Chapter 4

High-Field fMRI

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Abstract

Magnetic resonance imaging (MRI) allows detection of signal from constituent of biological tissues. Hydrogen (1H) is the most widely used element from which spectra and images are detected due to its abundance and high sensitivity manifested in its gyromagnetic ratio. The high contrast for soft tissue have afforded scientists invaluable information about brain structure and function. Among many parameters determining quality of MRI images, field strength is the most decisive one as it determines signal strength in fMRI images. Considering the low inherent sensitivity of fMRI, high magnetic field are the only way that activation contrast of neurofunctional studies could be increased. This is why there has been a relentless drive towards higher field strength in human imaging raising it up to 11.7 T to date. Technology of 7-T has become more widely available in scanners with fMRI capability. Development of many technologies such as multichannel RF coils, strong and fast gradients, simultaneous slice excitation, and brain-stimulation protocols have contributed to the expansion of fMRI as the method of choice for study of whole brain function. In this chapter, challenges of high-field fMRI in human studies are discussed among which signal to noise, susceptibility artifacts, multichannel RF coil designs are highlighted.

Key words High field, fMRI, Neuroimaging, Magnetic field, High resolution

1 Introduction

The high water content of biological tissues makes acquisition of anatomically accurate images of biological tissues possible [1, 2]. Imaging of structures are hinged on the contrast based on relaxation rates that are sensitive to the composition of tissues. The same mechanism is also used to visualize changes in signal as a function of physiology [3]. These facts have made fMRI a powerful tool for the study of neuroscience as it detects the changes in signal during the brain activities in response to specific stimulation designed to activate specific regions of the brain [4–10]. The mechanism based on which brain function is detected by fMRI depends on changes in the brain of magnetization caused by external stimulations of neurons. This process is successful only if responses to external cue stimulate enough neurons in the same

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region. Field strength of fMRI determines its sensitivity to the response of neuronal clusters. This makes differential response to the external stimulus a complex entity that can better visualize brain function. MR signal of brain activation is valid if it stems from a change caused by neuronal activity. Simultaneous detection of direct neuronal currents in the human brain has not yet been reported due to the sheer number of neurons involved and a lack of sensitivity to the neuron currents. However, neuronal activity produces a change in magnetic susceptibility of hemodynamics that modifies the magnetic field in the brain that can be detected as change in MRI signal [3]. Although, the mechanism that connects neuronal activity to hemodynamic response is still not well understood [11], the correlation of stimulus pattern with hemodynamic signals is well established in fMRI. This correlation has been observed for sensory, motor, and cognitive paradigms. These features have turned fMRI into a reliable tool for neuroscience and neurology research and with the improvement in MRI hardware and pulse sequences it is rapidly penetrating into psychiatry, neurosurgery, and psychology too.

Brain function can be noninvasively detected if the changes caused by its activity produce electromagnetic signals strong enough for high spatial localization and temporal resolution. Unlike invasive techniques that operate at the cellular or single neuronal level, whole brain access visualization with sensitivity for functional response is required to simultaneously detect all activated regions. The distinct advantage of fMRI is in its ability to acquire functional information from regions with vastly different anatomical geometry such as cortical regions and skull based brain tissues. Presently, only MRI can noninvasively access brain function and can be repeatedly applied on the same subject in multiple studies. The capability of fMRI to access different brain regions responding to a specific stimulation while simultaneously imaging the location of the functional regions makes it indispensible for the studies of brain normal function and dysfunction. But, we must keep in mind that fMRI signal is not a direct measure of neuronal activity. Computations for neuronal currents (nc) MRI has predicted a few part per billion (2–5 ppb) disturbance in MRI signal that is below noise floor. Such estimations demonstrate challenges involved in making of ncMRI a reality. Sensitivity of MRI to paramagnetic entities, however, brings hemodynamic and its coupling to neuronal activity to rescue [3, 11]. Diamagnetic nature of biological tissues makes blood with its rich iron content an ideal medium for the detection of physiological changes. The blood oxygen level dependent (BOLD) is an effect that measures changes in MR signal from deoxygenated hemoglobin (dHb) to oxygenated hemoglobin (O_2Hb) required by neuronal activation which modifies the magnetic field around the regions of oxygenation to the extent that changes in MR signal-to-noise ratio (SNR) can be measured in a comparative measurement. In

fMRI studies, this change in signal ($\Delta R/R$) is taken as accurately representing neuronal activity. Higher magnetic susceptibility (χ) of dHb compared to that of O_2Hb is enough at fields above 1 Tesla (T) to raise $\Delta R/R$ to about 1%/T which with modern instrumentation is detectable. Dependence of BOLD strength on the static magnetic field (**B0**) is a valuable feature of fMRI, which presently is benefiting from availability of 7.0 T whole body magnets for the study on human subjects.

The BOLD effect, however, depends on a number of physiological factors. The primary ones being cerebral blood flow (CBF), cerebral blood volume (CBV), and cerebral metabolic rate of oxygen (CMRO2). BOLD-based fMRI studies consider CBF, CBV, and CMRO2 mechanisms as being induced by changes in neuronal activities. To more effectively use fMRI in neuroscience research, the neurovascular coupling that relates neuronal activities to hemodynamics (BOLD) must be understood. As high magnetic field enhances BOLD signal it will play a vital role in determining the nature of MR signature of neuronal activities. The use of BOLD in study of diseases such as multiple sclerosis will become more widespread as evidence for involvement of gray matter in this disease becomes more available. Assessing the specifics of the cortical damage with fMRI depends on the ability to establish reliable correlation with specific physical and cognitive disability that needs high sensitivity and specificity to brain physiology. High-field fMRI could help with establishing an association of cortical activity with clinical relapses.

2 MR Signal

Strong magnets exert a torque on small magnets like protons. Such torque puts the spinning proton into a precession with a specific frequency called Larmor frequency. If an electromagnetic waves with the exact frequency as proton's Larmor frequency, usually in radio frequency (RF) range, is aimed at such proton, its energy will be absorbed to excite the proton from its ground state to an excited state [12, 13]. Magnets used in MRI scanners induce a resonance frequency in about 100 MHz range (10^8 Hz). At 3 T, for example, where proton Larmor frequency is 128 MHz, an RF wave with this exact frequency will be able to transfer its energy into the protons causing them to deflect from alignment with **B0**. Following this disturbance, proton magnetic dipole moment (μ) will return to its equilibrium position emitting an RF wave that will be picked up by the RF coil [14, 15]. The RF magnetic field (**B1**) that is induced into the coil circuit is mixed with signal from other events in the body that produce similar signals. The collective effect at a protons of μ magnetic moment at a frequency of ω is detected by the RF coil. The RF coil is trusted with the task of detecting the narrow frequency bandwidth that is created by the resonance condition.

The design of the RF coils, hence, is a rather critical matter and it is amply covered in the literature. While RF coils must operate at a narrow frequency range, they should be capable of operating in a very wide power range since kW RF power is required to excite the sample while a few milliseconds after excitation the coil should be able to detect a signal 1000's times weaker than the transmitted power. This remarkable resilience is constructed into a device that provides coverage to the entire head and accurately records the response of every cell that will get unraveled into images by computer programs of reconstruction routines.

Relaxation values govern the time course of the signal decay. So while the population of the protons (μ) aligned with **B0** is a function of **B0**, the signal will only persist within a time course comparable to spin–lattice (T_1) relaxation and spin–spin (T_2) relaxation [16]. Images can be produced where the tissue intensity represents relative T_1 values, the T_1-weighted (T_1W) contrast during which the T_2 relaxation must be kept at minimum. T_2 relaxation is a process of loss of coherence among aligned protons, while T_1 is the time during which excited dipoles return to their original orientation where they are unable to contribute to the signal. Considering a typical T_1 value of 1 s for brain tissues, a whole head image with 256×256 matrix takes about 5 min to acquire with no acceleration factors applied. The relatively long T_1 values set the acquisition time, as realignment of protons occur with that time scale. Acceleration of image acquisition is possible by simultaneous acquisition of multiple *k*-space lines for each excitation. In addition to T_1, spin–spin relaxation or T_2 decay, is also a mechanism that slows down MR image acquisition. Due to the inherent insensitivity of MRI, the population of magnetic moment required to produce detectable signal within a voxel is the difference (ΔN) between the parallel protons (N+) and anti-parallel protons (N-) which is relatively large. The sum of μ's (ΔNμ) within a voxel, i.e., magnetization vector or **M** determines the size of the signal. High magnetic field increases ΔN and through that the MR signal. Consequently, high fields can produce detectable signal from smaller voxels producing higher resolution images. As fMRI uses a fast imaging sequence, echo planar imaging (EPI), with T_2^* contrast it has high sensitivity to magnetic susceptibility. T_2^* depends on the sum of two mechanisms causing signal decay, i.e., spin–spin and local **B0** inhomogeneities that accelerate the loss of coherent precession of **M** over time [16, 17]. The contrast-to-noise ratio (CNR) of EPI-based BOLD signal used in fMRI depends on T_2^* changes caused by the difference in magnetic susceptibility of oxy- and deoxyhemoglobin. Since T_2^* is much shorter at high fields, high-field fMRI more accurately represents local magnetic field inhomogeneities caused by BOLD. As smaller voxels can be imaged with high-field fMRI, faster and stronger gradients are being designed and used to also increase temporal resolution to produce information more directly related to neuronal activity [8, 9].

3 B_0 Effects

Signal strength in MRI depends on **B0**, RF coil design, and relaxation values. **B0**, however, determines excess proton population that sets the limit of MR signal detectable by any magnet. In addition, the high magnetic susceptibility endows high field with dual advantages of high SNR and high susceptibility contrast. This fact is best at display with images acquired from 7 T scanners (Fig. 1). Among the parameters affecting image quality, **B0** is the single parameter whose effect on SNR and BOLD will expand the use of fMRI in assessment of physiological signatures of neurological disorders. It should be mentioned that dependence of MR signal on relaxations, susceptibility, CNR, and hardware creates both advantages and disadvantages at high field. Susceptibility artifacts in the regions with large cavities make the choice of premium field strength for fMRI studies a nontrivial matter. Susceptibility-based contrast can be used to image brain microstructure and to detect high brain iron as it has been suspected to play a role in many neurodegenerative diseases. However, the challenges

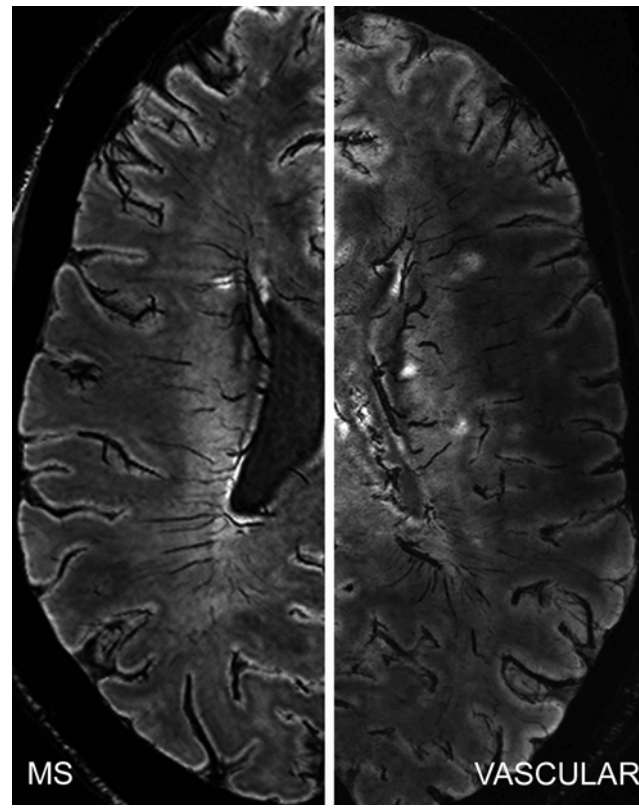

Fig. 1 A 7 T FLAIR* image of an MS patient vs. a vascular patient, in which a central vessel running through the MS lesion is clearly visible while absent through the vascular lesion. Courtesy of Prof. I.D.. Kilsdonk, VUMC, the Netherlands

involved in dealing the susceptibility artifacts of high-field fMRI has prevented its widespread use. Clever techniques such as high-order shimming, parallel transmit and receive (PTX), and short TE sequences could reduce the magnetic susceptibility artifacts at high field. These developments hold the promise to suppress the negative effects of high field and turn blights into blessings. Success in this front has far reaching implications on fMRI and its application in neurodegenerative diseases.

4 Relaxation Effects

In addition to high SNR, relaxation effects make 7.0 T an attractive field strength compared to 3.0 T and 1.5 T for fMRI studies (Fig. 2). For anatomical images, typical voxel size at 1.5 T is about 5 mm^3, high SNR at 7.0 T allows image from biological tissues with 1-mm^3 resolution in less than 10 min. The MR signal, however, is a function of the relaxation values, which will reduce the time that the magnetization vectors are available for sampling in transverse plane. High-field effects of susceptibility artifacts and BOLD effect make fMRI resolutions and its CNR a complex factor for researchers to optimize. While fMRI requires phase encoding an entire volume in one

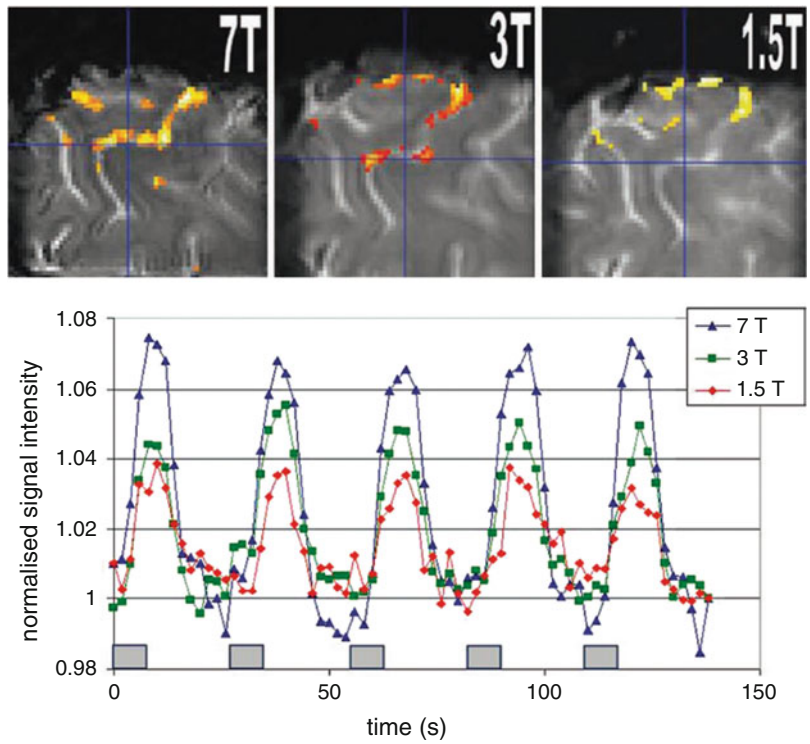

Fig. 2 fMRI study at 1.5, 3.0, and 7.0 T performed on Philips Achieva. Courtesy of University of Nottingham, UK

shot as in EPI, the artifacts of phase encoding gradients cannot be sufficiently refocused at high field. The high temporal resolution of single-shot EPI might have to be forsaken at high field because the spatial resolution and image quality suffer in single-shot EPI-at high-field fMRI. The geometric distortions caused by the phase encoding of single-shot EPI makes accurate coregistration of functional maps with anatomical images more complex than in lower fields. Furthermore, the point-spread functions (PSF) are broadened due to the long acquisition window during which higher signal decay occurs. One parameter that plays a critical role in determining many of these quantities is TE and its selection is critical in high field. But, the optimal TE is not always possible to find when large in-plane matrices are chosen to reach higher resolutions in fMRI studies. Variations of T_1 values with field strength are also important. T_1 values reported for gray matter (GM) at 7.0 T are about 2 s and for white matter values around 1.3 s [17–20]. Similar measurements at 3.0 T, have found T_1 values of about 1.5 s for GM and about 0.8 s for white matter [18–20]. T_1 values at 1.5 T reduce to about 1.2 s for GM and about 0.6 s for white matter [21]. Due to a need for fast encoding of the entire images in a time comparable to T_1 value, its absolute value does not have a large effect on fMRI images. However, T_2^* relaxation has a direct effect on the BOLD activation signal. This is especially true due to drastic change in T_2^* as a function of field strength. A multi-field measurement has reported [17] T_2^* for GM, WM, and putamen, respectively, to be 84.0, 66.2, and 55.5 ms at 1.5 T; 66.0, 53.2, and 31.5 ms at 3.0 T; and 33.2, 26.8., and 16.1 ms at 7.0 T. This shows that the difference between T_2^* of GM/WM has reduced from 18 ms at 1.5 T to 7 ms at 7.0 T. These results show a drop by a factor of about 2.5 in T_2^* of these tissues for a field increase from 1.5 to 7.0 T. Such changes have great implications on the outcomes of fast sequences at high field. For example, as T_2^* of some tissues of putamen drops to a value close to 10 ms, it will reduce the possibility of phase encoding the structure in a single-shot image for high-resolution images. This means that role of high field in producing high-resolution functional images must be further investigated.

Another challenge for high-field fMRI to exploit its advantages is the need for stronger gradients. Higher gradient amplitudes and faster switching rates can produce effects that can better be utilized at high fields. The new strong gradients of 80 mT/m that have become available on some 3 T and 7 T scanners will reduce the encoding time for a resolution of 1 mm to be 1 ms/line. This makes the total encoding time for 192 phase encoding steps to be 192 ms. The T_2^* of the human brain at 7 T is about 30 ms while T_2 of GM and WM are 93 ms and 76 ms, respectively. Thus, readouts of about 100 ms might be needed for SE EPI or partial *k*-space filling in GE EPI. Stronger gradients are going to be useful in reading a signal that lasts 30 ms. The fast decay induced by high magnetic

susceptibility during readout causes strong blurring of images that must be suppressed before the advantages of EPI at high field could be exploited. More robust gradients are becoming available that are improving sensitivity and specificity of BOLD fMRI at high field. This will enable the high-field BOLD fMRI to more accurately localize and coregister with the high-resolution anatomical images at 7 T. BOLD sensitivity does increase at higher fields, which can only be fully utilized when their high-resolution maps are produced from the entire brain including tissues in the near proximity of the skullbase and brain regions near air/tissue boundaries.

5 Imaging the Brain Function

The best way to image brain function would be to directly detect neuronal activities. Absence of such a technique has provided an opportunity for indirect observation of brain function through BOLD, which can measure changes in hemodynamics as a result of controlled neuronal activation. The coupling of neuronal activity and vascular hemodynamics makes BOLD dependents on the details of communication between neurons, glia, and blood vessels. Furthermore, BOLD is an indication of the existence of a tight level of vascular reactivity between neuronal network and vascular system.

Accurate fMRI representation of the brain function depends on the understanding of mechanism of neurovascular coupling, i.e., how neuronal activity affects hemodynamic response and its MR signal. Such relationship will enable us to account for pharmacological or disease-induced modulations of neurovascular coupling that could use BOLD signal changes, or perfusion, for the assessment of drug efficacy and pathological modification of physiology. In addition, fMRI has become an important tool in studies in psychology, psychiatry research, and basic cognitive neuroscience research [11]. This is primarily due to the fact that fMRI has proven to be able to provide a veritable readout of mental contents.

Organization of the brain allows the functional studies to identify the neuronal basis of behavior, or at least the hemodynamic manifestation of that. The measure of neuronal activity is obtained by constructing activity maps from the functional units involved in various brain networks [4, 22, 23]. The functional units, commonly called cortical columns are made up of neuronal networks involved in the implementation of a specific function. They form an organized structure that interacts with other units of the system that repeatedly occur in the cortex. This organized structure and its columnar activation contribute to elucidate the function of specific cortical areas [24]. Imaging with a resolution allowing to detect the simultaneous activation of these units, i.e., the collective response of all columns involved in a specific external stimulation, would greatly

enhance the credibility of fMRI studies. This is due to the fact that such resolution can establish the spatial localization of functional units. Resting-state fMRI, which can detect spatially dispersed but functionally connected regions that share information with each other, offers information on functional connectivity (FC) of the brain. Such FC maps are best utilized at high field, when they are capable of offering the temporal dependency of neuronal activation patterns of anatomically separate brain regions with high temporal resolution. High-field FC offers a measure of interaction between isolated clusters of columns involved in implementation of a function that will elucidate functional specialization of units and local networks at columnar level, as well as new insights in the overall organization of functional communication of brain networks. High-field fMRI is capable of whole brain imaging at both high temporal and spatial resolution, which together offer valuable information about the core aspects of the human brain, providing an overview of these novel imaging techniques and their implication to neuroscience. High-field fMRI offers the opportunity of the (1) use of spontaneous resting-state fMRI in determining functional connectivity, (2) to investigate the origin of these signals, (3) how functional connections are related to structural connections in the brain network and (4) how functional brain communication relate to cognitive performance. Analysis of functional connectivity patterns using graph theory, focusing on the overall organization of the functional brain network, is also a promising technique that takes advantage of these new functional connectivity tools in examining connectivity diseases, like multiple sclerosis, dementia, schizophrenia, and Alzheimer's disease. The potential to further empower FC fMRI with high-resolution maps based on functional units of the brain [5–8, 22] is another reason that makes high field an exciting technology for brain studies.

The primary advantage of high-field fMRI, however, remains the possibility of studying the brain physiology noninvasively with a high spatial and temporal resolution at the same time. FC fMRI reveals brain networks in resting state or based on experiments that measure brain activation due to the execution of a specific task. This is a unique capability that avails the entire brain for investigation at once. As such, it is critical that this capability is not compromised as field strength increases. Diagnoses based on functional mapping require high spatiotemporal resolution over the whole brain as field strength increases. The heterogeneity of the brain causes susceptibility-induced signal dropouts that worsen as the field strength increases. Unfortunately, this is the same mechanism that makes functional measurement of hemodynamics possible. So, we must develop reliable techniques to suppress signal dropouts while keeping susceptibility based CNR high. These conflicting needs may provide new incentives to move fMRI toward direct detection of neuronal correlates rather than the present

mechanisms of BOLD or perfusion. This is where high field can change the paradigm rather than just improving resolution. In the meantime, efforts to boost both spatial and temporal resolution of functional brain studies are focusing on susceptibility suppression.

The potential of 7 T fMRI (Fig. 2) has been shown in its ability to take advantage of the magnetic susceptibility and the BOLD effect to obtain [25] high-resolution images and functional maps. Such advantage could increase linearly or even more than linearly with **B0** as more technology in hardware and software is developed for high field. For example, the high SNR of SE BOLD could eliminate contributions to the signal from large draining veins at fields of 3.0 T and higher. This way, BOLD from microvascular networks directly on or near the site of neuronal activity could be detected [26]. Such tool is capable of dealing with more fundamental question in quantification of the signal. An fMRI signal with resolution high enough to consistently quantify blood flow and energy consumption provides a valuable insight into the relationship between neuroenergetics and neuronal activity. Such relationship has not received attention in fMRI studies. Most of fMRI studies, instead, have concentrated on experimentally proving cognitive neuroscience theories. High field can provide more powerful tools and quantifiable measures for such endeavors.

Besides BOLD, arterial spin labeling (ASL) sequences have also provided reliable measurements of CBF. This feature makes perfusion-based fMRI a complement to BOLD. A version of ASL called continuous, or CASL, has shown particular potential to take advantages of high-field strengths to obtain high SNR and CNR. ASL is implemented by tagging (normally with inversion RF pulse) the blood flowing to the brain in the neck. After a delay time, the slice select RF pulse is followed by an acquisition sequence. The blood with its water magnetically labeled flows into the brain and has its transverse magnetization decaying at the rate of T_1. So, T_1 duration is important in detection of tissue perfusion. The signal in perfusion imaging is a function of regional blood flow and the longitudinal relaxation time T_1. The T_1-dependent part of perfusion signal makes perfusion SNR a function of magnetic field. At high field, perfusion will benefit from increase in T_1 as it provides more transverse magnetization in the image slice. At high field, perfusion can provide quantitative measures of absolute CBF, a more direct representation of neuronal activity than the BOLD signal.

5.1 Fast Imaging

Image acquisition in MRI is slower than in other techniques such as computed tomography and positron emission tomography. This is mostly due to the relaxation phenomenon. Fast imaging techniques are not widely popular for structural imaging due to the poor image qualities and technical limitations. Relaxations and dephasing requires refocusing of signals in the intervals of the order of TE and realignment of spins with the main magnetic field every TR seconds,

where TR is called the repetition time. Refocusing can be achieved by gradient reversal or RF pulses. Depending on the acceleration rate and safety concerns, one or the other method can be used. For detection of physiological signals, however, the image acquisition rate should match the rate of physiological event. For brain functional imaging, this rate is of the order of a second. So, there is a need for imaging the entire brain within that timescale. For resolutions of the order of $5 \times 5 \times 5$ mm, the whole brain coverage requires 30–40 slices. For an image with 64 phase-encoding steps there is only 300 ms for refocusing and readout. These facts leave very few sequences for imaging at such rate. EPI is one such sequence. Its sequence details and the implications of its execution at high fields need close scrutiny in order to fully exploit its potentials in high-field functional imaging studies.

5.1.1 Echo-Planar Imaging

Fast imaging techniques achieve their speed by multiple refocusing of the spin ensemble during one TR. EPI as a GE-based technique is the fastest sequence and has a very low RF power content [27]. This aspect of EPI makes it suitable for high-field applications as RF absorption increases at high fields increasing the RF requirements. On the other hand, other aspects of EPI such as geometric distortion, blurring artifacts, and T_2^* signal loss are aggravated at higher fields [28, 29]. For instance, the geometric distortion that is caused by off-resonance effects will be further aggravated by long readout train of EPI. A phase offset that increases with TE will be created that will establish a linear phase gradient over *k*-space in the phase-encoding direction [30]. The image signal from these spins will get shifted as image is reconstructed. At high fields, this effect is proportionally stronger resulting in larger frequency shifts. However, the effect of long readouts can be drastically reduced by using parallel imaging. This will reduce geometrical distortions, but the T_2^* signal decay and blurring on the images will still remain. Other techniques have been introduced to deal with T_2^* relaxation causing distortion in images due to the decay in the signal along the *k*-space trajectory. Minimization of magnetic field inhomogeneities and susceptibility-induced effects requires the choice of TE close to T_2^*. As **B0** increases, T_2^* decreases and hardware and safety considerations often makes the minimum TE of single-shot EPI longer compared to T_2^*, which causes signal loss due to the phase dispersion caused by such choices of TE. Higher bandwidth could alleviate this problem but possibility of peripheral nerve stimulation will limit the use of much stronger gradients to achieve this. Other techniques have been proposed that will effectively restore T_2^* relaxation-induced signal loss and blurring. GE slice excitation profile imaging (GESEPI) is one such method that, combined with multichannel parallel receiver technology, such as sensitivity encoding (SENSE), will significantly enhance high-field EPI image qualities [31, 32].

Other EPI artifacts such as Nyquist ghost are independent of field strength and are inherent to the sequence *k*-space trajectory with various solutions applicable to their minimization at all field strengths [33]. Nyquist artifact is due to the time-reversal asymmetry of even and odd echoes and its ghosts overlap with the image causing a reduction in EPI SNR.

Next to its speed, the most important characteristic of EPI is the high magnetic susceptibility weighting it casts on images (Figs. 2 and 3). In fact, fMRI as the most important application of EPI takes advantage of EPI sensitivity to susceptibility change due to blood oxygenation. Unlike fMRI applications in which susceptibility enhances BOLD contrast, susceptibility weighting of EPI is not considered an advantage in applications such as diffusion-weighted imaging. As such, understanding of susceptibility is essential in enhancing its role where it helps fMRI and suppressing its undesirable aspects where it hurts data quality. A brief account of magnetic susceptibility of biological tissues is presented here to help appreciate the role of susceptibility in EPI-based BOLD signal changes.

5.2 Magnetic Susceptibility

Magnetic susceptibility, χ, is at the core of BOLD-based fMRI studies. When matter is exposed to strong magnetic field it will be magnetized [34]. In formation of χ, magnetic field ($\mathbf{H}$), magnetic induction ($\mathbf{B}$), and magnetization ($\mathbf{M}$) play roles. $\mathbf{H}$ is the entity that exists in vacuum and its penetration through space, i.e., free space of permeability $\mu_0 = 4\pi \times 10^{-7}$ H/m, is given by $\mathbf{B} = \mu_0 \mathbf{H}$. The magnetization, $\mathbf{M}$, represents the total magnetic moments per unit volume $\mathbf{M} = \sum \mu / v$. $\mathbf{M}$ is caused by $\mathbf{H}$ according to $\mathbf{M} = \chi \mathbf{H}$. $\mathbf{B}$ and $\mathbf{H}$ in SI unit system have units of Tesla and Ampere/meter, respectively. Inside a body placed in a magnetic field a magnetization $\mathbf{M}$ is generated that will produce a magnetic field of $\mathbf{B} = \mu_0(\mathbf{M} + \mathbf{H})$. Replacing $\mathbf{M}$ in this expression will yield $\mathbf{B} = \mu \mathbf{H}$ where $\mu = \mu_0(1 + \chi)$ will be the magnetic permeability of matter. As such, susceptibility of an object is a measure of enhancement of the magnetic field within its volume. This is important as it will determine how uniform a magnetic field ($\mathbf{B0}$) can be established inside the body in MRI. In μ, the characteristics of the free space and how its magnetic properties are modulated by matter through χ are hidden. $\mathbf{B}_0$ in turn, changes locally by χ causing the so-called susceptibility artifacts in MRI particularly in the areas of air/tissue interface [34, 35]. This effect causes a change in magnetic field as it is sensed inside a tissue and for heterogeneous tissues a contrast is generated between tissues, which are **B0** dependent. Difference in susceptibility, $\Delta\chi$, between adjacent tissues are small at low fields. If susceptibility-based inhomogeneity is smaller than inherent **B0** inhomogeneity it could be used for generating contrast for better visualization of tissues such as GM. High $\Delta\chi$ as exists at the air/tissue interfaces causes large variation in **B0** that is responsible for signal dropouts interfering with studies focused on these regions [29]. fMRI studies of regions near the ear canal, nasal cavity, and inferior frontal lobe suffer from this phenomenon.

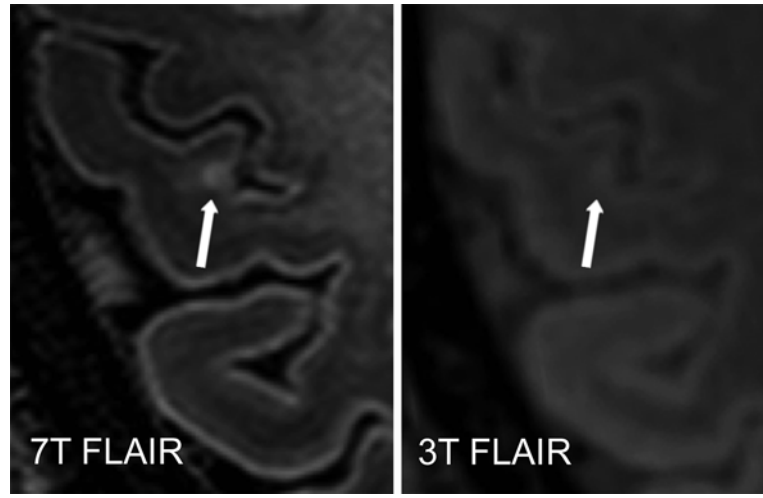

Fig. 3 An axial image showing cortical GM MS lesion acquired by 7 T FLAIR vs. 3 T FLAIR. (Courtesy of I.D. Klisdonk, VUMC, the Netherlands)

The most distinct role of susceptibility effect in MRI is in fMRI. It is based on the fact that **M** within a voxel is linearly proportional to $\mathbf{B}_0$ determining the role of high field in susceptibility-based enhancements of CNR. Specifically, T_2^* values decrease allowing paramagnetic molecules such as dHb to generate more dephasing in collective proton precession at high magnetic fields. Figures 2 and 3 show how high activation induces high functional CNR on the images taken at 7.0 T compared to lower fields. The short T_2^* values due to paramagnetic properties of dHb causes the veins and structures with high-density vasculatures to have their dimensions exaggerated as shown in Fig. 1. This mechanism affects $\mathbf{B}_0$ through χ making a larger variation in susceptibility, $\Delta\chi$, in brain tissues around activated neurons at high field subsequent to a perturbation. In brain activation studies, the stimulus causes change in volume and flow of oxygenated blood in the near proximity of activated brain regions. For the same activation, high field will use higher $\Delta\chi$ for better visualization of vasculature network which is coupled into the neuronal system in the brain.

Furthermore, high-field SNR allows the use of in vivo vascular imaging in establishing a relationship between brain tissue vascular density and functional imaging results. Independent information from vascular density could be attained from MR angiography to help better analysis of the fMRI data. In addition, such vascular density information could be used for the study of various topics from brain development and brain tumor staging to multiple sclerosis (MS). High-field fMRI in MS could better assess the effect of any changes in cortical activation during a particular task such as attention, memory, motor, etc. As high field enables better spatialized maps of the response to stimuli, fMRI could help assess the extent of neuropsychological problems. As fMRI becomes faster,

more detailed brain activation in MS patients could be used to assess their normal motor function as is done clinically today. As the strength of response signal varies depending on the activated region of the brain and the accessibility to the detector, i.e., RF coil, high field could allow a wide range of regions and paradigms to be designed to compare performance of MS patients with healthy controls. Such quantitative assessment of functional performance of the brain will provide a valuable tool in enhancing the disease management. Structural MRI, however, has had great success in visualizing lesions of demyelination [36–38]. But, lack of specificity has prevented MRI from being established as a reliable one-shop stop for diagnosis of MS. A reliable fMRI technique with resolution to reveal accurate cerebral functional response to controlled stimulations will complement the existing structural MRI tools in better understanding of MS. Such potential is entirely due to inherent sensitivity of fMRI to hemodynamic changes induced by cognitive perturbation and will provide information independent of structural changes of the disease. In this regard, a unique aspect of high field, i.e., high susceptibility and SNR, offers a tool that, although is MR in nature, its attributes are not equally available at lower fields. The **B0**-dependent susceptibility contrast, furthermore, provides potential for depiction of microvascular structures that will further enrich the tool box of high-field magnets [39].

Magnetic susceptibility of blood is governed by the same effects as discussed above. It is high enough to generate the BOLD effect just due to the change in its oxygenation state. A dHb molecule contains four paramagnetic iron ions. During oxygenation, dHb combines with four oxygen molecules which results in an O_2Hb molecule, which normally has no net paramagnetic moment. O_2Hb is in fact slightly diamagnetic. This will cause the magnetic susceptibility of blood to change by about 10^{-6} if the blood is fully oxygenated. Taking the susceptibility of O_2Hb as zero, then change in blood magnetic susceptibility with oxygenation constitutes the basis of BOLD contrast in fMRI. A detailed account of the effect of **B0** on BOLD through the susceptibility mechanism will further elucidate the impact of high field in fMRI.

5.3 Blood Oxygen Level Dependent

A change in magnetic susceptibility of $\Delta\chi = 10^{-6}$ (SI system) in blood as a result of oxygenation is possible and forms the basis of fMRI. Through $\mu = \mu_0(1+\chi)$, magnetic dipole strength of a voxel changes by $\Delta\chi$ and results in change in magnetization which constitute the basis of NMR signal. The maximum possible change in susceptibility due to blood oxygenation change is about one unit in SI. Assuming that $\Delta\chi = 10^{-6}$ is achieved during the activation, a corresponding 1.0×10^{-6} or 1 ppm change will result in magnetic field inhomogeneity. While at 1.5 T, 1 ppm inhomogeneity corresponds to about 63 Hz, at 7.0 T it could produce frequency shift of about 300 Hz. Such **B0** inhomogeneity will induce dephasing

of spin coherence which will reduce the signal causing dark regions on T_2^*-weighted EPI images. Even spin-echo sequence will bear reminiscences of such susceptibility-induced signal loss near the veins. While for stationary tissues RF does refocus the resulted dephasing of spins, for moving water molecules in veins protons rephrasing is not complete, making BOLD effective as a T_2 as well as T_2^* effect.

fMRI signal is believed to largely originate from BOLD effect around small vessels, i.e., arterioles, capillaries, and venules [25]. The extravascular areas surrounding the small vessels represent loci of neuronal activity. But, there are contributions from large vessels to the BOLD signal as well. Such contribution must be quantified to ensure an accurate account of the role of small vessels vs. large vessels in fMRI. High magnetic fields provide a powerful tool in this regard. A known magnetic field at any position puts spins in a well-defined precession whose frequency provides knowledge of its location to produce a map of proton density. Spatial homogeneity and temporal stability of the field are important requirements for creating images faithful to the structures being studied. **B0** field homogeneity of high-field magnets is around 0.5 ppm that using high-order shimming could improve it to about 0.1 ppm over the head. Beyond this, as it was discussed, dHb produces high magnetic susceptibilities leading into comparable local inhomogeneities in the static field within the brain. At high field, regions in the brain, such as temporal lobes and basal ganglia, demonstrate high magnetic susceptibility providing a high contrast from the surrounding tissues [40]. Different scenarios for change in T_2^* are possible depending on the occupation of the voxel by capillaries, large vessels, and extravascular and intravascular BOLD [8]. In general, it can be stated that T_2^* signal differential between activation and rest period from these regions increases as a function of magnetic field. For example, if typical acquisition parameters for fMRI studies are receiver bandwidth of 2 kHz/pixel; TR 4000 ms; TE 40 ms; FOV 190×190 mm^2; 30–40 slices; slice thickness, 5 mm; then implications of these parameters at 7.0 T can be contrasted to 1.5 T through a simple frequency shift. A typical BOLD effect of 0.5 ppm or 150 Hz frequency shift at 7.0 T could result in as high as 7% change in signal. Considering that BOLD has typically produced SNR, $\Delta R/R$, of the order of 1% at 1.5 T, this fact indicates that a linear increase in $\Delta R/R$ with **B0** is possible.

BOLD contrast acts as a change in T_2^* rate, ΔR_2^*. What are the factors affecting ΔR_2^*? First, ΔR_2^* is directly influenced by the change in concentration of dHb. In fact, the volume susceptibility is directly proportional to volume of dHb and as such on ΔR_2^* [34]. Assuming that dHb is proportional to blood volume, the fraction of the blood volume *fdHb* occupied by dHb will have direct effect on the signal. Models have been proposed that assign

dependence of magnetic susceptibility difference between blood O_2Hb and dHb, $\Delta\chi$, raised to a power between 1 and 2. For a venous oxygen saturation increasing from 60 to 95%, Davis et al. found a power of 1.5 fitting the simulated ΔR_2^* vs. $\Delta\chi$ curve best [41]. Such studies measure the oxygen consumption increase vs. blood flow increase as a result of functional stimulation of the brain, visual cortex in this case [41]. So, while there could be considerable differences between the increase in blood flow and oxygen consumption, there is a unanimous consent on the role of oxidative metabolism as a significant component of the metabolic response of the brain to externally induced neuronal activation.

A key role for oxidative metabolism during neuronal activation makes the role of high field more momentous in both settling such issues and enhancing the fMRI SNR. One needs to determine with certainty where the changes of the blood activation come from. They could come from the brain tissue or from the draining veins near the activated region. Many fMRI studies do not make any distinctions between these two contributions. This is partially due to the challenges involved in addressing the issue. As it was mentioned earlier, spin echo and diffusion weighting are used to differentiate contributions from different-sized vessels. Considering the small BOLD effect at low field, about 1% change in signal, an increase in fMRI signal is essential to enable suppression of BOLD signal through SE or diffusion in order to accurately investigate the source of activation. This is owing to the fact that SE EPI has more T_2 than T_2^* weighting reducing sensitivity to local susceptibility-based changes. The GE readout is responsible for the T_2^* contrast. The extent of T_2^* overlay on T_2 contrast of SE EPI is field dependent and drastic difference between T_2 and T_2^* at high field makes EPI readout in BOLD fMRI a good tool to investigate the exact location of the activated region.

Furthermore, changes in oxygenation induced by neuronal activation are complex. In the early stage of response, within the first 2–3 s, an increase in dHb is observed, which is called the "initial dip" [42]. At the end of this stage a decrease in dHb and an increase in O_2Hb are observed. High field can refine this hemodynamic behavior. The initial dip has not been so conspicuous at 1.5 T and as such not well documented. The strength of the initial dip has been reported to be more than five times stronger at 7.0 T compared to 1.5 T. Furthermore, the nature of the initial dip provides insight into the mechanism of oxygen utilization vs. cerebral blood flow. In this regard, the initial dip could be used as another tool at high field to study the correlation between hemodynamics and neuronal activities.

5.4 Physiological Noise

In the absence of physiological noise, fMRI at high field could produce functional maps of the brain with even higher resolution [43]. Scanners that already acquire submillimeter images at 7.0 T

will approach microscopic resolution in the absence of the limiting noise. Unlike thermal noise, which is temperature dependent, flat in frequency, not encoded by gradients, and hence constant at room temperature, physiological noise is a function of biological activities with relatively strong MR implications. As acquisition time of individual slices is around 10 ms, physiological noise during that time is not as debilitating as it is in the time series. Intensity of this time series noise in fMRI has shown variations which correlate with the respiratory and cardiac cycles, indicating physiological modulation of BOLD by lung and cardiac function. In fact, these signals have variations independent of stimulation paradigm and thermal noise. Physiological noises and their correlation with various physiological functions are independent of field strength. Nevertheless, there are some indications that physiological noise might have some components in brain activation as well [43, 44]. Nevertheless, physiological noises have BOLD-like signal with low-frequency and TE-dependent variations [45]. It has also been shown that physiological noise could be dependent on the signal strength and its brain regional dependence. In this regard, it has been shown to have greater magnitude in cortical GM than in white matter [43]. The possibility of physiological noise dependence on the signal strength could not be related to magnetic field strength. However, conversion of brain metabolism into MR signal might produce a "resting-state" signal that will not correlate with external stimulations and consequently degrades the fMRI SNR. It has been proposed that relative strength of physiological noise could also be due to the choice of imaging resolution. This could be caused by a large voxel size which results in an increase in physiological noise which in turn degrades the activation signal [46]. These optimum voxels become smaller as field strength increases. However, if there is any vascular cause of physiological noise the inverse relation between the field strength and optimum voxel size will be limited.

6 High-Resolution fMRI

High spatial resolution (submillimeter voxels) is an expected outcome of imaging at high magnetic fields. The information content of fMRI data can best be extracted by using an accurate account of the effect of neural activity on fMRI signals. In order to make fMRI images directly depicting cortical information, it is crucial to image at the scale of functional units of cortical structure, i.e., cortical columns [47]. Details of structures of cortical columns are the most prominent features of the architecture of the cortex. The cortex is organized in layers parallel to its outer surface (horizontal layers). Layers are specialized in the cell types they contain. Both the cell types and their connections with other neurons are unique

in each layer. Nevertheless, there are distinct units connecting neurons in the vertical direction (perpendicular to the outer surface). From the outer surface of the cortex inward, these neuronal units are piled up deep into the cortex and participate in producing response to the same external stimulations. The fact that these vertical structures penetrate though the entire cortical thickness gives them the attribute of cortical columns. The cortex is made up of about 20 billion neurons and contains progenitor cells and glial cells and their structure is organized in units of minicolumn each constituted of about 100 neurons. These minicolumns are tied to each other to form cortical columns [47]. fMRI at high field is capable of visualizing these columnar units.

To date, high-field fMRI of columnar organization has been concentrated mostly on the visual systems. Since neurons involved in the specific functions are incorporated in the same columns with average dimension of 0.5 mm along cortex surface, fMRI resolutions comparable to this dimension are essential for their observation. At lower fields, fMRI has shown to be able to detect site of the BOLD signal to within 5 mm at 1.5 T down to <1 mm at 7.0 T. But the point spread functions make the relationship between susceptibility-based BOLD and loci of neuronal activity a function of correlation between hemodynamics and neuronal response which is not known with certainty [48]. It has been reported that submillimeter in-plane resolution and the negative bold response (NBR) or "initial dip" can be used to locate the site of neural activation in the visual cortex (V2) of anesthetized cats at 7.0 T [49, 50]. Such findings at the columnar level will bestow fMRI a new capability in functional mapping of the brain. Also, it is clear that low-field fMRI cannot achieve similar results due to lower susceptibility and poor SNR and CNR in reduced voxel volumes. The spatial resolutions required for positive identification of sites of neuronal activities require resolutions in hundreds of microns range which are only possible at high magnetic field, i.e., >4.0 T. The neurophysiology of neuronal columns has to be reflected in BOLD response in a way to increase specificity and spatial resolution of fMRI. This places the spotlight on high magnetic fields. One major requirement of an imaging technique that is to elucidate the neurophysiology of the central nervous system using the BOLD dynamics is to reach high spatial and temporal resolution at the same time. High-field fMRI has shown to have such potential.

6.1 RF and Gradient Coil Technology

Gradients and RF coils are the two components of MRI scanners at the forefronts of signal generation and detection. As such, their less than ideal performance is the source of great many nuisances collectively referred to as artifacts [51]. To eliminate the high-field distortions of fMRI images, a variety of solutions are available [52]. Postprocessing techniques are proposed to correct for some of the distortions with known origins. Strong gradients also help reduce

distortions as they increase the receiver bandwidth which in comparison, susceptibility induced changes will reduce. High-field works have also shown that multishot EPI has been able to reduce distortions causing an increase in acquisition time. For those measurements in which temporal resolution and spatial resolution do not have to be at maximum multiecho EPI is a viable approach. However, due to the low frequency nature of physiological noise, longer acquisition will increase the signal variations of physiological functions.

RF coil technology appropriate for high field has many design aspects in common with coils used in lower fields [15]. However, due to the nature of RF distribution at higher field, RF engineering needs many advances for adaptation to high field [53–55]. The popular bird-cage designs will be unable to take full advantage of high field. In particular, lumped element technology in which capacitors and inductors are used is a design based on circuit analysis using quasistatic field approximations [15]. But this analysis is only valid at low fields since the RF wavelength required for spin excitation decreases as the field strength increases. Specifically, RF wavelength in air at 1.5, 3.0, and 7.0 T are about 5, 2.5, and 1 m long. Taking into account the dielectric constant of biological tissues which are around 80, the wavelength inside the body reduces by a factor of inverse of square root of dielectric constant to around 50, 25, and 10 cm, respectively. Comparing the typical dimension of an RF coil, say 20 cm diameter, with these numbers makes it clear that quasistatic approximations are only valid for fields below 1.5 T where the RF coil dimension is much smaller than the wavelength of the RF field. At 7.0 T, the resonance frequency of 300 MHz makes the in-tissue wavelength to be about 10 cm. Since typical dimensions of the human head are comparable to this wavelength, the wave nature of the RF pulse becomes dominant within the head. Consequently, full wave Maxwell equation solutions are required to estimate the magnetic field (**B1**) and electric field (E_1) of the RF as it penetrates into the body during the spin excitations [54]. Such solutions are only possible through the use of sophisticated numerical computations, such as finite difference time domain (FDTD). This approach treats the RF coil interaction with the human body as a full wave electromagnetic modeling that not only provides an accurate map of distribution of **B1** field over the subject but also offers a precise measure of specific absorption rate (SAR), which is an important indication of RF heating.

Inhomogeneous images acquired at high field (Fig. 1) demonstrate the effectiveness of the techniques developed for alleviation of inherent inhomogeneities of high-field images. These images point to a need for change in paradigm in the use of RF in high-field MRI. Use of computational tools for coil design is one pillar of the new paradigm. In addition, potential for excessive heat deposition predicted early in the history of MRI due to RF power constitutes a major safety issue that high field will have for a long time. Another issue that is

highlighted at high field is dielectric effects that have revealed their presence in high-field images due to focusing of RF power at the central regions of the imaged body [56]. In studies at high field which are mostly done on the human heads, this effect shows strong inhomogeneous spread of RF reducing the power required in the peripheral regions for spin excitation. Dielectric effects or dielectric resonance problems at high field is an issue of concern for coil designers and must be taken into account in the use of high-field scanners and analysis of the data acquired by these systems.

Another pillar of the new paradigm is parallel imaging. Recent techniques for acceleration of image acquisition based on parallel imaging, SMASH-like methods and SENSE-like methods [57, 58], have shown promise in alleviating RF inhomogeneities at high field. Both methods use surface like coil element which have an RF profile stronger in the proximal regions than in the deep regions of the body. While the immediate use of multichannel coil technology (parallel imaging) is in the receiver mode to accelerate signal reception, parallel transmit will also play an important role by restoring RF distribution over the whole head [59]. Possibility of the use of multichannel receive and transmit technology will allow high-field fMRI to further accelerate and enhance image qualities with potential to achieve microscopic resolution BOLD and perfusion-based images with high temporal and spatial resolution.

Need for more powerful gradients is another necessity of high field that has been highlighted recently as the receiver bandwidth increases in high-field scanners. Although modern scanners are equipped with more robust gradients, the increase in gradient strength and slew rate continues. During the 1980s, clinical scanners were equipped with gradients of 20 mT/m strength and 50 T/m/s slew rate. Today, 40-mT/m gradients with 150 T/m/s slew rate are available in most clinical scanners. Such hardware has helped many fMRI studies at 3.0 T and has helped research in the development and use of more powerful gradients.

Gradients also are the source of many image artifacts. At high field, artifacts due to EPI are aggravated and research has achieved many successes in minimizing image artifacts. Advances have been also achieved in gradient coil design and gradient amplifiers. Technologies such as active shielding (AS) of gradient have been realized. Considerable reduction in eddy current and its artifacts are reported by the use of AS gradients. Improved technology in pre-emphasis also has contributed in making modern gradients capable of higher performance even compared to the recent generations. Manufacturers of specialty high-field gradients offer products with strengths of 50–100 mT/m with capability of 150–300 μs switch time. Such gradients can clock slew rate up to 200–500 T/m/s. High-field fMRI is the primary beneficiary of this technology, as strong gradients capable of faster switching rates can be used to recover signal losses due to inhomogeneities through

suppression of T_2^* artifacts. There are, however, disadvantages such as dB/dt which emerge as switching time reduces in gradients. Faster switching increases dB/dt, which induces stronger electric fields in conducting tissues of the body causing nerve stimulation in the subject. Both designers and users of MRI scanners are made aware of the potential hazards of high gradient-induced electric fields and their use is governed by software and hardware safety supervisors to prevent incidents, such as ventricular fibrillation. Fortunately, fMRI uses sequences such as EPI which is very similar to the conventional gradient recalled echo sequence and it acquires the entire image in a single shot. The artifacts due to susceptibility and fast switching have been addressed in solutions, such as interleaved EPI and discontinuity in k-space, which have been dealt with by flip angle adjustments. In all, solutions in cleaning up EPI and other fast imaging techniques are making strong gradients more useful for application in high-field fMRI studies.

Another approach for using strong gradients without their undesirable side effects is through asymmetric designs, where the gradient field is produced only over the intended body part. For fMRI of the brain, this is particularly useful as it allows the establishment of stronger and faster gradients while at the same time keeping the heart isolated from induced electric fields. As the field strength increases, head-only scanners are gaining more attention. While high-field advantage of SNR is independent of higher gradient strength or slew rate, the additional in-plane resolution and slice thickness that can be achieved by using powerful gradients will help achieve isotropic voxels and ultimately microscopic map of brain function.

7 Conclusion

Functional imaging has achieved much success due to the MRI inherent soft-tissue contrast and its capability of detecting paramagnetic-based brain activation signals. The proportionality of SNR with field strength is an opportunity that has the potential of achieving microscopic brain mapping. High-field fMRI uses the SNR currency to enhance sensitivity and specificity in probing neurophysiology. Many high-field advantages can be utilized through realizable improved ancillary technologies such as RF coils, new excitation/detection schemes, artifact reduction, gradient technology, and parallel imaging. Low-field fMRI has already produced data from brain function that allows much insight into cognitive neuroscience. High field, in turn, has shown potential of further unraveling brain mysteries by detecting activation caused by controlled external stimulations with resolution that is approaching dimensions of functioning units of the brain. Such is the true potential of high-field fMRI.

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