Submillimeter T2 weighted BOLD fMRI of human visual cortex

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Submillimeter T₂ weighted BOLD fMRI of human visual cortex

Valentin G. Kemper

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Submillimeter T₂ weighted BOLD fMRI of human visual cortex

Dissertation

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Abbreviations, acronyms, variables

B_0	Static magnetic field
$B_1^{+/-}$	Transmission (+)/receive (-) radio frequency magnetic field
BOLD	Blood oxygen level dependent signal
CBF	cerebral blood flow
CBV	cerebral blood volume
CMRO2	cerebral metabolic rate of oxygen
CNR	Contrast-to-noise ratio
CSF	Cerebrospinal fluid
EPI	Echo planar imaging
fMRI	functional magnetic resonance imaging
FoV	Field of View
FSE	Fast spin echo (RARE equivalent)
FWHM	Full width at half maximum
GE-/SE-	Gradient-echo / spin-echo
GLM	General linear model
GRASE	gradient and spin-echo
GRE	Gradient (recalled) echo
HASTE	Half Fourier acquisition single-shot turbo spin-echo
hMT+	human homologue of middle temporal complex (also V5)
LGN	lateral geniculate nucleus
MB	Multiband
MION	monocrystalline iron oxide nanoparticles
MPRAGE	Magnetization-prepared rapid gradient-echo
MRI	Magnetic resonance imaging
MTF	Modulation transfer function
NMR	nuclear magnetic resonance
ODC	ocular dominance column
PET	positron emission tomography
RARE	Rapid acquisition with relaxation enhancement
RF	Radiofrequency
ROI	Region of interest
PSF	Point-spread function
SAR	Specific absorption rate
SMS	Simultaneous multi slice
SNR	Signal-to-noise ratio
(b)SSFP	(balanced) steady-state free precession
T_1	Longitudinal relaxation time
T_2	Transversal relaxation time
T_2^*	Effective transversal relaxation time
TE	Echo time
TI	Inversion time

TR	Repetition time
TSE	Turbo spin echo (RARE equivalent)
tSNR	temporal signal-to-noise ratio
V1	primary visual cortex
V2	secondary visual cortex
VASO	Vascular space occupancy
VFA	variable flip angle

Chapter 1

Introduction

Magnetic resonance imaging (MRI) employs a combination of static and fast alternating magnetic fields to obtain information about the inner structure of the studied object. Not only is MRI a mainstay in medical imaging, it can also be used to trace neuronal activity in the brain indirectly by detecting dynamic signal changes associated with changes in blood oxygenation, which are induced by the changed metabolic demand of the involved neurons. Over the past two decades, this fascinating technique called functional MRI (fMRI) has developed to become one of the most important methods in cognitive neuroscience, and fMRI experiments have yielded extensive insight to the functional organization of the living brain. Most fMRI experiments are conducted at temporal resolution of two to three seconds and spatial resolution of several tens of microliters to assess which brain regions are involved in a given task and to what extent. However, key mechanisms of cognitive processes are organized at a finer spatial scale, e.g. the inner layout of a brain region tangentially to the cortical sheet or the laminarization across cortical depth. Investigation of such fine-grained functional structures requires advanced techniques. This thesis deals with such high spatial resolution fMRI techniques. For the successful application in neuroscientific experiments, a solid foundation is required of both the methodological background, and the subject of study, i.e. functional organization at the scale of cortical layers and columns (mesoscale). Therefore, in the following introduction we set out to outline both appropriately. First, the milestones of the development of modern magnetic resonance imaging will be highlighted. Then an account of blood oxygenation level dependent fMRI and neurovascular coupling is given. Advantages of T_2 weighted BOLD fMRI follow. A brief review of the architecture of cortical gray matter at the scale of layers and columns is given with special interest in early visual cortex, and particularly primary visual cortex (V1). Then, aspects of prime relevance for high resolution imaging are considered. The point spread function of echo-train sequences is described mathematically, and finally, the 3D-GRASE sequence will be described briefly. An overview of the following chapters is given at the end of this introduction.

Beginnings of Magnetic Resonance Imaging

An electric current causes a magnetic field. This classical electro-magnetic observation is paralleled in quantum mechanics: charged elementary

particles like electrons or the constituents of a proton possess a magnetic field caused by a constant rotation about its own axis, its spin. The fact that atomic nuclei possess such a magnetic moment was first described by Isidor Isaac Rabi in 1938, who thereby extended the findings of Otto Stern and Walther Gerlach on the quantization of electron spins. Rabi used molecular beams traversing homogeneous and opposing inhomogeneous magnetic fields. Under the influence of radiofrequency (RF) waves at specific frequencies, the trajectory of the beam was altered, because the magnetic state of the atoms had been manipulated by the RF field. More specifically, if the Larmor frequency¹ of the nuclei in the beam were matched by the transmitted RF field, transitions of energetic levels associated with the orientation of the nuclear spin moment with regard to the external magnetic field were facilitated, and the altered magnetic configuration with respect to the external magnetic field caused deflection of the beam. Felix Bloch and independently Edward Mills Purcell experimented later, in 1946, with nuclear magnetic resonance (NMR) in solids and liquids. Bloch also provided great parts of the theoretical description of the precession of the nuclear magnetic moments in the external magnetic field. Although in comparison to nuclear beams, the separation of magnetic states is much weaker in solids, the abundance of atoms in solids compared to molecular beams allowed studying the resonance effects with more simple methods. It should be noted that the so-called Zeeman splitting (the difference of energetic states of magnetic levels) of protons at room temperature and 1 Tesla field strength is only 1.8×10^{-7} electron volts², and that as a consequence of the Fermi-Dirac distribution, the higher energetic state is only approximately 10^{-6} less occupied than the lower state. In other words, the observable magnetization stems from only one millionth of the total nuclear magnetic moment. The original saturation method was improved by the application of pulsed methods, to generate both free induction decays (Hahn, 1950a) and spin-echoes (Hahn, 1950b). This way, NMR spectroscopy could reveal information about the compounds of solids and their chemical environment, e.g. in which molecules hydrogen is bound.

¹ Named after Joseph Larmor (1857-1942). The frequency at which a magnetic dipole precesses in an external magnetic field.

² 1 Electron volt (eV) equals 1.602×10^{-19} Joule.

The usage of static field gradients for spatial encoding of the signal source was introduced by Paul Lauterbur. This way, a projection of the object spin density onto the axis of the gradient could be obtained (Lauterbur, 1973; 1974). Peter Mansfield identified the possibility to sample multiple echoes after a single excitation (Mansfield, 1977), which laid the foundation for echo planar imaging (EPI). This technique could significantly increase the acquisition speed. Additional important contributions to modern (nuclear) magnetic resonance *imaging* were provided by Richard R. Ernst and colleagues (Kumar et al., 1975), and Donald Twieg (Twieg, 1983). They made more explicit that in MRI one could acquire different spatial frequencies of the object in its dual space, k-space. The relevance of NMR and MRI to life sciences was showcased in the fact that the longitudinal relaxation time (T_1) and transverse relaxation time (T_2) differ between tissue types (Damadian, 1971), and further in what can be considered the first human body MRI image (Damadian et al., 1977). In the following years many improvements and developments in the domains of hardware, theoretical concepts, and imaging pulse sequences made MRI more accessible to neuroscientists and clinicians.

The BOLD effect and neuro-vascular coupling

Functional MRI (fMRI) started in the early 1990's. Functional imaging of the human brain was demonstrated using the external susceptibility contrast agent gadolinium-diethylenetriamine pentaacetic acid (Gd-DTPA, Belliveau et al., 1991). Meanwhile, it could be shown, that also deoxyhemoglobin could serve as a natural, endogenous contrast agent (Ogawa et al., 1990). Hemoglobin in red blood cells contains iron atoms, which lead to an overall diamagnetic behavior when oxygenated (oxyhemoglobin), and to paramagnetic behavior without the oxygen (deoxyhemoglobin). The paramagnetic state causes faster loss of phase-coherence of the magnetization in the vicinity of the molecules, i.e. shorter effective transverse relaxation time, T_2^* , and hence reduced signal intensity in T_2^* weighted images. In other words, the oxygen concentration itself in blood vessels yields a differential signal and can be used to register the location of neuronal activity in the brain. Three groups were in close competition to publish the first experimental human fMRI results using the newly established contrast mechanism (Bandettini et al., 1992; Kwong et al., 1992; Ogawa et al., 1992), followed by Blamire et al. (1992), Frahm et

al. (1992), and Turner et al. (1993). The name for the new method given by Ogawa (Ogawa et al., 1990) stuck: Blood oxygenation level dependent contrast, BOLD contrast. Ogawa et al. (1992) employed a 4 Tesla scanner and an unspoiled gradient-echo imaging sequence (FISP), but most sites quickly adapted to using EPI (at any field strength). These first experiments used visual (“photic”) stimulation or finger tapping for motor cortex activation in block designs consisting of on/off periods of multiple tens of seconds duration. Several reasons quickly motivated more research groups to study the cerebral functional organization using fMRI. Above all, BOLD imaging is non-invasive and allows application in healthy human volunteers and in patients. Measurements can be repeated virtually infinitely without harming the subject. Also, fMRI is not limited to the cortical surface or areas which can be easily exposed in animal models for optical imaging. This makes other brain areas accessible to the technique.

An important prerequisite for the interpretation of the BOLD effect is the understanding of vascular coupling to neuronal activity, i.e. where and how the blood oxygenation changes due to neuronal activity. The close spatial link of neuronal activity and increased provision of oxygen and metabolites had been hypothesized for over one-hundred years at that time then (Roy and Sherrington, 1890), and refined over the preceding decades (e.g. Roland and Larsen, 1976; Roland et al., 1980). At the time, it was evident from positron emission tomography (PET) studies that this spatial correspondence was given at least to the scale of cortical areas. In animals, this correspondence was already used at an even finer scale in optical imaging (Grinvald et al., 1986). More recent evidence shows the control of blood flow also at the capillary level (Duong et al., 2001; Attwell et al., 2010; Hall et al., 2014).

At the site of neuronal activity, the metabolic demand increases and more oxygen is extracted from the blood, i.e. the cerebral metabolic rate of oxygen (CMRO₂) is increased. Although the shorter T_2^* of deoxygenated blood should lead to signal reduction, an increase in the order of a few percent is observed. The reason is that the BOLD effect is the result of several mechanisms happening in close temporal relation: The increase of CMRO₂ is accompanied by an increase of cerebral blood flow (CBF) and cerebral blood volume (CBV). Both are triggered by a complex cascade of biochemical events (Uludag et al., 2005), which is still not fully understood. Increased CBV also attenuates the signal because of the shorter T_2^* of

blood than in brain parenchyma. Increased CBF increases the signal, because deoxygenated blood is exchanged for oxygen-rich blood. The exact timing and amplitude changes relative to their baselines determine the resultant dynamic signal evolution. All three aspects can be assembled in the hemodynamic response function (Boynton et al., 1996; Friston et al., 1998). The main concomitant BOLD response is positive because the increase in CBF over-compensates the increase in both CMRO₂ and CBV (Fox and Raichle, 1986). The “initial dip”, a small negative signal change immediately follows neuronal activity. Although it is not observed everywhere, and the exact underlying mechanism are not perfectly clear (Grinvald et al., 1991; Ernst and Hennig, 1994; Buxton, 2001; Uludag, 2010), it seems that the initial dip signal yields better spatial specificity than the positive response (Duong et al., 2000; Yacoub et al., 2001; but see also Hu and Yacoub, 2012; Watanabe et al., 2013; Siero et al., 2015). When increased CMRO₂ and CBF have decayed back to baseline, the overall CBV is still above its baseline resulting in a so-called post-stimulus undershoot (Buxton et al., 1998). Again, the exact physiological mechanisms of the post-stimulus undershoot are not clear, and contributions of a CBF undershoot or elevated transient CMRO₂ (Donahue et al., 2009) are discussed (Buxton, 2012). However, the post-stimulus undershoot also holds the potential to yield higher spatial specificity than the positive response (Yacoub et al., 2006). An important distinction in this context must be made between the origin of the BOLD signal, which can be extravascular (meaning stemming from the surrounding tissue of a blood vessel) or intravascular. The BOLD response is generated in both compartments, but their temporal dynamics and implications for specificity differ (Yacoub et al., 2006; Bianciardi et al., 2011). Additionally, a distinction between arterial and venous signals is being made, and the main BOLD response is attributed to venous signals (intra- and extravascular).

Higher functional specificity by high-field spin-echo BOLD fMRI

Shortly after the discovery of the BOLD effect it was found that BOLD imaging could also be done employing T₂ weighted spin-echo sequences (Bandettini et al., 1994). At first, this finding is counterintuitive because the magnetization near paramagnetic deoxyhemoglobin dephases more quickly than without its presence. In spin-echo imaging, this very dephasing

effect is reversed by the refocusing RF pulse and when the echo forms, the magnetization is in phase again. However, this is only true for static spins. The water molecules in the brain constantly fulfill a diffusing motion. Hence, an individual spin experiences different static field strengths in the presence of a field gradient caused by deoxyhemoglobin. While the macroscopic dephasing is reversed by the spin-echo, the dephasing due to this diffusion motion remains. The source of the field inhomogeneity has to be sufficiently small so that a diffusing spin can sample enough field variations along its trajectory in the time between excitation and readout. Only then can the T_2 weighted BOLD effect take place. Importantly, the critical spatial scale is in the order of a few micrometers, the size of cortical capillaries, arteriols and venules (Duvernoy et al., 1981), rendering the extravascular T_2 weighed BOLD effect sensitive to these blood vessels, but to a lesser extent to larger ones. This difference in sensitivity to small and large vessels increases with increasing field strength. The intravascular T_2 weighted BOLD contributes the majority of the overall signal at lower field, whereas this contribution is diminished at higher fields because of the short T_2 of blood itself compared to tissue T_2 (Boxerman et al., 1995a; Boxerman et al., 1995b; Duong et al., 2003; Uludag et al., 2009)³. In T_2^* weighted BOLD imaging, the extravascular signal from both large and small vessels increases with field strength. Therefore, T_2^* weighted BOLD imaging is not spatially more specific at high field than at lower field strength (Uludag et al., 2009; Geißler et al., 2013) despite the early optimistic view (Gati et al., 1997). In summary, T_2 weighted BOLD at high field yields a better spatial specificity than T_2^* weighted BOLD (at any field strength) (Yacoub et al., 2005).

The difference in spatio-temporal signal spread between T_2 and T_2^* weighted BOLD can be parametrized by their functional point-spread functions. Besides numerical simulation studies, two main groups of experimental designs to assess functional point spread of a given imaging sequence may be distinguished. In one group, experiments followed the strategy of using response patterns from functional paradigms with spatially well-known functional (e.g. retinotopic) organizations. By contrasting two conditions with neighboring cortical responses,

³ Assuming that the echo time is equal to tissue T_2 .

conclusions about the spread of information can be drawn⁴. It could be shown that at 7 T, the T_2^* weighted BOLD contrast has a spread of about 2 mm (full width at half maximum) and that the spread of T_2 weighted BOLD is narrower (Engel et al., 1997; Parkes et al., 2005; Shmuel et al., 2007; Panchuelo et al., 2015). In cat visual cortex at 9.4 T, T_2 weighted BOLD point spread was found to be about 1.0 mm (Park et al., 2005). This type of experiments does not necessarily require submillimeter resolution. However, the applicability of the results to high resolution fMRI is somewhat problematic, because an implicit assumption in the model is an isotropic, shift-invariant hemodynamic response. At high spatial resolution the details of the vascular organization (e.g. distribution across the cortical depth or varying density of intracortical veins) contravene this assumption, which may have a strong effect on the specificity (Norris, 2012). Hence, another group of experiments assesses the specificity by investigating laminar differences in activation patterns. It is well known (see below) that cortical area V1 receives most of its input in layer IV, and hence, most activation is expected there rather than at the cortical surface for a strong bottom-up visual stimulus. Experiments have shown that T_2 weighted BOLD imaging reflects this behavior more closely than T_2^* weighted BOLD (Zhao et al., 2004; Goense and Logothetis, 2006b; Harel et al., 2006; De Martino et al., 2013). Given the anisotropic differences in vascularization tangential or radial to the cortex, and moreover also depth-dependent differences, Polimeni et al. (2010) suggested distinguishing also directional (tangential and radial), and positional (depth-dependent) aspects of the BOLD point-spread function (see also Discussion chapter).

It must be mentioned that also other, more direct measures exist to assess the components of the BOLD effect individually for high resolution fMRI. Specifically, it could be shown that CBF (Zappe et al., 2008; Goense et al., 2012) and CBV (Harel et al., 2006; Jin and Kim, 2008a; Jin and Kim, 2008b; Goense et al., 2012) yielded cortical activity depth profiles more in line with the expectation described above. These CBV experiments performed on animals employed monocrystalline iron oxide nanoparticles (MION) to increase the CBV contrast. This is not possible in the human. However, the vascular space occupancy dependent (VASO, Lu et al., 2003) technique has

⁴ In the model, neuronal spread by lateral excitatory or inhibitory connections is ignored, and the spread is attributed solely to vasculature.

recently been developed further for application in humans without exogenous contrast agents (Hua et al., 2013a; Huber et al., 2013; Huber et al., 2015a).

The functional point-spread function takes signal spread into account which is attributed to the vascularization and the contrast mechanisms of the imaging sequence. The signal spread due to the imaging process itself is ignored in numerical simulations of the functional point spread function and only implicitly accounted for in experiments (because it is unavoidable). It must, however, be considered because different contrast mechanisms require the use of different imaging sequences, and the imaging point spread functions may differ. The explicit formulation of the imaging point spread function follows further below.

Mesoscopic organization of the cerebral cortex

The structural and functional organization of the human cerebral cortex can be broadly divided into three spatial scales: Macroscopic, mesoscopic and microscopic. In-vivo, the macro- and mesoscale are nowadays accessible by MRI approaches, but the microscale remains the domain of other methods (although microscopic composition can be inferred from MR data, e.g. spectroscopic, relaxometric or diffusion data). At the macroscale, one distinguishes four different lobes (frontal, temporal, occipital, and parietal) in the two hemispheres, which accommodate multiple cortical gray matter areas. These can be distinguished based on their microscopic properties. First systematic accounts of this organization were given by the study of post-mortem specimen (Brodmann, 1909), in which different neurons and neuronal cell densities as well as different connectivity patterns were observed. Brodmann distinguished about 52 different areas across the brain by the means of histological staining techniques (Ramón y Cajal, 1899), which were based on the method of Camillo Golgi (1843-1926). To the contemporaries, it was already evident that the different anatomical structures must also serve different functional, behavioral purposes. Such functional localization in different brain areas could also be concluded from lesion case studies, e.g. (Broca, 1865; Harlow, 1868; Wernicke, 1874; Damasio et al., 1994). Since these early days, a multitude of methods including lesion studies, but also fMRI, has detailed the knowledge of functional specialization, and many areas with involvement in specific tasks could be identified. Prominent examples

from the visual domain include visual areas V1-V4, V5/hMT+, the fusiform face area (Kanwisher et al., 1997), the extrastriate body area (Downing et al., 2001), and the parahippocampal place area (Epstein and Kanwisher, 1998). To what extent macroanatomical folding patterns are respected by the functional areas, and whether their boundaries are strictly linked to microanatomical differences is still topic of current research (Zilles and Amunts, 2009; Wilms et al., 2010; Frost and Goebel, 2012). Across the brain, maps can be found which are large enough to be considered also macroscopic: Retinotopy in visual areas (Engel et al., 1994; DeYoe et al., 1996; Wandell et al., 2007; Silver and Kastner, 2009), tonotopy in auditory cortex (Formisano et al., 2003), (gross) somatotopy in motor areas and somatosensory areas (Lotze et al., 2000; Buccino et al., 2001), while finer bodily differences (e.g. single digits, Besle et al., 2014) also have more fine-grained representations.

The mesoscale of the cerebral cortex can best be understood when mentally unfolding the macroscopic gyri and sulci to obtain a flat sheet of the thickness of the cortical gray matter. Perpendicular to this sheet, along the cortical depth, a generic model of six cortical layers has proven useful (Brodmann, 1909). These are numbered from the outer (pial) surface increasing towards the inside, towards the white matter. In various brain areas, the neuronal organization within the layers and the intracortical connectivity between layers is similar (Vogt and Vogt, 1919; Nieuwenhuys, 2013). In a simplified model, feed-forward connections from earlier stages of processing, e.g. visual information entering the cortex in primary visual cortex, V1, from the lateral geniculate nucleus (LGN, a pulvinar thalamic nucleus, which relays the information from the retina of the eye), terminate mostly in distinct sublayers of cortical layer 4. Within V1, the information transverses across the layers, and feed-forward connections to higher areas start from cortical layers 2, 3, 5 and 6. Feedback connections from higher areas terminate in layers 2, 3 and 5. The full connectivity is more complex (Gilbert, 1983; Douglas and Martin, 1991; Felleman and Van Essen, 1991; Douglas and Martin, 2004; Sincich and Horton, 2005).

fMRI studies probing human cortical depth dependent activation have become possible in recent years e.g. (Ress et al., 2007; Koopmans et al., 2010; Polimeni et al., 2010; Koopmans et al., 2011; Zimmermann et al., 2011; Olman et al., 2012; De Martino et al., 2013; Huber et al., 2015a). In the light of the extensive knowledge about laminar structure from other

methods, their impact to neuroscience is to date rather limited. Rather, thus far, they are informative about possibilities and limitations of the method itself. Applications mostly focused on visually evoked response profiles across cortical depth. Nevertheless, the potential of cortical depth dependent fMRI studies is exemplified in studies targeting different signal pathways such as magno- and parvocellular pathways (Olman et al., 2012), or feedforward or feedback connections (Muckli et al., 2015).

Within brain areas, tuning of the neurons parallel to the cortical sheet is not uniform, nor are neurons with similar tuning properties scattered across the area at random. Instead, a more fine-grained organization exists. Based on micro-electrode recordings in cat somatosensory cortex, Mountcastle (1957) postulated the presence of elementary processing units with highly similar tuning properties, which span the entire cortical depth forming a cortical column. This pioneering work was followed up by Hubel and Wiesel, who found also a columnar organization in visual cortex of cats and primates (Hubel and Wiesel, 1962; 1965; 1968; 1974) using also micro-electrode recordings, lesion studies in the LGN, or the injection of [3H]proline into one eye (Wiesel et al., 1974). Across these studies, the insight emerged that the primary visual cortex consists of domains of eye preferences, termed ocular dominance columns (ODCs). Using autoradiography, the complete pattern of ocular dominance columns could be presented in the macaque monkey (LeVay et al., 1985). These patches resemble zebra-stripes and are of several hundreds of micrometers in thickness. In the following years, multiple additional tuning characteristics of V1 neurons were observed: Preference for stimulus orientation, direction of motion, spatial and temporal frequency (Hubel and Wiesel, 1963; Bonhoeffer and Grinvald, 1991; Blasdel, 1992; Weliky et al., 1996; Shoham et al., 1997). These are closely linked to specific parallel thalamocortical and cortico-cortical connections to, from, and within V1, and their distinct projection zones in V2 (see (Sincich and Horton, 2005; Shapley and Hawken, 2011) for review).

In the human brain, ODCs have been shown in post-mortem samples using cytochrome oxidase staining in monocular blind (Horton and Hedley-Whyte, 1984; Adams et al., 2007), after it had been validated that cytochrome oxidase staining and [3H]proline injections yielded the same ODC patterns in animals (Horton, 1984). Using fMRI, ODCs could be visualized also in-vivo in the human brain (Menon et al., 1997; Dechent and

Frahm, 2000; Cheng et al., 2001; Goodyear and Menon, 2001; Yacoub et al., 2007). With the exceptions of orientation columns in V1 (Yacoub et al., 2008), temporal frequency (Sun et al., 2007) and axis-of-motion selective columns in hMT/V5 (Zimmermann et al., 2011; De Martino et al., 2013), no further columnar structures could be reliably *mapped* using fMRI in humans thus far (but informational content could be inferred, see Discussion chapter). This circumstance likely reflects conceptual controversies (Horton and Adams, 2005; Adams and Horton, 2009; Ts'o et al., 2009; da Costa and Martin, 2010), but more importantly technical and methodological limitations.

Imaging considerations for high-resolution fMRI

BOLD imaging is perfectly suitable to study cognitive processes in the human brain at the temporal scale of seconds and spatial scale of several cubic millimeters, probing of the involvement of macroscopic brain areas in a given task. Coverage of the entire brain is feasible at increasingly higher temporal and spatial resolutions thanks to various fast (Feinberg et al., 1986; Frahm et al., 1986; Margosian et al., 1986) and ultra-fast imaging techniques (Mansfield, 1977; Poser et al., 2010) and accelerated imaging techniques (Pruessmann et al., 1999; Griswold et al., 2002; Breuer et al., 2006). Most recently, the development of simultaneous multi-slice (SMS, also multiband, MB) imaging has significantly increased imaging speed and/or spatial resolution further (Larkman et al., 2001; Feinberg et al., 2010; Moeller et al., 2010; Setsompop et al., 2012). This development was made possible and further nourished by the introduction of multiple receive RF coil elements with spatially independent receive profiles (Sodickson and Manning, 1997; Wiggins et al., 2009). When aiming for high spatial resolution, special care must be taken to maintain sufficient sensitivity to identify functionally induced signal changes. Some means for higher sensitivity are the same as at lower resolution, but others differ markedly.

For high sensitivity, the contrast-to-noise ratio (CNR) has to be high. CNR is proportional to the effect size (i.e. BOLD signal change) and the temporal signal-to-noise ratio (tSNR). tSNR, in turn, scales with the signal-to-noise ratio (SNR) of the individual images in a time series. At low resolution, physiological noise dominates the tSNR. That is, signal fluctuations induced by physiological processes such as respiration and cardiac pulsation limit

the tSNR more strongly than the thermal noise affecting the acquisition (Triantafyllou et al., 2005; Triantafyllou et al., 2011). A considerable number of acquisition techniques (Zhang et al., 2006; Kundu et al., 2012) and post-processing techniques (Hu et al., 1995; Glover et al., 2000; Birn et al., 2008; Chang and Glover, 2009) have been successfully employed to reduce the effect of physiological noise. Ironically, the presence of physiological noise alleviates the effect of sub-optimal imaging at low resolution, because the thermal noise plays a subordinate role altogether (Gonzalez-Castillo et al., 2011). This is, however, not the case at higher resolution. At high resolution, any reduction of SNR, e.g. due to sub-optimal flip angles, reduces tSNR approximately proportionally.

Among others, SNR is proportional to the voxel volume (Edelstein et al., 1986). Thus, the increase of spatial resolution from 1 mm isotropic (1 mm^3) to 0.8 mm isotropic (0.512 mm^3) costs almost a factor of 2 in terms of SNR. But high resolution causes additional sensitivity reduction, because the image acquisition takes longer. This may reduce the temporal sampling rate and thus the number of sampling points per unit time, but a minimum number of independent observations is required to discriminate a real activation from spontaneous noisy fluctuations (Murphy et al., 2007). Additionally, it can cause sub-optimal choices of imaging parameters such as TE in the case of echo-train imaging sequences such as EPI. Moreover, partial Fourier or higher acceleration factors may be required to counteract the delay. This, however, comes at an SNR cost of the undersampling factor and an additional “geometry factor” (g-factor), which accounts for the introduction of noise from the imperfect disentanglement of spatial locations in the aliased, under-sampled images. Improvements in coil element decoupling and image reconstruction (Roemer et al., 1990; Triantafyllou et al., 2011; Sotiropoulos et al., 2013) as well as improved volumetric distribution of the aliases (Breuer et al., 2006; Bilgic et al., 2015) can reduce the g-factor penalty. These improvements can be particularly relevant to high resolution acquisitions because the distance between two aliased voxels is smaller if the voxel size is smaller (given a fixed matrix size). Two mechanisms can help to recover sensitivity in high resolution fMRI: 1) In smaller voxels, partial volume effects are reduced and distinct signals might emerge, which would otherwise be clouded by adjacent noise sources or cancel out with opposite signals (De Martino et al., 2011). 2) Small voxels reduce intra-voxel dephasing caused by strong macroscopic

static field gradients (Young et al., 1988; Reichenbach et al., 1997). Using high resolution may therefore recover signal from areas with strong susceptibility differences, e.g. orbitofrontal cortex or near the ear canals (Weiskopf et al., 2006; Weiskopf et al., 2007)(but see also other approaches: z-shimming, e.g. Gu et al. (2002), and tailored RF pulses, e.g. Cho and Ro (1992)).

Long EPI echo-trains bring about another difficulty, namely image distortions. k-space lines are acquired at different echo times in an EPI train leading to differences in the accumulated phase of the signal depending on local offresonance frequency (Reichenbach et al., 1997). The image distortions hinder the precise co-registration with anatomical reference images which are typically acquired with a T_1 weighted 3D magnetization-prepared rapid gradient-echo imaging sequence (MPRAGE, Mugler and Brookeman, 1990) or more recent sequence variant such as MP2RAGE (Marques et al., 2010) or MEMPR (van der Kouwe et al., 2008). The latter variants are more apt to counter RF inhomogeneity (but see also Van de Moortele et al., 2009), which is problematic at ultra-high field⁵. The mismatch between structural images and fMRI data can severely limit the interpretability of high-resolution fMRI results because the spatial extent of the investigated structures may only be a few voxels. For example, if the cortical thickness is assumed to be 3 mm, a misplacement of one 0.75 mm voxel will misattribute the cortical depth by 25 %, which is the thickness of at least one cortical layer. Susceptibility induced image distortions can be alleviated in the image-reconstruction or by post-processing techniques. An additional B_0 field map (Hutton et al., 2002; Cusack et al., 2003), a reversed or alternated phase-encoding scheme (Andersson et al., 2003; Smith et al., 2004), or reference scans (Zaitsev et al., 2004; Chung et al., 2011; Dragonu et al., 2013) are required. Recent developments in this field are further discussed in the discussion chapter.

Finally, it must be reiterated that ultra-high field scanners afford higher image SNR (Uğurbil et al., 2003 and references therein; Pohmann et al., 2015), because more spins contribute to the available magnetization. This

⁵ The term ultra-high field refers to field strengths at which the Larmor frequency of hydrogen falls into the range of ultra-high frequency (UHF), 300 Mhz – 3000 MHz, which is the case at 7 T and above.

is the case because less spins occupy the state anti-parallel to the external magnetic field. BOLD imaging receives additional gains because the effect size increases with field strength, so that overall, a supra-linear increase of CNR with field strength is observable for both T_2 and T_2^* weighted BOLD, irrespective of their changes in sensitivity with field strength, which are described above. Since physiological noise ultimately limits the achievable tSNR, the increased SNR from ultra-high field is well invested to counter the SNR reduction by high spatial resolution.

Point-spread function in the presence of signal decay during echo-train sequences

High spatial resolution acquisitions using EPI require long echo trains to sample all k-space lines. The acceleration techniques mentioned in the previous section can reduce the required number of lines. However, the detrimental effect on image SNR has also been mentioned. Besides distortions, long echo trains can also have a detrimental effect on the image point spread function. The latter will be formally introduced in the following section.

In the most common imaging technique in MRI, k-space signals $s(\vec{k})$ are acquired and Fourier transformed to obtain an image,

$$s(\vec{k}) = \int \rho(\vec{r}) \exp(i\vec{k}\vec{r}) d\vec{r} \quad (*)$$

$$\begin{aligned} I(\vec{r}) &= \mathcal{F}(s(\vec{k})) = \frac{1}{2\pi} \int \left(\int \rho(\vec{r}') \exp(i\vec{k}\vec{r}') d\vec{r}' \right) \exp(-i\vec{k}\vec{r}) d\vec{k} \\ &= \rho(\vec{r}), \end{aligned}$$

where $\rho(\vec{r})$ is the measurable spin-density⁶ at a given point $\vec{r}$, and the integral is evaluated in all space (be it 2D or 3D encoding). If the k-space signal is modulated by a filter (modulation transfer function, MTF),

$$s'(\vec{k}) = m(\vec{k}) s(\vec{k}),$$

the resultant image is as the convolution of the Fourier transform of k-space data and the Fourier transform of the filter function⁷ (convolution theorem),

$$\begin{aligned} I(\vec{r}) &= \mathcal{F}(s'(\vec{k})) = \mathcal{F}(s(\vec{k}) m(\vec{k})) = \mathcal{F}(s(\vec{k})) * \mathcal{F}(m(\vec{k})) \\ &= \rho(\vec{r}) * \mathcal{F}(m(\vec{k})). \end{aligned}$$

This is the defining equation for the point spread function (PSF): The PSF is the function, which is convolved with the ideal measurable spin-density yielding the resultant image (Rossmann, 1969; Robson et al., 1997),

$$I(\vec{r}) = \int \rho(\vec{r}') PSF(\vec{r} - \vec{r}') d\vec{r}'.$$

For example, the image resolution is limited by the maximum extent of sampled k-space, which can be formalized by the application of a boxcar filter $m_{trunc}(k_x, k_y)$ truncating the sampling of the infinite k-space in a 2D Cartesian grid:

$$m_{trunc}(k_x, k_y) = \begin{cases} 1 & \text{if } |k_x| < k_{x,max}, |k_y| < k_{y,max}, \\ 0 & \text{otherwise} \end{cases}$$

The Fourier transform of $m_{trunc}(k_x, k_y)$ is a sinc function, and hence, any edge or peak in the image has attenuated side lobes. This phenomenon is known as Gibbs ringing and is exemplified qualitatively in Figure 1-1 a.

⁶ The measurable spin-density takes contrast preparation (e.g. T_2^* weighting) into consideration, but constant, global scaling factors are neglected here for simplicity. In the literature, such scaling factors may also be attributed to the point spread function.

⁷ Leaving more complex dependencies aside. I.e., it is assumed that the image is composed of isoplanatic patches, that is areas that are approximately shift-invariant, see (Rossmann, 1969) and (Robson et al., 1997).

When k-space lines are acquired consecutively in echo train sequences, attenuation due to signal decay occurs. In the case of an EPI sequence with linear phase-encoding, the modulation is

$$\begin{aligned} m_{T_2^*}(k_x, k_y) &= \exp\left(-\frac{t_{es}n\Delta k_y + t_s m\Delta k_x + \text{const.}}{T_2^*}\right) \\ &= m_{T_2^*}(k_x(m), k_y(n)) \end{aligned}$$

where t_{es} is the echo spacing and t_s is the sampling time within one readout. Δk_y and Δk_x denote the sampling step sizes and n and m denote sampling indices in the respective direction. The constant term stems from a non-zero starting time and may be ignored further, because it does not modulate the sampling *differentially*. Since the sampling time is typically much smaller than T_2^* and the echo spacing ($t_s \ll t_{es}, t_s \ll T_2^*$) its effect can be ignored in an approximation. Then, the modulation occurs only in phase-encoding direction y . In this approximation, the effect of T_2^* decay on the phase-encoding direction can be treated analogously to the effect of T_2^* decay on the read-direction in a simple gradient-echo imaging sequence (with a long read-out) and the combined effect of truncation and T_2^* decay is (Haacke et al., 1999 eq. 13.54; Qin, 2012 Eq. 17)

$$PSF_{trunc+T_2^*}(y) \propto \frac{\exp\left(-i\pi \frac{y}{\Delta y}\right) - \exp\left(i\pi \frac{y}{\Delta y}\right) \exp\left(-\frac{T_s}{T_2^*}\right)}{\frac{1}{2\pi} \frac{T_s}{T_2^*} - i \frac{y}{\Delta y}} \quad (**)$$

In the above equation any constant scaling factors were omitted for the sake of clarity. As can be seen, the asymmetry of the T_2^* decay during the acquisition time T_s with linear ordering yields a complex PSF (Figure 1-1 b). The expression yields the pure sinc-modulation of the truncation when $\lim(T_s/T_2^*) \rightarrow 0$.

Equation (**) is also applicable to the case of T_2 decay along a multi-echo spin echo sequence like RARE or HASTE with linear ordering when replacing T_2 for T_2^* . T_s then stands for the time between consecutive spin-echoes (often labeled 2τ). Finally, with these replacements, this filter is also appropriate for the partition direction of the 3D-GRASE sequence employed in this thesis when using linear ordering. When using center-out ordering (that is $k_0, k_{-1}, k_1, k_{-2}, k_2, \dots$), the modulation is nearly symmetric

about the k-space center and the resulting PSF can be approximated by Qin, 2012 (Qin, 2012 Eq. 22)

$$PSF_{trunc+T_2^*}(y) \propto \frac{\frac{1}{\pi} \frac{T_s}{T_2^*} + \exp\left(-\frac{T_s}{T_2^*}\right) \left[\frac{y}{\Delta y} \sin\left(\pi \frac{y}{\Delta y}\right) - \frac{1}{\pi} \frac{T_s}{T_2^*} \cos\left(\pi \frac{y}{\Delta y}\right) \right]}{\left(\frac{1}{\pi} \frac{T_s}{T_2^*}\right)^2 + \left(\frac{y}{\Delta y}\right)^2}$$

Last, the case of a spin-echo or a spin-echo EPI shall be considered. It should be noted that typical depictions of the signal evolution around the spin-echo can be misleading because they might suggest a symmetric envelop due to T_2^* decay around the echo. Rather, the signal amplitude is as follows (Haacke et al., 1999 Eq. 8.18):

$$s(t) = s(0) \begin{cases} \exp\left(-\frac{t}{T_2}\right) \exp\left(-\frac{TE-t}{T_2'}\right) & \text{for } \tau < t < 2\tau = TE \\ \exp\left(-\frac{t}{T_2}\right) \exp\left(-\frac{t-TE}{T_2'}\right) & \text{for } t > 2\tau = TE \\ = \exp\left(-\frac{t}{T_2^*}\right) \exp\left(-\frac{TE}{T_2'}\right) & \end{cases}$$

where τ is the delay between excitation and refocusing pulse, and

$$\frac{1}{T_2^*} = \frac{1}{T_2} + \frac{1}{T_2'}$$

The approximation of a symmetric signal evolution is only justified when $T_2^* \ll T_2$, and the signal drops off quickly on the sides. For brain parenchyma, this is not the case, because $T_2^* \approx 0.5 T_2$. In that case, the branch before the spin-echo is almost constant in signal amplitude. In the example in Figure 1-1 c, $T_2^*/T_2 = 1/3$ (blue) and $T_2^*/T_2 = 1/6$ were chosen.

Again, in consequence of the asymmetric decay, the resulting PSF is complex. The complex nature of the PSF is somewhat difficult to grasp, which is why often in the literature and also in this thesis (but see Huber et al., 2015b), a simplified and more practical approach using the magnitude of the PSF is used. A complex PSF entails that the effect on adjacent voxels in the (magnitude) image must also be considered as a vector sum in the complex plane.

Although analytical expressions for the above PSFs may be derived using Fourier transforms and the convolution theorem, a numerical treatment of these effects is convenient, because it flexibly allows studying e.g. different ordering schemes or the effect of random noise contributions. Further, it is well suitable to account for the discrete sampling. Also, the analytical expressions can quickly become complicated diminishing their elegance and clarity. The truncation effect can be mimicked easily by performing the calculations on a much higher spatial resolution than the actual imaging resolution, e.g. 1 μm . Then, only the central part of k-space is filled. This is important when considering multiple filters at once. For example, partial Fourier acquisition using zero-filling misses up to half of the k-space required for the imaging resolution (Feinberg et al., 1986; Margosian et al., 1986). This fraction, however, becomes significantly smaller when working in the high resolution (1 μm -) space. In advanced image reconstruction, the (idealized) conjugate symmetry of k-space of a real object is exploited and the missing k-space information is filled by known data from the opposite site (Haacke et al., 1991; Noll et al., 1991; McGibney et al., 1993). In theory, these techniques could recover the full nominal resolution, but because of the experimental imperfections in the acquired data, the effect on the PSF is not easily quantifiable.

Finally, it may be noted that the same framework is used to assess and correct for image distortions in PSF mapping techniques for EPI (Robson et al., 1997; Zeng and Constable, 2002; Zaitsev et al., 2004). In this approach, the spatially dependent off-resonance contributes a complex phase in the integral in equation (*) in addition to the intended $\vec{k}$ encoding:

$$s(\vec{k}) = \int \rho(\vec{r}) \exp\left(i(\vec{k} + \vec{k}')\vec{r}\right) d\vec{r}$$

In consequence, the signal is misplaced in the resulting image (Reichenbach et al., 1997). The off-resonance has a stronger effect on the phase-encoding direction than on read-direction because of the different time-scales at which they are sampled. The fact that the PSF has a finite spread is disregarded in these distortion-correction methods because the shift is modelled only by the shift of the peak intensity in the PSF mapping data.

← **Figure 1-1:** Qualitative examples of MTFs (left) and corresponding PSFs (right) for different filters. The PSF plots are zoomed in x to the center. **a)** truncation without any decay, **b)** truncation and asymmetric exponential decay (e.g. phase-encoding direction in EPI, partition direction in 3D-GRASE with linear ordering), **c)** phase-encoding of spin-echo EPI experiment. Solid lines indicate magnitudes, dashed, darker lines indicate the real part of the PSFs.

3D-GRASE

The superior functional specificity of T_2 weighted BOLD compared to T_2^* weighted BOLD as well as the detrimental effect of long echo trains on image distortions and blurring have been described above. Besides accelerated imaging and partial Fourier acquisitions, reduced field of view (FoV) acquisitions can be employed to reduce the duration of the echo train. Various techniques to achieve reduced fields of view exist and are discussed in Chapter 2, but because of its high relevance to this thesis, the 3D inner volume gradient and spin-echo (3D-GRASE) sequence (Feinberg et al., 2008) will be described in more detail in this section. GRASE combines two different fast imaging techniques, EPI and rapid acquisition with relaxation enhancement (RARE) (Hennig et al., 1986), nowadays better known as turbo-spin echo (TSE) or fast spin echo (FSE). In RARE, multiple pairs of refocusing RF pulses and readouts are applied after a given excitation instead of a single pair. This approach reduces the acquisition time of T_2 weighted images immensely. In GRASE, multiple echoes are acquired after each refocusing pulse in an EPI fashion (Feinberg and Oshio, 1991) accelerating the acquisition even further because less refocusing pulses are needed than in RARE. Volumetric acquisition can be achieved in a 2D multi-slice or 3D approach. In anatomical imaging, the EPI factors are typically held modest, and a small, odd number of gradient-echoes (e.g. 3 or 5) are acquired between consecutive refocusing pulses (Trampel et al., 2013). Each gradient-echo receives its own phase-encoding via pre-phaser gradients and phase-encoding gradient blips. While the signal phase is refocused at the central spin-echoes throughout the echo train, this is not the case for the non-central gradient-echoes in the case of off-resonance (Figure 1-2 b). Also, the T_2 and T_2^* weighting varies between the echoes (see Figure 1-2 a, c). Many phase-encoding strategies have been suggested to address these issues, see (Bernstein et al., 2004) for details.

Figure 1-2: 3D-GRASE sequence diagrams (not to scale). **a)** Signal attenuation due to T_2 (dashed line) and combined effect of T_2 and T_2^* (solid line) throughout the readout. **b)** Phase evolution in the presence due to off-resonance. **c)** Simplified pulse diagram only displaying the excitation (Exc) and refocusing pulses (Refoc) and readouts (ADCs) without gradient activity shown. Diagram is not to scale. **d)** Inner volume selection mechanism: The selected volume is the mutual volume of excited and refocused slabs. **e)** Exemplary 3D k-space readout. Linear ordering in kz -direction is shown. Color-coding corresponds to the temporal order in **c**.

Two unique features separate the 3D-GRASE technique employed in this thesis from most anatomical acquisition techniques and those for perfusion imaging, in which GRASE is also often utilized. First, the 3D-GRASE is a single-shot technique in which the entire volume is read out after a single

excitation pulse. Second, in order to keep the duration of the acquisition short, it uses inner volume selective refocusing pulses to reduce the field of view in the phase encoding direction. The latter is done as follows: For excitation, a slab-selective 90° RF pulse is used. The slab-selective refocusing pulses are then executed orthogonally to the excitation pulse plane. In consequence, only the mutual volume receives both excitation and refocusing pulses and produces echoes when the read-out is performed (Figure 1-2 d). Two of the three spatial dimensions are thus limited because any tissue outside the mutual volume is either not excited or not refocused. These two imaging directions are well suited for phase-encoding (primary and secondary phase-encoding direction, or in-plane direction and partition direction phase-encoding), while the third direction is sampled as the read-direction (frequency encoding direction, x-direction in Figure 1-2 e). The in-plane phase encoding is linear as in an EPI whereas the partition direction is encoded in center-out or linear fashion. In either case, the signal magnitude and phase do not experience any discontinuities due to off-resonance or different decay due to T_2 and T_2^* but a smooth evolution along the two directions. The effect of these modulations on the imaging point spread function is described in the section above. Figure 1-3 shows a more detailed sequence pulse diagram including gradients.

← **Figure 1-3:** 3D-GRASE sequence pulse diagram (not to scale). Note that slab-selective gradients for excitation and refocusing are executed in partition (Par) and phase-encoding (PE) direction, respectively. For T_2 weighting, a short delay time is required after each EPI readout, indicated by the dashed additional read-out gradients. Crusher and pre-/post-phaser gradients were combined for increased speed. Three phase-correction scans are acquired immediately after the excitation. Center-out partition encoding is displayed.

Chapter overview

The introduction outlined the scientific background for the following chapters of this thesis including the basics of MRI, the BOLD effect, neurovascular coupling, the functional cerebral organization at the mesoscale, imaging considerations for high resolution fMRI, the image point spread function, and the 3D-GRASE imaging pulse sequence. All following results refer to high resolution human MRI at ultra-high field. In Chapter 2 we report the results of a comparison of two T_2 weighted imaging sequences for application in high resolution fMRI, spin-echo EPI and 3D-GRASE, at 7 T. The main findings are that 3D-GRASE offers better functional sensitivity and specificity than SE-EPI while its spatial coverage and imaging acuity are limited. For these reasons, 3D-GRASE was further developed employing variable flip-angle refocusing pulses to increase coverage and improve the imaging PSF. The results are reported in Chapter 3. In Chapter 4, these methodological advances are put into practice in a high-resolution 9.4 T experiment. We performed population receptive field mapping demonstrating the capability to perform routine visual experiments with high quality results at 9.4 T. High-resolution T_2^* weighted anatomical imaging showed differences in cortical depth profiles between visual areas V1 and V2. These results are paired with preliminary results of ocular dominance using 3D-GRASE. Finally, a few aspects of high-resolution fMRI acquisition and analysis are discussed in Chapter 5, partly incorporating the results of the reported studies.

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Chapter 2

Submillimeter T_2 weighted fMRI

at 7 T: comparison of 3D-GRASE and 2D SE-EPI

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Abstract

Functional magnetic resonance imaging (fMRI) allows studying human brain function non-invasively up to the spatial resolution of cortical columns and layers. Most fMRI acquisitions rely on the blood oxygenation level dependent (BOLD) contrast employing T_2^* weighted 2D multi-slice echo-planar imaging (EPI). At ultra-high magnetic field (i.e. 7 T and above), it has been shown experimentally and by simulation, that T_2 weighted acquisitions yield a signal that is spatially more specific to the site of neuronal activity at the cost of functional sensitivity. This study compared two T_2 weighted imaging sequences, inner-volume 3D Gradient-and-Spin-Echo (3D-GRASE) and 2D Spin-Echo EPI (SE-EPI), with evaluation of their imaging point-spread function, functional specificity, and functional sensitivity at submillimeter resolution. Simulations and measurements of the imaging point-spread function revealed that the strongest anisotropic blurring in 3D-GRASE (along the second phase-encoding direction) was about 60 % higher than the strongest anisotropic blurring in 2D SE-EPI (along the phase-encoding direction). In a visual paradigm, the BOLD sensitivity of 3D-GRASE was found to be superior due to its higher temporal signal-to-noise ratio. High resolution cortical depth profiles suggested that the contrast mechanisms are similar between the two sequences, however, 2D SE-EPI had a higher surface bias owing to the higher T_2^* contribution of the longer in-plane EPI echo-train for full field of view compared to the reduced field of view of zoomed 3D-GRASE.

Introduction

Since its discovery more than two decades ago (Bandettini et al., 1992; Kwong et al., 1992; Ogawa et al., 1992), non-invasive functional magnetic resonance imaging (fMRI) has evolved to become a primary method to study human brain function. The majority of fMRI experiments have been conducted using the blood oxygenation level dependent (BOLD) method (Ogawa et al., 1990), relying on T_2^* changes in gradient-echo based echo-planar imaging (GE-EPI, Mansfield, 1977) acquisitions. However, it has been shown in simulations (Boxerman et al., 1995b; Uludag et al., 2009; Pflugfelder et al., 2011) and experiments at submillimeter (Duong et al., 2003; Yacoub et al., 2003; Yacoub et al., 2007) or lower resolution (Harmer et al., 2012; Boyacioglu et al., 2014; Panchuelo et al., 2015), that at high field strength (7 Tesla and above) imaging strategies utilizing T_2 weighted contrast yield higher spatial specificity than T_2^* weighted contrast. This becomes particularly relevant when the investigated functional organization is on the order of 1 mm or smaller, requiring avoidance of pial vein effects that have been shown to be stronger in T_2^* weighted acquisitions (Yacoub et al., 2005). Cerebral blood flow or blood volume based approaches present an alternative approach to high-resolution fMRI (see e.g. Jin and Kim, 2008a; Goense et al., 2012; Huber et al., 2015a).

By far, most T_2 weighted fMRI experiments have been conducted using 2D spin-echo EPI sequences ((Bandettini et al., 1994), see (Norris, 2012) for review). The EPI echo train increases the temporal and the specific absorption rate (SAR) efficiency as compared to purely T_2 weighted sequences such as RARE/FSE (Hennig et al., 1986; Constable et al., 1994; Poser and Norris, 2007) or to balanced and non-balanced steady-state free precession sequences (b-SSFP/nb-SSFP) (Auerbach et al., 2002; Bieri and Scheffler, 2007; Miller and Jezzard, 2008; Barth et al., 2010; Goa et al., 2014). However, the EPI echo train causes blurring in the phase-encoding direction due to T_2' weighting (Constable and Gore, 1992) and increases the T_2^* weighting as demonstrated by Goense et al. 2006.

As an alternative, inner-volume excitation approaches, such as 3D Gradient-and-Spin-Echo (3D-GRASE) (Oshio and Feinberg, 1991; Feinberg et al., 2008) or single slice inner volume 2D-SE EPI (Duong et al., 2002; Yacoub et al., 2003) have been proposed for T_2 weighted submillimeter fMRI in humans. The 3D-GRASE sequence combines EPI-

readouts with fast spin-echo acquisition schemes (RARE/TSE) by acquiring multiple EPI readouts separated by refocusing pulses. Several secondary phase-encoding steps (referred to as “partitions” throughout this manuscript) are acquired after a single excitation pulse thus overcoming the single slice limitation of zoomed inner volume EPI. Slab-selective refocusing pulses are applied perpendicularly to the slab-selective excitation pulse to limit the required phase-encoding steps (Feinberg et al., 2008). This inner-volume selection allows for shorter EPI echo-trains, minimizing both T_2^* contrast and blurring in the in-plane phase-encoding direction. At the same time, short EPI echo-trains keep the overall echo train length short to minimize blurring along the partition direction related to T_2 decay. Centric ordering of the partitions is typically chosen to sample k-space center at maximal SNR (minimal TE). Compared to 2D spin-echo EPI sequences, 3D-GRASE offers a potential SAR advantage because it uses fewer radiofrequency (RF) pulses due to the necessity of only one excitation pulse for the entire 3D volume and a reduced number of refocusing pulses due to partial Fourier acquisitions along the partition direction. The parsimony in SAR can be used to improve the excitation and refocusing slab profiles by increasing the bandwidth-time product of the RF pulses or to shorten the RF pulse duration in order to shorten the overall echo train length. Cortical depth-specific and columnar fMRI studies have been successfully conducted using 3D-GRASE (Zimmermann et al., 2011; Olman et al., 2012), and it has been shown that 3D-GRASE yields a more specific signal than GE-EPI (De Martino et al., 2013). However, thus far, a systematic comparison of 3D-GRASE and 2D SE-EPI has been missing.

Therefore, this study compares 3D-GRASE and 2D SE-EPI for submillimeter resolution fMRI experiments at 7 T. We do so by simulating and measuring the imaging point-spread function (referred to as PSF through this manuscript) reflecting the anisotropic spread of information in the image stemming from an idealized point source. The point-spread function is defined here as the magnitude of the Fourier transform of the complex optical transfer function, a function reflecting a modulation of k-space data (i.e. truncation associated with the finite nominal image resolution and signal reduction by relaxation weighting at different positions in k-space), whose magnitude is the so-called modulation transfer function (MTF) (Robson et al., 1997). T_2 or T_2^* weighting along an echo-train and truncation of k-space thus impose limits on the effective resolution of the image.

Further, we measure temporal stability (temporal signal-to-noise ratio, tSNR), functional responses to visual stimulation, and the cortical depth profiles of the two acquisitions.

Methods

All measurements were performed on a 7T Siemens Magnetom scanner equipped with a body gradient system (70 mT/m maximum amplitude, 200 mT/m/s maximum slew rate) and a dedicated surface coil (16-channel receive and a separate 4 channel transmit coil with a pre-determined static B_1 phase set optimized for homogeneity over the visual cortex; Live Services, Minneapolis, MN, USA) covering the posterior part of the subjects' heads. Compared to a whole brain coil, this RF coil offers better transmit efficiency (reduced SAR) in occipital areas and a wide angle for visual stimulation. Three subjects (two females, age (28.3 ± 1.5) years) were scanned for imaging point-spread function (PSF) and functional measurements. Three additional male subjects (age 33.3 ± 3.5) were scanned for the PSF measurements only (see below). All subjects were scanned after giving informed written consent and in compliance with the local ethical board.

Visual stimulation protocol

Functional data were acquired while the subjects were performing a visual stimulation task. High contrast concentric flickering checkerboard patterns were displayed centrally on a screen in the magnet bore with a visual angle of 39 degrees. A block design was chosen with 14 blocks of 10 seconds stimulation and 12 seconds rest. The subjects were instructed to fixate a point in the middle of the screen.

Simulations

The signal evolution throughout the echo trains of 3D-GRASE and 2D SE-EPI were simulated in MATLAB (The MATHWORKS Inc., Natick, MA, USA). The same imaging parameters were used in the PSF measurements as in the functional experiments (see below). For the 2D SE-EPI, the signal modulation transfer function (MTF, Robson et al., 1997) was modeled as an exponential decay with a time constant (T_2) of 50 ms (see Uludag et al., 2009, for review of relaxation times) in addition to an exponential decay with a time constant (T_2') of 63 ms (where $T_2^* = 1/(1/T_2 + 1/T_2') = 27.8\text{ms}$)

symmetrically on both sides of the central spin-echo (Bernstein et al., 2004), such that the outer k-space lines experience a stronger modulation. To account for partial Fourier acquisitions (Feinberg et al., 1986), the missing k-space lines were zero-filled. Accelerated imaging was accounted for by assuming the acquisition of missing k-space lines interspersed equidistantly between the acquired lines such that the total echo-train duration was maintained.

The in-plane phase-encoding part of the 3D-GRASE sequence was simulated as in the 2D SE-EPI case, whereas the partition direction was simulated to experience an exponential decay with the same time constant ($T_2 = 50$ ms, equivalent to perfect 180° refocusing pulses). Centric reordering was taken into account and the same procedure to mimic partial Fourier acquisition was applied.

In the model it was assumed that the modulation along the phase-encoding direction is separable from the modulation along the partition direction in 3D-GRASE. In order to obtain the simulated PSF at a $1\mu\text{m}$ resolution the simulated MTF was Fourier transformed after zero-filling to account for the truncated k-space acquisition. This simulation was repeated for the phase-encoding direction of both sequences and the partition direction of 3D-GRASE. All parameter sets used in the experiments were considered. A normal distribution was fitted to the magnitude of each PSF using a linear least squares regression with four free parameters, amplitude, offset, standard deviation and baseline. A Gaussian was chosen because it well approximated the shape of the central lobe of the PSF (i.e. the convolution of the decay filter and a sinc-kernel due to the k-space truncation) and it allows to easily parameterize the full width at half maximum (FWHM).

Point-spread function measurements

PSF measurements were performed with the same imaging parameters as the functional measurements (see below) and the simulations, except for the number of measurements and a lower image scaling factor to adjust the dynamic range to accommodate the high image intensity in the k-space center. The vendor's product 2D SE-EPI sequence was used after implementing the option to turn off the phase-encoding gradients. Further, the gradient polarity of the refocussing gradient was inverted to allow low-SAR fat suppression (Park et al., 1987; Volk et al., 1987; Gomori et al., 1988;

Ivanov et al., 2010) in the PSF measurements and the functional measurements.

Four volumes were acquired to reach a steady state. In the fifth repetition, the phase-encoding gradients were switched off, so that the k-space center was acquired in every readout line. This procedure yields non-Fourier-encoded images (Fourier-encoded only along the readout direction), which are processed in the image reconstruction pipeline nonetheless. Since the acquired data does not contain any spatial information, but does experience the MTF (i.e. the weighting due T_2 and T_2^* decay), the resulting image reflects the point-spread function due to the acquisition and reconstruction (Mugler et al., 1992; Robson et al., 1997; Zaitsev et al., 2004; Park et al., 2007). In the ideal case with no signal decay, all acquisition lines would be identical leading to a reconstructed image with a delta-function like intensity distribution along the non-encoded directions. However, in practice, due to the non-uniformity of the MTF, the peak has a finite width and exhibits side lobes in the case of partial Fourier acquisitions.

The data were analyzed as follows. After standard image reconstruction, individual lines (in phase-encoding or partition encoding direction) were admitted to the analysis if their maximum pixel value was at least 25 % of the global image intensity to avoid noise-only lines. These lines were centered on their respective maximums. Then, data were interpolated using a spline interpolation and a normal distribution was fitted as to the simulated data described above. In the 2D SE-EPI acquisitions, as many peaks as the GRAPPA acceleration factor appear in the data due to the aliasing, but only the maximum peak was used for fitting. This makes the results more comparable to the 3D-GRASE data and reduces an overestimation of the PSF due to the collapsing of the PSF over the entire field of view (FoV, see discussion for details).

In order to assess the slice profile of 2D SE-EPI (i.e. the point spread function along the slice direction), we simulated profiles of the used excitation and refocusing pulses by Fourier transforming the vendor-provided RF pulse shapes. Perfect 90° and 180° pulses were assumed at the slice center. The resulting slice profiles were calculated as $\sin(\alpha_1) \times \sin^2(\alpha_2/2)$, where α_1 and α_2 denote the spatially dependent excitation and refocusing angles, respectively. The final slice profile was obtained by

assuming saturation recovery from the excitation pulse during one TR at the original slice location and during half a TR at the location of the neighboring slices (approximating interleaved slice acquisition). Saturation recovery from both a fully relaxed system (longitudinal magnetization $m_z = 1$) and an Ernst steady state were considered in a range of T_1 values between 1200 ms and 1800 ms (step size of 100 ms).

Functional measurements

Five different acquisitions were repeated two times in each scanning session in a pseudo-random order. All acquisitions had a nominal isotropic resolution of $(0.8 \text{ mm})^3$ and repetition time (TR) of 2000 ms. All used nominal excitation/refocussing flip angles of $90^\circ/180^\circ$. Additional acquisition parameters are listed in Table 2-1. 3D-GRASE 2 is identical to 3D-GRASE 1 except the image volume was rotated about the read-direction such that the phase-encoding direction of 3D-GRASE 1 was the same as partition encoding direction of 3D-GRASE 2 and vice versa. The slices in all measurements except 3D-GRASE 2 were placed parallel to calcarine sulcus (anterior-posterior (ant-pos)), and orthogonally to that in 3D-GRASE 2 (inferior-superior (inf-sup)). Phase-encoding direction left-right was chosen for all 2D SE-EPI acquisitions to keep the FoV to a minimum, while avoiding aliasing in the region of interest. Although the echo spacing of the 2D SE-EPI acquisitions had to be slightly increased with respect to 3D-GRASE to avoid critical peripheral nerve stimulation, phase-encoding direction left-right allowed much shorter EPI echo train durations than anterior-posterior in 2D SE-EPI.

Automatic second order shimming routines were used to homogenize the static magnetic field (B_0) in a region of interest big enough to accommodate the 2D SE-EPI FoV. The shim was adjusted manually for further improvements of the homogeneity, until the FWHM of the measured Larmor frequencies was well below 40 Hz. Macroscopic inhomogeneities further cause a reduction in the apparent T_2^* . We obtained a macroscopic, volumetric T_2^* of $17 \pm 2 \text{ ms}$ (mean $\pm$ SD across all six participants). The individual subjects' volumetric T_2^* values were also used in the PSF simulations in addition to the theoretical T_2^* values for cortical gray matter. A constant shim was then used throughout all functional and PSF measurements. The transmit field (B_1^+) was measured using a pre-saturation based B_1 mapping sequence provided by the scanner

vendor. The transmit voltage was adjusted to yield the correct flip angles in the approximate location of the calcarine sulcus.

	3D- GRASE 1	3D- GRASE 2	2D SE- EPI 1	2D SE- EPI 2	2D SE- EPI 3
TE (ms)	36	36	36	50	50
field of view	30×120 ×10	30×120 ×10	120×120 ×16	120×120 ×16	120×120 ×16
Echo spacing (ms)	1.01	1.01	1.02	1.02	1.03
EPI/total echo train duration (ms)	30 / 216	30 / 216	46	46	31
GRAPPA accel. factor	--	--	2	2	3
Partial Fourier slice orientation	5/8 (partition direction) ant-pos	5/8 (partition direction) inf-sup	6/8 (phase direction) ant-pos	6/8 (phase direction) ant-pos	6/8 (phase direction) ant-pos

Table 2-1: Acquisition parameters of the five functional imaging protocols

Anatomical measurements

Structural images were acquired for anatomical reference using a T_1 weighted MPRAGE sequence (isotropic resolution of 0.6 mm; TR = 3100 ms; TI = 1500 ms; TE = 2.52 ms; flip angle = 5 degree; GRAPPA acceleration factor = 3; FoV = 230x230x154 mm³). Additional proton density weighted images were acquired using identical imaging parameters (except TR = 1440ms) without the inversion module. These additional images were used to alleviate inhomogeneities across the FoV in post-processing by dividing the T_1 weighted image pixel values by those of the proton density weighted images (Van de Moortele et al., 2009).

Functional data analysis

Data analysis was performed using BrainVoyager QX 2.8 (Brain Innovation, Maastricht, The Netherlands) and custom-written routines in MATLAB. Standard preprocessing of the fMRI data consisted of 3D rigid body motion correction and temporal high-pass filtering by a General Linear Model (GLM) with three cosine cycles and a linear trend regressor for each run. The average motion parameters for all acquisitions were 0.32 ± 0.31 mm translation and 0.31 ± 0.28 degree rotation (mean $\pm$ SD of absolute deviation of both parameters). No difference between 3D-GRASE and 2D SE-EPI acquisitions was observed. SE-EPI data was additionally slice-time corrected using a sinc-weighted interpolation. These data were then co-registered with the structural images using positional information of the acquisitions. Manual adjustments were performed using edge information in the fMRI data. For this purpose, the fMRI data was averaged across time after preprocessing to yield a single high quality image, with fine-grained structural information (i.e. CSF/gray matter and white matter/gray matter boundaries), for alignment. When image distortions were too strong to guarantee good alignment of the entire volume, multiple alignments were performed specifically in order to optimize the co-registration for the targeted regions, in which cortical depth profiles were generated. Finally, functional images were resampled in the 3D anatomical volume at a resolution of 0.8 mm using a sinc interpolation.

A standard GLM was used to assess the functional activation. The visual stimulation predictor was created by convolving the visual activation blocks with a standard hemodynamic response function (HRF). For each imaging sequence, both runs were analyzed together on a single subject level without additional confound predictors.

Temporal Signal-to-Noise (tSNR) maps were created by dividing the voxelwise temporal mean intensity by the temporal standard deviation. To produce tSNR maps, preprocessing included only high-pass filtering, using four cosine cycles and linear trend removal. No motion correction or slice-time correction was applied to avoid additional spatial interpolation. The effect of the visual stimulation was removed from the voxels' time course using univariate regression (i.e. GLM).

For the cortical depth profile analysis, high resolution cortical depth grids were created similar to as described in De Martino et al. (2013) based on

anatomical data after segmenting cortical gray and white matter and delineating the boundary between gray matter and cerebrospinal fluid (CSF). The automatic segmentation in BrainVoyager QX was used and refined manually in the regions of interest to ensure correct classification of white matter, gray matter and other tissue types. In each region of interest, a stack of five cortical grids were created starting from cortical thickness measurements (Jones et al., 2000). Grids were placed at regular intervals of cortical depth, and neighboring sampling points within a grid were regularly spaced. A single grid would sample $8 \times 8 \text{ mm}^2$ on a flat piece of cortex. A total of 10 regions of interest were defined within the foldings of the calcarine sulcus. Figure 2-1 displays an exemplary cortical depth sampling region of interest.

Figure 2-1: Exemplary high resolution cortical grid sampling prescription. Cortical depth dependent grids were prescribed at 10 % (red), 30 % (green), 50 % (dark blue), 70 % (yellow), and 90 % (light blue) cortical depth as defined between the white matter-gray matter boundary and the gray matter-CSF boundary (light gray lines), as segmented based on the anatomical reference images.

After the creation of relative cortical depth grids, the local cortex normal vectors (the vectors orthogonal to the cortical sheet) were approximated linearly by calculating the difference vector between the grid points at 10 % cortical depth and the corresponding grid points at 90 % cortical depth. The angle between these cortex normal vectors and the orientation of the partition directions of both 3D-GRASE 1 and 3D-GRASE 2 were calculated.

Results

Imaging point-spread function simulations and measurements

Figure 2-2 shows the results of the simulations and the imaging PSF measurement for all acquisitions, demonstrating good agreement between experimental data and simulations for both the MTF (top) and the PSF (bottom). Prior to the creation of the MTFs, the raw data from the PSF measurements were coil-combined (sum-of-squares combination). The maximum of each readout line (i.e. the echo) was selected and averaged across the other imaging dimension (slices/partition direction for phase-encoding direction; phase-encoding direction for partition direction), and normalized in the range [0, 1]. Note the asymmetry in MTF with higher intensities in the echoes before than after the central spin-echo as expected from combined T_2 and T_2' modulation. This signal characteristic is often neglected in over-simplified models assuming only a symmetric T_2^* signal decay around the spin-echo.

Acquisition	Direction	FWHM (pixel)		
		Measurement	Simulation GM T_2^*	Simulation Exp. T_2^*
3D-GRASE 1	PE	1.8 ± 0.3	1.2	1.3 ± 0.0
2D SE-EPI 1	PE	2.3 ± 0.2	2.0	2.3 ± 0.1
2D SE-EPI 2	PE	2.2 ± 0.1	2.0	2.3 ± 0.1
2D SE-EPI 3	PE	2.0 ± 0.1	1.8	2.0 ± 0.1
3D-GRASE 1	partition	3.6 ± 0.5	4.4	

Table 2-2: FWHM of the PSFs of the different acquisitions (mean $\pm$ standard deviation).

Table 2-2 reports the mean across lines and subjects of the full width half maximum of the PSF (mean $\pm$ standard deviation). The FWHM of the partition direction in 3D-GRASE 1 was found to be 3.6 ± 0.5 pixels, which is about 56 % and 63 % higher than the FWHMs of the phase-encoding direction of 2D SE-EPI 1 and 2. Phase-encoding direction of 2D SE-EPI 3 and 3D-GRASE 1 acquisitions have smaller FWHMs due to the reduced number of phase-encoding steps. The experimental findings are in good agreement with the simulations. The agreement is enhanced when using the experimentally obtained volumetric T_2^* values (right column) in the simulation rather than literature values for gray matter (middle column).

Figure 2-2: Averaged modulation transfer functions (MTFs, top) and point-spread functions (PSFs, bottom). The top panel shows averaged MTFs in phase-encoding direction (thick lines) and partition encoding direction for 3D-GRASE sequences (thin lines). Solid lines represent averaged experimental results across all subjects, dashed lines represent simulations. The dimension of the horizontal axis in the top panel is relative k -space. In the bottom panel, the dimension of the horizontal axis is pixels in absolute numbers (cropped to center) for better comparison. Error bars indicate standard deviation across subjects.

Figure 2-3: Simulated 2D SE-EPI slice profile of a single slice (top) and with consideration of neighboring slices and saturation recovery (bottom). Profiles are displayed relative to nominal slice thickness.

The simulation results of the 2D SE-EPI slice profile are displayed in Figure 2-3. The FWHM (indicated by the vertical dashed line in the figure) was found to be 1.3 ± 0.2 times the nominal slice thickness (mean $\pm$ SD across different T_1 values and saturation scenarios). Due to the wide saturation bands of neighboring slices, the effective slice profile resembles a triangle rather than the desired rectangle. When taking into account the saturation bands of neighboring slices, the integral of the attainable signal is reduced by 49 ± 5 percent compared to a single slice without T_1 saturation effects and by 35 ± 5 percent compared to a single slice with T_1 saturation effects.

Temporal signal-to-noise ratio

Figure 2-4 displays central slices of the tSNR maps and full volume tSNR histograms. The 2D SE-EPI data were cropped to the same in-plane FoV as the 3D-GRASE 1 acquisition (disregarding increased image distortions in 2D SE-EPI). The images and histograms show that the tSNR is substantially higher in 3D-GRASE than in all 2D SE-EPI acquisitions. 3D-GRASE 2 yields similar tSNR as 3D-GRASE 1 (not shown because of its different slice orientation). The 2D SE-EPI 1, 2, and 3 (short TE ($R = 2$), long TE ($R = 2$), long TE ($R = 3$)) yield tSNR in descending order as expected due to T_2 relaxation, undersampling (R), and noise amplification (g-factor) from higher acceleration. Similar results were found for all other subjects (not shown).

Visual activation

All functional acquisitions elicited significant responses to the visual stimulation in and around the calcarine sulcus. Figure 2-5 displays results of the functional experiment overlaid on both an anatomical reference (sagittal cut, left), and on averaged functional slices (single central slice). The same statistical threshold was chosen for all acquisitions, and no multiple comparison correction was used in order not to favor the reduced FoV acquisitions. Note the absence of activated voxels in white matter regions in all acquisitions. BOLD sensitivity is significantly lower in the 2D SE-EPI acquisitions as a consequence of the reduced tSNR (see Figure 2-4).

Figure 2-6 displays histograms of the BOLD signal changes (top) and t-values (bottom) for all three subjects. For each acquisition, voxels were included in the analysis if they responded significantly ($p < 0.05$ uncorrected). Only the mutually covered region was considered. Border voxels were discarded to exclude artefacts from motion or slow scanner drift. The histograms reveal that in each subject, smaller BOLD signal changes surpass the significance threshold using 3D-GRASE, indicative of smaller variability in the responses. In consequence, more active voxels are detected in 3D-GRASE 1 than in any of the 2D SE-EPI acquisitions (see Figure 2-6 bottom).

Figure 2-4 (double page): Temporal signal-to-noise-ratio maps. Maps of the five different acquisitions in a single subject (left) and corresponding histograms (right) are displayed. The 2D SE-EPI images are cropped to the same FoV as 3D-GRASE 1. All maps have the same color scale. Histograms display the tSNR distribution of the same in-plane FoV in all 3D-GRASE slices and 2D SE-EPI slices corresponding to 3D-GRASE 1.

Figure 2-5: BOLD responses overlaid on anatomical reference and averaged functional slices. Mid-sagittal slices of the reference anatomical scan (left) and central functional slices (right) are shown, as indicated by the dashed lines. Note the oblique coronal orientation of 3D-GRASE 2. The same statistical threshold was applied to all acquisitions ($t > 3.0$, $p < 0.003$ two-sided t-test on single voxel level, cluster threshold of 4 voxels). The position of the sagittal cut is shown on a transversal slice in the bottom left corner. The extent and orientation of the functional slices as well as the displayed slice position (dashed lines) are indicated by the colored boxes in the sagittal images.

Figure 2-6: Histograms of significant voxels. Counts of BOLD signal changes (top) and t-values are shown for voxels, which responded significantly to the stimulation ($t > 2.0$, $p < 0.046$).

Cortical depth profiles

Figure 2-7 displays cortical depth profiles from individual regions and their average from 3D-GRASE 1, 2D SE-EPI 1 and 2D SE-EPI 3. 2D SE-EPI 2 was similar to 2D SE-EPI 1 and 2D-SE-EPI 3 (not shown for clarity). Grid points were included in the spatial average, if at least one of the three displayed acquisitions elicited significant responses ($p < 0.05$, uncorrected) in at least one of the five cortical depths. The responses measured with these protocols are similar showing BOLD signal changes mostly between 1 % and 3 %. In both 2D SE-EPI and 3D-GRASE the BOLD signal change is significantly higher at 50 % cortical depth than at 10 % (two-sided Wilcoxon signed-rank test, $p < 0.02$, uncorrected). The 2D SE-EPI acquisitions increase further towards the pial surface (signal change is different between 50% and 90% at $p < 0.02$, two-sided Wilcoxon signed-rank test, for 2D SE-EPI 1 and 2, not significant for 2D SE-EPI 3), whereas the 3D-GRASE profile shows a trend to decrease towards the surface.

In order to assess the potential effect of the imaging PSF on the cortical depth profiles dependent profiles, we repeated the cortical depth profile analysis after smoothing the 2D SE-EPI 1 data using an anisotropic Gaussian kernel. We used two different sizes of the smoothing kernel (FWHM of 2.4 and 4.7 pixels) in slice direction (no additional smoothing in other directions) a range that includes the estimated FWHM of 3D-GRASE 1 in the partition direction. The comparison of normal and blurred data is shown in Figure 2-8. The noted increase towards the pial surface in 2D SE EPI remains despite the smoothing. All profiles differ significantly between 10 % and 90 % cortical depth (two-sided Wilcoxon signed-rank test, $p < 0.002$, uncorrected).

We also evaluated the difference between 3D-GRASE 1 and the orthogonally oriented 3D-GRASE 2 in four of the individual regions which were sufficiently covered by both acquisitions (ROIs 2, 5, 7, and 10 in Figure 2-7). Histograms of the angle (limited between 0° and 90°) between the cortex normal vectors and the partition directions of both 3D-GRASE 1 and 2, are presented at the top of the Figure 2-9. The averages of the cortical depth profiles in these regions are displayed at the bottom in the same figure. Despite the difference in acquisition orientation the depth dependent functional profiles are similar to one another, and are similar to

the 3D-GRASE 1 profile in Figure 2-9 although only a subset of ROIs was used.

Figure 2-7: Cortical depth profiles in individual regions. Single regions (small graphs) and their average (large graph, bottom right) of 3D-GRASE 1 (blue), 2D SE-EPI 1 (yellow), and 2D SE-EPI 3 (pink). Error bars represent standard errors across grid points (individual ROI graphs) and across regions (average graph).

Figure 2-8: Cortical depth profiles in individual regions. Single regions (small graphs) and their average (large graph, bottom right) of 2D SE-EPI 1. Original data is compared to blurred data of two different blurring kernel sizes.

Discussion

In this study, we compared 3D-GRASE to 2D SE-EPI acquisitions in a high spatial resolution BOLD fMRI experiment at 7 T. Simulations, PSF measurements and a simple visual activation paradigm with robust functional responses were used to assess differences with regard to voxel blurring, functional sensitivity, and functional (BOLD) specificity as indicated by cortical depth dependent profiles. Our findings suggest that the anisotropic blurring in 3D-GRASE is higher than in 2D SE-EPI. Further,

Figure 2-9: Comparison of 3D-GRASE 1 and 3D-GRASE 2. Top: Histograms of angle between cortex normal and partition encoding direction of both, 3D-GRASE 1 (dark blue) and 3D-GRASE 2 (light blue), in degrees. Bottom: Mean cortical depth profiles. Error bars represent standard errors across regions.

3D-GRASE yields a more sensitive BOLD signal and less macrovascular weighting as indicated by the smaller superficial effect in the cortical depth profiles. Based on these findings, we conclude that with the used experimental set-up 3D-GRASE yields valuable advantages over 2D SE-EPI for high-resolution fMRI applications provided the more limited coverage is sufficient to the experimental setup. The ability to discriminate small, differential signals at a length-scale on the order of 1 mm depends on the product of tSNR and effect-size (Murphy et al., 2007), which is proportional to the contrast-to-noise ratio (CNR). The measured effect-size (i.e. difference in BOLD signal) depends on the image blurring, and hence depends on the orientation of the structure with respect to the anisotropic image blurring. It can be shown that, for the protocols employed here, the

superior tSNR of 3D-GRASE outweighs detrimental effects of the stronger image blurring, and that the CNR will be below that of 2D SE-EPI only if the investigated structure is closely aligned (~ 0 deg.) with the partition direction of 3D-GRASE.

Our results are in general agreement with previous studies investigating 3D-GRASE (De Martino et al., 2013) or 2D SE-EPI (Goense and Logothetis, 2006a; Harel et al., 2006; Jin and Kim, 2008a), independently. The different protocols we used followed practical considerations and were performed similarly to previously published studies while also matching parameters such as resolution and echo time. Compared to previous studies, the imaging FoV of the 3D-GRASE acquisitions was reduced to account for the slower switching of the body gradient coil (SC72) that was used here.

Inner-volume selection was previously proposed to reduce the echo train length in 2D SE-EPI using spatially orthogonal refocusing pulses to acquire a single slice (Yacoub et al., 2007; Yacoub et al., 2008). Multi-slice acquisitions with this approach are sub-optimal because of saturation effects. Outer-volume suppression (OVS, Heidemann et al., 2012) and 2D spatially selective RF pulses (Pauly et al., 1989; Finsterbusch, 2010; Finsterbusch, 2013) have also been proposed. However, magnetization transfer effects in OVS would reduce the tSNR of 2D SE-EPI further, while additional RF-pulses would tighten the SAR constraints (Pfeuffer et al., 2002; Wargo and Gore, 2013) leading to a reduced number of slices. The use of segmented acquisitions would require techniques to mitigate the effects of subject motion (e.g. the use of bite-bars or advanced image reconstruction techniques) and would be significantly less time efficient. Finally, a surface receive coil with an even more limited FoV (Koning et al., 2013) was not available to us and may represent an alternative way to achieve zoomed imaging in 2D multi-slice imaging.

Imaging point-spread function

3D-GRASE was found to exhibit a wider PSF in partition direction than the 2D SE-EPI acquisitions in phase-encoding direction or slice direction (as expected from simulations). The blurring in the phase-encoding direction of 3D-GRASE was minimal because of the short EPI echo train duration due to the reduced FoV.

The PSF was assessed based on non-phase-encoded data from the entire FoV. Two concomitant sources of possible confounds should be taken into consideration. First, different spatial locations have different PSF properties due to the relaxation properties of their underlying anatomical tissue. Since T_2 of white matter and gray matter is almost identical at 7 T (Yacoub et al., 2003; Deistung et al., 2008; Cox and Gowland, 2010) and T_2^* of white matter is only slightly shorter (Peters et al., 2007; Deistung et al., 2008), one can expect this influence to be small. CSF, which has a much longer T_2 , occupies only a small volume fraction in the chosen FoV and is partly saturated due to its long T_1 ($T_1 \sim TR$). Other tissue compartments, which have much shorter T_2 , contribute relatively little to the signal at TE. It can therefore be expected that the presence of various tissue types does not significantly affect the PSF estimation. Second, static field inhomogeneities across the FoV lead to an overestimation of the global PSF by a broadening of the measured signal. Local off-resonances shift the voxel-by-voxel peak along the phase-encoding direction. The sum of the shifted peaks is broader than an individual one would be. Also, the effective volumetric T_2^* is shortened. Either of these effects (tissue or field specific inhomogeneities) would lead to an overestimation or larger PSF. As such, our measurements can be regarded as a worst-case approximation of the local blurring. The simulations using gray matter T_2^* , on the other hand, reflect the ideal case and can be seen as a lower bound of the local blurring, not subject to either experimental imperfections affecting the local blurring or the global overestimation affecting only our measurements. The reasonable agreement of these numbers suggests that the detrimental effects of the global estimation are limited. An alternative approach, circumventing these possible confounds, would be to employ an acquisition scheme similar to the one by (Zeng and Constable, 2002; Chung et al., 2011), which was used for distortion correction in EPI images. In this study, we chose an approach that did not depend on image reconstruction, which is desirable when comparing different imaging pulse sequences.

This work focused on imaging related effects on the PSF and we did not consider the additional effect of the BOLD related spatial spread of the signal (i.e. the functional PSF), both of which need to be accounted for in determining the ultimate resolution of the fMRI signals. The latter is normally measured by considering differential paradigms with a known spatial distribution of responses and comparing it to the measured spatial

distribution (Shmuel et al., 2007). In light of the results presented here, it is worth noting that a wider spatial imaging PSF will not cancel out high spatial frequency information in differential fMRI paradigms. Rather, when adjacent areas respond to different functional conditions, a wider spatial imaging PSF has a similar effect as a wider functional PSF and results in a reduction of CNR between the functional conditions (Yacoub et al., 2008). Thus, the combination of a differential fMRI paradigm, along with a high functional CNR with reduced contamination from pial veins, explain why columnar or cortical depth dependent fMRI analyses (Zimmermann et al., 2011; Olman et al., 2012; De Martino et al., 2013), with blurring levels (in 3D GRASE acquisitions) comparable to the data presented here, are possible.

tSNR and BOLD sensitivity

The sensitivity to detect small, significant BOLD changes was found to be clearly superior in 3D-GRASE in this study (Figures 2-5 and 2-6). This is a straight-forward consequence of the higher tSNR (Figure 2-4). The tSNR advantage of 3D-GRASE is likely to stem from two sources: First, being a 3D sequence 3D-GRASE is more SNR efficient because of the longer effective sampling time per volume (Edelstein et al., 1986). This is particularly relevant since such high-resolution fMRI typically operates in the thermally dominated noise regime (Triantafyllou et al., 2005), in which tSNR scales linearly with SNR. Second, the inner volume selection in 3D-GRASE obviated the need for parallel imaging in 3D-GRASE, whereas it was necessary in 2D SE-EPI causing a loss in static SNR and hence tSNR by under-sampling and g-factor penalty. Additionally, although the FWHM of the 2D SE-EPI acquisitions was wider in the slice direction than expected (1.3 ± 0.2 times the nominal slice thickness) the large overlap of neighboring slices in the multi-slice 2D acquisitions reduces the available magnetization because of saturation effects (Figure 2-3). Improved slice profiles could therefore improve both tSNR and point-spread.

The origin of the greater sensitivity of the 3D-GRASE sequence seems not to originate from differences in functional contrast (i.e. 3D-GRASE did not exhibit greater response amplitudes, as seen in the functional response profiles, which is also consistent with less contribution from pial vessels), but rather the higher sensitivity seems to originate from a more robust signal (i.e. less noise). The higher sensitivity permitted 3D-GRASE to detect

more subtle BOLD signal changes than 2D SE-EPI, while larger responses were detected about equally.

Contrast mechanisms and functional specificity

All acquisitions employed in this study elicit primarily T_2 weighted contrast, with varying contributions from other mechanisms. As such, the bulk of the detected BOLD signal changes have absolute amplitudes below five percent, in agreement with the literature (Yacoub et al., 2005), however, it should be noted that differences in tasks, acquisition parameters (e.g. echo time, Koopmans et al., 2011), or sampling strategies may all result in differences in the observed functional signal changes. Contributions from T_2^* (T_2') are not negligible due to the duration of the EPI echo trains, which was on the order of magnitude of the T_2^* of the brain tissue. The T_2^* contribution is expected to be higher in the 2D SE-EPI acquisitions than in 3D-GRASE because of the longer EPI echo trains and in-plane partial Fourier acquisitions, as discussed in the section on the image point-spread function. The later (non-center) partitions in the 3D-GRASE echo-train are sampled at a later effective TE than the nominal TE, which was matched with the TE of 2D SE-EPI 1. Therefore, the T_2 contribution is higher in 3D-GRASE because later partitions experience more T_2 weighting and additional T_2 weighted stimulated echo weighting than the center partition (Goerke et al., 2007). In addition, blood vessels have a particularly sharp spatial profile (compared to smoother gray or white matter structures), which manifests itself in the k-space regions corresponding to high spatial frequencies. High k-space lines of an EPI readout, in turn, experience the strongest T_2^* weighting. Note that, in reduced FoV acquisitions, the same effect takes place. However, given the shorter EPI readout times, the high k-space lines are acquired closer to the spin-echo, thus reducing the effect size.

Finally, more diffusion weighting is aggregated along the readout train of 3D-GRASE due to the readout and crusher gradients. Moderate diffusion weighting has been shown to suppress macrovascular signals (Lee et al., 1999; Duong et al., 2003; Yacoub et al., 2003).

In consequence of the aforementioned differences in contrast between 3D-GRASE and 2D SE-EPI, the cortical depth profiles differ such that 2D SE-EPI exhibits an increase of the signal change towards the pial surface, whereas 3D-GRASE remains mostly flat. Such increasing cortical depth profiles have

previously been associated with reduced functional specificity in SE-EPI (Goense and Logothetis, 2006a) and GE-EPI (Polimeni et al., 2010; De Martino et al., 2013), because they reflect T_2^* induced weighting of macrovasculature. We follow this line of argument and conclude that under the experimental conditions employed here, 3D-GRASE is less biased by large superficial effects as indicated by the layer profiles (Figure 2-7).

Our imaging PSF results raise the question of whether the observed difference in layer profiles is a mere consequence of the stronger blurring in the partition direction of 3D-GRASE. We show that this is not the case in two ways. First, we smoothed the 2D SE-EPI 1 data with anisotropic Gaussian filters exceeding the width of the PSF of 3D-GRASE along the partition direction. The characteristics of cortical depth profiles, and more specifically the increase towards the pial surface, are preserved (Figure 2-8). Second, when looking at the angle between the partition encoding direction and the direction of the cortical depth (Figure 2-9 top), on average there is not a bias of alignment between the partition direction and the grid direction (i.e. smaller angles between the directions). The curvature of the cortex prevents this from occurring and ultimately protects the cortical depth measures from the partition blurring of both 3D GRASE 1 and 3D GRASE 2, despite their orthogonal prescription. Further, the differences in angle distributions between the two acquisitions did not even elicit any significant difference in the layer profiles (Figure 2-9).

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Chapter 3

Variable flip angle 3D-GRASE for high resolution fMRI at 7 T

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Abstract

This study evaluates the use of variable flip angle refocusing pulse trains in single-shot 3D gradient and spin-echo (3D-GRASE) in order to reduce blurring and increase the spatial coverage for high spatial resolution T_2 weighted functional MRI at 7 T. Variable flip angle refocusing schemes in 3D-GRASE were calculated based on extended phase graph theory. The blurring along the slice (partition) direction was evaluated in simulations, as well as phantom and in-vivo experiments. Further, temporal stability and functional sensitivity at 0.8 mm isotropic resolution were assessed. Variable flip angle refocusing schemes yielded significantly reduced blurring compared to conventional refocusing schemes, with the full width at half maximum being about 30-40 % narrower. Simultaneously, spatial coverage could be increased by 80 %. The temporal signal-to-noise ratio was slightly reduced, but functional sensitivity was largely maintained due to increased functional contrast in the variable flip angle acquisitions. Signal-to-noise ratio and functional sensitivity were reduced more strongly in areas with insufficient RF transmission indicating higher sensitivity to experimental imperfections. We conclude that variable flip angle refocusing schemes increase usability of 3D-GRASE for high-resolution fMRI by reducing blurring and allowing increased spatial coverage.

Introduction

Simulations and experiments have shown that at ultra-high field (i.e. 7 T and above) the T_2 weighted blood oxygen level dependent (BOLD) signal is more specific to the site of neuronal activity than T_2^* weighted BOLD (at either high or low field), because T_2 weighted BOLD is less sensitive to large draining veins (Duong et al., 2003; Yacoub et al., 2005; Uludag et al., 2009). However, regardless of the increased signal to noise ratio available at higher field (Edelstein et al., 1986; Pohmann et al., 2015), purely T_2 weighted acquisition strategies (Constable et al., 1994; Poser and Norris, 2007; Barth et al., 2010; Goerke et al., 2011; Hua et al., 2013b; Goa et al., 2014) have been hindered in high-resolution applications by their long acquisition time, lower sensitivity, and/or the high specific absorption rate (SAR). The temporal efficiency and (relative) SAR parsimony of spin-echo echo planar imaging (SE-EPI, Bandettini et al., 1994) partly alleviate these issues. However, EPI readouts introduce T_2^* contrast, depending on the echo train length, compromising purely T_2 weighted contrast (Goense and Logothetis, 2006b). To counteract this, outer-volume suppression (Pfeuffer et al., 2002; Heidemann et al., 2012), inner-volume selection by orthogonal radio-frequency (RF) pulse train prescriptions (Feinberg et al., 1985), and segmented EPI trains have been used (Yacoub et al., 2005).

In the study of human brain function, the successful use of the latter two methods has been showcased by a single-slice 2D SE-EPI with anisotropic resolution (Yacoub et al., 2007; Yacoub et al., 2008). Despite this success, the method did not find applicability outside a flat piece of cortex in primary visual areas. Extending this approach, to overcome the limitation of acquiring a single anisotropic slice, 3D inner-volume gradient and spin echo (3D-GRASE, Feinberg and Oshio, 1991; Feinberg et al., 2008) has been proposed. 3D-GRASE acquires a full 3D volume after a single excitation pulse by sampling k-space with a combination of EPI echo trains and multiple spin-echoes. The refocusing RF pulses select a perpendicular slab achieving inner-volume selection. We have recently shown that 3D-GRASE is functionally more specific and more sensitive than 2D SE-EPI with a large field of view (FoV) (Kemper et al., 2015b), however, blurring along the secondary phase-encoding direction (partition direction) and the small FoV of 3D-GRASE still limit its usability. In particular, the FoV of 3D-GRASE cannot easily be extended as doing so introduces T_2 decay induced blurring (additionally T_2^* blurring and T_2^* functional contrast when increasing the in-

plane FoV). To alleviate the blurring introduced by T_2 decay, the signal strength would have to be sustained throughout the echo train (Qin, 2012). This can be achieved by variable flip angle refocusing RF pulse trains, which introduce alternative signal pathways (stimulated echoes and additional primary spin-echoes of various pairs of RF pulses). They are designed based on extended phase graph theory (Hennig, 1988) and are routinely employed in T_2 weighted turbo spin echo (RARE/FSE/TSE) (Hennig et al., 1986) structural imaging (known as SPACE, VISTA or CUBE) (Busse et al., 2006; Busse et al., 2008).

In this proof-of-concept study, we apply VFA refocusing trains in high spatial resolution single-shot 3D-GRASE. We validate the method in phantom acquisitions and demonstrate two cases of successful in-vivo application to (a) reduce the blurring and to (b) simultaneously reduce blurring and extend the imaging FoV. Accelerated imaging (Pruessmann et al., 1999; Griswold et al., 2002) as a potential alternative to increase the in-plane FoV is also explored.

Methods

All measurements were performed on a 7T Magnetom Siemens scanner equipped with a body gradient system (70 mT/m maximum amplitude, 200 mT/m/s maximum slew rate). A 32-channel phased-array head coil (Nova Medical, Wilmington, MA, USA) was used in phantom measurements and a 16-channel phased array surface coil (Live Services, Minneapolis, MN, USA) covering the posterior part of the subjects' heads was used for in-vivo experiments. Eight healthy volunteers (5 female; mean age 27 ± 4 years) were scanned after giving informed written consent and in compliance with the local ethical board. One subject (S 5) was excluded from functional analyses, because she reported sleepiness after the measurements. Second order automatic static field shim routines were applied and refined manually to reach good static field homogeneity (in-vivo: Larmor frequency full width at half maximum ≤ 45 Hz, $T_2^* = 15.1 \pm 1.4$ ms). RF transmission voltage was adjusted based on a pre-saturation based B_1 mapping sequence provided by the scanner vendor. A small region of interest in the center of the imaging volume was used to determine the correct voltage.

Variable flip angle refocusing design

The variable flip angle pulse trains were calculated offline using MATLAB (The MATHWORKS Inc., Natick, MA, USA). It was assumed that the signal evolution along the partition encoding direction could be treated separately from the decay due to T_2 and T_2' , which affects the phase encoding direction. Further, it was assumed that the Carr-Purcell-Meiboom-Gill (CPMG) condition was met for the central spin-echoes of the EPI echo trains. An exponential target signal decay was calculated taking into account TE, number of slices (also accounting for k-space truncation), partial Fourier (assuming zero-filling), the desired maximum blurring along the partition-direction, and the relaxation properties of the target tissue ($T_2 = 40$ ms, $T_1 = 400$ ms for agar phantom, $T_2 = 50$ ms, $T_1 = 1800$ ms for gray matter). The calculation of the VFA echo train for a given target signal shape was then done as suggested in (Busse et al., 2006) based on (Hennig, 1988; Hennig et al., 2003). Finally, the flip angles of the last third of the echo train were raised quadratically in the in-vivo scans to maximize the signal intensity. The last refocusing flip angle was raised to the maximum of the echo train rather than to 180° that would otherwise require longer refocusing pulses. Care was taken that the resulting signal intensities of the alternated last refocusing flip angles were all higher than in the exponential decay to ensure blurring would not become stronger due to the alternation.

Point-spread function measurements

Global point-spread function measurements were performed by acquiring non-Fourier-encoded images (Kemper et al., 2015b). After four volume acquisitions in order to reach a steady state, the phase-encoding gradients in the in-plane and partition directions were switched off for the fifth repetition. Instead of sampling a full k-space, the k-space center line was acquired repeatedly in every read-out, modulated by the modulation transfer function (MTF). The resultant data can be reconstructed in the reconstruction pipeline exhibiting the anisotropic image point-spread function (PSF), reflecting effects of the acquisition (i.e. signal modulation due to T_2 and T_2^* decay) and the reconstruction (i.e. filtering) (Mugler et al., 1992; Zaitsev et al., 2004; Park et al., 2007). The ideal case of a homogeneous MTF would result in a sharply peaked intensity distribution along the non-encoded directions. However, in practice, the obtained PSF

has a finite width. In order to characterize the PSF, we computed the full width at half maximum (FWHM) by interpolating the magnitude of the PSF using a spline interpolation. This approach was chosen rather than a Gaussian fit (Kemper et al., 2015b) because it characterized the different peak shapes of the VFA acquisitions better.

Phantom measurements

A spherical agar phantom was used to test the VFA approach systematically in a wide range of parameter combinations. VFA pulse trains were calculated for each of the $4 \times 3 \times 3$ combinations of 1) FWHM of PSFs of 2, 2.5, 3, and 4 pixels, 2) coverage of 10, 16, and 20 slices, and 3) partial Fourier acquisition of 5/8, 7/8, and 8/8 (except Partial Fourier 5/8 at 2 pixel FWHM was not performed with 10 slices because it would require a constant MTF). Other imaging parameters were as in the in-vivo REF measurement (see below).

In-vivo measurements

Four different 3D-GRASE measurements were acquired with each subject: 1) a conventional 3D-GRASE acquisition with nominal 180° refocusing pulses (REF); 2) a variable flip angle acquisition with otherwise same protocol as REF with reduced blurring (VFA1); 3) a variable flip angle acquisition to extend the FoV in partition-direction and with reduced blurring (VFA2); 4) the same protocol as REF, except GRAPPA factor 2 and doubled FoV in in-plane phase encoding direction (R2). TE in VFA1 and VFA2 could be slightly reduced compared to REF because of the shorter RF pulse lengths required for the smaller flip angles. See Table 3-1 for additional imaging parameters. The nominal refocusing flip angles used for VFA1 were (109° , 63° , 62° , 63° , 75° , 109°), and for VFA2 (90° , 49° , 45° , 43° , 43° , 42° , 43° , 46° , 51° , 58° , 67° , 77° , 90°). All acquisitions used 90° nominal excitation flip angles, linear phase ordering in in-plane direction, and centric ordering of the partition direction.

Variable flip angle 3D-GRASE				
	REF	VFA1	VFA2	R2
TE / TR (ms)	37.9 / 2000	36.9 / 2000	35.9 / 2000	37.9 / 2000
Matrix size	120×30×1	120×30×1	120×30×1	120×60×1
	0	0	8	0
Image volume (mm ³)	96×24×8	96×24×8	96×24×14. 4	96×48×8
Turbo factor	6	6	14	6
Echo train duration (ms)	227	221	504	227
Nominal refocusing flip angles	180°	62° to 109°	42° to 90°	180°
Echo-spacing (ms)	1.03	1.03	1.03	1.03

Table 3-1: Imaging parameters used in in-vivo measurements.

A T_1 weighted MPAGE sequence (isotropic resolution of 0.6 mm; TR = 3100 ms; TI = 1500 ms; TE = 2.52 ms; Flip angle = 5°; GRAPPA acceleration factor = 3; FoV = 230×230×154 mm³; duration 8:49 min.) was used to acquire structural images for anatomical reference. Additionally, a proton density weighted MPAGE with identical imaging parameters except without an inversion module (and: TR=1440 ms, duration 4:06 min.) was acquired to alleviate inhomogeneities across the FoV in post-processing by dividing the T_1 weighted image by the proton density weighted images (Van de Moortele et al., 2009).

Visual stimulation paradigm and functional data analysis

Subjects fixated a central point on a screen in the magnet bore while high contrast concentric flickering checkerboard patterns were displayed (visual angle of 39 degrees) via an angulated mirror attached to the RF coil. One run consisted of 36 blocks of 8 seconds stimulation interspersed with 10 to 14 seconds rest totaling a duration of 12:12 minutes.

Data analysis was performed using BrainVoyager QX 2.8.2 (Brain Innovation, Maastricht, The Netherlands) and custom-written routines in MATLAB. Preprocessing of the fMRI data included 3D rigid body motion correction and temporal high-pass filtering by a GLM with four cosine cycles and linear trend. The data were then co-registered with the structural images using positional information of the acquisitions. Manual

adjustments were performed using edge information of the fMRI data. Finally, functional images were resampled in the 3D volume at a resolution of 0.8 mm using sinc interpolation.

A standard GLM was used to assess the functional activation. The visual stimulation regressor was created by convolving the visual activation blocks with a standard 2-gamma-function hemodynamic response function. Each run was analyzed on a single subject level with confound motion regressors (3 translational and 3 rotational).

To produce temporal signal-to-noise ratio (tSNR) maps, preprocessing included only high-pass filtering. No motion correction was applied to avoid additional spatial interpolation. The effect of the visual stimulation was removed from the voxels' time course using a GLM. We then computed tSNR dividing the voxels' temporal mean by the temporal standard deviation.

Results

Phantom measurements

Figure 3-1 displays the employed RF pulse trains used for the phantom measurements and the corresponding measured and simulated echo signal intensities. Measured data were coil-combined using sum-of-squares. As expected, smaller flip angles are employed in order to sustain the signal longer throughout the echo train. Good agreement between theoretical prediction and experimental results can be observed for all parameter combinations.

→**Figure 3-1:** (a) RF pulse flip angles employed in the phantom measurements for different numbers of slices (rows), different partial Fourier factors (columns) and different target PSF FWHM (in pixels, graph colors, annotated in top right graph). (b) Corresponding signal intensities. Markers and lines represent experimental data and simulations, respectively. Simulations and experimental data were scaled by their individual means. Size: Double-column width.

Point-spread function simulations and measurements

The results of the simulations and measurements of in-vivo PSF in partition direction are summarized in Table 3-2. As expected, VFA1 and VFA2 have narrower PSFs than the REF acquisition in both measurements and simulations.

Acquisition	Measurement	Simulation
REF	4.0 ± 0.5	4.8
VFA1	2.6 ± 0.3	2.3
VFA2	2.9 ± 0.3	2.3

Table 3-2: FWHM (pixel, mean $\pm$ std) of PSF in in-vivo measurements.

Temporal signal-to-noise ratio

Mean signal and tSNR maps of a representative subject are shown in Figure 3-2 (all subjects in Figure 3-3). The reference acquisition, REF, yields the strongest tSNR; VFA1 and VFA2 have slightly reduced tSNRs. The GRAPPA acquisition, R2, has poor tSNR in comparison to the other acquisitions. All maps reveal reduced tSNR values in the left hemisphere (right side of the image, radiological convention) associated with RF transmission asymmetry. This reduction is more pronounced in the VFA acquisitions.

Figure 3-2: (a-d) Mean signal maps of REF (top), VFA1 (top middle), VFA2 (bottom middle), and R2 (bottom). A single, transversal oblique central slice is shown for each acquisition (identical anatomical position). (e-h) Temporal signal to noise ratio maps at position corresponding to maps in a-d. The same color scale is used for all maps. (i) Relative RF transmission (B_1^+) map of same location and interpolated to same resolution. The in-plane imaging FoVs of the functional acquisitions are indicated by the dashed (REF, VFA1, VFA2) and dotted (R2) boxes, respectively.

Figure 3-3 (double page): Temporal signal to noise ratio maps of all subjects (S 1 – S 8) and all acquisitions. Single, transversal oblique central slices (identical anatomical position, same color scale) are shown for each acquisition.

Bottom: Relative RF transmission (B_1^+) maps of same location and interpolated to same resolution. The in-plane imaging FoVs of the functional acquisitions are indicated by the dashed (REF, VFA1, VFA2) and dotted (R2) boxes, respectively.

Functional activation

Maps of functional activation of a representative subject are displayed in Figure 3-4. All displayed acquisitions, REF (top), VFA1 (middle), and VFA2 (bottom), show robust activation patterns. The strongest activation is confined to regions of gray matter and (in smaller proportion) CSF. The GRAPPA acquisition, R2, is not shown because it revealed very little functional responses. Figure 3-5 displays activation maps of all subjects.

To quantify the differences, we calculated within-subject medians of absolute percent signal changes and absolute t-values for all acquisitions using a gray matter mask derived from the anatomical reference data in the mutually covered volume. BOLD signal changes were found to be 14 % (18 %) higher in VFA1 (VFA2) than in REF ($p = 0.02$, uncorr., two-sided Wilcoxon sign rank test). Further, VFA1 and VFA2 did not reveal significantly different t-values than REF. R2 had significantly lower t-values than the other acquisitions ($p < 0.02$), although BOLD signal changes were not significantly different from REF, indicating the same contrast mechanism as in REF but lower tSNR. Individual subject data is provided in Table 3-3 and Figure 3-6.

→**Figure 3-4:** Visual activation patterns (t-values, two-tailed Student's t-test, $p < 0.01$, uncorrected, 4-voxel cluster-threshold) overlaid on anatomical reference in sagittal, transversal, and coronal cuts. The imaging volume cross section is indicated by the colored boxes in the sagittal cuts and the anatomical reference image at the top (blue: REF, light green: VFA1, dark green: VFA2). Size: Double-column width.

Figure 3-5 (double page): Visual activation maps (t-values, two-tailed Student's t-test, $p < 0.01$, uncorrected, 4-voxel cluster-threshold) overlaid on anatomical reference in coronal, sagittal, and transversal cuts.

Discussion and Conclusions

We demonstrate the application of variable flip angle refocusing schemes in high resolution 3D-GRASE acquisitions in order to improve the image PSF and spatial coverage in T_2 weighted submillimeter fMRI applications at 7 T. In short, the variable flip angle refocusing approach reduces the signal intensity at early echo times and increases it at later echo times. This results in the following: a) Reduced blurring across partitions and/or increased coverage. b) reduced tSNR (in center-out reordering). c) Increased BOLD contrast. We showed that the enhanced BOLD contrast largely counterbalances the reduced tSNR in VFA while image blurring was reduced and therefore conclude that VFA refocusing is a valuable improvement of the single-shot inner-volume 3D-GRASE sequence.

Our method is similar to that of Liang et al. (2014), who recently presented a VFA 3D-GRASE technique for low-resolution whole-brain perfusion measurements using arterial spin labeling at lower field to improve the PSF. Although the scope is different, the employed VFA refocusing RF pulse trains are similar because the ratio of sequence timings and tissue T_2 at 3 T and 7 T are comparable. However, it should be noted that the stronger T_2 weighted stimulated-echo contrast induced by the VFA refocusing has different implications in BOLD imaging than in perfusion imaging, where minimal T_2 contamination is desirable. Further, our study extends the quantitative assessment of the blurring by *direct*, empirical in-vivo measurements of the PSF.

Subject	t-values				Percent signal changes			
	REF	VFA1	VFA2	R2	REF	VFA1	VFA2	R2
1	1.61	1.65	1.43	1.15	1.20	1.46	1.47	1.29
2	1.85	1.69	1.95	1.07	1.26	1.40	1.58	1.37
3	1.48	1.15	1.27	1.06	1.10	1.11	1.19	1.06
4	1.15	1.18	1.48	0.88	0.80	1.08	0.81	1.00
6	2.12	1.95	2.10	1.44	1.22	1.40	1.44	1.31
7	1.62	1.50	1.70	1.11	1.06	1.19	1.25	1.24
8	2.26	2.36	2.57	1.83	1.33	1.59	1.74	1.28

Table 3-3: Individual subject medians of t-values and percent signal changes of all acquisitions.

Figure 3-6: Scatterplot of differences of individual subject medians with respect to REF acquisition. Colors represent different subjects, open markers represent median across subjects.

Image point-spread function

Our method was validated using phantom and in vivo measurements. In the phantom scans we noted excellent agreement of simulations and measurements. Compared to conventional refocusing schemes, in-vivo VFA measurements exhibit significantly reduced blurring. With the VFA approach we were able to obtain a similar PSF to that of large FoV 2D SE-EPI along the phase-encoding direction (Kemper et al., 2015b). In addition, the coverage of VFA2 was almost doubled compared to REF. REF is in good agreement with (Kemper et al., 2015b). Deviations stem from the longer TE and the different fitting approaches. Note that experimental imperfections in the 180° refocusing pulses can be advantageous for the PSF while this is not necessarily the case for lower flip angles. This explains why in REF, the experimental blurring is smaller than theoretically expected. VFA2 exhibits slightly higher blurring than theoretically expected and compared to VFA1. This may be because of physiological noise sources introducing phase shifts

throughout the much longer echo train, which could potentially be mitigated using more sophisticated image-reconstruction algorithms (Kim et al., 2015). Finally, constant flip angle schemes employing angles below 180° (Fernandez-Seara et al., 2005) would yield a much smaller improvement over 180° pulses than the presented VFA acquisitions. For 140° constant refocusing flip angles we found a reduction of blurring FWHM of 8 % in simulations and 3-8 % in measurements (tested in four subjects), compared to 180° (REF).

tSNR and functional sensitivity

The tSNR in both VFA acquisitions was smaller compared to REF. The reduction was most apparent in regions experiencing insufficient RF transmission (see Figure 3-2 bottom), to which the VFA acquisitions were more sensitive than the conventional measurement. Importantly, less RF efficiency, which is typically linked to improved homogeneity (e.g. in B_1 shimming approaches (Metzger et al., 2008; De Martino et al., 2012)), would be acceptable, because of the low SAR of the VFA acquisitions.

Image SNR is commonly known to be dominated by the signal intensity of k-space center (in our case proportional to $\sin(\alpha_0) \times \sin^2(\alpha_1/2)$, where α_0 is the excitation flip angle and α_1 the first refocusing angle) and to scale with the square root of the sampling time (depending on the number of slices and partial Fourier acquisition (Edelstein et al., 1986)). This explains the reduction of tSNR in VFA1 while the latter partly recovers tSNR in VFA2, because it employs a longer sampling time.

Higher functional signal changes were observed in both VFA acquisitions, thereby preserving the contrast-to-noise ratio and hence functional sensitivity. Higher signal changes are expected because a higher fraction of the sampled signal experiences long echo times (in spin-echo pathways) or long mixing times (in stimulated echo pathways). Thus, in both signal pathways spins experience longer diffusion times in the presence of microscopic magnetic field gradients surrounding capillaries and venules containing deoxygenated blood (dynamic averaging) (Yacoub et al., 2003; Goerke et al., 2007; Uludag et al., 2009). This mechanism increases the BOLD contrast. Differential responses from small, adjacent cortical patches or cortical layers can be clouded by image blurring reducing the contrast-to-noise ratio (Yacoub et al., 2008; Kemper et al., 2015b). The reduced blurring using VFA will therefore improve the functional sensitivity in

differential functional paradigms (when the areas are aligned with the partition direction of the imaging slab).

Alternative ways to increase FoV

For comparison, in-plane accelerated data were acquired, as an alternative approach to increase the FoV. These did not yield satisfying results. The likely reason is insufficiently distinct RF receive profiles. A different coil design might be advantageous for this application (Koning et al., 2013), allowing for reduced g-factors. Further, a high resolution receive coil grid with smaller elements might allow for acceleration along the smaller partition direction. Alternatively, independent multi-slab as well as multi-banded (Larkman et al., 2001) multi-slab acquisitions have been demonstrated (Chen and Feinberg, 2013; Vu et al., 2013). These approaches allow imaging multiples of the FoV in separate locations; however, acquiring an increased, contiguous FoV might be limited by saturation effects from imperfect slab profiles and insufficiently distinct receive RF coil sensitivity profiles, for the separation of the multi-banded slabs in high spatial resolution acquisitions. A larger, contiguous FoV is preferable for applications that focus on imaging larger cortical areas. Note, however, that the VFA technique could straightforwardly be combined with in-plane accelerated imaging and/or these multi-slab approaches.

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Chapter 4

9.4 T anatomical and functional investigation of human primary and secondary visual cortex

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Abstract

Ultra-high field functional magnetic resonance imaging (fMRI) employing the T_2 weighted blood oxygenation dependent (BOLD) effect provide sufficient specificity and sensitivity to sample cortical structures at the submillimeter scale. Anatomical MRI at ultra-high field affords novel applications because of stronger contrasts and higher resolution. Thus far, little experience exists for human fMRI at field strengths above 7 Tesla. This study provides preliminary evidence for the potential of field strengths higher than 7T in the delineation of functional and anatomical properties of visual cortical areas. We employed a human 9.4 T scanner to obtain T_2^* and T_2 weighted BOLD functional data and high resolution T_1 and T_2^* weighted anatomical images. We delineated visual areas V1 and V2 using population receptive field mapping and gradient-echo echo planar imaging. Within these retinotopically defined cortical regions (corresponding to Brodmann areas 17 and 18, respectively) we analyzed the anatomical contrast from T_2^* weighted data (0.35 mm isotropic resolution) and found distinct differences in their cortical depth dependent contrast profiles. Further, we report preliminary results of ocular preference in early visual cortex from monocular stimulation and T_2 weighted inner-volume single-shot 3D-GRASE acquisitions. Our preliminary analysis shows that high resolution T_2 weighted functional data allow detecting functional differences in organization of ocular dominance between V1 and V2. Primary visual cortex exhibits higher functional specificity to either eye and the specificity was spatially organized in one of two subjects. The organization in V1 was consistent across cortical depth forming ocular dominance columns.

Introduction

Blood oxygenation level dependent (BOLD, Ogawa et al., 1990) functional magnetic resonance imaging (fMRI) allows investigating human brain function non-invasively and has greatly advanced the knowledge about its organization. One of the early applications of fMRI was the functional segregation of individual visual areas, such as primary visual cortex (V1) and secondary visual cortex (V2). To date, more than twenty visual areas (Silver and Kastner, 2009; Wandell and Winawer, 2011) can be identified by the means of retinotopic mapping (DeYoe et al., 1996; Engel et al., 1997) which defines the preferred polar angle and eccentricity of a given cortical location. Recently, population receptive field (pRF) mapping has been introduced to obtain the receptive field size of neuronal populations and more accurate estimates of preferred retinotopic location (Dumoulin and Wandell, 2008).

A characterization of early visual areas can also be obtained using anatomical contrast *in vivo*. Early visual cortex, V1-V3 (Brodmann areas 17 and 18), is known to be highly myelinated and this information can be mapped using cortical myelin mapping techniques that use (combinations of) T_1 weighted, T_2 and/or T_2^* weighted imaging (Glasser and Van Essen, 2011; De Martino et al., 2014; Lutti et al., 2014). Overall myelination allows the distinction between early and higher level visual cortices as validated with post mortem probabilistic atlases (Abdollahi et al., 2014). However, the average myelination across cortical depth does not allow the distinction of areas within early visual cortex (e.g. V1 from V2). To do so myelin information needs to be extracted in a cortical depth dependent manner by T_2^* weighted magnitude or phase imaging or susceptibility weighted imaging (Duyn et al., 2007; Fukunaga et al., 2010; Budde et al., 2011; Budde et al., 2014a) as laminar profiles are clearly different both in terms of myelin and cytoarchitecture (Ramón y Cajal, 1899; Brodmann, 1909; Vogt and Vogt, 1919; Nieuwenhuys, 2013). Good agreement between cortical depth dependent anatomical contrast in V1 and V2 and retinotopically defined borders has been demonstrated (Bridge et al., 2005; Sánchez-Panchuelo et al., 2012).

At the functional level V1 can be characterized on the basis of the preference to stimulus features other than retinotopic position albeit at a smaller spatial scale. Besides preference with respect to right or left eye

(ocular dominance columns, ODCs, Hubel and Wiesel, 1965; 1977; Grinvald et al., 1991), preference to spatial and temporal frequency (Shoham et al., 1997), and to orientation (Blasdel and Salama, 1986; Bonhoeffer and Grinvald, 1991) have been observed in animals. ODCs form stripes of varying width and with bifurcations and other irregularities (LeVay et al., 1985). They tend to be oriented orthogonally to the V1/V2 border, where they end abruptly (Ts'o et al., 1990). In human V1, ODCs have been shown in post-mortem samples using cytochrome oxidase staining in monocular blind (Horton and Hedley-Whyte, 1984; Horton et al., 1990; Adams et al., 2007). The mean width of a single column is approximately 0.8-1.1 mm (Adams et al., 2007; Yacoub et al., 2007).

ODCs have been mapped in-vivo using ultra-high field (i.e. ≥ 7 Tesla) fMRI. Early experiments targeting ODCs mostly used segmented gradient-echo echo-planar imaging (EPI) techniques fMRI (Menon et al., 1997; Dechent and Frahm, 2000; Cheng et al., 2001; Goodyear and Menon, 2001). At ultra-high field, the T_2 weighted (spin-echo) BOLD effect is less dominated by large veins which drain larger portions of gray matter than T_2^* weighted (gradient-echo) BOLD. Thus, spin-echo BOLD is more specific to changes on a small spatial scale, i.e. the functional point spread function is narrower. This has been confirmed in experiments and simulations (Duong et al., 2003; Yacoub et al., 2005; Yacoub et al., 2007; Uludag et al., 2009). Spin-echo based imaging approaches have yielded more precise maps of ODCs despite the lower contrast-to-noise ratio of T_2 weighted fMRI in single conditions without differential contrasts (Yacoub et al., 2007). In either case, T_2 weighted or T_2^* weighted imaging, researchers have used thick slices with high in-plane resolution positioned tangentially to small, flat pieces of calcarine sulcus. For this reason, ODCs have not been studied systematically in extended portions of V1 or its surroundings using fMRI. 3D inner-volume gradient- and spin-echo (3D-GRASE, Feinberg and Oshio, 1991; Feinberg et al., 2008) overcomes the limitation of the anisotropic resolution and could therefore be used to map the functional organization also in folded cortical regions outside V1 (Zimmermann et al., 2011; De Martino et al., 2013). It yields a T_2 weighted contrast similar to the segmented inner-volume T_2 weighted BOLD imaging approach chosen in imaging ODCs and orientation columns in V1 (Yacoub et al., 2008). Moreover, it was demonstrated to yield better specificity than full-field-of-

view spin-echo EPI (due to the shorter EPI echo train duration of 3D-GRASE (Kemper et al., 2015b)).

Both anatomical and functional studies targeting fine-scaled structures have been greatly facilitated by the continuous improvements of spatial resolution as well as sensitivity at higher magnetic field strengths. As 7 Tesla magnets become increasingly available to neuroscientists, higher field strengths such as 9.4 T bear the potential to push the limits even further (Pohmann et al., 2015). Thus far, only few anatomical or functional studies have been performed at 9.4 T human systems (Budde et al., 2011; Ehses et al., 2013; Budde et al., 2014a; Budde et al., 2014b; Ehses et al., 2014; Bause et al., 2015; Scheffler and Ehses, 2015) due to the limited accessibility and technical difficulties. The challenges are similar as at lower field strength, e.g. 7 T, but more pressing. The RF wavelength is shorter at higher field (higher Larmor frequency) leading to increased power deposition and increased spatial excitation inhomogeneity. Static field inhomogeneity due to susceptibility differences is enhanced, transverse relaxation times (T_2 , T_2^*) are shorter, and the longitudinal relaxation time is longer. Only after overcoming these hindrances, the increased SNR of 9.4 T can be exploited. Variable flip angle 3D-GRASE can meet these challenges. T_2^* contamination is minimized by the use of inner-volume selection in conjunction with fast gradient switching of a dedicated head gradient system. T_2 blurring and SAR can be reduced by the application of a variable refocusing flip-angle approach (Liang et al., 2014; Kemper et al., 2015c). Therefore, this study sets out to extend the experience in high-resolution functional and anatomical imaging of human visual cortex. We report pRF mapping using standard gradient-echo EPI, high-resolution T_2^* weighted anatomical imaging of cortical depth dependent signals in V1 and V2, and mapping of ocular dominance volumetrically at isotropic resolution using T_2 weighted 3D-GRASE.

Methods

Two healthy female volunteers (mean age 25 ± 1) were scanned in two sessions on a 9.4 T MRI (Siemens, Erlangen, Germany) equipped with a head-only gradient coil (max. 80 mT/m at 400 mT/m/s slew rate) and an 8-channel transmit 24-channel receive surface coil (Life Services, Minneapolis, MN, USA) covering the posterior part of the subjects head. A static, non-subject-specific B_1^+ phase shim was used throughout the

measurements, after it had been validated that this approach generated sufficiently efficient and homogeneous RF fields in early visual areas in various subjects (Kemper et al., 2015a) using DREAM B_1 mapping (Nehrke and Börnert, 2012; Tse et al., 2014). Only the global scaling factor (reference voltage) was adjusted to the individual subjects after acquiring a pre-saturation approach based flip angle map. SAR supervision was maintained by imposing the maximum local SAR level observed in simulations as global RF power deposition limits.

Second order shimming was applied to homogenize the B_0 magnetic field in a manually drawn region of interest in early visual areas using a custom-made dual-echo field mapping GRE sequence and MATLAB (The MATHWORKS Inc., Natick, MA, USA) routines.

Visual stimulation

Visual stimulation was provided using a projector and a frosted screen near the subject's head, seen via a tilted mirror. Population receptive field mapping was performed using randomly moving bars (Senden et al., 2014; Goebel, 2015). Horizontal, vertical, and oblique full contrast flickering checkerboards bars (flickering rate 7.5 Hz) were presented at 12 different positions spanning 0.63° visual angle each with maximum eccentricity of 7.5° (square-shaped). During anatomical acquisitions, subjects watched animated cartoon movies.

For binocular eye stimulation, subjects wore anaglyph glasses (Lee filters, Andover, Hampshire, UK; red #026, cyan #116) throughout the entire second experimental session. The stimulus colors were adjusted such that the eyes could be stimulated individually using the pass-band optical wavelength of the filter plates. Subjects were instructed to fixate a central fixation dot, while full field concentric flickering checkerboard patterns were presented. The fixation dot was moved 2.5° upwards, such that more of the lower visual field was stimulated. A block design switching between right and left eye every 48 seconds was chosen (Yacoub et al., 2007). In the beginning and end 24 seconds of gray screen were presented at the same luminance as the non-stimulated eyes perceived. Seven runs of 7:12 min duration each were performed. Figure 4-1 shows a drawing of the binocular stimulation set-up.

Figure 4-1: Cartoon display of binocular stimulation using anaglyph glasses.

Imaging pulse sequences

Anatomical reference images were acquired with a T_1 weighted MPRAGE sequence (TE/TI/TR = 2.5/1200/3600 ms; nominal flip angle = 4° ; matrix size = $384 \times 384 \times 256$; GRAPPA acceleration factor 3, partial Fourier factor 6/8 (partition direction); total duration 8:54 min.). In addition, a proton density weighted MPRAGE without the inversion module (identical imaging parameters except TR = 1620 ms and total duration = 4:01 min.) was acquired to correct for transmission and receive coil biases (Van de Moortele et al., 2009). TI and flip angle were adapted from 7 T protocols based on literature values for T_1 and proton density in white and gray matter at 7 and 9.4 T and the equations in Deichmann et al. (2000) and Marques et al. (2010).

Population receptive fields mapping was performed using a gradient-echo EPI sequence (1.05 mm isotropic nominal resolution; TE/TR = 14.6/2000 ms; in-plane FoV 105×105 mm; 54 coronal slices; nominal flip angle 70° ; echo spacing 0.64 ms; GRAPPA 2, partial Fourier 7/8; 13:20 min. duration, 3 repetitions)

Anatomical high resolution T_2^* weighted images were acquired using a 2D GRE sequence with limited FoV (0.35 mm isotropic nominal resolution (0.043 mm^3); TE/TR = 20/1500 ms; in-plane FoV 100×100 mm; 48 slices;

nominal flip angle; 70°.; bandwidth 80 Hz/Pixel; no parallel imaging, no partial Fourier; 7:09 min. duration, 6 averages).

Ocular dominance imaging was performed using a high-resolution inner-volume 3D-GRASE sequence (TE/TR =30.85/2000 ms; in-plane FoV 22.4×105 mm; 12 slices; nominal flip angles (90-107-60-56-53-54-54-58-70-107)°; echo spacing 0.75 ms; partial Fourier 6/8 (partition direction); 8:00 min. duration, 7 repetitions). Images were acquired at a nominal isotropic resolution of 0.7 mm, and were then interpolated to 0.35 mm isotropic resolution using the complex, uncombined coil data. This was done in order not to introduce any resolution losses due to co-registration or motion-correction. Refocusing flip angles were adjusted based on extended phase graph theory simulations to yield reduced across-slice blurring of estimated 2.3 voxels (Kemper et al., 2015c).

Data analysis

Functional data analysis was performed using BrainVoyager QX 2.8.4 (Brain Innovation, Maastricht, the Netherlands) and MATLAB routines. Preprocessing of the population receptive field data included slice-time correction, 3D-motion correction, and high-pass filtering. Additionally, data was distortion-corrected using acquisitions with reversed phase encoding direction and the COPE plug-in (v0.5) in BrainVoyager (Andersson et al., 2003; Fritz et al., 2014). The three runs were averaged and analyzed to generate pRF estimates for each voxel. Model time courses for pRFs of receptive field positions between $\pm 7.5^\circ$ eccentricity in horizontal and vertical position and size (Gaussian full width at half maximum) between 0.2° and 10° were calculated, to which the experimental data was compared to find the best match (highest correlation). Functional data were co-registered to the intra-session reference anatomical data using positional and edge information. Anatomical alignment across sessions was used to align all (functional and anatomical) data to the anatomical reference image of the second (ocular dominance) session. The resulting maps for voxel-wise retinotopic eccentricity, polar angle, and pRF size were projected onto the surface representations of the hemispheres (see below). Visual areas V1 and V2 were delineated by the reversal of polar angle at the vertical meridian. Delineation was possible down to an eccentricity of approximately 2° . Below this limit, the polar angle did not yield sufficient information.

Preprocessing of the ocular dominance functional data only included 3D-motion correction and linear trend removal. Individual runs were aligned with one-another and co-registered with the T_1 weighted anatomical acquisition using positional information. Fine-tuning of the alignment was performed manually using image edge information. A general linear model was calculated using the right and left eye condition predictors after convolution with a standard 2-gamma-function hemodynamic response function. Additionally, motion parameters were used as confound predictors (three translational and three rotational per run). As a measure for eye preference, we calculated selectivity, s , as the normalized relative contribution between the BOLD responses to the right and left eye ($s = (\beta_R - \beta_L) / (\beta_R + \beta_L)$). The following three criteria were used to identify voxels with reasonable characteristics to analyze eye preference on: 1) Voxels had to have a small eccentricity in the population receptive field measurement below 5° visual angle. This limit was chosen because subjects reported ocular rivalry “creeping in” from peripheral visual field areas, such that, at times, subjects would perceive the color-shaded gray background in the non-stimulated eye more pronounced than the checkerboards in the stimulated eye. Such effects are more likely to occur at higher eccentricity (Blake et al., 1992). 2) BOLD responses to right or left eye individually had to be significant ($p < 0.001$) and both positive to rule out areas of negative BOLD responses. 3) BOLD signal changes above a threshold of 7 % were discarded as likely macrovascular contributions. The group of voxels that fulfilled the criteria 1-3 (small eccentricity, small BOLD % signal change, significant activation for right or left eye individually) was considered to have sufficient signal quality for ocular dominance to be observed if present.

Permuting the spatial distribution of the selectivity index s allowed us to assess the null distribution of the median absolute s ($\text{median}(|s|)$) in V1 and V2 and thus the significance of the difference between V1 and V2. Spatial permutations were created by swapping at random N voxels from V1 and V2 (where N was determined as 70% of the smaller number of voxels fulfilling criteria 1-3 in V1 and V2). This procedure was repeated 1000 times to obtain the empirical null distribution of selectivity values against which the selectivity of V1 and V2 were compared.

The anatomical high-resolution T_2^* weighted images were co-registered to one-another and then averaged. Prior to that, the images were cropped

such that no fold-in in phase-encoding direction was present. The averaged dataset was divided by a strongly spatially smoothed version of it (Garcia, 2010) this step retained local anatomical contrast but eliminated low-spatial-frequency image inhomogeneity stemming from the RF coil profiles. The brain was masked for this step based on intensity so that the local average was not reduced at the edges. The resulting image was co-registered with the MPRAGE anatomical reference.

The T_1 weighted anatomical reference images were divided by the proton density weighted images. Further, low-spatial frequency inhomogeneity correction was applied. Automatic image segmentation of white matter (WM) and gray matter (GM) was performed and refined manually. Finally, the hemispheres were separated and individual surface representations were created from the mid-GM sheet.

Results

Population receptive fields

Figure 4-2 summarizes the results of the population receptive field mapping. Early visual areas could be readily identified. Multiple polar angle reversal, which mark the transitions from V1 to V2 and from V2 to V3, are readily observable in the surface maps, both ventrally and dorsally. Additionally, at least hV4, LO1, and LO2 can be distinguished.

Anatomical cortical depth profiles

Figure 4-3 shows an exemplary transversal cut along with the T_1 weighted reference and an overlay of the segmentation from subject 1. The Stria of Gennari was visible in the T_2^* weighted high resolution anatomical images in both subjects. Average cortical depth profiles of the T_2^* weighted anatomical contrast were generated after grouping the data according to the functional delineation from the population receptive field mapping. The results for both participants are shown in Figure 4-4. The average V1 profile exhibits a marked reduction of signal intensity in the middle of the cortical depth, whereas the V2 profile is rather continuously increasing.

→**Figure 4-2:** Population receptive field results of both subjects and both hemispheres (columns). Surface maps from left to right: Eccentricity, polar angles, prf size, and delineation of areas V1 and V2. Only the dorsal part of V2 was labeled.

Figure 4-4: Cortical depth profiles of high resolution T_2^* weighted anatomical data sampled within V1 (green) and V2 (red) as determined from the population receptive field measurements. Both subjects and both hemispheres are shown as well as their average (average $\pm$ std. error). For comparison, myelin stains were taken from Nieuwenhuys (2013) Fig. 29.

← **Figure 4-3:** Transversal cuts through anatomical data. Left column: T_1 weighted MPRAGE divided by proton density weighted MPRAGE. Right column: T_2^* weighted GRE data. Middle row: Overlaid boundary of cortical gray matter (white lines). Bottom row: Visual areas V1 (green) and V2 (red) as determined from the population receptive field measurements overlaid. Note the clear appearance of the Stria of Gennari in the T_2^* weighted image (black arrows) and dark lines just underneath the gray matter in white matter (white arrows).

Ocular dominance

Figure 4-5 displays the selectivity as extracted from the 3D GRASE data at middle cortical depth on surface maps. A patchy organization can be observed in all hemispheres, but only little preference for the right eye is registered in subject 1. Selectivity for both eyes is similarly distributed in V1 of subject 2.

The bar plots in Figure 4-5 show the ratio of the subset of selective voxels (right vs. left significant, student's t -test $p < 0.05$, uncor.) within the group of voxels fulfilling criteria 1-3. This analysis was performed in the volume space. When the chance level of criterion 3 (significant activation for right or left eye individually) is reduced (lower p , higher t -value), the ratios increase as expected, because significant differences between left and right eye are more easily detected in more robust voxels. In all hemispheres, the ratio of selective to non-selective voxels is higher in V1 than in V2 across a wide range of chance levels. Figure 4-6 shows the results of the spatial permutation tests. The selectivity was found to be significantly different between the retionotopically defined V1, V2, and the permuted region of interest in all hemispheres.

Figure 4-7 displays volumetric representations of high resolution cortical depth sampling grids from a region of interest within V1 of subject 2. For both hemispheres, maps of selectivity and of binarized ocular dominance are shown. Selectivity maps were only masked using criteria 1-3, but no significance thresholding for the difference right versus left was used. The binary ocular dominance maps were thresholded using the same statistical values as in (Yacoub et al., 2007). A high degree of consistency across cortical depth is observed in both types of maps and in both hemispheres. The maps are split up to facilitate comparison across cortical depth.

Figure 4-5: Surface maps of selectivity index for right versus left eye ($(\beta_R - \beta_L)/(\beta_R + \beta_L)$). Right side: bar plots for the same hemispheres of significant eye preference within group of voxels fulfilling criteria 1-3 (see text for details).

Figure 4-6: Spatial permutation test results. Bar graph of median absolute selectivity index s when sampled from V1, V2, or from both ROIs at random. Bar colors indicate medians and 95 % confidence intervals as obtained from the repeated random subset drawings from the ROIs (1000 repetitions).

Discussion

The present study investigated human early visual cortex anatomically and functionally at high spatial resolution using 9.4 T MRI. Few functional studies have thus far been performed in-vivo in humans at 9.4 T (see introduction for references) due to the technical challenges associated with it. In our study, the limitation to early visual areas allowed for the use of an RF coil with transmit and receive sensitivity confined to a small region for better B_1^+ efficiency and high SNR. In fact, SAR was at such a low level that it did not impede the temporal efficiency of the imaging protocols or the achievable flip angles. In the case of the T_2 weighted acquisitions, this is also due to the variable flip angle 3D-GRASE approach.

Figure 4-7: 3D representation of selectivity maps and binary ocular dominance maps from high resolution cortical depth sampling grids in V1 of subject 2. Maps are shown between 10 and 90 % cortical depth. The orientation is similar to surface maps in Figure 4-5 (lat: lateral; med: medial; CSF cerebrospinal fluid; WM: white matter). For the binary maps, the same statistical thresholds were used as in (Yacoub et al., 2007).

A routine visual experiment (i.e. retinotopic mapping) was successfully conducted at a relatively high resolution (1.05 mm isotropic) and yielded excellent results. Further, we demonstrated the achievement of high quality anatomical images. These were obtained at 0.35 mm nominal isotropic resolution isotropic (0.043 mm³), which has rarely been reported previously in-vivo (Budde et al., 2014a; Forstmann et al., 2014). Cortical depth profiles obtained from these T_2^* weighted anatomical data reflected differences in the laminarization between V1 and V2 as defined by the

population receptive field retinotopic measurements. We also present preliminary findings of ocular dominance employing 3D-GRASE for 0.7 mm nominal isotropic resolution (0.34 mm^3). In both subjects, the specificity of response to either eye was different between V1 and V2. In one of the two subjects, ocular dominance maps in V1 were characterized by spatially clustered responses that alternated in preference for either eye when moving tangentially to the cortex. This organization was consistent across cortical depth suggestive of ocular dominance columns.

Population receptive fields

We presented population receptive field mapping at 1.05 mm isotropic nominal resolution using a gradient-echo EPI sequence. The purpose of these measurements was to delineate V1 and V2 accurately and precisely, which we succeeded in due to the high SNR of the 9.4 T. Our results are in agreement with the literature results from lower field strengths, e.g. (Goebel et al., 1998; Dumoulin and Wandell, 2008; Silver and Kastner, 2009; Winawer et al., 2010; Wandell and Winawer, 2011). The presented surface maps have a small, uncharted area at the occipital poles. This could be the consequence of two factors. First, imperfections in the EPI data due to acquisition strategy (i.e. distortions because of the left-right phase-encoding direction) may degrade the signal in this region. Studies typically choose anterior-posterior phase-encoding, which yields more benign image distortions in this anatomical location. Our particular choice is justified in order to shorten the echo train duration and exploit the RF coil geometry for better SNR. Second, because the location of the uncharted area coincides with the foveal confluence, where the cortical magnification factor is extreme, attention effects and micro-saccades in conjunction with the fact that the fixation dot was static might impede the pRF mapping (Schira et al., 2009; Wandell and Winawer, 2011).

Anatomical cortical depth profiles

Our high resolution T_2^* weighted anatomical data revealed a cortical depth-specific difference in contrast between V1 and V2, and the results are in agreement with the literature (Duyn et al., 2007; Fukunaga et al., 2010; Budde et al., 2011). A dark band in middle cortical depth can be identified by visual inspection in all hemispheres. This signature seems to exist beyond the retinotopically defined boundary between V1 and V2. This dark band likely corresponds to the Stria of Gennari. T_2^* weighted images are

sensitive to differences in iron concentration, which has been demonstrated to be closely co-localized with myelin (Fukunaga et al., 2010). Further, Lee et al. (2010) have shown that endogenous deoxy-hemoglobin has a negligible effect, which allows the conclusion that the dark band is not related to the denser capillary bed in the middle cortical vascular layer 3.

When analyzing the average cortical depth profile throughout V1 and V2 broadening or blurring of the profiles takes place because of local differences in cortical depth, curvature, segmentation, and alignment inaccuracies. The laminar depth profiles in Figure 4-4 appear fuzzier than in previous publications because the data was averaged across a large region of interest, while localized profiles have been presented in publications of other groups. Alignment inaccuracies could be (virtually) eliminated if the gray/white matter segmentation could be performed on the data itself, or at least a dataset with the same distortions (Clare and Jezzard, 2001; Renvall et al., 2014). However, the image contrast in the present data was not sufficient, likely being the cause for the dissimilar V1 profile in the left hemisphere of subject 2. An additional acquisition with T_1 weighting with otherwise same imaging modalities would be beneficial. Alternatively, even a combined T_1 - T_2^* weighted acquisition with varied TEs, TRs and/or TIs would be an option. Further, it has been demonstrated (Waehnert et al., 2014) that cortical layers follow cortical thickness more closely when assessed in an isovolumetric approach than in the approach based on the Laplace equation chosen here (Jones et al., 2000; Zimmermann et al., 2011). How much this change in “laminar” assignment would affect our average profiles will be matter of future investigations. The application of prospective motion correction might further increase the spatial resolution (Zaitsev et al., 2006; Callaghan et al., 2015) by reducing intra-run motion. Eventually, obtaining high image quality that allows classifying whether a small cortical patch belongs to V1, V2, or other cortical areas would be desirable, as has been done with histological data (Annese et al., 2004) and post-mortem diffusion weighted data (Bastiani et al., 2015). A border between V1 and V2 defined in such an approach would be more accurate than curvature-based (Hinds et al., 2008) or post-mortem atlas based approaches (Wohlschläger et al., 2005; Hinds et al., 2009; Wilms et al., 2010) and potentially more reliable than visually identified borders. It has to be noted that the V1/V2 border identified based on retinotopy and

cortical depth dependent myelination have been shown to be in good agreement, although small deviations exist (Bridge et al., 2005; Sánchez-Panchuelo et al., 2012).

Ocular dominance

The ocular dominance measurements using 3D-GRASE with variable flip angle refocusing revealed that the selectivity in V1 was significantly higher than in V2. This suggests that fMRI is able to detect functional differences between these two areas on the basis of eye preference. In one subject the spatial organization of selectivity alternated between both eyes (subject 2) resembling the patterns that have been reported in previous studies (Menon et al., 1997; Cheng et al., 2001; Goodyear and Menon, 2001; Yacoub et al., 2007), and this organization was consistent across cortical depth. For the first subject instead we found an overall bias for the left eye. This could have been caused by the different eye dominance of the subjects. Subject 1 was left eye dominant (as measured from behavioral performance). If the experimental stimuli were not balanced sufficiently but had a bias towards the left eye, the representation of the left eye may have been enhanced in subject 1 maps. Such an imbalance of stimulation might be caused by the application of anaglyph glasses (for the lack of a monocular stimulation device in the narrow 9.4 T scanner bore), or the stimulation paradigm, which, however, closely followed the paradigm employed in earlier, successful studies (Yacoub et al., 2007).

Previous fMRI studies of ocular dominance have mostly ignored responses in areas other than V1 by masking (Cheng et al., 2001) or were limited spatially to V1 (Menon et al., 1997; Goodyear and Menon, 2001; Yacoub et al., 2007). We investigated eye preference also in V2. Despite the significant difference in overall selectivity between V1 and V2, our data showed regions with high selectivity to either eye outside of V1. Hubel and Wiesel (1965) reported that a majority of the investigated neurons in cat V2 had a medium to strong preference for the contralateral eye, in fact more pronounced than in V1. However, while neurons in V1 cluster spatially according to ocular dominance in ODCs and develop more lateral connections to neurons with the same eye preference (Katz et al., 1989; Malach et al., 1993; Yoshioka et al., 1996), in V2, neither seems to be the case (Matsubara et al., 1987; Adams et al., 2007). The fact that ODCs end abruptly at the V1/V2 boundary has been observed in optical imaging (Ts'o

et al., 1990) and post-mortem cytochrome oxidase staining studies (Horton et al., 1990; Adams et al., 2007). The observed stripy pattern of cytochrome oxidase in V2 has a different spatial frequency and is associated with different stimulus properties than ocular input.

Figure 4-8: Observed mismatch between ocular dominance pattern and V1/V2 boundary as defined by the pRF mapping and accordance with high resolution T_2^* weighted anatomical data. Left: Surface map of S2 RH (lateral view). Consecutive transversal cuts (top to bottom: superior to inferior position) with superimposed V1/V2 border from pRF mapping (magenta) with (middle column) and without (right column) overlay of selectivity. The yellow arrowheads indicate the visually identified end of the Stria of Gennari representing the anatomical boundary between V1 and V2.

The expected orthogonal organization of ODCs with respect to the V1/V2 border could not be confirmed based on our data. We did, however, notice a patch of orthogonal ODCs on the side of V2 as defined by the pRF results

(see Figure 4-8). In closer inspection we found that these coincided with areas, which still revealed the V1 typical cortical depth profile in the T_2^* weighted anatomical data. This suggests a close spatial correspondence of the anatomical definition of V1 and the presence of ODCs and an erroneous definition of the V1/V2 border based on the GE-EPI based retinotopy. Although preliminary, our results show the potential of having three independent functional and anatomical markers of V1 and V2.

Methodologically, the ocular dominance measurements continue our effort of high isotropic resolution T_2 weighted BOLD fMRI. As such, we succeeded in exploiting the higher signal strength afforded by the 9.4 T scanner to increase the spatial resolution as compared to previous 7 T experiments using 3D-GRASE or GE-EPI. The fast switching dedicated head gradient coil, high SNR RF coil optimized for occipital cortex, and the variable flip angle 3D-GRASE sequence allowed us to obtain fMRI data of unique quality at such high resolution.

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Chapter 5

Summary and discussion

MRI acquisitions present an abundance of trade-offs and compromises between competing factors for optimal results, and fMRI techniques constitute no exception to this rule. The choice of the optimal functional contrast mechanism (T_2^* weighted BOLD, T_2 weighted BOLD, CBV, CBF) for a given application is fundamental and by no means trivial (but often dictated by practical considerations). After opting for a basic experimental design and imaging sequence type, the imaging parameters need to be set to satisfy the needs of a given application (e.g. high spatial resolution mapping, encoding/decoding of brain states, whole-brain resting state) for subject safety (SAR and peripheral nerve stimulation limits), spatial resolution, temporal resolution, spatial coverage, distortions, short experiment duration, functional specificity, and functional sensitivity all at the same time (see Figure 5-1). All current high resolution fMRI approaches have their pros and cons, and the fact that a remedy for a typical downside of a given approach in special cases might be at hand makes things only more confusing. The methodological contributions of this thesis extend the knowledge in the field of T_2 weighted ultra-high field fMRI, exploring possibilities and limitations of the acquisition and analysis techniques for this contrast mechanism. In this chapter, we will summarize our empirical findings and then explore two aspects of particular relevance to high resolution fMRI further: Avoidance of macrovascular signals and precise co-registration with anatomical reference images. Finally, we will give an account of personally presumed future developments and open challenges.

Summary

In Chapter 2 we have shown how two T_2 weighted fMRI sequences, 3D-GRASE and 2D SE-EPI compare at 7 T in a submillimeter resolution experiment. 3D-GRASE yielded superior specificity and sensitivity over SE-EPI with large field of view. Spatial coverage and image blurring were better in SE-EPI. The superior sensitivity was reflected in more robust activations in a visual task. Besides the SNR-beneficial 3D acquisition in 3D-GRASE, the 2D multi-slice slice profiles were identified to hamper the tSNR in 2D SE-EPI. In high resolution cortical depth profiles, 2D SE-EPI revealed an increase of BOLD signal changes towards superficial layers, resembling previously observed GE-EPI profiles but with a smaller slope. The fact that in deep cortical gray matter the signal changes were similar suggested that principally, similar contrast mechanisms were at work, however, the

increase towards the surface was in line with a higher T_2^* contrast contamination in 2D SE-EPI. Moreover, we demonstrated that the difference in superficial layers was not a mere consequence of blurring by an analysis of smoothed 2D SE-EPI data and of the angle between the cortex normal and the 3D-GRASE slabs in two orthogonal orientations. We concluded that 3D-GRASE is the preferred method for the investigation of fine functional structures, however acknowledging the limited spatial coverage and strong slice blurring.

Figure 5-1: Example profiles of required characteristics of fMRI applications. Multiple properties (dimensions) are displayed in a polar diagram.

In Chapter 3, we addressed these issues of 3D-GRASE by introducing a variable flip angle refocusing approach for 3D-GRASE based on extended phase graph theory. This made a simultaneous improvement of coverage and image blurring possible. The VFA approach grants more flexibility in the use of 3D-GRASE to find balance points of the acquisition properties mentioned above which suit the application best. Specifically, coverage and image blurring could be significantly improved compared to the standard

180° refocusing approach at little cost in functional sensitivity. Moreover, SAR becomes significantly less of a limitation using the smaller refocusing angles. Despite the fact that tSNR was reduced in the VFA approach, functional sensitivity was partly maintained due to a small observed increase in functional contrast in the functional experiment at 7 T. This is mediated by a shift of signal towards the longer TE pathways in stimulated echo pathways. The agreement of simulations and experimental data was first validated in phantom measurements. In-vivo, we were able to obtain blurring similar to that observed in 2D SE-EPI in chapter 1. The VFA approach was more susceptible to B_1^+ inhomogeneity yielding reduced tSNR and functional sensitivity when the transmission was insufficient.

In Chapter 4, we explored the possibilities of human anatomical and functional MRI at 9.4 T further. With a specialized RF coil with spatially limited transmit- and receive profiles, we were able to conduct the experiments well within the SAR limits using a non-subject-specific B_1 shim with high RF efficiency and sufficient homogeneity. Good anatomical contrast was observed in T_1 weighted MPRAGE acquisitions adapted to the relaxation times at 9.4 T. Further, high resolution (0.35 mm isotropic) T_2^* weighted data yielded sufficient information to observe clear differences in cortical depth dependent profiles between visual areas V1 and V2 associated with the co-localization of iron with myelin in the Stria of Gennari. A routine population receptive field experiment yielded excellent results affirming the expected SNR advantage of ultra-high field beyond 7 T. By the means of the VFA approach, we were able to apply 3D-GRASE also at 9.4 T for a functional mapping experiment at 0.7 mm isotropic nominal resolution. These measurements showed significant differences in ocular dominance between retinotopically defined V1 and V2. Further, our preliminary results revealed a patchy organization of ocular dominance in V1 of one of the two volunteers. This organization was found to be consistent across cortical depth.

Avoiding macrovascular signals in T_2^* and T_2 weighted BOLD data

Functional specificity is the key advantage of high field T_2 weighted BOLD over T_2^* weighted BOLD fMRI, which has previously been demonstrated extensively (in methodological and application studies, see Introduction for details). However, in most imaging aspects aside of functional specificity, GE-EPI sets high standards, particularly functional sensitivity. Could it be

that the overall higher sensitivity over-compensates the lower specificity, or is the higher specificity of T_2 more beneficial? A few aspects of this question will be outlined in the following section.

To begin with, taking a purely quantitative stand-point, it must be noted that the expected signal changes from micro-vasculature are not fundamentally different between T_2 and T_2^* weighted BOLD imaging. For both, extravascular signal changes are simulated to be between 1 and 2 % at ultra-high field (Uludag et al., 2009). The intravascular component is negligible. Empirically, Yacoub et al. (2005) reported the T_2^* signal to be on average 1.3 ± 0.1 times higher than the T_2 signal in gray matter at high spatial resolution at 7 T. Stronger differences in sensitivity must be the result of lower tSNR, and in fact, lower tSNR is reported in comparative studies when different TEs and relaxation times are taken into consideration (Harmer et al., 2012; Boyacioglu et al., 2014). This reduction in tSNR in T_2 weighted data could be a consequence of poor slice profiles and saturation effects, as discussed in Chapter 2 of this thesis. The spin-echo signal suffers more strongly from imperfect slice profiles because of the combined $\sin(\pi \cdot f/2)^3$ -dependence on the RF scaling factor f of excitation and refocusing pulse, as compared to $\sin(\alpha_E \cdot f)$ in gradient-echo, where α_E is the Ernst angle. Technical imperfections could thus explain a significant part of the difference in sensitivity - irrespective of potential differences in physiological noise contributions. The discrepancy of results between Yacoub et al. (2005) and Triantafyllou et al. (2009) with regard to physiological noise in T_2 weighted data is however noted: While the former reported a constant ratio of physiological to thermal noise with increasing voxel size, the latter reported a similar increase as in T_2^* weighted data. Panchuelo et al. (2015) used retinotopic response patterns to demonstrate that the CNRs of T_2 and T_2^* weighted BOLD imaging converge when the cortical distance between neighboring responses is reduced to 1 mm. Unfortunately, the study did not investigate smaller distances, which would reveal whether T_2 weighted BOLD excels at higher resolution.

One argument for the utility of a sensitive but unspecific approach is that non-specific signals should cancel each other out in a differential fMRI approach. However, this is only true for balanced conditions, in which the unspecific signals are zero-mean (Polimeni et al., 2010). Further, unrelated signal changes impede the quality of activation estimates (e.g. predictors in a GLM are less efficient). As a remedy, it has been suggested to mask image

positions which are known to contain large vessels, particularly large pial vessels (Barth and Norris, 2007; Koopmans et al., 2010) in T_2^* weighted data, or, in a more drastic form to ignore all data except from middle cortical depth altogether (Goncalves et al., 2015). This approach exploits that large vessels appear dark and tend to have high dynamic signal changes (Olman et al., 2007), or the position of large vessels is obtained from other, co-registered scans. This approach is viable under two conditions: 1) The spatial resolution is sufficiently high to rule out partial volume effects from surface vessels in middle layers (and below). 2) It can be afforded to discard the tissue affected by the vessels, which may be near or far away. This can be the case, e.g. when the aim of the study is to find evidence for the presence of information in a given region or cortical layer using multi-variate pattern analysis (Haxby et al., 2001; Smith and Muckli, 2010; Muckli et al., 2015), or when data can be averaged across a larger cortical region of interest. However, if the intention is to *map* a given region, the approach does not present a solution. In particular, ignoring signals from superficial layers preempts the possibility to draw any conclusions about columnar (that is vertical, depth-dependent) organization or to target feedback connections which terminate in superficial layers (Muckli et al., 2015). At best, the knowledge about the presence of macrovasculature may give a good estimate of the reliability of the functional data at a given location, as has also been demonstrated at lower resolution (Winawer et al., 2010). Nonetheless, Muckli et al. (2015) were able to decode, which partly occluded visual scene subjects viewed, from superficial cortical layers using GE-EPI in a retinotopic quadrant, which did not receive any visual input. The decoding accuracy was improved after removing non-specific venous signals. T_2 weighted 3D-GRASE measurements in the same subjects yielded lower decoding accuracies. This underscores the potential of T_2^* weighted BOLD for *decoding* applications, even in superficial layers.

Recent experiments (Moerel et al., under review) show that at high resolution the fidelity of gray matter voxels is inversely correlated with the distance to the nearest (medium-sized to large) blood vessel (both tangentially or radially to the cortex) as detected by a time of flight angiography. This is also in line with the observation that physiological noise affects superficial cortical layers stronger than deeper layers (Polimeni et al., 2015) and the concomitantly reduced spatial specificity in

superficial layers (Polimeni et al., 2010). To what extent responses in middle and deep layers are affected by pial vein reactions is not clear yet. When critically assessing the successful early reports of ODCs and orientation columns using thick tangential slices (Menon et al., 1997; Cheng et al., 2001; Yacoub et al., 2007; Yacoub et al., 2008) it must be stated that the columnarity was informed from knowledge from invasive animal research and post-mortem human data. Which cortical depths (or laminae) contributed to the collapsed maps is unknown, and without the similarity to primate cortical organization, strictly speaking one could only draw the very limited conclusion that tuning e.g. for ocular preference is not opposite at different cortical depths and hence does not cancel out. Importantly, such inference from animal literature is not given for higher cognitive function, where the non-invasiveness of fMRI truly unfolds its power. Whether sampling only deep layers using GE-EPI would yield spatial maps more similar to those obtained using more specific SE-EPI is unknown, however, experimental findings showed that the specificity of GE-EPI is slightly lower than that of 3D-GRASE at deep and middle cortical depth, and biases may be introduced in GE-EPI independent of cortical depth (De Martino et al., 2013). This may be either due to long-range effects of large pial vessels, or due to the contribution of intracortical veins, which drain a territory of several square millimeters in deep layers (types V4 and V5), and even transport venous blood from the white matter underneath (type V5) across the cortex (Duvernoy et al., 1981).

A relevant controversy for this context was initiated when it was shown that the orientation of visually presented grating stimuli could be decoded from responses in early visual cortex using multivariate pattern analysis (Kamitani and Tong, 2005), although orientation columns are much smaller than the used low imaging resolution in the GE-EPI experiment. The hypothesis was that the origin of the differential signals were slight sampling biases of orientation columns, but it was countered by showing that a broad-scaled organization could explain the high decoding accuracy (Freeman et al., 2011). Similarly, at higher resolution, GE-EPI might provide enough overall sensitivity to provide *information* about the brain state, however, resulting spatial maps must be treated very carefully because of the functional point-spread. This was demonstrated by Shmuel et al. (2010) reanalyzing the GE-EPI ODC data from Yacoub et al. (2007). Test-retest stability is an important indicator for the reliability of obtained maps.

Mixed results with GE-EPI might point at insufficient functional resolution for the investigated structure (Yacoub et al., 2007). As a consequence, more recent studies investigating fine-grained structures (Zimmermann et al., 2011; Goncalves et al., 2015) have adapted a modeling approach similar to as by Chaimow et al. (2011) to examine the possibility of picking up biases rather than real topographic representations of unknown spatial scale. In this modelling approach, a putative columnar organization of various sizes and other properties is modelled, and the effects of BOLD point-spread and image sampling are considered.

Finally, the question has to be addressed carefully to what extent larger vessels go unnoticed and are included in the analysis. Draining venules in the cortex have a diameter of 20 to 150 μm (Duvernoy et al., 1981; Polimeni et al., 2010). In this regime, there are already distinct differences in the sensitivity of T_2 and T_2^* weighted BOLD due to the static broadening effect (Uludag et al., 2005), however, despite the signal reduction also surrounding the vessel in T_2^* weighted imaging, these may not be seen even at high spatial resolution fMRI. Hence, fine-grained laminar functional organization might still be clouded by the non-differential response stemming from these. Finally, the notion that cortical vascularization is at least linked to the functional architecture which it supports, has been proposed (Gardner, 2010). If future research proves this hypothesis right to a finer scale than currently known (Harrison et al., 2002), researchers may worry a little less about sensitivity to medium sized blood vessels in the cortex.

Co-registration with structural images

The study reported in Chapter 4 pushes the spatial resolution both in functional and anatomical acquisitions. In this high resolution domain, the co-registration with structural images with strong anatomical contrast, particularly WM/GM contrast has proven useful, but distortions of high spatial resolution functional data impose difficulties. The reduced distortions of short EPI trains as in zoomed 3D-GRASE have been mentioned at the appropriate places in the previous chapters. However, when larger areas require a precise alignment, the residual distortions will again impede the analysis. Sequences which are virtually free of distortions may present a solution. Promising candidates, which also provide a contrast similar to T_2 weighting have recently been presented (Auerbach et

al., 2002; Ehses et al., 2013; Goa et al., 2013; Hua et al., 2013b; Goa et al., 2014; Scheffler and Ehses, 2015). It should, however, be noted that even these sequences have distortions because of gradient nonlinearities and susceptibility induced B_0 inhomogeneity. When they are acquired with a different slice prescription than the reference images, residual distortions still hamper the alignment. Moreover, the structural reference scans are also slightly distorted (although the PSF has been improved by the application of variable flip angle echo trains and improved acquisition order (Mugler et al., 1992; Deichmann et al., 2000; Stöcker and Shah, 2006) and accelerated imaging (Van der Kouwe et al., 2014)). Nonetheless, the co-registration might not fulfill the strict requirements of high-resolution fMRI so that segmentation on the basis of the functional data itself (e.g. averaged across time for better SNR) may be the only alternative. This is possible when the functional data has sufficient anatomical contrast. If this is not the case, the closest proxy to this is an anatomical acquisition with the same distortions and same slice prescription. This approach has recently been revived for T_1 weighted inversion recovery EPI data (Clare and Jezzard, 2001; Renvall et al., 2014), and may hold great potential for high resolution fMRI.

Challenges and future directions

The number of research centers operating high field MRI scanners has increased steadily in recent years. Soon, commercial 7 T systems with clinical CE and FDA approval will be on the market. The growing user group will hopefully nourish further methodological advances in the field of high resolution fMRI and enable exciting applications in the human brain. Experimental set-ups are exploring double digit field strengths (10.5 T operational at CMRR, Minnesota), and chances are that technical developments necessitated by higher field also translate to improved imaging at lower field strength, as it was the case between 7 T and 3 T. Time and again, innovations have revolutionized the way MRI is performed – compressed sensing (Lustig et al., 2007) and MR fingerprinting (Ma et al., 2013) to name just two recent examples. If one ventures a prediction, one can only start out from the currently conceivable techniques. In the following, we will therefore try to identify areas of development in the domain of high resolution fMRI acquisition.

Image acquisition and reconstruction

The importance of the imaging PSF has been stressed in this thesis. The blurring effect of signal decay throughout an echo train in EPI, 3D-GRASE, or TSE has been well characterized in the literature, but an additional blurring effect occurs from inconsistencies of the phase along the direction in question. Characterizing and correcting such phase inconsistencies caused by subject motion or other physiological contributions would further improve the PSF of 3D-GRASE. fMRI sequences with better point spread have been mentioned in the above section. They are promising for precise measurements; however, for serious application in submillimeter resolution fMRI, sufficiently high functional sensitivity remains to be demonstrated as of now. The lower temporal efficiency than in echo-train sequences impedes their sensitivity and typically requires moderately high acceleration factors for acceptable temporal resolution (Hua et al., 2013b; Scheffler and Ehse, 2015). Application of reduced field of view imaging to T2prep-GRE or SSFP approaches might overcome these hindrances.

Such reduced field of view techniques can be realized using parallel transmission (pTX) (Katscher et al., 2003; Zhu, 2004), which will see wider application in high field fMRI, especially in T_2 weighted BOLD imaging. Zoomed imaging approaches can benefit from pTX, whether in the form of more efficient outer-volume suppression or of 2D or even 3D spatially selective pulses. Tightly linked to improved RF coil designs, pTX has great potential to improve the image acquisition because of the crucial dependence on the precision of RF pulses in spin-echo sequences (particularly echo-train sequences such as 3D-GRASE), and the currently limiting factor of power deposition (SAR). PTX pulse design can accommodate both aspects (Wu et al., 2013). This way, SNR and spatial coverage in multi-slice imaging will be improved. Further, pTX will improve simultaneous multi-slice acquisitions (Poser et al., 2014), which have undergone substantial developments themselves to set new standards in imaging speed (Setsompop et al., 2013; Ugurbil et al., 2013; Xu et al., 2013).

Concomitantly, the supervision of safe operation with regard to power deposition and tissue heating is in need of future improvement at two levels. Fundamentally, possible divergence of SAR and tissue heating currently require additional safety margins (Shrivastava et al., 2008 and

references therein). Improvements in this aspect would be highly desirable, e.g. direct, precise, and accurate temperature measurements. However, given the slow pace in this domain thus far, this may not be within reach soon. Practically, the current supervision by virtual observation points (Eichfelder and Gebhardt, 2011) slows down the system operation hindering the effective use of multiple different pTX pulses altogether, and improved computations would facilitate the application.

Comparison of different acquisition approaches

Competing characteristics of the image acquisition such as spatial coverage, functional specificity, and functional sensitivity have been mentioned in the beginning of this discussion. In the multi-dimensional space spanned by these characteristics, different applications require very different profiles (see Figure 5-1). Methodological improvements help to extent the accessible volume in this space. Ideally, one axis, e.g. spatial resolution, could be extended thanks to an innovation without compromising another one, but realistically, most if not all novel approaches have their drawbacks (at least in the moment of their introduction). Over time, a large diversity of different functional contrasts and acquisition methods has developed and to this end, no overall optimal strategy for all high resolution fMRI studies in humans has been found. 2D GE-EPI is the de facto standard, and comparisons between divergent “branches” of methods are scarce. More comparisons would be desirable to obtain a more coherent, informed picture of the pros and cons of different approaches. Research collaborations between centers to fuse the expertise in the various approaches seem to be a necessary requirement for the successful and neutral assessment of different techniques. Establishment of a reference experiment with a known “gold standard” would be desirable. Such a gold standard would have to be based on well-known examples of neuronal activity.

The assessment of different approaches should go hand in hand with an advance in theoretical modeling at multiple levels. To this end, many experimental design choices are still led by intuition rather than solid simulations. For example, when intending to map a columnar structure, to what extend are partial Fourier and/or accelerated imaging acquisitions beneficial given the difference in SNR, distortions, and image blurring? Given the profile of BOLD activations in k-space (which differs from that of

static images), is tSNR the optimal target property to be maximized or could the acquisition be tailored to capture BOLD patterns best? Can the slightly higher sensitivity to capillaries of GE-EPI afford its lower specificity compared to T_2 weighted BOLD, or should researchers invest more time in techniques with even lower sensitivity and higher specificity such as perfusion or CBV based contrasts? Given the *spatio-temporal* BOLD PSF, would joint changes in stimulus presentation and data acquisition produce better results? It is evident that the answers to such questions differ depending on the specific application, e.g. mapping versus decoding. However, answers could only be found in synergy of simulations and empirical studies such that eventually, critical balance point values of diverse imaging characteristics might be found.

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Knowledge Valorization

According to the “National Valorization Committee”, the term knowledge valorization refers to “the process of creating value from knowledge, by making knowledge suitable and/or available for social (and/or economic) use and by making knowledge suitable for translation into competitive products, services, processes and new commercial activities” (Regulations governing the attainment of doctoral degree, UM, App. 4, §23), and the doctoral candidate is requested to write “an approximately five-page addendum” on the topic, which, however, shall not be a part of the dissertation itself.

So, how can the insights of the present thesis be “valorized”? The present thesis is mostly methodological in nature, that is, for the most part it deals with the question of how T2 weighted high resolution BOLD fMRI in visual cortex can be performed better for cognitive neuroscientific applications. Since these applications lie within the field of fundamental natural sciences, the thesis can also be allocated in this domain. Fundamental sciences and the concept of “valorization” are considered diametrically opposed to one another by many, and this conflict has been pointed out in the valorization addendums appended to recent dissertations in the department for cognitive neuroscience (see e.g. R. L. Rademaker, “Internal representations of the brain” (2015); G. Lange, “Psychophysical investigations of perceptual learning and attention” (2016)). However, the results of fundamental research may yield immeasurable value to society in the future via complex and unforeseeable paths. In this light, the answer to the question posed above can impossibly be answered exhaustively. It is clear to see that the degree to which the knowledge is straight-forwardly applicable scales inversely with the “distance” of the specific application to the centers of attention of the present work. In an attempt to illustrate this view, Figure 1 displays a classification of various applications of magnetic resonance imaging. It is needless to say that this binary hierarchical classification is extremely simplified for the purpose of clarity and underestimates the variety and complexity of applications. Some levels may as well be swapped, e.g. the distinctions in species and purposes (otherwise e.g. neuroscientific research on rodents or a diffusion scan for the diagnosis of a brain tumor in a race horse could not be

accommodated). Further, the branches which do not lead to the BOLD technique are kept very general and are not detailed further.

To the first order, the considerations with regard to “valorization” may be limited to the displayed realm of applications of MRI. The core claim of this chapter will be that the concepts presented in this thesis are applicable in other side branches at *all* hierarchical levels in figure 1. In other words, any information provided in this thesis may influence decision-making with regard to the techniques for any applications in magnetic resonance imaging. As stated above, the direct applicability to different nodes of the graph then scales inversely with the “distance” (i.e. shortest path in the graph). In the following, we will provide some examples of this.

The most direct application of the findings of this thesis is in other modalities or other functional domains. 3D-GRASE has been used for arterial spin labeling fMRI, and the variable flip angle technique (Chapter 3) can improve the data quality in this application, as has also recently been shown by other authors. The thesis discusses advantages and disadvantages of T2- and T2*-weighted BOLD fMRI at length (e.g. Chapter 5), and these apply to other functional domains, e.g. any sensory domains, memory, emotions, decision-making etc. just like in the visual domain. The suitability of 2D SE-EPI or 3D-GRASE for these applications may be guided by the findings in Chapter 2.

The application of the variable flip angle technique proposed for the 3D-GRASE imaging pulse sequence in Chapter 3 is most beneficial at long spin-echo train duration compared to T2 and long T1. These conditions are not only given in brain imaging (functional and structural (anatomical), for which 3D-GRASE is also employed), but may occur in various applications, in various materials and organic, human or non-human tissue types. Examples range from human lung imaging and musculoskeletal imaging to non-hydrogen (“X-Nuclei”) imaging in soft tissue, e.g. sodium imaging in knee cartilage, or imaging in solid inorganic materials. The additional degrees of freedom enabled by the variable flip angles may be exploited in larger spatial coverage, reduced image blurring, or higher nominal spatial resolution. Further, the significantly reduced power deposition may enable new applications, especially when SAR is a delicate issue.

Figure 1: Classification of various applications of magnetic resonance imaging (strongly simplified). Top: Hierarchical binary tree, bottom: Same structure displayed to scale under the assumption of equal binary composition and a random placement of BOLD imaging among other applications.

The work presented in this thesis relies on ultra-high field imaging. By the methodological advancements in it, it makes ultra-high field imaging more accessible to the various applications mentioned above. The improved signal-to-noise ratio at higher field strength is unquestioned and may be translated to stronger contrast-to-noise ratio, shorter imaging time, and/or higher spatial resolution, all of which may be helpful in clinical routines. These factors would facilitate the diagnosis of known pathologies, but moreover enable diagnosis of previously elusive diseases. Ultimately, these factors will help, e.g. to start patient treatment earlier, and improve its monitoring throughout the process, thereby improving quality of life and life expectancy. Economically, this potential is showcased by the introduction of the first commercially available 7T scanner with CE and FDA approval, the “Terra” manufactured by Siemens Healthcare about fifteen years after the world’s first human 7 Tesla MRI scanner was installed at University of Minnesota in 1999. In this context we may also refer to the development of novel RF transmission and receive coil designs. A close link between manufacturers (e.g. Life Services, Minneapolis, MN, USA) and the scientific research institute enabled the customized design for the RF coils used in the studies reported here. Based on this experience (e.g. with regard to the spatial distribution of coil sensitivities and coupling) additional RF coils have been and will be designed for advanced imaging applications, which pushes research forward worldwide. Finally it is worth mentioning that innovations from the ultra-high field domain have previously also translated to improvements at lower field strength, and this process is likely to continue. Given that 1.5 T and 3.0 T machines are the mainstay of clinical MRI, methodological improvements at ultra-high field already enhance clinical routine to the benefit of patient care.

Currently, there are merely a handful of operational human MRI systems worldwide which exceed 7T field strength, and our anatomical and functional study at 9.4 T (Chapter 4) is still one of the first of its kind. Whether this even higher field strength will eventually also find its way into clinical routine remains to be seen. However, our study is a door opener in the sense that it demonstrated the feasibility of 9.4 T scanning in the human brain without the requirement of complicated parallel transmission pulses. This circumstance facilitates the access to 9.4 T for application in different fields and possibly without the close monitoring by MR physicists after appropriate training of non-expert users.

It was stated above that the limitation of the “valorization” considerations may be limited to the organization according to Figure 1 *to the first order*. What was meant by this is that the “valorization” is most direct in this framework. As though this would not already present a (perhaps infinitely) large amount of improved techniques and new possibilities, they themselves open up new paths for improved techniques and new possibilities in other domains – *second order* – and so on. This cascade describes the sum of marginal utility and leads eventually to an infinite “valorization” potential, as held by all scientific projects.

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I truly enjoyed the time in the department of cognitive neuroscience, which is characterized by such a positive, constructive spirit of partnership and joint effort. The list of people who contribute to this pleasant atmosphere is almost endless, but I would like to say “thank you” explicitly to the people working in the background for the smooth operation, most of all to Christl, Riny, and Eva. I enjoyed also the work with the Scannexus technicians Lotty, Esther, and the others. Also, I appreciate the companionship of all fellow scientists in Rainer’s (ERC) group, in the MR physics group, the CN R&D team, Brain Innovation, and diverse lunch- and coffee break groups. Please rest assured that our exchange – whether professional, private, or (as often the case) anything in between – is highly valued. This goes particularly for my paranymphs Helen and Thomas, and office mates Sanae, Britta, Jochen, Jessica, and Amaia. You guys make coming to Uni fun. Finally, I would like to state my deep thankfulness to my parents, brothers, and Maren. Life would not be the same without you.

Curriculum Vitae

Valentin was born on October 19, 1985, in Coesfeld, Germany. After finishing his secondary education at Cypress Bay High School, Weston, FL., USA, and Schillergymnasium Münster, Germany, in 2005 (Abitur grade 1.3), he studied Psychology and Physics at WWU University of Münster. Valentin graduated from RWTH Aachen University (Diplom-Physiker) in solid-state physics minoring in computer science and biomedical engineering. His diploma thesis under the supervision of Prof.dr. N. Jon Shah and dr. Ana-Maria Oros-Peusquens at INM-4 of Jülich Research Centre dealt with “Decomposition of Signal Decay and Recovery of T2* Information in Quantitative MRI”. In 2011, he started a PhD project under the supervision of Prof.dr. Rainer Goebel and dr. Federico De Martino of Maastricht University, and Prof.dr. Essa Yacoub of University of Minnesota. After finishing his thesis entitled “Submillimeter BOLD fMRI of human visual cortex” Valentin will continue working in the department for Cognitive Neuroscience in Maastricht under the supervision of dr. De Martino and Prof.dr. Elia Formisano.

Publication List

Peer reviewed journal articles

- Kemper, V.G.**, De Martino, F., Vu, A.T., Poser, B.A., Feinberg, D.A., Goebel, R., and Yacoub, E. (2015). Sub-Millimeter T2 Weighted fMRI at 7 T: Comparison of 3D-GRASE and 2D SE-EPI. *Frontiers in Neuroscience* 9. doi: 10.3389/fnins.2015.00163.
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- Riecke, L., Peters, J.C., Valente, G., **Kemper, V.G.**, Formisano, E., and Sorger, B. (under review). Frequency-selective attention in auditory scenes recruits frequency representations throughout human superior temporal cortex.
- Sengupta, S., **Kemper, V.G.**, Roebroek, A., Poser, B.A., Zimmermann, J., De Martino, F., Goebel, R., and Adriany, G. (in preparation). A 4 channel phased array Tx and 16 channel receive coil for high resolution visual cortical imaging at 7T.
- Kemper, V.G.**, De Martino, F., Emmerling, T., Yacoub, E., and Goebel, R. (in preparation). 9.4 T anatomical and functional investigation of human primary and secondary visual cortex.
- Emmerling, T.C., Valente, G., Zimmermann, J., **Kemper, V.G.**, Frost, M., and Goebel, R. (in preparation). Overlapping feature representations in human visual cortex: Binocular disparity and axis-of-motion tuning mapped in human area MT using ultra-high field fMRI.
- Moerel, M., De Martino, F., **Kemper, V.G.**, Schmitter, S., Vu, A.T., Ugurbil, K., Formisano, E., and Yacoub, E. (in preparation) Sensitivity and specificity considerations for fMRI encoding, decoding, and mapping of voxel preferences at ultra-high field.
- Reithler, J., Kashyap, S., Ivanov, D., **Kemper, V.G.**, de Weerd, P., and Goebel, R. (in preparation) Linking hippocampal pattern separation to subsequent recognition memory performance: a 7T fMRI study.

Conference Contributions

- Kemper, V.G.**, Oros-Peusquens, A-M., and Shah, N.J. (2011). Spatially resolved two-dimensional T1-T2 relaxometry in the human brain using inversion recovery spin-echo measurements and NNLS. *19th Annual Meeting of ISMRM*, 2757.

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- Riecke, L., Peters, J.C., Valente, G., **Kemper, V.G.**, Formisano, E., and Sorger, B. Attention on tonotopy: Task- and stimulus-driven audio-frequency representations in human supratemporal cortex.
- Plantinga, B., Roebroek, A., Bastiani, M., **Kemper, V.G.**, Kuijf, M., Uludağ, K., ter Haar Romeny, B., and Temel, Y. (2014). Ultra-high resolution ex vivo connectivity and parcellation of the human subthalamic nucleus; *XXI Congress of the European Society of Stereotactic and Functional Neurosurgery*.
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