulation can influence retinal activity, which would provide evidence for the existence of such corticofugal fibers. The application of single magnetic pulses results in the stimulation of neurons through a short lasting electrical current in the brain, often accompanied by artificial percepts (phosphenes) (Marg and Rudiak, 1994; Taylor et al., 2010). The pilot study reported here presents first results, showing retinal slow potentials and high frequency activity following TMS in both subjects. Furthermore, the study shows the feasibility of this approach and alludes to necessary refinements in the study protocol.

1.3 Approaches to low SNR signals

Paper titles like “Finding gamma” (Fries et al., 2008) or “Cortical gamma responses: searching high and low” (Crone et al., 2011) imply that gamma activity is something that is hard to measure and challenges the researcher. Indeed, higher frequencies have a considerably smaller SNR compared to lower frequency bands, which is due to the fact that the frequency spectrum of brain rhythms follows a 1/f shape. Thus, signals in high frequencies have smaller amplitudes, while
measurement-related and environmental noise is unaffected. Furthermore, gamma activity often is restricted to smaller brain areas than, for example, widely spread alpha desynchronizations (Lachaux et al., 2007; Miller et al., 2009b).

One way to improve SNR is the application of spatial filters (Sekihara et al., 2004; Väisänen and Malmivuo, 2009; Dalal et al., 2011a), i.e., the source reconstruction of magneto-/electroencephalography (MEEG) data with beamformers (van Drongelen et al., 1996; Van Veen et al., 1997). Another powerful approach is the use of multivariate decoding techniques, since those methods leverage the information across several dimensions (i.e., space, time, and frequency) instead of applying myriads of tests with the need to correct for multiple comparisons (Stokes and Spaak, 2016). Furthermore, some decoding algorithms are more sensitive towards weak or non-linear effects in the data (e.g., Strobl et al., 2009).

Chapter 3 of this work comprises two studies focusing on the low SNR aspect of high frequency activity. The first study combines beamformer source reconstruction with a decoding approach to investigate the predictive value of single-trial gamma power, while the second study examines the effects of several methodological factors on beamformer performance in a simulation. These two projects will briefly be outlined in the following sections.

### 1.3.1 Decoding gamma

Recently, studies showed trial-to-trial variations in LFP high frequency activity (Lundqvist et al., 2016; Lowet et al., 2016), which attracted new interest in single-trial analyses (Stokes and Spaak, 2016). **Study 3** investigates the predictive value of single-trial source space gamma power towards the discrimination of stimulus modality (visual versus auditory stimulus presentation) by adopting a classification algorithm. In order to decode the information about the stimulus modality from the source data, the random forest classification algorithm (Breiman, 2001) was used. This method aims at partitioning the data into subsets with respect to auditory
and visual stimulus presentation, thereby identifying the most informative MEG features in time, frequency, and space. The classification was embedded in an across-subjects framework, which yields additional information about the inter-individual consistency of gamma activity patterns.

1.3.2 Beamformer performance and channel count

Beamforming is among the most widely used methods for source reconstruction. This method estimates the activity of source locations by applying a set of weights, the spatial filter, to the sensor data (Hillebrand et al., 2005).

In the past decades, the number of channels in state-of-the-art MEEG systems considerably increased and reached 200 and more channels. The impact of increasing channel count on beamformer performance is investigated in Study 4. This simulation study also considers further important factors, namely the quality of the data covariance matrix and the forward model, which are both used to estimate the weights of the beamformer, and the input SNR. The aim of this simulation is to identify those parameters that are crucial for good beamformer performance in different settings, for example with low SNR signals like gamma activity.
Chapter 2

Escaping the boundaries of the neocortex: High frequency activity in retinocortical interactions
2.1 Study 1

Faster than the brain’s speed of light:

Retinocortical interactions differ in high frequency activity when processing darks and lights

Some studies suggest that the processing of darks benefits from greater neural resources in the visual system and potentially occurs faster. However, evidence from the human is still sparse, especially with respect to retinocortical interactions. We recorded retinal and cortical responses to 480 ms light flashes simultaneously with electroretinography (ERG) and magnetoencephalography (MEG) in ten participants and analyzed the high frequency responses to the flash onsets and offsets.

We show that high frequency oscillations for flash offsets occur earlier than flash onsets in the cortex but not in the retina. Interestingly, while the onset activity involved a wide range of frequencies (55–195 Hz in the retina, and 55–145 Hz in the cortex), the offset response was restricted to the 75–95 Hz frequency band in both retina and cortex. The results suggest faster propagation times but not earlier retinal processing for darks than lights, suggesting a thalamic role. They also support previous findings that the retinal high frequency activity is transmitted to cortex. Furthermore, the outcomes add to the ongoing discussion about the function of narrowband oscillations in the human visual system.
2.1.1 Introduction

In 1938, Hartline discovered that the processing of light increments and light decrements is done separately by two pathways in the retina, the ON- and OFF-pathways, which commence with sign-inverting and sign-conserving bipolar cells at the first synapse of the photoreceptors (Werblin and Dowling, 1969). These channels have long been treated as parallel, however, studies suggest functional and neuronal asymmetries in these pathways.

A behavioral advantage for the detection of dark objects or light decrements over light objects has been reported in several psychophysical studies (e.g., Blackwell, 1946; Krauskopf, 1980; Bowen et al., 1989; Chubb and Nam, 2000; Buchner and Baumgartner, 2007). More recently, Komban et al. (2011) reported faster and more accurate reactions for dark squares compared to light squares on a uniform binary noise background at suprathreshold but not threshold levels. This advantage for dark stimuli, however, vanished if the binary noise background was corrected for the irradiation illusion, which is the effect that light objects on a dark background seem larger than their dark counterparts (Galilei, 1632; von Helmholtz, 1867). These results raise the question at which stage of the visual system do potential functional asymmetries in the ON and OFF pathway emerge – and what precisely are the neural underpinnings of these often reported behavioral advantages of darks over lights.

In visual cortex, responses to light decrements are found to be stronger than responses to light increments in both electroencephalography (EEG) and functional magnetic resonance imaging (fMRI) recordings (Zemon et al., 1988; Zemon et al., 1995; Olman et al., 2008). Multiunit recordings from cat visual cortex show faster response latencies (defined as 40% of maximum response) in OFF-dominated cortical sites (Komban et al., 2014). The number of geniculate afferents at the representation of the area centralis in cat visual cortex is higher in the OFF-pathway (Jin et al., 2008). Otherwise, Yeh et al. (2009) reported more black-dominant
neurons in layers 2 and 3 of primary visual cortex (V1) of macaque monkeys, but a balanced amount of black- and white-dominant neurons in the thalamic input layer 4c of visual cortex and thus conclude that advantages for the processing of darks are generated or at least amplified in the visual cortex and not the thalamus. Subsequently, they showed that the neural circuitry in V1 seems to enhance responses to darks: they found a temporal advantage in the processing of darks in the thalamic input layer 4c, but not in the later stages of cortical visual processing (Xing et al., 2010). A potential advantage for dark stimuli at the thalamic level is further supported by a study of Jin et al. (2011), which reported faster processing for light decrements than increments in the lateral geniculate nucleus (LGN) of the cat thalamus. Thus, studies which focused on cortical and thalamic processing of darks and lights suggest that there are greater neural resources for darks, however, they do not agree at which stage of the visual system these advantages are introduced.

At the retinal stage, evidence for functional asymmetries in the ON- and OFF-pathways is mixed. While some studies find no asymmetries at all (Kremers et al., 1993; Benardete and Kaplan, 1997; Benardete and Kaplan, 1999), others do report differences in ON and OFF processing. For example, it has been shown that OFF bipolar cells outnumber ON bipolar cells in the central retina by twofold (Ahmad et al., 2003). OFF ganglion cells seem to have narrower dendritic and thus narrower receptive fields than their ON counterparts (Wässle et al., 1981; Morigiwa et al., 1989; Dacey and Petersen, 1992; DeVries and Baylor, 1997), which show more overlap than ON dendritic fields (Borghuis et al., 2008). This suggests that more resources are allocated to the OFF pathway (Balasubramanian and Sterling, 2009). Furthermore, OFF neurons respond fairly linear with light decrements, whereas ON neurons reveal a pronounced non-linearity and saturate their responses even with small increases in luminance (Chichilnisky and Kalmar, 2002; Kremkow et al., 2014). It has also been shown, however, that OFF cell currents are rectified by
ON cells (Zaghloul et al., 2003; Liang and Freed, 2010). Regarding the response kinetics of ON and OFF retinal cells, it has been hypothesized that OFF bipolar cells are faster, since no biochemical sign inversion of the light response is needed – in contrast to ON bipolar cells (Nawy and Jahr, 1990; Chichilnisky and Kalmar, 2002). Indeed, the initial response (defined as 5% of maximum response) was shown to be slightly faster for OFF-bipolar cells (Chichilnisky and Kalmar, 2002). This finding is strengthened by several studies which also show faster responses for light decrements in the retina (Copenhagen et al., 1983; Zaghloul et al., 2003; Burkhardt et al., 2007; Gollisch and Meister, 2008; Nichols et al., 2013). However, Chichilnisky and Kalmar (2002) reported this temporal advantage only for the initial response, whereas the time to peak was shorter for ON bipolar cells and not OFF bipolar cells (also see Lankheet et al., 1998).

In summary, while there is an evident advantage for darks over lights on the behavioral level, the potential functional asymmetries in the ON and OFF pathways throughout the visual system are less well understood and especially evidence from the human visual system is still sparse. In the present study, we aim at investigating the shape and timing of activity patterns elicited by flash onsets and offsets in the human visual system by recording retinal and cortical responses simultaneously.

**Retinal potentials and high frequency oscillations** Retinal potentials in response to full-field flashes have been used in the clinical assessment of retinal function for some decades (Marmor et al., 1989; Marmor et al., 2009) and are therefore well described. These potentials, which are seen in the electroretinogram (ERG), reflect the summed activity of the retinal network and arise from different processing stages (Frishman, 2013). The first negative deflection of the human ERG in response to a light flash is the a-wave, which originates from the photoreceptors (Perlman, 2001; Frishman, 2013). It is truncated by the rising flank of the positive b-wave, a potential that is mostly driven by ON bipolar cells (Sieving et al., 1994;
2 High frequency activity in retinocortical interactions

Frishman, 2013; Vukmanic et al., 2014). At the offset of long duration light flashes, a potential referred to as the d-wave can be seen: this positive deflection has its origin in the OFF bipolar cells (Sieving et al., 1994; Perlman, 2001; Frishman, 2013); in the photopic ERG, a contribution of the cone receptors is assumed (Evers and Gouras, 1986; Frishman, 2013).

A peculiarity of the ERG is the oscillatory potential, an onset locked high frequency oscillation that has first been described by Fröhlich (1914). It is characterized as a millisecond precise oscillation on the rising flank of the b-wave, with a frequency centered around 120 Hz, and sometimes described as involving frequencies up to 200 Hz (Kozak, 1971; Munk and Neuenschwander, 2000; Todorov et al., 2016). Mechanisms and cellular origin of the oscillatory potential are still unknown, an involvement of ganglion, amacrine and bipolar cells, possibly in a negative feedback loop, is discussed (Doty and Kimura, 1963; Perlman, 2001; Kenyon et al., 2003; Frishman, 2013). Kozak (1971) describes a similar but slower oscillation (75–125 Hz) in response to light offset.

Retinocortical propagation The visual system involves several stages of processing: commencing in the retina, information is passed to the LGN in thalamus and then projected to the occipital cortex. There is evidence, that the retinal oscillatory potential is directly transmitted to visual cortex (Lopez and Sannita, 1997; Castelo-Branco et al., 1998; Sannita et al., 1999; Heinrich and Bach, 2001; Neuenschwander et al., 2002; Todorov et al., 2016). Other studies, however, come to the conclusion that retinal and cortical gamma are two distinct processes (Doty and Kimura, 1963; Molotchnikoff et al., 1975; Heinrich and Bach, 2004). Reconciling these opposite findings, it has been proposed that two different types of cortical high frequency activity exist, one inherited from the retina and one generated locally after visual stimulation. Munk and Neuenschwander (2000) suggest that the oscillatory potential, incorporating frequencies from 60 to 120 Hz, is transmitted
from the retina to cortex, whereas slower cortical gamma activity below 60 Hz is
generated locally. A recent study by Saleem et al. (2017) reports that cortical
narrowband gamma responses are inherited from thalamus and proposes different
channels for thalamocortical (narrowband) and corticocortical (broadband) infor-
mation transfer.

The present study investigates the retinal and cortical responses to light flash
onsets and offsets and aims to compare their temporal dynamics and oscillatory
patterns. The simultaneous recording of retinal and cortical activity further en-
ables a direct comparison of retinal and cortical high frequency activity and its
propagation through the visual system.

2.1.2 Methods

Participants 10 healthy participants (four female, average age 34.1 years; s.d. =
6.31) took part in the study. 6 participants were contact lens wearers, since expe-
rience showed that they usually tolerate the eye electrode used to record the ERG
very well. Contact lens wearers did not wear their lenses during the experiment.
All participants provided written informed consent and the study was approved by
the Ethical Committee of Central Denmark Region and carried out in accordance
with the Declaration of Helsinki.

Experimental design and data acquisition The experimental stimuli were
full field light flashes which were presented using the Presentation software (Neu-
robehavioral Systems, Inc., Berkeley, CA). The white flashes had a duration of
480 ms and were followed by a black screen which was shown for a random time
interval between 2000 and 2500 ms. A total of 250 flashes was shown and the ex-
periment lasted approximately 12 min. The flashes were projected onto a screen
inside the MEG chamber using a ProPixx projector (VPixx Technologies Inc.,
Saint-Bruno, Canada) with a 60 Hz refresh rate and symmetric rise and fall times. Participants were seated in an upright position, the projection screen was at 70 cm distance from the subjects. The flashes were as full-field as possible subtending the central 28° (vertical extent) and 48° (horizontal extent) of the visual field and had a brightness of 280 cd m\(^{-2}\).

MEG data was recorded using a 306-channel MEG system (102 magnetometers and 2 × 102 gradiometers, Elekta Neuromag TRIUX, Elekta Instruments, Stockholm, Sweden) in a magnetically shielded room. Data was sampled at 5 kHz with a recording bandwidth of 0.1–1650 Hz. Bilateral ERG was recorded using disposable Dawson-Trick-Litzkow (DTL) fiber electrodes. Additionally, horizontal and vertical electrooculogram (HEOG and VEOG) were recorded using a bipolar montage. The ERG electrodes were referenced to the ipsilateral HEOG. Prior to data acquisition, the head position indicator (HPI) coils and three fiducial points (left and right periauricular points and nasion) were digitized using a Polhemus Fastrak 3D scanner (Polhemus, Colchester, VT, USA) for later coregistration with the structural magnetic resonance image (MRI) of the subjects. The on- and offsets of the flashes were recorded with a photodiode during the whole experiment.

**Data analysis** Analysis of MEG and ERG data was conducted using the open-source toolboxes FieldTrip (Oostenveld et al., 2010) and NUTMEG (Dalal et al., 2004; Dalal et al., 2011a) for MATLAB. Epochs of light onsets and offsets were identified using the photodiode traces. Trials with eye-movements were rejected based on the HEOG and VEOG activity. Subsequently, trials including muscle artifacts or MEG channel jumps were excluded as well, leaving on average 183.4 trials (\(std = 24.06\) per subject and condition. The data was downsampled to 1000 Hz.
For ERG data analysis, only data from the left ERG was used. Data was baseline corrected and detrended and the epochs were then averaged with respect to light onset and offset. The peak latencies for the retinal potentials (a-, b- and d-wave) were identified on the averaged time series for every subject. A paired samples Wilcoxon signed rank test was conducted on the b-wave and d-wave measurements, as well as on the a-wave and d-wave peaks. To obtain the oscillatory potentials after light onset, ERG data was highpass-filtered at 55 Hz (Hanning windowed finite impulse response (FIR) filter, onepass-zerophase, 6 Hz transition width). For light offset, data was highpass-filtered at 75 Hz and lowpass-filtered at 95 Hz using the same filter definitions.

For MEG data analysis, only the 102 magnetometers were used. Boundary element head models with three layers (brain, skull, scalp) were constructed for every subject based on the individual structural MRI using OpenMEEG (Gramfort et al., 2010; Gramfort et al., 2011). The source grid spanning the whole brain had a resolution of 10 mm. Sources were reconstructed using the linearly constrained minimum variance (LCMV) beamformer (Van Veen et al., 1997) with normalized weights (Van Veen et al., 1997; Sekihara and Nagarajan, 2008). The covariance matrices passed to the beamformer were computed based on the minimum covariance determinant estimator, providing a robust covariance matrix estimate. The beamforming approach was combined with the Hilbert transform to acquire source space Hilbert amplitude and phase for five frequency bands: 55–75, 75–95, 105–125, 125–145, and 155–195 Hz. To generate these frequency bands, separate high- and lowpass filters were adopted (Hanning windowed FIR filter, onepass-zerophase, 6 Hz transition width). For every frequency band and condition, a spatial filter was constructed as described above, and the single trials were projected through the filter to yield virtual electrodes at every grid point. Subsequently, the time courses of the virtual electrodes were Hilbert transformed, providing amplitude estimates for every frequency band. Intertrial coherence (ITC) was computed based on the
Hilbert phase estimates. To allow for comparison of retinal and cortical high frequency activity, the ERG data was filtered and Hilbert transformed in the same manner.

For both MEG and ERG data, the Hilbert amplitude time courses were normalized against the distribution of baseline time points using the Wilcoxon rank sum test for every frequency band and subject. The z-values obtained from this step were tested against the baseline distribution across subjects with the Wilcoxon rank sum test. The derived statistics were corrected for multiple comparisons by controlling the false discovery rate (FDR). ITC peaks were identified for every subject; in source space, the maximal ITC was searched among all occipital voxels based on the Automated Anatomical Labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002) for every subject. Due to a polyphasic response, the retinal light offset ITC for one participant was smoothed by lowpass filtering the ITC time series (cutoff: 40 Hz) to identify a clear peak latency. Light onset and offset ITC peak times were then tested using the paired sample Wilcoxon signed rank test for both retinal and cortical activity.

2.1.3 Results

Retinal evoked potentials The across-subjects average of retinal activity following light onset revealed the characteristic ERG flash response (Figure 2.1A). The negative a-wave had an average latency of 24.2 ms across subjects, followed by the positive b-wave at 79.9 ms. The data also shows the c-wave, which is generally seen with longer flashes, but of no further interest in this study. Figure 2.1B shows the retinal response to light offset with the d-wave peaking at 25.2 ms (n = 8: for two subjects the peak was not identifiable). The comparison of d-wave and b-wave latencies using a non-parametric paired-sample test (Wilcoxon signed-rank test)
revealed a significant difference \((R = 36, p = 0.0078)\) with the d-wave being faster across subjects. There was no peak latency difference between the a-wave and the d-wave: \(R = 13, p = 0.5469\).

**Retinal and cortical high frequency activity**  As illustrated in Figure 2.2A, high-pass filtering the light onset ERG data at 55 Hz reveals a high frequency burst. This oscillatory potential has high inter-trial and even inter-individual fidelity and can thus still be seen in the average across subjects. A comparable pattern in the light-off data is only evident when looking at a narrow frequency band of 75–95 Hz (Figure 2.2B). This is supported by the fact that across subjects, only this frequency band shows a significant increase in ITC after light offset compared to baseline by adopting a Wilcoxon rank sum test (Figure 2.2C).

To evaluate high frequency activity in the MEG data, Hilbert amplitudes of five frequency bands were computed in source space. In response to light onset, all but the highest frequency band show significant increases in Hilbert amplitude (in comparison to baseline, Wilcoxon rank sum test across subjects). Figure 2.3A shows this broadband response (the black boxes indicate significant time periods, \(p < 0.001\), FDR-corrected) and suggests that the activity in higher frequency bands occurs earlier than changes in lower frequencies. This gamma band activity spans occipital regions, including V1 as well as visual upstream regions (Figure 2.3B, masked for \(p < 0.001\), FDR-corrected). The brain’s activity following light offset comprised a narrowband response of 75–95 Hz localized to occipital cortex (Figure 2.3C and D, masked for \(p < 0.001\), FDR-corrected), which is the same frequency band as for the retinal response to light offset.

It has recently been shown in rats that the flash-induced retinal oscillatory potential is transferred via the optic nerve to the occipital cortex (Todorov et al., 2016). To investigate and compare retinal and cortical oscillatory potentials in this
Figure 2.1: **Retinal evoked potentials.** A Retinal potentials following flash onset, averaged across subjects. B ERG response to light offset, averaged across subjects.

Figure 2.2: **Retinal oscillatory potentials.** A Oscillatory potential after light onset. The data is highpass filtered at 55 Hz and averaged across subjects. B The oscillatory potential after light offset. Data is bandpass filtered from 75 to 95 Hz and averaged across subjects. C Intertrial coherence for light offset, tested against baseline across subjects (Wilcoxon rank sum test), black box marks significant area ($p < 0.05$, FDR-corrected).
Figure 2.3: **Occipital high frequency activity.** Both light onset and light offset evoked cortical high frequency activity. Hilbert amplitudes in different frequency bands are tested against baseline across subjects with the Wilcoxon rank sum test. Depicted for each frequency band is the time courses of the maximum voxel. **A** Occipital high frequency activity following light onset. Black boxes indicate time periods with $p < 0.001$ (FDR-corrected). **B** Voxels with significant activity in the different frequency bands following light onset, activity is masked for $p < 0.001$. The red cross hairs mark the maximum voxels. **C** High frequency activity following light offset in visual cortex. **D** Localization of flash offset activity, the cross hairs mark the maximum voxel.
study, we calculated intertrial coherence for those frequency bands that revealed significant power increases (see above). Figure 2.4A shows the ITC time course in response to light onset for the ERG (depicted in pale blue, median and inter-quartile range across subjects) and for occipital cortex (pale red), where the cortical ITC time course is computed as the across-subjects median of individual occipital maximum ITC. It is evident that the retinal oscillatory potential after light onset is followed by phase consistent activity in the cortex. This pattern is most obvious for the higher frequency bands: in the 105–125 Hz band, the cortical ITC peak follows after 51.0 ms (median difference between retinal and cortical peak across subjects, number of peak relations \( n = 9 \), since the retinal onset ITC peak was not identifiable for one subject). In the 125–145 Hz band, cortical activity follows the retinal ITC peak after 32.0 ms (\( n = 9 \)). As illustrated in Figure 2.4B, light offset led to a comparable pattern: an increase in trial-wise phase consistency in the ERG (depicted in dark blue) is followed by increased ITC in occipital cortex 21.0 ms (\( n = 7 \)), which is shown in dark red (also compare Table 2.2).

**High frequency activity: comparing light onset and offset** To assess whether the latencies of retinal and cortical high frequency bursts differ between light onset and offset, ITC peak times were tested across subjects with the Wilcoxon signed rank test. Since light offset was characterized by a narrowband response (75–95 Hz), the different onset frequency bands were all tested against this one offset frequency band. The retinal ITC peak latencies (cf. Figures 2.5A) show no significant difference between light onset and offset for the frequency bands of 55–75 Hz, 75–95 Hz, and 125–145 Hz (cf. Table 2.2). In the 105–125 Hz frequency band, the light onset ITC peak (27.0 ms, \( n = 9 \)) was significantly earlier than the 75–95 Hz light offset peak (34.0 ms, \( n = 7 \); \( R = 0.0, p = 0.0312 \)). In the cortex, however, the offset response at 75–95 Hz shows a significantly earlier ITC peak time (57.0 ms, \( n = 10 \)) than the light onset oscillatory potentials of the 75–125 Hz
Figure 2.4: **Retinal and cortical intertrial coherence.** Shown are median time courses across subjects, shaded areas represent the inter-quartile range. **A** Time courses of ITC following light onset for the frequency bands with significant activity (cf. Figure 2.3A). Retinal ITC courses are depicted in pale blue, the cortical ITC in pale red. Cortical ITC time courses represent the median across subjects’ individual maximum ITC activity in occipital cortex. **B** ITC time course in response to light offset for the 75–95 Hz narrowband response (cf. Figure 2.2C and 2.3C). The retinal response is shown in dark blue, the median response across individual occipital maximum voxels is shown in dark red.

frequency range (75–95 Hz: 71.5 ms, $n = 10$): $R = 49$, $p = 0.0254$ and 105–125 Hz: 77.0 ms ($n = 10$), $R = 40$, $p = 0.0352$. There was no difference for the other light onset frequency bands of 55–75 Hz and 125–145 Hz (cf. Table 2.2 and Figure 2.5B). Thus, whereas offset high frequency oscillations peak faster than onset responses in the brain, they seem to peak equally fast or even slower in the retina. This pattern suggests that the narrowband light offset response is transferred faster to cortex than the onset response: the light offset ITC peaks significantly later in the retina than the light onset response for 105–125 Hz, but earlier in the brain.
Table 2.1: **Intertrial coherence peak latencies.** Retinal and cortical peak times for the ITC of different frequency bands for both light onset and offset. Shown are peak times for frequency bands with significant activity (cf. Figures 2.2 and 2.3). Specified as well are the number of identifiable peak times per condition (subjects, \(n\)). The last column shows the results from a Wilcoxon signed rank test of light onset peak latencies of the different frequency bands against the 75-95 Hz light offset peak latency. The last section of the table shows the propagation times (median across subjects), defined as the difference between the cortical and retinal ITC peak time.

<table>
<thead>
<tr>
<th></th>
<th>Light onset</th>
<th>Light offset</th>
<th>Wilcoxon test</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Retina</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>55-75 Hz</td>
<td>31.5 ms, (n = 8)</td>
<td></td>
<td>(R = 7.0) (p = 0.6250)</td>
</tr>
<tr>
<td>75-95 Hz</td>
<td>34.0 ms, (n = 9)</td>
<td>34.0 ms, (n = 7)</td>
<td>(R = 9.5) (p = 0.8750)</td>
</tr>
<tr>
<td>105-125 Hz</td>
<td>27.0 ms, (n = 9)</td>
<td></td>
<td>(R = 0.0) (p = 0.0312)</td>
</tr>
<tr>
<td>125-145 Hz</td>
<td>27.0 ms, (n = 10)</td>
<td></td>
<td>(R = 3.0) (p = 0.0781)</td>
</tr>
<tr>
<td><strong>Occipital cortex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>55-75 Hz</td>
<td>69.0 ms, (n = 9)</td>
<td></td>
<td>(R = 36.0) (p = 0.1250)</td>
</tr>
<tr>
<td>75-95 Hz</td>
<td>71.5 ms, (n = 10)</td>
<td>57.0 ms, (n = 10)</td>
<td>(R = 49.0) (p = 0.0254)</td>
</tr>
<tr>
<td>105-125 Hz</td>
<td>77.0 ms, (n = 10)</td>
<td></td>
<td>(R = 40.0) (p = 0.0352)</td>
</tr>
<tr>
<td>125-145 Hz</td>
<td>58.0 ms, (n = 9)</td>
<td></td>
<td>(R = 23.5) (p = 0.9414)</td>
</tr>
<tr>
<td><strong>Propagation times retina – cortex</strong></td>
<td></td>
<td></td>
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<td>55-75 Hz</td>
<td>40.0 ms, (n = 7)</td>
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<td></td>
</tr>
<tr>
<td>105-125 Hz</td>
<td>51.0 ms, (n = 9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>125-145 Hz</td>
<td>32.0 ms, (n = 9)</td>
<td></td>
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</tbody>
</table>
2.1.4 Discussion

There are studies showing advantages for the processing of darks on different levels of the visual system (e.g., Zemon et al., 1988; Yeh et al., 2009; Jin et al., 2011; Komban et al., 2011; Nichols et al., 2013; Komban et al., 2014), however, evidence from the human brain is still sparse. In the present study, we simultaneously recorded retinal and cortical activity to flash onsets and offsets in order to investigate the differences and similarities in the respective activity patterns. The focus was hereby on oscillatory activity in the high frequency range in order to map the retinal oscillatory potential (Fröhlich, 1914) and its potential transmission to occipital cortex (Todorov et al., 2016).

Are darks processed faster than lights? Especially behavioral studies suggest a faster processing of darks compared to lights: reactions to dark objects and light decrements are faster and more accurate (Blackwell, 1946; Chubb and Nam, 2000;
Buchner and Baumgartner, 2007). On cortical, thalamic, and retinal level, evidence for faster processing of darks is mixed (e.g., Lankheet et al., 1998; Chichilnisky and Kalmar, 2002; Gollisch and Meister, 2008; Jin et al., 2008; Yeh et al., 2009), although numerous studies report greater neural resources for the processing of darks (e.g., Balasubramanian and Sterling, 2009).

We compared retinal and cortical ITC peak times in the high frequency range as well as retinal evoked potentials in response to light onsets and offsets to conclude on temporal differences in processing and propagation in the visual system.

The first obvious difference between light onset and offset high frequency activity is the frequency range itself: whereas the retinal oscillatory potential in response to light onset contains frequencies from 55 to 195 Hz, the retinal high frequency activity following light offset is restricted to the 75–95 Hz band. A very similar pattern emerges in visual cortex: the light onset high frequency response comprises frequencies between 55 and 145 Hz, while the flash offset activity is limited as well to 75–95 Hz. The cortical onset activity’s upper limit at 145 Hz is presumably due to a lower signal-to-noise ratio related to very high frequency content in MEG recordings.

In visual cortex, the narrowband 75–95 Hz light offset response is faster than the activity in the two main frequency bands for light onset, 75–95 Hz and 105–125 Hz. For the 55–75 Hz and 125–145 Hz flash onset response, no significant temporal difference to light offset was found. This finding corroborates the assumption that darks are processed faster than lights at the cortical level (Komban et al., 2014).

In the retina, the picture is not as homogeneous: while there is no significant difference concerning light onset and offset peak times in most frequency bands, the main onset frequency band of 105–125 Hz has an earlier peak time than the 75–95 Hz offset response. Thus, the retinal high frequency activity shows an opposite pattern to the cortical oscillatory responses.
When looking at the retinal evoked potentials, studies on the generators of these potentials suggest to compare the b-wave (light onset) to the d-wave (light offset), since both are presumably driven by bipolar cells (Sieving et al., 1994; Perlman, 2001; Frishman, 2013; Vukmanic et al., 2014). In our data, the d-wave is significantly faster than the b-wave. However, the fact that the b-wave peaks as late as 79.9 ms which is even later than the ITC peaks of high frequency activity in cortex (58.0 to 77.0 ms) raises the question whether this is a just comparison. The d-wave latency (25.2 ms) is around 10 ms earlier than the latency of the offset oscillatory potential (34.0 ms). The same is true for the light onset activity when comparing the a-wave latency (24.2 ms) to the peak times of the different frequency bands (27.0–31.5 ms), whereas the b-wave peaks over 45 ms after this high frequency activity. When taking the oscillatory potentials as an anchor, considering that they are reflecting a rather late mechanism in retinal processing (possibly feedback loops between different retinal cell types, see Doty and Kimura, 1963; Perlman, 2001; Kenyon et al., 2003; Frishman, 2013), then it becomes apparent, that the d-wave and b-wave might not reflect related cell activities after all. When instead comparing the d-wave to the a-wave, there is no difference in timing, however, the a-wave and d-wave are supposedly not generated by the same cell population (Sieving et al., 1994; Perlman, 2001; Frishman, 2013).

Looking at the peak latencies of oscillatory activity, our data suggests faster processing of darks on the cortical, but not on the retinal level. The evidence on retinal level is mixed: while the main onset frequency band peaks faster than high frequency activity in response to light offset, a comprehensive interpretation of retinal potential latencies is questionable.

Emerging from the retinal and cortical peak latencies of oscillatory activity, the propagation time of information is faster for darks (21.0 ms) than lights (32.0–51.0 ms). The light onset propagation times replicate previous findings of Heinrich and Bach (2001), who reported a time lag of 48 ms. The faster propagation of
light offset information suggests a thalamic role, which is supported by the finding of a faster processing for light decrements in the LGN of cats (Jin et al., 2011). Correspondingly, Xing et al. (2010) described a temporal advantage for darks in the thalamic input layer of V1 in macaque monkeys, however, it must be noted that they report no time differences in upstream visual areas. One possible explanation for the faster transmission time for darks could be a lesser informational content for darks compared to lights. Light onset could evoke more features of visual scene processing, e.g., stereo vision, which renders potential thalamic processing faster. Alternatively, the faster transmission times could be explained by asymmetries in the ON and OFF pathways as it has been suggested that more neural resources are allocated to the OFF pathway (Balasubramanian and Sterling, 2009).

In summary, our results strengthen findings of faster processing for darks in visual cortex and thereby deliver a possible explanation for any behavioral advantages of darks over lights. On the retinal level, we did not find faster processing of light decrements. Instead, light increments seem to be processed equally fast or even faster than light decrements. Due to the fact that the ERG represents the summed activity of different cell types and due to the lack of knowledge regarding the origin of the retinal oscillatory potential, it is hardly possible to speculate about the precise underlying retinal mechanisms of this finding. Information transmission to visual cortex, however, seems to happen faster for light offset than onset, suggesting a thalamic involvement.

**Are retinal oscillatory potentials transmitted to cortex?** Whether the retinal oscillatory potential gets transmitted to visual cortex has been a controversial topic. Some studies come to the conclusion that this is not the case: Heinrich and Bach (2004), for example, describe different peak frequencies in retina and cortex and Molotchnikoff et al. (1975) report a lack of cortical high frequency activity following flash-stimulation despite a clear retinal response. Doty and Kimura (1963)
find a link between retinal and cortical gamma band activity in monkeys but not in cats. Other studies, however, show strong evidence for a propagation of the oscillatory potential through the visual system (Lopez and Sannita, 1997; Sannita et al., 1999; Heinrich and Bach, 2001; Munk and Neuenschwander, 2000; Neuenschwander et al., 2002; Koepsell et al., 2009). Castelo-Branco et al. (1998) described strong correlations between retinal, thalamic and cortical high frequency activity (60–120 Hz) in cats. More recently, Todorov et al. (2016) reported high coherence between the retina, the optic chiasm and visual cortex in rats, however, they note different wave shapes in these three stages of the visual system and therefore argue against a merely passive spread of the oscillatory potential.

The current data shows evoked oscillatory activity following light onset and offset in both retina and cortex. This activation comprises similar frequency bands in the retina and in visual cortex: the light onset response is broadband in the retina (55–195 Hz) as well as in cortex 55–145 Hz. The lack of significant flash-evoked activity in the 155–195 Hz frequency band in visual cortex is presumably due to the low signal-to-noise ratio of such high frequencies. Equivalently, the offset response is restricted to the same frequency band (75–97 Hz) in both retina and visual cortex. This activation pattern is consistent with a propagation of the retinal oscillatory potential to visual cortex. Furthermore, the faster propagation time for light offset responses suggests thalamic involvement and indicates that the propagation of the oscillatory potential to the visual cortex is not a mere passive spread (Todorov et al., 2016).

The role of narrowband and broadband gamma responses in the visual system As outlined above, light onset evoked a broadband high frequency response in the retina and visual cortex, whereas light offset was followed by a narrowband response in the 75–95 Hz range. Narrowband oscillatory activity in the visual system has been observed in response to stationary or moving grating stim-
uli (e.g., Adjamian et al., 2004b; Hoogenboom et al., 2006; Muthukumaraswamy et al., 2010) and has been shown to vary in peak frequency depending on different stimulus features like eccentricity or movement (Swettenham et al., 2009; van Pelt and Fries, 2013). Narrowband gamma responses were also described with focused attention (Vidal et al., 2006). However, there is a debate about the origin as well as functional implication of such narrowband responses, for example, about the question if they are solely induced by grating stimuli (Hermes et al., 2014; Hermes et al., 2015), or also by natural stimuli (Brunet et al., 2014). In the present study, the narrowband gamma response was elicited by light offset and is thus presumably linked to the OFF pathway of the visual system. This finding suggests that gratings could trigger an exceeding involvement of the OFF pathway which is apparent in cortical narrowband responses.

A recent paper shows narrowband gamma oscillations in the visual system of mice: Saleem et al. (2017) report that visual broadband and narrowband activity is not correlated: with higher contrast, broadband gamma increases while narrowband oscillations decrease. They show that the narrowband gamma response is inherited from thalamus and propose a model with two different channels for information transfer: the narrowband gamma enabling thalamocortical communication and the broadband gamma allowing for corticocortical interactions. In the present study, we show that both narrowband and broadband gamma are transmitted from retina to cortex. However, they still comprise different information, possibly even different levels of informational value. Light contains per se more information than darkness, and supposedly evokes more features in visual scene processing, which could be an explanation why more frequency bands are involved in carrying the information, as well as why the transmission is faster for light offset responses.
In summary, our data supports faster processing of darks on the cortical but not retinal level. The oscillatory potential gets transmitted to visual cortex, and this propagation is faster for light offset responses. Furthermore, we show that light onset high frequency activity comprises a broad range of frequencies, whereas the response to light offset evokes a narrowband oscillation in the range of 75–95 Hz in both retina and cortex.

Acknowledgments We thank Christopher Bailey for his assistance in data collection and Tzvetan Popov and Ursula Lommen for their help with a pilot recording. Further, we thank Juan Vidal for valuable discussions about this study. This work was supported by the Zukunftskolleg of the University of Konstanz, ERA-Net NEURON via the Bundesministerium für Bildung und Forschung (BMBF grant 01EW1307), and the European Research Council (Starting Grant 640488).
2.2 Study 2

Does transcranial magnetic stimulation of occipital cortex affect the retina? – A pilot study

The functioning of corticofugal neurons in the human visual system is still relatively unexplored. Although the existence of such fibers is corroborated in some anatomical studies, physiological evidence is still ambivalent. By combining transcranial magnetic stimulation (TMS) of visual cortex with electroretinography, we hope to provide further evidence of corticoretinal pathways in the human brain. This pilot study aims to demonstrate the feasibility of this approach.

TMS-evoked potentials were observed in both subjects. Sham stimulations and a phantom head investigation could rule out most of the suspected artifacts as a cause for this activity. The presented results are consistent with the stimulation of a corticoretinal pathway through TMS of visual cortex. Furthermore, this pilot study offers valuable clues on crucial improvements for the planned full study.

2.2.1 Introduction

Clearly, the retina transfers massive amounts of information to the cerebral cortex. However, whether any information flows in the opposite direction in humans, i.e., from cortex to retina, has only been explored by a handful of studies (Wasserman et al., 2010) despite the fact that an analogous system in the auditory domain has attracted research interest: after the olivochochlear bundles have been first described by Rasmussen in 1946, numerous studies investigated this efferent network that originates in the auditory cortex and projects to the cochlear receptors (see
Terreros and Delano, 2015, for a review). It has been shown that the auditory cortex can modulate cochlear activity, for example by deactivating the auditory cortex in chinchillas (Léon et al., 2012) or through investigation of sleep/wake cycles in guinea pigs (Vellutti et al., 1989). Several studies have even shown an influence of selective attention on cochlear responses (e.g. Oatman, 1971, in cats, or Smith et al., 2012 and Srinivasan et al., 2012, in humans).

In the human visual system, the functioning and role of corticoretinal fibers is still hardly examined. Wasserman et al. (2010) even speak of an “urban legend” about the non-existence of efferent retinal neurons.

The first anatomical characterization of efferent visual fibers in animals dates back to 1888, when Ramón y Cajal described fiber bundles that terminated in the avian retina. The existence of such neurons in mammals has been controversially debated for a long time, but with the rise of modern histological methods and retrograde nerve fiber tracers, many studies have claimed the existence of centrifugal fibers in numerous mammals – and some also in humans. Reviews by Repérant et al. (2006) and Ortiz et al. (2016) cite studies which described centrifugal fibers in the human retina (e.g., Liss and Wolter, 1956; Ventura and Mathieu, 1959; Wolter, 1965; Honrubia and Elliot, 1968; Repérant and Gallego, 1976; Wolter, 1991). According to these examinations, the human centrifugal visual system consists of very few – rarely more than 10 – large axons (compared to for example over 10,000 in the chicken (Uchiyama et al., 1996), but only one to five in rats (Gastinger et al., 1999)). These axons branch widely and can innervate up to a whole retinal quadrant (Repérant and Gallego, 1976).

Animal studies on the function of retinopetal neurons in mammals have shown increased retinal responses after optic nerve sections in macaque monkeys (Jacobson and Gestring, 1958; Maffei et al., 1985) and modulated firing pattern of retinal cells in response to light flashes after cryoblocking of the visual cortex in rats (Molotchnikoff and Tremblay, 1986). Retinal activity patterns are also modulated
by sleep/wake cycles in rats (Galambos et al., 1994; Galambos et al., 2001). Thus, there is evidence for the efferent visual system to exert comparable influences on the retina as does the auditory centrifugal system on the cochlea.

Studies investigating such effects in the human visual system, however, are rare and physiological evidence is still somehow equivocal (cf. Ortiz et al., 2016) and controversially debated. Comparing monocular to binocular retinal stimulation yielded mixed evidence, where some studies found larger amplitudes in the electroretinogram (ERG) for monocular recordings and others did not (Wirth, 1951; Bagolini, 1959; Steindler et al., 1981). In a comparable experiment, recording from the occluded eye in monocular stimulation lead to the observation of effects in the non-illuminated eye (e.g., Marg, 1953). Positive evidence of these studies could be interpreted in line with the impact of a corticofugal visual system; an alternative explanation could be found in retino-retinal feedback (cf. Tang et al., 2016). Clinical studies after unilateral optic nerve trauma and nerve damage yield equivocal results as well (see Ortiz et al., 2016 for a review). In a spatial attention task, Eason et al. (1983b) showed larger ERG amplitudes for flashes in the attended compared to the unattended field, but Mangun et al. (1986) failed to replicate this finding.

The aim of the planned study is to investigate whether cortical stimulation can influence retinal activity, which would provide strong functional evidence for the existence of corticofugal fibers to the retina and a mechanism for top-down modulation of retinal responses. This chapter presents a pilot study undertaken to establish the feasibility of our approach. To this end, we combined for the first time TMS of visual cortex and electroretinography, and computed ERG averages time-locked to the cortical stimulation (cTMS-evoked ERG potentials).
TMS is known to be able to exert excitatory and inhibitory effects on the visual cortex. Applying weak single pulse TMS to visual areas elicits phosphenes, artificial percepts in the form of faint light flashes and flares (e.g., Marg and Rudiak, 1994; Ray et al., 1998; Kammer, 1999; Kammer et al., 2005; Taylor et al., 2010), whereas strong stimulation leads to a suppression of visual perception or the impression of scotomas (Amassian et al., 1989; Kammer, 1999; Kammer et al., 2005). In this study, phosphenes were used as a benchmark of cortical excitability (Meyer et al., 1991; Gerwig et al., 2003).

We hypothesize that if the stimulation of visual cortex through TMS is transmitted via corticofugal neurons, effects of this stimulation should be seen in the electroretinogram. Undoubtedly, such a hypothesis can not be confirmed in a pilot study with only few subjects. The particular aim of this pilot experiment is to show the feasibility of combining ERG with TMS regarding data collection, data analysis, and data interpretation and to further develop the methods for the planned exhaustive study.

2.2.2 Methods

Participants and experimental design The present pilot study was run with three healthy participants. Of those, two (one male, one female) were included in the further analyses, the third subject did report only few phosphenic percepts. Data for subject A was collected in two different sessions.

TMS single pulses were applied over visual cortex (targeting primary and secondary visual cortex, V1 and V2) using a “Magstim Rapid2” transcranial magnetic stimulator (Magstim Co, Whitland, UK) and a figure-eight coil (7 cm wingspan). To target the visual areas as precisely as possible, neuronavigation based on the participant’s magnetic resonance image (MRI) was adopted. Within the circumscribed brain region of V1 and V2, coil positions where phosphenes could be elicited were searched. Prior to the actual experiment, the individual’s phosphenic thresh-
old was determined with the modified binary search procedure (MOBS; Tyrrell and Owens, 1988). Stimulation intensity was subsequently kept just above this threshold to ensure a higher number of phosphene percepts (at 60 and 70% of maximum machine output for subject A, and 40% for subject B).

Retinal activity was recorded bilaterally using Dawson-Trick-Litzkow (DTL) fiber electrodes. To monitor eye movements, horizontal and vertical electrooculogram (HEOG and VEOG) electrodes were attached. Additionally, scalp electrodes (Fz and Fpz) were used. Data was recorded using an average reference, but re-referenced during data analysis. The ground electrode was placed on the right cheek.

During the experiment, the recording chamber was dark and subjects were asked to keep their eyes open and still. TMS pulses were applied through a foot switch by the experimenter. The participant verbally reported phosphene percepts trial by trial.

For subject A, additionally two sham conditions were realized. To administer any potential effects that are not related to the magnetic stimulation of the brain tissue, the coil was turned 180 degrees such that the magnetic field was facing away from the subject. The second sham condition consisted of motor cortex stimulation to account for possible activations which are due to the stimulation but not depending on the stimulation site, like for example startle reflexes or volume conduction.

Data analysis All data analyses were done using FieldTrip (Oostenveld et al., 2010), an open source MATLAB toolbox for MEEG data analysis. Data were epoched with respect to the TMS pulses. The TMS pulse artifact was identified and its extent (−8 ms and +14 ms relative to the TMS trigger) replaced with a cubic interpolation. Channels were first re-referenced to Fz, subsequently, the electrooculogram (EOG) channels were re-referenced following a bipolar montage
and the ERG channels were re-referenced to the ipsilateral HEOG electrode. Data were highpass filtered at 1 Hz and lowpass filtered at 250 Hz using finite impulse response (FIR) filter (onepass-zerophase, Hamming window, transition width: 0.5 Hz for the highpass and 10 Hz for the lowpass filter). To reduce line noise in the data, a discrete fourier transform (DFT) filter was applied for 50, 100 and 150 Hz.

Based on the EOG data, all trials with blinks, saccades, muscle and other artifacts were rejected. For the motor sham condition, all trials where the subject had reported any activation of facial nerves and muscles were excluded from further analysis as well. Overall, this resulted in 135 trials for subject A, 35 trials for subject B, 55 epochs in the sham condition and 34 in the motor sham condition (cf. Table 2.2). Subsequently, data were sorted into phosphene and non-phosphene trials. cTMS-evoked potentials were computed by averaging trials within these two categories. To uncover high frequency activity, data were bandpass filtered between 105 Hz and 145 Hz (Hamming-windowed FIR filter, onepass-zerophase, transition width: 6 Hz for both highpass and lowpass filter) and the Hilbert transform was calculated.

**Phantom head investigation** The experiment was simulated with a conductive phantom head to account for potential direct effects of the magnetic pulse on the ERG electrodes. An ERG electrode, reference, and ground were attached to the dummy and embedded in a conducting solution. Seven single pulses were applied to the back of the phantom head. The obtained data was processed in the same way as described for the real data above.

### 2.2.3 Results

**Phosphene trials** The ERG average across trials with phosphene percepts shows a slow positive potential centered around 90 ms after the TMS pulse to visual cortex (compare Figure 2.6, left column). This evoked response is similar in shape
across participants and recording sites (left and right ERG) except for the left ERG of subject B. Preceding the positive potential, the ERG recorded high frequency activity that can clearly be seen in the averaged data. Computing the analytic amplitude of the signal for 105 to 145 Hz shows that this high frequency activity is lasting approximately from 30 to 70 ms and peaking at \( \approx 45 \text{ ms} \) (Figure 2.7, left-hand side). Precise peak timings for both the evoked potential and high frequency activity are listed in Table 2.2.

The EOG of subject A did not record any TMS-locked activity (Figure 2.6, top right plot). The VEOG of subject B, however, shows a positive deflection comparable to the ERG potential. This could either point to saccadic eye movements or reflect a recording of retinal activity by the VEOG electrodes.

As Figure 2.8 shows, the Fpz electrode, which was referenced to Fz and the only scalp electrode in this pilot experiment, recorded a slow potential as well. However, in both subjects, it peaks later than the ERG (cf. Table 2.2), thus, volume conduction can be ruled out.

Table 2.2: **Peak latencies.** Peak latencies for the slow potential and the high frequency activity (analytic amplitude for 105 to 145 Hz).

<table>
<thead>
<tr>
<th>Participant</th>
<th>Slow potential</th>
<th>Hilbert amplitude</th>
<th>trials</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Right ERG</td>
<td>Left ERG</td>
<td>Fpz</td>
</tr>
<tr>
<td><strong>A</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>percepts</td>
<td>89.36</td>
<td>85.45</td>
<td>103.50</td>
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<tr>
<td>non-percepts</td>
<td>85.94</td>
<td>84.47</td>
<td>103.50</td>
</tr>
<tr>
<td><strong>B</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>percepts</td>
<td>89.84</td>
<td>n.i.*</td>
<td>94.25</td>
</tr>
<tr>
<td>non-percepts</td>
<td>87.40</td>
<td>n.i.*</td>
<td>103.00</td>
</tr>
</tbody>
</table>

*Values are reported as peak times of the averages in ms, except for the last column, which shows numbers of trials per category.*

*n.i.: not identifiable, compare Figure 2.6*
Figure 2.6: Retinal responses to transcranial magnetic stimulation of V1. **A:** ERG activity. The left panel shows the ERG responses in trials where subject A (top) and B (bottom) reported phosphenes percepts. The dark blue and light blue traces correspond to the right and left ERG, the grey area marks the time points that were interpolated after removal of the TMS artifact. The middle column shows the trials where the participants did not report any phosphenes. **B:** EOG activity in phosphene trials. The HEOG and VEOG are depicted in light and dark green, respectively, the right ERG is shown in dark blue. Note that the ERG was scaled by a factor of 0.33 to make it comparable to the EOG recordings and that this has an impact on the leading edge of the ERG potential.

**Non-phosphenene trials** When comparing the trials without phosphene reports to the phosphene trials, there is not much of a difference: The averages show a similar positive potential (Figure 2.6) and high frequency activity (Figure 2.7) as the phosphene trials. As Table 2.2 shows, the timing of all peaks is comparable as well. Furthermore, the EOG and Fpz also recorded similar activity patterns as the averages from the percept category.

**Sham conditions** For participant A, two sham conditions were realized during the pilot experiments. In one condition, the coil was turned 180 degrees such that no magnetic pulse reached the brain tissue. The ERG and EOG results from this control condition are shown in Figure 2.9 (top panel): there is no response com-
Figure 2.7: Hilbert analytic amplitude. The Hilbert amplitude was computed for the frequency band of 105 to 145 Hz and is shown here for the ERG electrodes (right and left ERG in dark and light blue, respectively). Both in trials with phosphene perceptions (left column) and without phosphene reports (right column), an increase in high frequency activity is noticeable.

Figure 2.8: Comparison of ERG potentials to Fpz activity. The Fpz electrode (referenced to Fz) recorded a slow potential (shown in pink). Compared to the ERG potential in dark blue, the Fpz potential peaks later. Note that the ERG was scaled by a factor of 0.2 to make it comparable to the Fpz recordings and that this gives a misleading representation of the leading edge of the ERG potential, which is considerably steeper and precedes the Fpz potential’s leading edge.
parable to the results of the stimulation trials (cf. Figure 2.6). Also in the second sham condition, where motor cortex instead of the visual areas was stimulated, no TMS-locked effects are present (Figure 2.9, bottom panel).

Figure 2.9: Sham conditions. The figure shows the results from two control conditions. A: In the sham condition, the TMS coil was turned such that the magnetic field was facing away from the subject. B: In the motor sham condition, the motor cortex instead of primary visual cortex was stimulated. All data are from subject A; y-axes are made comparable to Figure 2.6.

**Phantom head** In the data from the conductive phantom head test, no pulse-locked effects apart from the TMS pulse artifact itself were present. After removing and interpolating the TMS pulse artifact, neither slow decay artifacts nor any pulse-locked high frequency activity could be identified. The averages from this test are provided in Figure 2.10.
2 High frequency activity in retinocortical interactions

Figure 2.10: **Results from phantom head experiment.** When stimulating an ERG electrode attached to a conductive phantom head, TMS system did not induce any artifacts in the ERG electrode after the 5 ms duration of the TMS pulse itself (removed and interpolated here), as can be seen on the left hand side of this figure. The high frequency noise is not locked to the TMS pulse, as the analytic amplitude in the right column of this plot shows.

2.2.4 **Discussion**

The present pilot study aimed to check the feasibility of combining transcranial magnetic stimulation of visual cortex with the recording of retinal activity by electroretinography. Although it is impossible to draw any generalizable conclusions from this small pilot sample, it is nevertheless interesting to cautiously review the present results and their potential implications.

Figure 2.11: **Flash-evoked retinal potential.** The subject was stimulated with short, bright flashes, while the left eye was occluded. The a-wave (negative deflection) and b-wave (positive potential) are clearly visible in the right ERG. Data stems from subject A, and was recorded during a pilot experiment for another project in the same lab.
Following transcranial magnetic stimulation of visual cortex, a slow potential and high frequency activity were recorded from the retina in both subjects, whereas sham stimulation did not produce any comparable outcomes.

Especially remarkable about this effect is, that the cTMS-evoked ERG potential is very similar to what can be recorded following flash stimulation of the retina. Figure 2.11 shows a flash-evoked retinal response: the first negative deflection of this average is the a-wave, which is generated by the photoreceptors in the retina (Frishman, 2013). The large positive potential following the a-wave is the b-wave, which is mostly generated by depolarizing ON bipolar cells (Frishman, 2013; Vukmanic et al., 2014). Comparing the results in Figure 2.6 to this well-studied flash-response, there is an intriguing resemblance of the cTMS-evoked positive potential to the b-wave. Another similarity between the cTMS- and flash-evoked recordings is the high frequency activity prior to the positive potential: as Figure 2.6 demonstrates, it can still be seen in the average of trials. This is a characteristic of the so-called oscillatory potential in flash-induced retinal responses (Fröhlich, 1914; Todorov et al., 2016), whose origin remains unsettled, but is likely to partially arise from retinal ganglion cell activity (Doty and Kimura, 1963; Kenyon et al., 2003; Frishman, 2013). The resemblance of our recordings to flash-evoked retinal activity is an indication that we indeed recorded genuine retinal activity following TMS of visual cortex.

Interestingly, there are no noteworthy differences between phosphene and non-phosphene trials. We used the report of phosphene perceptions at first hand as a measure of cortical excitability and as a control over stimulation intensity. Phosphene-induced effects in the electroencephalography (EEG) are rather late, 160 to 200 ms after the TMS pulse (Taylor et al., 2010), occurring considerably later than the retinal potentials we observed. Taylor et al. (2010) take this as evidence that phosphenes are not a local phenomenon, but are generated by a network of visual areas; which is supported by studies that show phosphene per-
ceptions following stimulation of parietal cortex (Marzi et al., 2009; Fried et al., 2011). Furthermore, it has been found that phosphene perception is linked to pre-stimulus alpha in posterior-occipital and frontocentral regions (Romei et al., 2010; Dugué et al., 2011). Based on these studies, it is valid to suggest that phosphene perceptions and the stimulation of the corticofugal pathway do not necessarily depend on each other. However, another possible explanation for the similarity of phosphene and non-phosphene trials is that the ERG response was triggered by the TMS pulse itself and not through the stimulation of efferent pathways, for example by provoking a blink, micro-saccade, muscle twitch, or even by direct effects on the electrode itself.

The phantom head investigation demonstrated, that the ERG fiber electrode does not react differently to the magnetic pulse than the other electrodes that we used. Apart from the TMS pulse artifact that could easily be removed and interpolated during data processing, neither pulse-locked slow effects nor high frequency activity was found. Therefore, not only the resemblance to well-studied retinal activity, but also the outcomes of this test make it rather unlikely that the TMS-evoked ERG activity in this study stems solely from a direct effect of the magnetic pulse on the ERG electrodes.

A rather compelling alternative explanation for the ERG activity are eye movements, e.g., small saccades or blinks. They could be triggered by a startle response to the sound or the tingling feeling accompanying the TMS pulse or even through a mechanism evoked by the stimulation of visual areas. Since none of the two sham conditions that were realized with subject A show any TMS-evoked activity, it is unlikely that the ERG responses in the phosphene conditions are startle reflex related activity. Especially in the motor sham condition, any eye movements that were related to the sensation of the TMS pulse should still be present or even enhanced. To have direct control over eye movements, EOG was recorded during all experiments. However, the interpretation of the EOG is not straight forward:
whereas the EOG is clean for subject A, the VEOG of subject B picked up a slow potential which was similar to the slow wave in the ERG. There are two explanations for this: firstly, the cause for this potential could be a vertical eye movement – and this eye movement is what is picked up by the ERG as well. However, there is no such VEOG activity in subject A despite apparent ERG potentials. Alternatively, it could be the other way around and the VEOG of subject B picked up the retinal potential: some retinal changes are visible in the EOG (Eason et al., 1983a; Frishman, 2013) and can even be reconstructed from frontal MEG sensors (Wong et al., 2014). Nevertheless, this is an apparent shortcoming of the present pilot study and should be resolved in the future investigation.

The potential recorded by the Fpz electrode, a slow response time-locked to the TMS stimulation, peaks after the retinal activity. This reassures that the retinal activity is not due to volume conduction of posterior activity. Instead, the centroparietal electrode could have picked up TMS-evoked activity in occipital cortex – but to draw any conclusions on this, a full EEG montage would be necessary.

**Feasibility and outlook**  Clearly, this pilot study can not lead to any reliable conclusions about the functioning of the corticofugal system – but it could show that the combination of electroretinography and TMS of visual cortex is viable: the ERG data are analyzable despite the magnetic pulses and most of the suspected artifactual influences (e.g., volume conduction or startle reflexes) could be ruled out within this subject sample.

The limitations of this pilot experiment will be addressed in the upcoming study: first of all, eye tracking will be added to be able to disentangle eye movements and retinal activity recorded by the EOG electrodes. Furthermore, a full EEG montage will shed more light on concurrent brain processes and their relation to the possible retinal effects. An eventual corticoretinal information flow could then be investigated with coherence and connectivity measures.
The study protocol will be changed such that true magnetic stimulation is interleaved with catch trials and a motor sham condition might be added for every subject.

**Conclusions**  This pilot study combined TMS to visual cortex and retinography for the first time and we could show that such a study protocol is feasible. The results from this small sample of subjects are consistent with the stimulation of a corticofugal pathway through TMS of visual cortex and the transmission of this stimulation to the retina. To be able to draw exhaustive conclusions, a thorough investigation with several subjects will be conducted.

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Chapter 3

The gamma chase: Approaches to low SNR signals
3.1 Study 3

Across-subjects classification of stimulus modality from human MEG high frequency activity

Single-trial analyses have the potential to uncover meaningful brain dynamics that are obscured when averaging across trials. However, low signal-to-noise ratio (SNR) can impede the use of single-trial analyses and decoding methods. In this study, we investigate the applicability of a single-trial approach to decode stimulus modality from MEG high frequency activity. In order to classify the auditory versus visual presentation of words, we combine beamformer source reconstruction with the random forest classification method. To enable group level inference, the classification is embedded in an across-subjects framework.

We show that single-trial gamma SNR allows for good classification performance (accuracy across subjects: 66.44%). This implies that the characteristics of high frequency activity have a high consistency across trials and subjects. The random forest classifier assigned informational value to activity in both auditory and visual cortex with high spatial specificity. Across time, gamma power was most informative during stimulus presentation. Among all frequency bands, the 75–95 Hz band was the most informative frequency band in visual as well as in auditory areas. Especially in visual areas, a broad range of gamma frequencies (55–125 Hz) contributed to the successful classification.

Thus, we demonstrate the feasibility of single-trial approaches for decoding the stimulus modality across subjects from high frequency activity and describe the discriminative gamma activity in time, frequency, and space.
3.1.1 Introduction

Since the first reports of cortical gamma band activity (Gray and Singer, 1989; Gray et al., 1989), these high frequency responses have been linked to a plethora of brain processes and mental tasks, for example visual perception and processing (Hoogenboom et al., 2006; Dalal et al., 2011b; Muthukumaraswamy et al., 2010; Hermes et al., 2014), auditory perception (Crone et al., 2001; Brosch et al., 2002) or memory (Fell et al., 2001; Osipova et al., 2006; Jensen et al., 2007; Staudigl and Hanslmayr, 2013). Although numerous theories about the origin and function of these high frequency oscillations and their relation with lower frequencies like theta and alpha have been proposed (e.g., Akam and Kullmann, 2014; Jensen and Mazaheri, 2010; Fries, 2015), there is an ongoing debate about whether gamma band responses reflect narrowband oscillations or broadband power increases, possibly echoing an increase in spiking activity (Miller et al., 2009a; Ray and Maunsell, 2010; Hermes et al., 2014). One obstacle in this quest is the 1/f characteristic of the brain’s frequency power spectrum and a low signal-to-noise ratio (SNR) of gamma band activity in magnetoencephalography (MEG) or electroencephalography (EEG) recordings. To increase SNR, trial averaging is a frequently used tool to cancel out random variance. However, this approach can potentially obscure or cancel meaningful brain activity (Stokes and Spaak, 2016). Indeed, local field potentials and electrocorticographic data from monkeys revealed systematic trial-to-trial variations in gamma power and frequency in a visual (Lowet et al., 2016) and a memory task (Lundqvist et al., 2016). Importantly, the averages across trials in these studies displayed the classic sustained gamma effect, indicating that single-trial responses are crucial to understand the brain’s dynamics (Stokes and Spaak, 2016). One powerful approach to assess single-trial information are multivariate decoding techniques. Whether such methods are applicable on low SNR gamma band MEG data, however, remains unclear. In the present paper, we investigate the predictive value of single-trial gamma power
regarding the modality of stimulus presentation (auditory or visual presentation of words) in human MEG data. While comparable contrasts have been used to test classifier performance or as example datasets (e.g., Guimaraes et al., 2007; Gramfort et al., 2013), our aim was to unravel single-trial high frequency patterns in human MEG data. To decode information about stimulus-modality from the time-frequency data, we used a combination of beamforming (Van Veen et al., 1997) and random forest classification (Breiman, 2001). This approach was embedded into an across-subjects cross-validation framework, where the classifier was tested on unseen subjects to assess the generality of the spatial time-frequency pattern. Our results confirm that gamma SNR in single trials is high enough to achieve stable classification accuracy significantly above chance. Interestingly, the classification model yields high informational value to a broad bandwidth in the gamma range. Furthermore, we show that the characteristics of the gamma activity are similar enough across trials and even subjects to yield reliable classification performance.

3.1.2 Methods

Participants A total of 24 participants (17 female; mean age=22 years, range=19 – 26 years; 21 right-handed) took part in this MEG experiment. Three participants were excluded due to technical problems, one due to excessive environmental noise. The data from the remaining 20 participants are presented here. All of the participants gave written informed consent prior to the experiment, in line with the Declaration of Helsinki, and received course credits or nominal financial compensation for participation. All participants were German native speakers and reported normal or corrected-to-normal vision, and no history of neurological disease.

Parts of this data have been published in Staudigl and Hanslmayr (2013), with respect to independent research questions and analyses.
Design, procedure, and material  The experiment consisted of a study phase and a subsequent recognition test. Only data from the study phase are reported here. In the study phase, participants were presented with words either visually (projected centrally on a screen) or auditorily (via nonferromagnetic tubes to both ears). The duration of the visual word presentation was determined by the duration of the respective audio file, i.e., the time to pronounce the word (mean duration = 697 ms, s.d. = 119 ms). Each word was followed by a fixation cross. The duration of the word and fixation cross together added up to 2000 ms. Participants were instructed to count the syllables of the word and indicate via button press whether the word had two syllables. A question mark (max. duration of 1500 ms) prompted the subject’s response. The button press ended the presentation of the question mark. A fixation cross with variable duration (1000–1500 ms) was presented before each item. After the encoding phase, participants performed a distractor task and a surprise recognition test phase.

The stimuli consisted of 420 unrelated German nouns, grouped into three lists with 140 words. Half of each list’s words had two syllables, the other half had one, three or four syllables. Two lists were presented during the study phase and one list during the test phase. The assignment of the lists to study or test phase was counterbalanced across participants. Items were presented in random order, with the constraint that not more than 5 words of the same modality and not more than 5 words from the same condition were presented sequentially.

MEG data acquisition and preprocessing  MEG data was recorded with a 148-channel magnetometer (MAGNES™ 2500 WH, 4D Neuroimaging, San Diego, USA) in a supine position inside a magnetically shielded room. Data was continuously recorded at a sampling rate of 678.17 Hz and bandwidth of 0.1–200 Hz, and later downsampled to 300 Hz to reduce computational load. All data processing prior to classification was done using FieldTrip (Oostenveld et al., 2010), an open-
source MATLAB toolbox for MEEG data analysis. Data was epoched into single trials, with epochs ranging from 1500 ms before item presentation to 4000 ms after item presentation. Trials were visually inspected for artifacts, contaminated trials were rejected. Thereafter, trials were corrected for blinks, eye movements, and cardiac artifacts using independent component analysis (ICA).

**Source reconstruction** For coregistration with the individual structural magnetic resonance image (available for 17 out of 20 participants; for the remaining three participants we used an affine transformation of an MNI-template brain; Montreal Neurological Institute, Montreal, Canada), the shape of the participant’s head as well as three markers (nasion, left and right ear canal) and the location of the head position indicator (HPI) coils were digitized prior to the experiment using a Fastrak Polhemus 3D scanner (Polhemus, Colchester, VT, USA).

Single-trial source space activity was reconstructed using a linearly constrained minimum variance (LCMV) beamformer (Van Veen et al., 1997) with weight normalization (neural activity index; Van Veen et al., 1997; Sekihara and Nagarajan, 2008). First, the spatial filter was computed adopting a realistic single shell head model (Nolte, 2003) based on the individual structural magnetic resonance image (MRI) and a source model with grid points covering the whole brain volume (resolution: 15 mm). The data covariance matrix was computed for −500 to 1000 ms relative to stimulus presentation. Subsequently, the spatial filter was applied to the single trials to obtain virtual electrodes at all grid point locations.

For the classification of the oscillatory activity, single-trial time frequency representations were calculated at every virtual electrode applying a Fast Fourier Transform. Gamma band activity was estimated using frequency smoothing (Slepian sequence multi taper approach), yielding 20 Hz-wide frequency bands centered at 35,
65, 85, 115 and 135 Hz. The power was calculated separately for 250 ms long time windows from −500 to 1000 ms and the post-stimulus activity was then expressed as relative change to baseline power.

**Random forest classification** The random forest algorithm (Breiman, 2001), an ensemble method, aggregates the results of several classifiers. These so-called base learners are classification and regression trees (Breiman et al., 1984), which partition the data by adopting binary splits. The aim of this partitioning process is to reduce the impurity regarding the class labels in the daughter nodes that result from this split: preferably, all observations from one class should arrive in the same node. In every split, the tree algorithm searches first for the predictor that maximizes the purity of the daughter nodes and then for the best split point within that predictor. Random forests now grow numerous trees; each of these trees, however, is built on a bootstrap sample of the original data and in every split only a random subsample of all predictors is searched. The variance introduced by this randomness leads to a robust prediction by the aggregated model. This approach furthermore enables random forest to cope particularly well with highly correlated predictor variables (Cutler et al., 2009), which is of special interest when working with MEEG data. Additionally, data with more predictors than observations (small n large p problems) are also handled effectively since the predictor variables are searched successively (Strobl et al., 2009), which makes this approach particularly interesting when dealing with high-dimensional source-space MEEG data. For every predictor, the algorithm returns an estimate of how important this variable was for the model’s prediction. The version used here is based on the impurity reduction introduced by a predictor variable across all trees, which is measured by the Gini index (Gini, 1912; Breiman et al., 1984; Cutler et al., 2009).
Random forest classification was performed using the scikit-learn module for Python (Pedregosa et al., 2011). The aim of the decoding was to classify trials regarding their stimulus modality: visual or auditory. The predictors were [voxel, time point, frequency band]-triplets, providing 16,624 predictors, overall. For every subject, the more prevalent class (auditory or visual stimulation) was downsampled such that every dataset contained equal trial numbers for both cases. The total trial number across all subjects was 4,270 trials.

The classification was embedded in a cross-validation framework across subjects: the classifier was trained on the data from all but one subject and then tested on the data of this left-out subject. This procedure was repeated for all 20 subjects, such that every dataset was used as test set once. This approach ensures that the classifier is never tested on data it was trained on and thus controls for possible overfitting of the classifier. Moreover, it allows the assessment of across-subjects predictability of the data regarding the response variable.

Each of the 20 cross-validation models aggregated the results of 15,000 classification trees, where every tree was built on a bootstrap sample of all observations in the trainings set. To ensure that the model incorporated a sufficient number of trees, classification performance was assessed with 25,000 trees for two folds (Liaw and Wiener, 2002), yielding comparable results as the sparser model. At each binary split, the algorithm considered $\sqrt{N_{\text{features}}}$ predictors to find the best split. The accuracies on the test datasets as well as the variable importances were merged across the cross-validation folds. The performance of the classifier was then tested against 50% chance level using a binomial test (Combrisson and Jerbi, 2015), since a permutation based test was computationally not feasible.
3.1.3 Results

To assess the predictive value of single-trial gamma power towards stimulus modality, we used MEG data from 20 subjects and adopted an across-subjects classification scheme. Data was first source reconstructed with an LCMV beamformer, subsequently, we used the random forest algorithm to classify the modality of stimulus presentation (auditory or visual).

The random forest model classified auditory versus visual trials with 66.44% accuracy, which is significantly better than chance (binomial test, \( n_{\text{trials}} = 4270, p < 0.001 \)). As the confusion matrix in Figure 3.1A shows, the accuracy was slightly better for auditory trials (69.60%) than for visual trials (63.19%). In the adopted 20-fold cross-validation scheme, every fold corresponded to the data of one subject, hence, the classifier was always tested on data of one subject which was not included in building the model. The classifier accuracy on the 20 cross-validation folds is depicted in Figure 3.1B. The performance on the different folds is diverse, ranging from 50.98 to 84.86%, however, the accuracy for all but three folds is above 60% (note that the folds, since they are part of the whole classifier model, are not tested for significance). The good classifier performance indicates that the gamma power patterns are remarkably stable across trials and even subjects.

The random forest classifier provides the variable importance as an importance estimate for every predictor in the model. This measure indicates the informational value of a given predictor towards the discrimination of the two classes, auditory and visual modality. Figure 3.2 reports the highest 2% of variable importance values, i.e., those [voxel, time point, frequency band]-triplets that were most informative for partitioning the data. Not only visual, but also auditory regions contributed to the model, even though visual areas yielded more information than the auditory cortex. Interestingly, the lower frequency bands of 25–45 Hz and 55–75 Hz did not rank as important as the 75–95 Hz band. Even frequencies above 100 Hz
contributed to the model in both visual and right auditory cortex. Gamma power beyond 125 Hz, however, did not add substantially to the classification model.

All time windows but the last one (750–1000 ms) supplied information to the classifier, in higher frequencies, the earlier time windows seemed to play a more pronounced role compared to the lower gamma frequencies. Figure 3.3 shows the time-frequency representations of variable importance for the visual and auditory peak voxels: the visual peak voxel (MNI coordinates: [-4 -100 12]) falls into left calcarine sulcus, the auditory peak voxel (MNI coordinates: [68 -20 10]) into right superior temporal gyrus (labels determined with the Automated Anatomical Labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002)). The time-frequency representations for those two peak voxels (Figure 3.3) confirm the pattern evident across all voxels (Figure 3.2). Thus, the 75–95 Hz band yielded a characteristic and stable activity pattern in both the auditory and visual cortex. The visual re-
Figure 3.2: Variable importances. The 2% most important predictors are shown across time, frequency and space. A higher variable importance score implies that this predictor had a higher informative value in the random forest model to partition the data into trials with auditory and visual perception. The orthogonal views are centered on the voxel showing the highest variable importance.
response was specifically characterized by a broadband gamma increase in the range of 55 to 125 Hz. The auditory response yielded informational value in an overlapping but narrower frequency range (75–125 Hz).

Figure 3.3: **Variable importances in visual and auditory peak voxels.** A Peak voxel locations for auditory and visual cortex (compare peak voxels from Figure 3.2) B Time-frequency representation of variable importances in those peak voxels. Black boxes indicate those variables which were among the 2% most informative predictors.

To investigate the underlying gamma power changes, the variable importance rankings were compared to the power differences between auditory and visual trials. To this end, auditory and visual power changes relative to baseline were averaged across trials and subjects, and the difference between the visual and the auditory condition was computed. These differences are depicted in Figure 3.4A: the spatial pattern of power is shown for the 250–500 ms time window and two frequency bands (75–95 Hz, top, and 105–125 Hz, bottom in Figure 3.4A). Red colors refer to higher gamma power in the visual condition and blue colors to higher power in the auditory condition. The black lines encircle those voxels which were among the 2% most informative predictors for the classifier. Figure 3.4B shows the underlying gamma power relations for the same peak voxels as presented in Figure 3.3. Interestingly, the classifier analysis based on single trials also rated predictors as highly informative where a difference in the averages is small, as is most evident for the time-frequency representation of the auditory condition (75–95 Hz, 500–750 ms).
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Figure 3.4: **Underlying gamma power.** This figure shows the difference in averaged gamma power between visual and auditory word presentation trials. **A** Spatial representation of gamma power for two frequency bands (75-95 Hz, top, and 105-125 Hz, bottom). Red hues represent a higher gamma power in the average of visual trials, the blue colors depict higher gamma power in the average of the auditory condition. Black boxes indicate the 2% most informative predictors as shown in Figure 3.2. **B** Gamma power in visual and auditory peak voxels. Shown is the difference between the visual and auditory condition, black boxes again indicate the most informative predictors for the classifier model.

### 3.1.4 Discussion

In the present work, we investigated the predictive value of single-trial gamma power to classify the stimuli’s modality. This was done in an across-subjects cross-validation framework which allowed us to estimate not only the gamma pattern stability across trials but also across subjects.

The decoding of MEEG high frequency activity on a single-trial basis can be challenging due to the low SNR: while intracranially recorded high frequency activity up to 180 Hz has been used to decode movements (Leuthardt et al., 2004; Rickert et al., 2005), comparable approaches with MEEG data were not successful (Waldert et al., 2008; Quandt et al., 2012). Some studies could show a contribution of high gamma power (along with lower oscillatory activity) to the overall classifier performance (Fuentemilla et al., 2010; Schulz et al., 2011). In this study, we successfully decoded stimulus modality exclusively from high frequency activity: the classifier model was able to correctly classify 66.44% of the trials based on their
source reconstructed gamma activity pattern, reliably distinguishing visual from auditory word presentation. Thus, the SNR of single-trial gamma power in source-level MEG data was high enough to successfully apply single-trial multivariate analyses. Interestingly, more auditory (69.30%) than visual trials (63.19%) were classified correctly, although visual areas yielded more information to the classifier. One possible explanation for this could be that the classifier-inherent cutoff values for gamma power in the visual voxels were rather conservative and therefore missed small gamma increases in visual cortex in visual trials, but still reliably detected the absence of visual activity in auditory trials.

The classification model was built across subjects, adopting a 20-fold across-subjects cross-validation, where the classifier was trained on 19 subjects and then tested on the data of the left-out 20th subject. Hence, the trials of any given subject were classified by a model which was built on the data from different subjects. Using this approach, we assessed the common patterns across trials and subjects. The accuracy pattern across the different folds was higher than 60% for all but three subjects. Low accuracies indicate either higher noise levels in these participants or activity patterns which deviate from the across-subjects consensus as uncovered by the random forest model. The overall classification accuracy of 66.44% is comparable to previous reports of across-subjects MEG data classification (e.g., Olivetti et al., 2014).

The variable importance indicates which predictors were used by the model to yield the classification performance, by providing the common pattern across trials and subjects that differentiated between the two conditions. Clearly, gamma band activity from both visual and auditory areas was exploited by the model, although the visual cortex was more important than the auditory cortices, expressed by higher ranking variable importances. Overall, a broad range of frequencies and a
time span of 750 ms included gamma band activation relevant to the random forest model.

In this study, we show the feasibility of applying the random forest algorithm (Breiman, 2001) to single-trial source-localized time-frequency data. With its non-parametric, non-linear approach and its capability to handle high dimensional datasets with highly correlated predictors, this method is well suited for MEG data (also see Fraiwan et al., 2012; Lehmann et al., 2007; Bentlemsan et al., 2014; Donos et al., 2015) and can detect subtle differences concealed in the averaged data.

Another advantage of this method is the possibility to directly compare predictors (e.g., frequency bands) to each other regarding their importance in the model: for example, we are able to state that the 75–95 Hz frequency band is the most important frequency band, and that the visual cortex has higher informational value for the classification than the auditory cortex.

In our data, the left primary visual cortex was most informative for the classification among all brain regions. Additionally, also higher visual areas ranked as highly informative, which is concordant with the localization of visual gamma band responses in intracranial electroencephalography (iEEG) and MEG studies (e.g., Tallon-Baudry et al., 2005; Swettenham et al., 2009; Muthukumaraswamy et al., 2010; Tan et al., 2016). The classification further identified auditory regions as informative. Although iEEG reliably shows high gamma responses to auditory stimuli (Edwards et al., 2005; Bidet-Caulet et al., 2007; Canolty et al., 2007; Edwards et al., 2009), auditory high frequency activity above 75 Hz has only rarely been shown in MEG studies: examples include high gamma responses to sound and pitch perception (Schepers et al., 2012; Sedley et al., 2012). Within the auditory regions, the most important voxel in our data was located in the right superior tem-
poral gyrus, which is in line with iEEG studies investigating phoneme and word processing (Crone et al., 2001; Edwards et al., 2009) and the above-mentioned MEG studies. Further important regions included Heschl’s gyrus and the planum temporale. Interestingly, the right auditory cortex showed higher importance with more voxels involved compared to the left auditory cortex, although the stimuli were words and should typically evoke language-related activity localized to the left hemisphere (Canolty et al., 2007; Edwards et al., 2009). This may be explained by the fact that both conditions used words as stimuli and thus, left-hemispheric language related activity is not able to distinguish between auditory and visual trials.

The time windows most important to the classification covered 0 to 750 ms after stimulus onset, while the last time window (750–1000 ms) did not show any high ranking variable importance values, implying that gamma activity was most informative to the classifier during presentation of a word (mean = 700 ms).

Informative predictors in auditory areas, however, were only found between 250 and 750 ms, although previous studies reported early auditory (high) gamma responses following phoneme or word stimuli (e.g., Crone et al., 2001; Edwards et al., 2009; Edwards et al., 2010; Steinschneider et al., 2011).

In both, visual and auditory brain areas, the most important frequency band was the 75–95 Hz band. Especially in the 250–500 ms window, this frequency band exhibited exceeding informative value for the classification. Yet, the visual areas overall provided informative predictors across a broad frequency range (55–125 Hz). This points to underlying broadband gamma activity in single trials rather than a narrowband response, which is typically elicited by high contrast stimuli such as gratings, (e.g., Muthukumaraswamy et al., 2010; Tan et al., 2016). The high frequency activity beneficial for classification is similar to visually induced broad-
band gamma activity reported in iEEG and MEG studies (Lachaux et al., 2005; Tallon-Baudry et al., 2005; Vidal et al., 2006; Siegel et al., 2007; Hermes et al., 2014). Vidal et al. (2006), for example, describe a lower frequency band of 45–65 Hz and high gamma activity of 70–120 Hz in their MEG study on visual grouping. Related to reading, broadband high frequency activity above 50 Hz has been reported in iEEG studies (Jung et al., 2008; Dalal et al., 2009; Hamamé et al., 2012; Hamamé et al., 2013). Furthermore, compared to the narrowband responses elicited by high contrast stimuli such as gratings, which are typically centered at lower frequencies, (e.g., 50 Hz reported by Muthukumaraswamy et al. [2010] or 60 Hz reported by Tan et al. [2016]), our results yielded the 75–95 Hz frequency band as most informative.

In the auditory areas, the most important variables were concentrated in the 75–95 Hz and 105–125 Hz Hz frequency bands. This is in line with iEEG studies on syllable and word processing, which report gamma responses from 80 Hz up to 200 Hz (Canolty et al., 2007; Chang et al., 2011). Thus, our results might reflect the lower end of the high gamma response described in these studies, potentially cropped by low SNR above 125 Hz.

To summarize, we have shown that single-trial gamma activity can be successfully used to classify stimulus modality. Importantly, the successful across-subjects classification suggested that single-trial gamma-band activity contains high inter-individual consistency. The classifier identified both visual and auditory areas as informative with high spatial specificity. Our results furthermore suggest that single-trial high frequency activity after visual word presentation is characterized by a broadband rather than a narrowband response.
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3.2 Study 4

Is more always better? The effect of sensor array density on beamformer performance

The latest MEEG systems have 200 sensors and more, yet it is unclear whether common source reconstruction methods profit from having so many channels. Here, we investigate the influence of sensor array density on beamformer performance. We simulated data using a real MEG configuration with 248 magnetometers and a realistic BEM-based head model. A “ground truth” forward model with no coregistration error was created to simulate dipole sources, and a second forward model with a typical coregistration error was added for source reconstruction. Dipole sources were simulated to cover the whole brain volume. The density of the sensor array was varied to yield between 20 channels and the full set of 248. Sources were reconstructed using an LCMV beamformer, with performance quantified using the output SNR and localization error at the peak voxels. The data covariance input into the beamformer and its inverse was calculated in different ways: 1) using the sample covariance, 2) using the known covariance analytically determined from the simulation parameters, and 3) additionally using the matrix inversion lemma for its inverse. For higher input SNRs, output SNR decreases with more sensors. This effect is influenced by both the covariance estimate and the coregistration error: when using the analytical covariance and a model without coregistration error, the output SNR did indeed increase with the number of sensors. The results suggest that larger channel counts may counterintuitively result in worse performance with a standard beamformer. This effect appears to result from increasing covariance inversion error, as demonstrated by the analytical covariance performance.
3.2.1 Introduction

The number of channels in state-of-the-art whole-head magnetoencephalography (MEG) and electroencephalography (EEG) systems has increased over the years to more than 200. Especially combined MEEG systems easily reach a high number of sensors. It is commonly assumed that more channels result in better source reconstruction.

Some previous work has examined the relationship between channel count and the quality of source reconstruction. However, a lot of this work focuses on source localization methods other than beamforming. For example, Michel et al. (2004) report better source reconstruction results in terms of localization precision with more channels for minimum norm estimation (MNE) techniques like LAURA or LORETA. Song et al. (2015) investigate the importance of electrode count and coverage in EEG for MNE models. They demonstrate that a higher number of electrodes and a good coverage of the head is beneficial for localization precision. Vrba et al. (2004) show that when using a synthetic aperture magnetometry (SAM) beamformer, the spatial resolution of a localized source increases with an increasing channel count (from 138 to 275 channels). However, they assume no forward model error in their simulations. Regarding the linearly constrained minimum variance (LCMV) beamformer, van Drongelen et al. (1996) state that a higher number of electrodes (64 compared to 32 and 20 channels) results in a higher resolving power in their simulation based on EEG data. However, anecdotal reports suggest that a high sensor count might not be beneficial for beamformer performance in applications with real data. Brookes et al. (2008) show in a theoretical framework that the number of channels is among the critical characteristics for a good beamforming solution. It is derived that a high channel count can increase the error in the data covariance matrix estimate. However, the authors do not further examine this relationship, i.e., they do not explore how many channels could be considered as “too much” when it comes to the accuracy of the covariance matrix estimate.
Hillebrand and Barnes (2005) report that inaccurate forward modeling has worse effects with more sensors. They note that this problem occurs when the resolution of the beamformer is high enough to capture the differences between the ground truth and the modeled lead field (also see Cox, 1973; Hillebrand and Barnes, 2003; Sekihara and Nagarajan, 2008).

A thorough investigation of these effects is still missing, to our best knowledge. Consequently, in this paper we systematically examine the effect of sensor array density on the beamformer solution in a simulation with special consideration of the forward model and the covariance matrix estimate.

In the following sections, the theoretical background for this simulation study will be given, highlighting the forward model and covariance matrix estimate and their use in beamforming.

**Source reconstruction with beamforming** The source reconstruction with beamforming is obtained by applying a spatial filter to the recorded MEG data. This spatial filter is determined by a set of weights that regulate the contribution of each sensor for each source location (Van Veen et al., 1997; Hillebrand et al., 2005). This can mathematically be expressed by:

$$\hat{s}_r(t) = w^T_r b(t),$$  \hspace{1cm} (3.1)

where $\hat{s}_r$ is the estimated source amplitude at a specific location $r$ in source space at time $t$, $w^T_r$ is the vector of weighting parameters at the target location, with $T$ denoting the transpose. $b_t$ is a column vector representing the magnetic field at time $t$.

Further, the weight vector can be calculated the following:

$$w_r = (L_r^T R^{-1} L_r)^{-1} L_r^T R^{-1},$$ \hspace{1cm} (3.2)
with $L_r$ denoting the forward model at location $r$ and $R$ being the covariance matrix of the data (cf. van Drongelen et al., 1996; Van Veen et al., 1997; Hillebrand and Barnes, 2005; Brookes et al., 2008).

This equation for the beamformer weights, i.e., the spatial filter, shows that the beamforming solution is entirely based on the forward model $L$, and the estimated data covariance matrix $R$. Thus, these are the ingredients that determine the quality of the beamformer solution. The estimation of the forward model and the covariance matrix will therefore be examined in greater detail in the following.

The forward model

The lead field matrix is dependent on the sensor configuration, the volume conductor model, and the source model (Hillebrand and Barnes, 2005). Especially inaccuracies in the volume conductor model can introduce sufficient error to degrade source reconstruction performance. One prominent issue is the accuracy of the head model in use (e.g., single shell model versus boundary element model). But also the coregistration error introduced by an inaccurate registration of MEG data to the individual magnetic resonance image (MRI) can cause inaccuracies in the forward model. These errors can lead to a decreased signal-to-noise ratio (SNR), especially for weaker sources, including, for example, high frequency activity and deeper sources (cf. Dalal et al., 2014 for EEG). We examine the role of coregistration error in our simulation by comparing a ground truth forward model without coregistration error to a forward model with a realistic coregistration error.

Estimation of the data covariance matrix

The covariance matrix must be estimated from the recorded data. A common approach to estimate the covariance between two channels $i$ and $j$ is:

$$R_{ij} = \frac{1}{N} \sum_{n=1}^{N} [m_i(t_n)][m_j(t_n)]$$

(3.3)
Here, $m_i(t_n)$ represents the magnetic field measurement at channel $i$ and time sample $t_n$, correspondingly, $m_j(t_n)$ describes the magnetic field measurement at channel $j$ of the same time point. $N$ depicts the number of samples recorded.

As Brookes et al. (2008) remark, the accuracy of the data covariance estimate depends on the number of samples, the SNR of the data and the channel count. That is, decreasing the number of samples or the SNR, or increasing the number of channels will result in an increasing error in the covariance estimate.

In this work, we will systematically examine the impact of channel count on beamformer performance, namely, output SNR and localization precision. Furthermore, the role of input SNR, the forward model, and the data covariance matrix in this relationship will be investigated.

### 3.2.2 Methods

To investigate the impact of sensor count on beamformer performance, sensor array density was systematically decreased in simulation. Furthermore, two different forward models (with and without coregistration error) were used, and different input SNRs were considered. To identify the role of the covariance matrix and its inverse, the data covariance input into the beamformer was calculated in different ways: 1) using the sample covariance, 2) using the known covariance analytically determined from the simulation parameters, and 3) additionally using the matrix inversion lemma for its inverse.

**Simulation** An overview of the simulation process is given in Figure 3.5. The simulation was based on a real MEG dataset acquired with a magnetometer system with 248 channels (4D Neuroimaging, San Diego). To obtain anatomical fiducials, a 3D-printed head model of the subject based on a scan obtained with a high-
Figure 3.5: **Simulation.** This flow chart illustrates the simulation process.
resolution 3D scanner with a measurement uncertainty of 0.1 mm (FaceSCAN3D, 3D-Shape GmbH, Erlangen, Germany) was used. The anatomical fiducials (nasion, left and right pre-auricular points) were needed to coregister the MEG sensor coordinates with MEG head space as well as with individual MRI space. These fiducials points were then digitized on the model head using the Flying Triangulation (FlyTri) 3D face sensor (Ettl et al., 2012; Ettl, 2015). To obtain a ground truth forward model, these anatomical fiducials were additionally digitized using the high-resolution FaceSCAN3D scanner. Coregistration between MEG head space and MEG sensor space was done for both the FlyTri and FaceSCAN3D coordinates with a rigid body transformation between the fiducials and the MEG sensor coordinates. Coregistration to MRI space was performed with the NUTMEG toolbox (Dalal et al., 2004; Dalal et al., 2011a). The error in fiducial distance for the FlyTri coordinates was 3.04 mm in MRI space compared to the FaceSCAN3D ground truth, which led to a mean error of 4.13 mm in MRI space for the sensor coordinates.

Sensor array density was varied by eliminating sensors based on the space between the sensor coordinates: increasing the allowed space between any two adjacent sensors resulted in a decreasing sensor count. In this way, increasing the spacing between the sensors from 15 to 70 mm in 5 mm steps yielded 12 different sensor counts ranging from the full set of 248 sensors to 20 sensors.

Two forward models were computed: one based on the ground truth FaceSCAN3D coordinates, and one model with a realistic registration error, which was based on the FlyTri coordinates. The subject’s MRI was used to generate brain, skull, and scalp surfaces with BrainVisa (http://brainvisa.info/). Following Oostendorp et al. (2000), a three-layer boundary element model with a brain : skull : skin conductivity ratio of 1 : 0.067 : 1 was constructed with OpenMEEG (Gramfort et al., 2010; Gramfort et al., 2011). The lead fields for both coordinate sets were generated to cover the brain space as a 5 mm grid. The simulated dipole source was synthesized as a 19 Hz oscillation sampled at 1000 Hz and placed at a predefined voxel
of the grid. This oscillation was then projected to the sensors using the forward model based on the FaceSCAN$^{3D}$ ground truth sensor coordinates. Simulated MEG datasets with an SNR ranging from $-30$ to $30$ dB were obtained by adding Gaussian noise to the MEG channels. The source was then reconstructed over space and time for both forward models with the LCMV beamformer implemented in NUTMEG using weight normalization. As described by Sekihara et al. (2001), the weight vector is calculated as follows when adopting weight normalization (compare to equation 3.2):

$$w_r = \left(\sqrt{l_r^T R^{-2} l_r}\right)^{-1} R^{-1} l_r,$$

(3.4)

with $l$ denoting the leadfield at source location $r$ with orientation $\eta_{opt}$. The optimal source orientation was defined as the orientation that maximizes the output SNR (Sekihara et al., 2004). For each of the twelve sets of sensors and the different input SNRs, the simulated source was placed at 99 different voxels of the grid, which were located on an evenly spaced lattice all over the brain volume. Output SNR was estimated at every voxel by subtracting 150 ms baseline activity from the 150 ms active window containing the oscillation and normalizing by the baseline activity. The peak voxel was defined as the voxel with the maximal output SNR and its distance to the simulated source was computed.

As discussed above, the beamformer weights are based on the forward model and the covariance matrix. Thus, also the impact of the covariance model was assessed in the simulation. In a parallel set of simulations, the analytically derived known covariance was used instead of the sample covariance, which is estimated from the data as stated in equation 3.3. The analytic covariance was given by:

$$R = \mu^2 I + \sigma^2 LL^T,$$

(3.5)
where $\mu^2$ is the uncorrelated noise power at the MEG channel level, $I$ denotes the identity matrix, $\sigma^2$ is the root mean square (r.m.s.) amplitude of the simulated source and $L$ the lead field for the simulated source. The inverse of this analytic covariance was derived using the matrix inversion lemma,

$$R^{-1} = (\mu^2 I)^{-1} - (\mu^2 I)^{-1} \sigma L [1 + \sigma L^T (\mu^2 I)^{-1} \sigma L]^{-1} \sigma L^T (\mu^2 I)^{-1},$$  \hspace{1cm} (3.6)$$

to assess the error introduced by the covariance matrix inversion.

### 3.2.3 Results

**Ground truth forward model** Figure 3.6A displays the output SNR in the peak voxel as a function of sensor count for the FaceSCAN\textsuperscript{3D} forward model. The output SNR is averaged across the 99 source reconstructions, where the simulated source was placed in different voxels of the grid. The left section of this figure displays the results for the sample covariance, the right section corresponds to the analytical covariance matrix and the matrix inversion lemma. For both covariance models, there is a clear effect of input SNR: for every sensor count, higher input SNR (depicted in lighter colors) results in higher output SNR. For the estimated covariance, however, the strength of the input signal interacts with the sensor count: for high input SNRs above $-10$ dB, there is a negative relationship between sensor count and output SNR. For moderately strong input signals, this relationship resembles an inverse U-shape, indicating that a critical point is reached with 72-86 sensors.

The right panel of Figure 3.6 presents the results from the analytical covariance with the conventional inversion (blue shades), and from the application of the matrix inversion lemma, depicted in orange. The respective output SNRs almost
completely overlap, which points to the conclusion that an analytical inversion of the covariance matrix does not lead to an additional improvement if the covariance matrix itself is analytically derived.

The localization errors resulting from the simulation with the ground truth forward model are shown in Figure 3.6B. Firstly, the outcomes for both covariance models, the data covariance (left panel) and the analytical covariance and matrix inversion lemma (right panel), look very similar, with a slightly higher localization precision with the analytical covariance matrix. Thus, the covariance estimation error does not seem to have a strong impact on localization precision. In contrast, both the input SNR and sensor array density show a clear relationship with localization error: higher input SNRs lead to smaller localization errors, yielding perfect localization with very strong input signals. For lower SNRs and with increasing sensor count, however, the localization error decreases. As with output SNR, the localization error results are almost overlapping for the analytical covariance and the matrix inversion lemma (here shown in gray).

Taken together, increasing sensor count leads to higher output SNR and smaller localization errors with an exact forward model and the analytical covariance (irrespective of the application of the matrix inversion lemma). Substituting the analytically derived covariance with the estimated covariance, the localization precision still improves with increasing sensor count, whereas the output SNR decreases with input SNRs above $-25$ dB.

**Realistic forward model** The simulation was repeated for a forward model with a realistic coregistration error (the error in fiducial distance compared to the ground truth forward model was 3.04 mm). The results of the simulation with this forward model are shown in Figure 3.7. Figure 3.7A shows the output SNR averaged across peak voxels as a function of sensor count for different input SNRs (lighter colors represent higher input SNRs). The left and right panels of this figure
Figure 3.6: **Beamformer performance with the ground truth forward model.**
Beamformer performance as a function of sensor count, adopting an exact forward model. 
**A** Output SNR averaged across peak voxels for the data covariance (left panel) and the analytical covariance/matrix inversion lemma. Lighter colors refer to higher input SNRs. In the right panel, the matrix inversion lemma results are depicted in orange. 
**B** Localization error averaged across peak voxels, figure composition as in A.
correspond to the estimated and analytical covariance, respectively. Overall, the output signal strength tends to be smaller compared to the simulation outcomes with the ground truth forward model.

With the data covariance (left panel), only the weakest input signal (−25 dB) shows a positive relationship of sensor count and output SNR. Moderately strong input signals yield an inverted U-shape relation between sensor count and output SNR, showing a maximum output SNR around 72-86 sensors. For an input signal of −10 dB, for example, the output signal strength shows a degradation of more than −10 dB when increasing the number of sensors from 86 to 248. The right panel of Figure 3.7 presents the output SNR from the analytical covariance (blue shades) and the matrix inversion lemma (depicted in orange, again almost completely overlapping with the results for the analytically derived covariance matrix). Again, higher input SNRs (above −10 dB) show decreased beamformer performance with high sensor count, whereas for very noisy signals (SNR below −10 dB), the output SNR increases with the number of sensors. Overall, the sensor count effect is less pronounced with the analytical covariance matrix/the matrix inversion lemma compared to the data covariance, the general pattern, however, is comparable.

Figure 3.7B presents the localization errors for the simulations with the realistic forward model. The localization precision is bounded at approximately 3–3.5 mm, corresponding to the coregistration error of 3.04 mm. Comparable to the outcomes from the ground truth forward model simulation, the results are only slightly better with the analytically derived covariance matrix. As can be seen, the localization precision improves with increasing sensor count for input SNRs below 10 dB. With stronger input signals, however, the localization precision decreases with higher sensor count: for an input SNR of 10 dB, the localization error worsens by almost 10 mm when increasing the number of sensors from 86 to 248.
To conclude on the realistic forward model simulations: with high input SNRs and increasing sensor count, the beamformer performance declines regarding both output signal strength and localization precision. These adverse effects are more pronounced with the estimated covariance matrix compared to the analytical covariance matrix.

Realistic forward model

![Graphs showing beamformer performance with a realistic forward model](image)

Figure 3.7: **Beamformer performance with a realistic forward model.** Figure composition as in Figure 1. **A** Output SNR. **B** Localization error.
Figure 3.8 directly compares the results from the different forward models and covariance estimation methods for selected input SNRs (−10, 0 and 10 dB, from left to right). The output SNRs from the matrix inversion lemma are not depicted since they are overlapping with the analytical covariance results (cf. Figures 3.6 and 3.7).

As can be seen, the difference in output SNR between the ground truth forward model (depicted in blue) and the realistic forward model (depicted in red) increases with higher sensor count, as well as with higher input SNR (Figure 3.8A). A similar pattern is observed for the difference between the two covariance matrix computations.

The localization precision shows a rather stable difference of approximately 3 mm between the exact and realistic forward model results, corresponding to the coregistration error (Figure 3.8B). Only with the highest input signal strength shown here (SNR of −10 dB), the localization error increases drastically with a high numbers of sensors for the realistic forward model.

In conclusion, these results illustrate that the differences in beamformer performance between the different covariance matrix estimations and forward models, which become evident with high sensor array density, expand with higher input SNRs (especially regarding output SNR). The discrepancies are particularly pronounced between the exact and realistic forward model, which points to the importance of accurate coregistration.
Figure 3.8: **Model comparisons.** Comparison of beamformer performance regarding exact and estimated forward model and covariance matrix for selected input SNRs. **A** Output SNR as a function of sensor count, shown for three different input SNRs (−10, 0 and 10 dB, from left to right). The ground truth forward model is shown in blue, while the realistic forward model is depicted in red. Lighter colors refer to the analytical covariance. **B** Localization error as a function of sensor count. Overall figure composition as in A. Green colors refer to the exact forward model and purple colors to the realistic forward model.
3.2.4 Discussion

Our simulations show an effect of sensor count on beamformer performance, i.e., output SNR and localization error. In particular, we demonstrate that high channel count can deteriorate beamformer performance under realistic conditions. Intriguingly, a high sensor array density hereby refers to channel counts which are easily exceeded in state-of-the-art MEEG systems: depending on the SNR of the input signal, adverse effects of high channel count can already be present with 60 or less sensors. We further identified factors influencing the relationship between beamformer performance and sensor array density, namely input SNR, forward model accuracy, and covariance matrix precision.

Ideally, beamformer performance should increase with increasing channel count – this was shown to be the case for other source reconstruction methods (Michel et al., 2004; Vrba et al., 2004; Song et al., 2015) and many researchers intuitively expect beamforming to perform similarly. In contrast, our simulations demonstrate a decline in beamformer performance if either the covariance matrix or the forward model are not accurate. Those are the crucial ingredients for the construction of the beamformer weights (compare Equation 3.2) and the source activity is then estimated by combining the weighted sensor measurements. The impact of sensor count varies with the strength of the input signal, showing stronger effects with higher input SNR.

Sensor count and forward model The forward model has a strong impact on the relation between sensor count and beamformer performance, its accuracy effects both performance measures, output SNR and localization error. The importance of accurate forward models in the construction of spatial filters has been extensively discussed (Hillebrand and Barnes, 2005; Brookes et al., 2008; Steinsträter et al., 2010; Dalal et al., 2014; Meyer et al., 2017). Our results highlight the value of
forward model accuracy in an additional context: to be able to exploit high sensor counts, it is crucial that the forward model is maximally accurate. This relationship has been theoretically formulated by Sekihara and Nagarajan (2008), who showed that an array mismatch between the exact and estimated forward model can cause a decrease in output SNR and that this effect scales with the number of sensors.

The adverse effects of high sensor counts especially play a role with high SNR signal. It has previously been shown that strong signals can deteriorate beamformer performance in the presence of coregistration error (Cox, 1973; Hillebrand and Barnes, 2003). This is due to a higher spatial selectivity of the beamformer with high input SNRs, resulting in signal cancellation if the true and estimated forward model exhibit a mismatch (Cox, 1973; Vrba, 2002; Hillebrand and Barnes, 2003; Dalal et al., 2014). Hillebrand and Barnes (2005) related this effect to the number of sensors, which was confirmed by our simulations: the deleterious impact of coregistration error in the presence of strong input signals increases with the number of sensors.

**Sensor count and covariance matrix** Brookes et al. (2008) defined a relationship between channel count and the covariance matrix, influenced by the strength of the input signal. They formulated that the accuracy of the estimated covariance matrix is depending on the number of sensors, such that more sensors lead to higher errors in the covariance matrix estimate. This relationship is confirmed by our simulations, where especially the output SNR is impacted by the combination of covariance matrix error and high sensor count.

In this study, we did not vary the number of samples used to estimate the covariance matrix. Clearly, the informational content of the covariance window is important and ideally, the covariance matrix would be estimated from an infinite
number of data points (Brookes et al., 2008). However, it is obvious that this is not possible – on the contrary, the number of samples is often quite limited in typical neuroscientific experiments.

Interestingly, the inversion of the covariance matrix has no further effect on the beamformer performance in our simulation: adopting the matrix inversion lemma instead of using a conventional inversion on the analytical covariance matrix yielded almost identical results.

With lower input SNRs, the accuracy of the covariance model has a stronger impact, while the accuracy of the forward model plays a more important role with stronger input signals. The localization precision, however, is depending on the accuracy of the forward model and input SNR, but does not show a relation with the covariance matrix.

**Future directions** There is a number of scenarios which the simulations of this study do not cover. First, we only simulated one source per simulation run. Thus, we cannot relate the impact of sensor count to the plausible condition of two or more sources. In this context, an important feature of beamformer performance is the ability to discriminate close sources. Boto et al. (2016) showed that more channels result in better discrimination of close sources. Thus, a trade-off between spatial resolution and output SNR is presumable when source reconstructing two or more sources.

Second, our simulations did not manipulate the amount of coregistration error. An error of 3.04 mm in the fiducial coordinates compared to the ground truth forward model is a moderate if not small coregistration error, the common error is estimated to be in the order of 5–10 mm (Adjamian et al., 2004a; Whalen et al., 2008). Dalal et al. (2014) showed that higher coregistration errors can have quite drastic effects on beamformer performance with EEG: high errors not only caused
imprecise source localization but also prevented the detection of weak sources. Whether these consequences varied with the number of sensors, however, was not tested.

Following from that, a third open question is whether the sensor count effect shown here for MEG data applies to EEG data as well. In general, incorrect forward models have a stronger effect with EEG data, since the electrical potentials generated in the brain are deflected by the differently conductive tissues before they are measured at the scalp surface. Furthermore, coregistration error impacts the relation between head model and channel positions differently in MEG and EEG data: On the one hand, MEG sensors exhibit a larger distance to the scalp than EEG electrodes, thus, the same error in fiducial distance causes a larger deviation in sensor positions. On the other hand, especially if EEG electrodes are digitized individually, the coregistration error can be inconsistent regarding quantity and direction among the electrodes, while the individual MEG sensors keep their spatial relations and are only shifted relative to the head model. Whether the adverse effects of forward model mismatch in EEG are impacted by channel count is an interesting follow-up question.

**Real data** The findings we report here are all based on simulations. Clearly, real data has different characteristics than synthetic data, for example noise in real data is typically correlated among sensors. To be able to draw final conclusions about the transfer of our results to real data analyses, a thorough investigation of the presented sensor count effect with real data is in progress. To this end, we use data recorded with a head cast (Troebinger et al., 2013; Troebinger et al., 2014; Meyer et al., 2017) to obtain a maximally accurate forward model. In order to introduce coregistration error, the fiducial points, which are used to coregister the sensor space with the individual MRI, are shifted in a systematic way. As a paradigm, somatosensory stimulation of the median nerve was chosen to obtain
data from a very strong and focal source. Input SNR is manipulated by using
different subsets of trials. This examination will ultimately quantify how sensor
count impacts beamformer performance in real data.

To conclude, we have shown in this simulation study that beamformer perfor-
ance is depending on sensor count under realistic conditions: While the beam-
former source reconstruction of weaker signals, e.g., high frequency activity, benefits
from high sensor array density, less sensors yield a better beamformer performance
with strong input signals. Intriguingly, our simulation shows that the number of
sensors relevant to this effect is not beyond the practical limits of MEEG systems,
but in a relatively low range (depending on the input SNR, 100 sensors and less).
The covariance matrix accuracy and especially the forward model precision influ-
ence this effect, highlighting the importance of accurate forward models with small
coregistration error.

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Chapter 4

General discussion

This dissertation explored different facets of high frequency activity: Chapter 2 investigated different aspects of gamma activity in the visual system, while Chapter 3 focused on the low signal-to-noise ratio (SNR) nature of high frequency activity.

**Study 1** showed retinal and cortical high frequency activity in response to light onset and offset. While the onset response was characterized by broadband high frequency activity, the light offset was followed by a narrowband gamma response, yielding a new perspective on narrowband versus broadband high frequency activity. The results further implied the propagation of high frequency activity from retina to visual cortex. Intriguingly, the transmission time was faster for light offset than light onset responses, illustrating that the understanding of early stage visual processing is vital for the comprehension of cortical visual activity.

**Study 2** demonstrated the feasibility of combining electroretinography (ERG) and the transcranial magnetic stimulation (TMS) of visual cortex. The results from this pilot study showed retinal activity following the stimulation of visual cortex. The retinal responses comprised a slow evoked potential as well as high frequency activity, which resembled flash-evoked responses. This observation indicates the
possibility that a corticofugal pathway was stimulated. Furthermore, this pilot study yielded insights that will further improve the design of the forthcoming full study.

**Study 3** examined the predictive value of single-trial gamma responses. By combining beamforming with random forest classification, the stimulus modality (visual or auditory presentation of words) was successfully decoded from high frequency activity in an across-subjects approach. The classification model allocated the highest predictive values to a broad range of gamma activity in both visual and auditory cortex. This study thereby demonstrated the feasibility of single-trial analyses on low SNR gamma activity.

**Study 4** explored the effects of high sensor array density on beamformer performance. Moreover, the influence of further factors was assessed, for example, input SNR or forward model accuracy. Surprisingly, higher sensor counts had an adverse effect on beamformer performance with high input SNRs. Thus, while the beamformer source reconstruction of low SNR signals like gamma activity benefits from higher sensor counts, using fewer sensors yields better results if the input signal is strong.

In the following, the findings of those four studies are collated and discussed with respect to three main questions:

1. Which findings on high frequency activity in retinocortical interactions did this work provide?

2. What is added to the topic of high frequency activity patterns, in particular, narrowband versus broadband gamma responses?

3. What are the conclusions about the analysis of low SNR signals, in particular, high frequency responses?
4.1 The role of high frequency activity in retinocortical interactions

The existence of high frequency activity in the visual system has been known for a long time (Fröhlich, 1914; Gray and Singer, 1989). However, the role of such gamma band activity is still debated both at the retinal (Doty and Kimura, 1963; Kozak, 1971; Perlman, 2001; Kenyon et al., 2003; Frishman, 2013) and cortical level (Ray and Maunsell, 2015; Cardin, 2016; Sohal, 2016). The following paragraphs will discuss the findings of Study 1 and Study 2 and relate them to recent theories and findings on gamma activity in the visual system.

4.1.1 Is visual cortex the first structure to substantially process visual information?

Despite the complex wiring and massive number of different cell types in the retina (Masland, 2001), its supposed role has often been restricted to the passive detection and transmission of visual information, particularly in human neuroscience. Referring to the visual system of the horseshoe crab, Gollisch and Meister (2010) argued that these tasks could effectively be achieved with the photoreceptors alone, yet, the human retina comprises 49 additional cell types, suggesting a high specialization on different aspects of visual processing – which has been shown for example in motion processing (e.g., Schwartz et al., 2007).

Nevertheless, magneto-/electroencephalography (MEEG) research on the human visual system mostly concentrates on the visual cortex, neglecting the possibility that the retina might already process visual information. Eventually, differences in cortical peak latencies could not relate to timing differences in cortical
processing alone but also be inherited from earlier processing stages within the visual system.

**Study 1** examined whether darks are processed faster than lights and whether these possible differences occur only in visual cortex or already at the retinal stage. This question was addressed by comparing high frequency responses to light onsets and offsets in retina and cortex. The oscillatory potential is presumably generated by the output layer of the retina (Doty and Kimura, 1963; Perlman, 2001; Kenyon et al., 2003; Frishman, 2013) and possibly transmitted to visual cortex (e.g., Lopez and Sannita, 1997; Neuenschwander et al., 2002; Todorov et al., 2016). In cortex, gamma activity represents the first response to short flash stimuli, occurring as early as 15 ms after the retinal peak (Dalal et al., in prep). Thus, high frequency activity constitutes a compelling approach to examine differences in retinocortical transmission latencies non-invasively.

Interestingly, while the retinal processing of darks and lights was shown to be equally fast (or even faster for light onset in the 105–125 Hz band), the high frequency activity peak in the visual cortex was significantly earlier for light offset than onset. This finding suggests a faster transmission of high frequency responses following light offset compared to light onset.

There are several plausible functional explanations for this: first, thalamus could be involved in the emergence of those latency differences by slower processing of light onset responses, which could be a consequence of more complex informational content in light stimuli. Second, differences in the ON and OFF pathways of the visual system could explain this finding as well. As discussed in Study 1, several such asymmetries have been reported, overall suggesting that more resources are allocated to the OFF pathway of the visual system (Dacey and Petersen, 1992; Ahmad et al., 2003; Balasubramanian and Sterling, 2009). Possibly, faster conduction speeds in the OFF pathway enable faster transmission times for darks. It has
also been shown that the parvocellular pathway transmits information slower than
the magnocellular pathway in macaque monkeys (Schmolesky et al., 1998), which
could contribute to overall slower propagation times for lights. Lastly, the latency
differences could arise from a higher excitability of cortical OFF neurons, leading
to an earlier response peak for darks.

Multi-unit activity (MUA) recordings from cat lateral geniculate nucleus (LGN)
showed faster processing for light decrements compared to light increments (Jin et
al., 2011), which implies that thalamus could indeed play a role regarding the
cortical peak differences observed in Study 1.

This finding challenges the notion that differences in cortical peak latencies re-
late to local cortical computation: if retinal or thalamic processing differs between
visual stimuli, latency variability measured in cortex could already be introduced at
earlier processing stages. Supporting this, recent results from our group show dif-
fences in the latencies of the retinal b-wave in response to different photographic
stimuli (Zeiller et al., in prep). Intriguingly, the retinal peak latencies are related
to the visually evoked potentials (N135) in cortex, providing further evidence that
visual processing might start in early visual stages already.

Thus, the understanding of retinocortical interactions is crucial for the compre-
hension of cortical processes in visual perception and probably even in higher-order
processes which build on visual perception.

### 4.1.2 High frequency activity is transmitted from the retina
to cortex – and back?

The ongoing discussion about the role, function, and origin of gamma activity in
the visual system comprises the question whether the high frequency activity ob-
served in visual cortex is inherited from thalamus (Saleem et al., 2017) or even the
retina (e.g., Koepsell et al., 2009) or generated locally. While some studies suggest
that the retinal oscillatory potential is transmitted via the optic chiasm and thalamus to visual cortex (e.g., Lopez and Sannita, 1997; Neuenschwander et al., 2002; Todorov et al., 2016), other studies find no or mixed evidence for such a propagation, implying that retinal and cortical high frequency activity are two distinct processes (Doty and Kimura, 1963; Molotchnikoff et al., 1975; Heinrich and Bach, 2004).

In this dissertation, **Study 1** presented support for the notion that the retinal oscillatory potential is transmitted to visual cortex. For both the light onset and light offset response the retinal peak in high frequency activity was followed by a cortical gamma activity peak 21.0 to 51.0 ms later. Importantly, the cortical gamma activity showed the same frequency pattern as the retinal activity—a broadband response to light onset and a narrowband response to light offset, which was restricted to 75–95 Hz. This pattern is consistent with a propagation of the retinal oscillatory potential to the cortex, affirming the results from earlier studies (Lopez and Sannita, 1997; Heinrich and Bach, 2001; Munk and Neuenschwander, 2000; Koepsell et al., 2009; Todorov et al., 2016).

As noted above, this propagation was observed for the light onset broadband response as well as for the light offset narrowband response following light offset. This finding contradicts a model recently introduced by Saleem et al. (2017), who proposed that narrowband gamma activity is transmitted from thalamus (and presumably the retina) to cortex, whereas broadband high frequency activity serves corticocortical interactions. In contrast, the results of Study 1 suggest that early cortical gamma responses to visual stimuli are inherited from the retina, regardless of their bandwidth.
The pilot recordings reported in **Study 2** imply that high frequency activity in the visual system might also be transmitted in the opposite direction: from the visual cortex to the retina. Following stimulation of visual cortex with TMS, retinal activity was observed in both subjects, comprising a slow potential as well as high frequency activity. Overall, this activity resembled typical flash-evoked responses. These preliminary results are consistent with the existence of a cortico-foveal pathway in the human visual system, which has been a highly debated yet rarely examined topic (Wasserman et al., 2010). However, to definitely rule out an artifactual source of these responses, the use of an eye tracker will be necessary in the full study.

The potential function of such an efferent pathway is unclear: while evidence from animal research suggests a modulating influence of visual cortex on the retina (Maffei et al., 1985; Molotchnikoff and Tremblay, 1986; Galambos et al., 1994; Galambos et al., 2001), studies regarding the human visual system yielded mixed results (Wirth, 1951; Steindler et al., 1981; Marg, 1953; Eason et al., 1983a; Mangun et al., 1986). Possibly, it enables feedback communication from the visual cortex to the retina.

If the planned full study confirms the preliminary results presented in this work, this could challenge a recently proposed theory on the role of gamma activity: it was suggested that gamma constitutes a feedforward mechanism, complemented by alpha as a feedback mechanism (Van Kerkoerle et al., 2014; Dougherty et al., 2015; Popov et al., 2017). Study 2, however, reported retinal high frequency activity transmitted in feedback direction. It could be argued, that TMS constitutes a strong, artificial stimulus, which could lead to unusual effects at the neural level. However, the potential propagation of this stimulation passes through thalamus – thus, any activity recorded from the retina should already have been converted to “neural code” (as is underpinned by the resemblance of the recorded activity to flash-evoked retinal responses). Therefore – given the preliminary results from
Study 2 can be replicated – this would indicate that feedback in the visual system could involve high frequency activity, possibly in addition to slower alpha rhythms (Van Kerkoerle et al., 2014; Popov et al., 2017).

### 4.1.3 Retinocortical interactions: Future perspectives

The simultaneous recording of ERG and MEEG constitutes a unique way to study the interplay of retina and cortex in the human visual system. The first two studies of this work illustrated the importance of retinocortical interactions towards the understanding of visual and potentially even higher-order processing.

Building on the result of Study 1 that darks are transmitted faster than lights and the findings from our group that different photographic stimuli yield different retinal and cortical peak latencies (Zeiller et al., in prep), further investigations on the temporal aspects of retinocortical interactions are required. Corresponding experiments could involve simple visual stimuli like edges, patterns, and noise stimuli, but also naturalistic photographs or stimuli of higher complexity, e.g., motion reversals.

Regarding the role of thalamus, recent work from our group showed thalamic activation after visual stimulation with 1 ms flashes, recorded with magnetoencephalography (MEG) (Dalal et al., in prep). This suggests that it should be possible to examine the thalamic contribution to different transmission latencies with MEG to draw further conclusions on the role of thalamus in any observed latency differences.

Finally, several neurological disorders have been related to changes in retinal or retinocortical processing, for example, multiple sclerosis (Feinsod et al., 1973) or Parkinson’s disease (Gottlob et al., 1987). Also some psychiatric disorders show anomalies in the ERG, e.g., seasonal affective disorder, autism or schizophrenia, presumably induced by alterations in the dopamine or serotonin levels (Lavoie et al., 2014a; for a review see Lavoie et al., 2014b). Often, stud-
ies and even clinical routines rely on slow retinal and cortical potentials (e.g., the b-wave and P50) to characterize abnormalities in processing and conduction delays from retina to cortex, for example in multiple sclerosis (Bobak et al., 1983; Parisi et al., 1999). Based on the finding that high frequency activity is most likely the first information transmitted from retina to cortex (Study 1 and Dalal et al., in prep), it would be interesting to investigate whether retinocortical propagation of high frequency activity could provide insight into the mechanisms underlying these disorders as well as form the basis for improved diagnostic techniques in the clinic.

Since the pilot study on potential corticofugal propagation confirmed the feasibility of combining ERG and TMS, the full study can be conducted. However, some limitations in the present study protocol were recovered: most importantly, the use of an eye tracker will simplify the identification of any possible stimulation-related eye movements. The simultaneous recording of electroencephalographic (EEG) data will enable the analysis of concurrent cortical processes and show whether the high frequency activity is present in visual cortex as well, which would suggest a feedback mechanism.

A further research question related to the potential retinopetal pathway is whether alpha oscillations are involved (cf. Jensen and Mazaheri, 2010; Van Kerkoerle et al., 2014; Bonnefond et al., 2017). The pilot data from Study 2 showed a slow positive potential, followed in some trials by a trough and another peak, which could point to the entrainment of a slow oscillation. Preliminary work from our group showed that eyes-closed alpha is not only present in visual cortex, but can also be recorded from the retina and that the retinal and cortical alpha oscillations had a consistent phase relation (Kaiser et al., 2014). This bears the question whether the retinal alpha activity could be inherited from visual cortex – or the other way around.
4.2 High frequency activity patterns

One of the most prevalent debates in contemporary visual neuroscience is the discussion about narrowband and broadband gamma activity and their functional role in the human brain. In Chapter 1, some of the theories and views on high frequency activity were introduced, ranging from the view that gamma increases merely reflect neural noise (Miller et al., 2009a) to distinguished theories on the function of (narrowband) gamma, for example the communication through coherence hypothesis (Fries, 2005; Fries, 2015). In this work, Study 1 and Study 3 contributed new findings to the discussion about narrowband and broadband gamma.

4.2.1 Narrowband and broadband activity in the interplay of retina and cortex

In Study 1, narrowband and broadband high frequency activity was observed in response to dark and light stimuli, respectively. Above, it was argued that this activity is potentially transmitted from retina to cortex. This could imply that the high frequency activity is involved in the coding and communication of visual information, mirrored by an increase in neural activation. The broader bandwidth of the light onset compared to the light offset response could be explained by the consideration that light contains more information than darkness. This could furthermore resolve why the transmission of the light onset response was slower compared to the light offset response.

Alternatively, the observed high frequency activity could also be explained by the communication through coherence hypothesis: the synchronization of retina and cortex through gamma-rhythmic inhibitory activity would enable the communication of information from the retina to visual cortex. The narrow bandwidth (75–95 Hz) of the observed light offset high frequency activity is coherent with a rhythmic modulation by inhibitory interneurons, proposed to enable an effective syn-
chronization. The light onset response, however, was a broadband high frequency response ranging from 55–145 Hz. Presuming the *communication through coherence* hypothesis, this broadband activity could reflect multiple “channels” of information transfer, potentially targeting different cell assemblies in visual cortex (cf. Crone and Hao, 2002; Akam and Kullmann, 2014). Such frequency multiplexing has been reported in the hippocampus (Colgin et al., 2009) or even the retina (Meister, 1996). However, Ray and Maunsell (2015) argue that long integration windows would be needed to differentiate the adjacent frequency channels, rendering frequency multiplexing a slow process. Furthermore, if the variability in the latencies of b-wave and N135 in response to different photographic stimuli (Zeiller et al., in prep) can be confirmed for high frequency activity as well, this would present phase variabilities in high frequency oscillations among stimuli, which argues against the representation of a stable mechanism for communication (cf. Henrie and Shapley, 2005; Burns et al., 2011). Based on a modeling study, Rolls et al. (2012) suggested that gamma band coherence might not be a mechanism for controlling signal flow, but rather a consequence of information transmission, supporting the concept of gamma activity more directly representing informational content.

To conclude, although the narrowband offset-response could be consistent with the *communication through coherence* hypothesis, it is difficult to reconcile the broad bandwidth of the light onset response with this view. Thus, considering both high frequency patterns, it is more likely that they represent visual information, mirrored by an increase in neural activity. That both cortical gamma responses are phase-locked to the stimulus, as reflected by a high intertrial coherence (ITC), could show that simple stimuli like light onset and offset are transmitted with highly reliable timing.
Considerations on grating-induced narrowband oscillations  Cortical narrowband gamma responses are typically elicited by high contrast stimuli (e.g., Adjamian et al., 2004b; Hoogenboom et al., 2006; Muthukumaraswamy et al., 2010; Tan et al., 2016), which are often characterized as non-natural stimuli and can even evoke negative sensations in some viewers (Wilkins, 1986; Wilkins, 1995). Noise stimuli or photographs, on the other hand, were shown to induce broadband high frequency activity (Hermes et al., 2014; Hermes et al., 2015).

These contrary findings can be linked to the outcomes from Study 1: the high frequency response to gratings could be explained by an excessive activation of the OFF channel in the visual system, resulting in a comparable narrowband response as observed for light offset in Study 1. Interestingly, early ERG studies using grating stimuli reported a high frequency response around 60 Hz (Sokol and Riggs, 1971; Cavonius and Sternheim, 1972), which corresponds to the center frequencies elicited by gratings in visual cortex (e.g., 60 Hz [Tan et al., 2016] or 50 Hz [Muthukumaraswamy et al., 2010]). This suggests the possibility, that cortical narrowband responses to grating stimuli could indeed be inherited from the retina, potentially through the same pathway as light offset responses.

Another possible explanation for the narrowband responses elicited by either grating stimuli or light offsets (Study 1) are inhibitory responses. Grating stimuli have been linked to a perceptual suppression of the surrounding (Bair et al., 2003; Angelucci and Bressloff, 2006; Jia et al., 2011), as well as to lateral inhibition in both the retina (Ratliff, 1965) and cortex (Blakemore and Tobin, 1972). Those processes involve gamma-aminobutyric acid (GABA)ergic inhibitory interneurons (Sillito, 1979; Sedley and Cunningham, 2013), which have been related to narrowband gamma responses (cf. Section 1.1.1; e.g., Llinás, 1992; Wang and Buzsáki, 1996). The cessation of light exposure, i.e., light offset, could trigger inhibitory activity as well (Singer and Creutzfeldt, 1970). Thus, the narrowband responses in
retina and cortex could be elicited by presumably independent inhibitory processes. How this can explain the similar frequency patterns in retina an cortex following both light onset and offset, however, remains unclear.

4.2.2 High frequency activity patterns in single trials

For an understanding of brain dynamics, the analysis of single-trial responses is crucial – brain processes do not operate according to the concept of trial averaging (Stokes and Spaak, 2016). In Study 3, the predictive value of single-trial gamma responses was investigated with a decoding approach. The classification of stimulus modality (auditory or visual presentation of words) reached 66.44% accuracy across subjects and yielded high informational value to a broad range of gamma power in both visual and auditory cortex. This suggests an underlying broadband activity in single trials rather than a narrowband response. Furthermore, since the classification was embedded in an across-subjects framework, the successful classification implies a high conformity of those responses across subjects. These results add to the narrowband versus broadband gamma discussion regarding natural stimuli: while grating stimuli reliably elicit narrowband gamma responses (see above), they are hardly shown in response to natural stimuli or noise stimuli (Hermes et al., 2014; Hermes et al., 2015, but see: Brunet et al., 2013; Brunet et al., 2014). One possible explanation for this lack of narrowband oscillations could be a high variability of narrowband response peak frequencies in single trials, appearing as a broadband response when averaged (cf. Lowet et al., 2016; Lundqvist et al., 2016). The decoding analysis in Study 3, however, indicates single-trial broadband gamma activity in visual cortex in response to words as visual stimuli.
4.2.3 Synthesis: Towards an integrative view of narrowband and broadband gamma

To conclude, the results from Study 1 and Study 3, in conjunction with previous research, suggest that narrowband high frequency activity is an exception, rather than the rule. While light onset (Study 1) and words (Study 3) as well as photographic stimuli (Hermes et al., 2014; Hermes et al., 2015) elicit a broadband gamma increase, the high frequency responses to light offset or grating stimuli comprise a narrow bandwidth, possibly both related to the OFF-channel in the visual system or inhibitory responses. The rare occurrence of narrowband gamma activity in response to various stimuli, as well as other factors (e.g., the stochasticity of gamma rhythms, see Henrie and Shapley, 2005; Burns et al., 2011), make a role of this activity as a fundamental mechanism in binding, communication or as clock implausible.

Broadband gamma, on the other hand, most likely reflects an increase in neural activity, as supported by the correlation of this activity with MUA (e.g., Csicsvari et al., 2003; Nir et al., 2007; Rasch et al., 2008; Whittingstall and Logothetis, 2009) and the blood oxygen level-dependent (BOLD) effect (Mukamel et al., 2005; Niessing et al., 2005; Lachaux et al., 2007; Ojemann et al., 2010), possibly echoing the local processing of information. Study 1 indicated that broadband (and narrowband) high frequency activity could mirror information transmitted from the retina, and that the bandwidth herein reflects the amount of information contained in the stimulus.
4.2.4 High frequency activity patterns: Future perspectives

The findings of Study 1 and Study 3, together with the consideration from Section 4.2.3, bear several questions for further research, which will be outlined in the following.

First, it would be interesting to examine whether the cortical narrowband gamma elicited by grating stimuli is in fact inherited from the retina, as similar retinal and cortical peak frequencies suggest (Sokol and Riggs, 1971; Tan et al., 2016).

To investigate the above posed hypothesis that the range of frequencies involved in a visual response is dependent on the level of information the stimulus contains, retinal and cortical high frequency responses to different photographic stimuli with variations in visual features, e.g., spatial frequency or contrast, could be analyzed. However, the challenge with this approach is to control the level of information contained in these stimuli. Furthermore, an investigation whether high frequency activity peak latencies show the same variability regarding different photographic stimuli as the slow potentials (Zeiller et al., in prep) could provide further interesting insights. Such timing differences would be accompanied by phase variability, which would raise further doubt regarding the plausibility that gamma activity represents functional mechanisms.

Finally, the decoding approach used in Study 3 could be adopted to examine single-trial gamma response patterns in further contrasts. For example, it would be interesting to attempt decoding of stimulus categories (faces, tools, houses, etc.) from broadband high frequency activity as it is possible with time-domain data (e.g., Van de Nieuwenhuijzen et al., 2013; Olivetti et al., 2014). Potentially,
such decoding strategies could also be useful with regard to the above proposed investigation of the link between high frequency activity bandwidth and the level of information in a visual stimulus.

4.3 High frequency activity and SNR

The detection and analysis of weak signals like high frequency activity can pose a challenge to the researcher. There are several approaches to increase SNR, among them beamforming and decoding methods. Study 3 and Study 4 of this work investigated different aspects of the analysis of low SNR signals.

4.3.1 Single-trial gamma power

One common way to increase SNR is the averaging of trials to cancel random noise. However, this approach can potentially also average out meaningful brain signals (Stokes and Spaak, 2016), which motivated the application of a decoding algorithm to single-trial gamma power in Study 3.

While multivariate analyses are a common tool in the fMRI community (Pol- drack, 2011), they seem to be less popular with MEEG data. One advantage of such methods is that they leverage power across several dimensions, e.g., time and frequency, instead of testing each time point or frequency band independently. This can potentially be a successful approach to weak signals (Stokes and Spaak, 2016), which encouraged the application of a multivariate model in Study 3.

A combined approach of beamforming and classification was used for single-trial-based analysis of source-reconstructed gamma power measured with MEG. The results revealed that high frequency activity has predictive value towards the discrimination of stimulus modality (auditory versus visual presentation of words).
The overall classification model yielded an accuracy of 66.44%, which was significantly better than chance level. For cross-validation, the model was trained on the data from all but one subject and then tested on the dataset of the left-out subject. This procedure was repeated such that every subject served as the test subject once. This across-subjects approach is considered to be difficult due to inter-individual structural and functional variability (Olivetti et al., 2014). The classification accuracy shown here matches previous reports of across-subjects classification performances in (time-domain) MEG data: e.g., an accuracy slightly above 60% for the decoding of syntactic and auditory violations in spoken sentences (Herrmann et al., 2012) or 62–65% for classifying the presentation of faces versus scrambled images, reaching 67% if the differences across subjects were explicitly modeled (Olivetti et al., 2014).

Consequently, Study 3 demonstrated that the decoding of stimulus modality information from low SNR single-trial high frequency activity is possible, even across subjects. As already discussed in Section 4.2.1, this approach furthermore provided interesting results on gamma patterns in auditory and visual cortex.

**Using random forests to decode brain activity** Study 3 used the random forest algorithm (Breiman, 2001) for decoding. Several attributes make random forest a particularly interesting classification algorithm for MEEG data decoding problems (used for example in Fraiwan et al., 2012; Lehmann et al., 2007; Bentlemsan et al., 2014; Donos et al., 2015). First, random forest predictions are not biased by highly correlated predictor variables. This is of particular interest in MEEG data analysis, since data points are correlated along several dimensions like time, frequency or sensor/source space. Furthermore, random forests are particularly well-suited for datasets with more predictors than observations, since the algorithm searches the predictor variables successively (Strobl et al., 2009). While many parametric multivariate models, e.g., the general linear model (GLM), are
ill-determined in such small $n$ large $p$ cases, random forest models are able to handle even extreme cases with thousands of predictors but less than 100 observations, which motivated its frequent application with genome data (Díaz-Uriarte and De Andres, 2006; Chen and Ishwaran, 2012).

In general, multivariate approaches avoid the multi-comparison problem common in MEEG data analysis, since all predictors are assessed in one model. Random forest models rank these predictor variables according to their predictive value within the model. This allows for a direct comparison of brain areas or frequency bands regarding their relevance, which is, for example, not achievable with cluster-based permutation tests (Maris and Oostenveld, 2007). In Study 3, this enabled the conclusion that the 75–95 Hz frequency band in primary visual cortex (V1) was most informative towards the discrimination of visual and auditory trials.

In a recent project, we exploited these strengths of the random forest algorithm to investigate differences in network communication during low and high demand for cognitive control (Popov et al., in prep). EEG data from 333 participants performing a color-word Stroop task were analyzed regarding inhibitory control, adopting a previously reported inhibitory network, which was based on functional magnetic resonance imaging (fMRI) data (Spielberg et al., 2015). The EEG data was source reconstructed with a linearly constrained minimum variance (LCMV) beamformer, yielding virtual electrodes at the nodes of the predefined network. Complementing Granger causality analysis, the random forest algorithm was used to predict the demand for cognitive control (incongruent versus congruent condition of the Stroop task) based on 1) reaction time, 2) trial-averaged theta power in the network nodes, 3) beta power, and 4) combinations of those features. Interestingly, this approach revealed that brain activity (theta and beta together) predicted executive control demands almost as good as the reaction time alone (Figure 4.1A). Combining brain activity and behavior boosted accuracy to 76% (theta and reaction time model).
While the averaged power showed theta decreases and beta increases throughout the whole network, the random forest approach enabled a ranking of nodes regarding their predictive value within the classification model. In the model built on theta power, the most informative node was the superior frontal gyrus (SFG) (Figure 4.1B, left panel). This complemented the Granger causality analysis, which revealed that the dorsal anterior cingulate cortex (dACC) and SFG were under top-down influence of the inferior frontal gyrus (IFG). The beta activity model showed that the precuneus contributed the most information to the classifier (Figure 4.1B, right panel), supporting the fronto-parietal feedback communication revealed by the Granger spectra. To summarize, the random forest model amended and supported the findings from the Granger causality analysis in this study, and furthermore provided interesting insights into how reaction times and electroencephalography (EEG) data complement each other regarding the prediction of demand for cognitive control.

Figure 4.1: **Decoding cognitive demand with random forest.** Results from *Popov et al., in prep.*, adopting random forest models to decode inhibitory control within a global brain network. **A** Comparison of different models regarding their classification accuracy. $\theta$: theta power in the network nodes, $\beta$: beta power in the network nodes, *rt*: reaction time. **B** Variable importance for the theta (left panel) and beta model (right panel). Red colors and larger node sizes illustrate a higher predictive value of the respective node within the classification model.
Decoding (high frequency) brain activity: Future perspectives

In a recent paper, Cichy et al. (2015) showed that it is possible to decode information about stimulus orientation from MEG data. This impressively underpins the potential of decoding approaches in MEEG research: while it is difficult to gain high-precision information about the cortical source of brain activity from MEEG data due to the ill-determined inverse problem of source reconstruction, it is still possible to exploit discriminative information regarding different brain states present in the data (Stokes et al., 2015). In Study 3, the classification approach demonstrated its potential in the analysis of low SNR signals like single-trial high frequency activity. Stokes et al. (2015) in any case predicted that decoding might “revolutionise MEG/EEG just as it did fMRI”.

4.3.2 Using beamformer with low SNR data

Another way to approach weak signals is the source reconstruction with spatial filters, since they can enhance effective SNR (Sekihara et al., 2004; Väisänen and Malmivuo, 2009; Dalal et al., 2011a). However, the performance of beamformers was shown to be sensitive to factors like covariance estimation error or coregistration error (Brookes et al., 2008; Dalal et al., 2014). Study 4 investigated the influence of a further factor, namely sensor count, on beamformer performance and linked the effect of sensor array density to input SNR, forward model accuracy, and covariance estimation error.

The simulation showed that sensor count indeed has an impact on beamformer performance: with strong input signals, the beamformer performance (output SNR as well as localization precision) decreased with increasing sensor count. For weak signals like high frequency activity, however, higher sensor counts yielded better beamformer performance. This relationship was further influenced by the data covariance estimation and especially the forward model. Thus, while weak signals can in general benefit from a higher sensor array density, the accuracy of the data
covariance matrix and the forward model are still crucial. Related to this, Dalal et al. (2014) investigated the impact of inaccurate forward models on beamformer source reconstruction with EEG data in a simulation study. While coregistration error led to an attenuated output SNR and imprecise localization for stronger signals, it completely prevented the detection of weak signals, highlighting the importance of accurate forward models in particular with weaker signals.

**Beamformer performance: Future perspectives** To be able to draw final conclusions about the impact of sensor count beyond simulations, an investigation with real MEG data is in progress. The data was recorded with a head cast (Troebinger et al., 2013; Troebinger et al., 2014; Meyer et al., 2017), enabling the comparison of an ideal forward model to forward models with an added coregistration error. The used median nerve stimulation response has a high SNR, which can be systematically decreased by using only subsets of trials. Furthermore, the signal also comprises a weaker high frequency response. The follow-up study will ultimately elucidate the relevance of sensor count in real data analysis.

Another successive study could be the examination of this sensor count effect in EEG data. Since beamforming with EEG data was shown to be very sensitive to forward model errors, especially with weak signals (Dalal et al., 2014), it would be interesting to relate the sensor count effect to the specificities of EEG source reconstruction.

To conclude, the analysis of weak input signals like high frequency activity can benefit from beamforming and decoding approaches. Beamformer performance was shown to decrease with higher sensor counts and strong signals, the beamformer source reconstruction of weaker signals on the contrary profits from a sensor counts.
4.4 Conclusions

This dissertation explored different facets of high frequency activity in the human brain. The first part investigated the role of gamma activity in the interplay of retina and cortex, the second part concentrated on approaches to low SNR signals like gamma power.

Beyond the scope of the single studies, this work proposed several implications with respect to the origin and role of gamma activity. First, it highlighted how important the understanding of retinocortical interactions is for the comprehension of cortical visual and higher-order processes: cortical high frequency activity seems to be inherited from the retina, manifesting latency differences which might also be inherited from earlier processing stages. Furthermore, visual cortex could possess a corticofugal connection to the retina, possibly exerting feedback influence mirrored by retinal high frequency activity.

Second, this work added to the ongoing discussion about narrowband versus broadband gamma: while both narrowband and broadband visual high frequency activity can be inherited from the retina, the narrowband responses in the visual system could arise from the specific stimulus features evoking the OFF pathway or from low informational content in those stimuli.

Third, concerning the analysis of low SNR signals, this dissertation showed the feasibility of single-trial decoding of gamma power. Furthermore, it described the relation between high sensor count and beamformer performance, showing that weak signals like high frequency activity benefit from a high sensor array density.

Finally, this dissertation elicited novel questions on the role of high frequency activity in the human brain – among them the questions whether the bandwidth of visual gamma activity could reflect informational content, whether the visual narrowband activity in response to grating stimuli is inherited from the retina
or whether it is possible to decode higher-order stimulus characteristics such as object categories from high frequency activity – thereby paving the way for further research on the role of high frequency activity in neural information processing.
Conducted studies and own research contributions

The studies reported in this dissertation were co-authored and supported by a number of colleagues. Below, the authors of the reported studies and my own research contributions are listed.

Study 1: Faster than the brain’s speed of light: Retinocortical interactions differ in high frequency activity when processing darks and lights
Authors: Britta U. Westner and Sarang S. Dalal
Own contributions: I conceptualized the experiment together with Sarang S. Dalal, I carried out the MEG measurements, analyzed the data, and drafted the manuscript.
Status: Submitted to bioRxiv. doi: https://doi.org/10.1101/153551

Study 2: Does transcranial magnetic stimulation of occipital cortex affect the retina? – A pilot study
Authors: Britta U. Westner, Mathis Kaiser, and Sarang S. Dalal
Own contributions: I designed the experiment together with Sarang S. Dalal, I carried out the transcranial magnetic stimulations, analyzed the data, and drafted the manuscript.
Status: In preparation.

Study 3: Across-subjects classification of stimulus modality from human MEG high frequency activity
Authors: Britta U. Westner, Sarang S. Dalal, Simon Hanslmayr, and Tobias Staudigl
Own contributions: The original study was conceptualized and undertaken by To-
bias Staudigl and Simon Hanslmayr. I developed the decoding study, analyzed the
data together with Tobias Staudigl, I applied the decoding analyses, and drafted
the manuscript.

*Status:* Submitted to *PLOS Computational Biology.*

**Study 4: Is more always better? The effect of sensor array density on beamformer performance**

*Authors:* Britta U. Westner, Matthew J. Brookes, and Sarang S. Dalal

*Own contributions:* I conceptualized the examination, programmed the simula-
tions, analyzed the data, and drafted the manuscript.

*Status:* In preparation.


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