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Physiological measurements using ultra-high field fMRI: a review

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Abstract

Functional MRI (fMRI) has grown to be the neuroimaging technique of choice for investigating brain function. This topical review provides an outline of fMRI methods and applications, with a particular emphasis on the recent advances provided by ultra-high field (UHF) scanners to allow functional mapping with greater sensitivity and improved spatial specificity. A short outline of the origin of the blood oxygenation level dependent (BOLD) contrast is provided, followed by a review of BOLD fMRI methods based on gradient-echo (GE) and spin-echo (SE) contrast. Phase based fMRI measures, as well as perfusion contrast obtained with the technique of arterial spin labelling (ASL), are also discussed. An overview of 7T based functional neuroimaging is provided, outlining the potential advances to be made and technical challenges to be addressed.

Keywords: ultra-high field, fMRI, ASL, brain, haemodynamics, resting state, layer

(Some figures may appear in colour only in the online journal)
1. Introduction

The technique of functional magnetic resonance imaging (fMRI) has grown to be the neuroimaging technique of choice for investigating brain function. fMRI was developed in the early 1990s following key developments: the invention of echo planar imaging (EPI) (Mansfield 1977) which allowed MR images to be collected on a physiological time scale, and the observation that an increase in oxygenation in capillaries and veins upon brain activation results in a detectable enhancement in the MRI signal, an effect termed as the blood oxygenation level dependent (BOLD) contrast (Ogawa et al 1990). Immediately after this discovery, real-time vascular changes were monitored in a cat’s brain by modifying the inhaled oxygen concentration (Turner et al 1991). Two independent studies (Ogawa et al 1992; Kwong et al 1992) followed showing that the BOLD effect can be used to image human brain function. This development of functional MRI using BOLD contrast constituted an enormous advance in the field of imaging brain function. fMRI offers excellent spatial resolution, relatively high temporal resolution, and whole brain coverage, making it possible to identify the entire network of brain areas engaged in a particular task. Most importantly, fMRI is entirely non-invasive, allowing repeated, multiple scans within the same individual. This, together with the ever-increasing availability of MR scanners, led the neuroscience community to quickly adopt fMRI for a wide range of applications, from identifying active brain areas while performing sensorimotor tasks, to studies of the neural basis of cognition and behavior, and resting state networks.

fMRI does not measure neuronal activity directly, rather local changes in vascular properties in response to neural activity which collectively give rise to the BOLD haemodynamic response. Figure 1 shows the MR methods to detect the haemodynamic and metabolic changes underlying the BOLD response: cerebral blood volume (CBV) alterations using dynamic susceptibility contrast agent (Smirnakis et al 2007), a method used in early fMRI studies (Villringer et al 1988; Belliveau et al 1991) and which has recently been applied to study activity across cortical layers (Goense et al 2012); cerebral blood flow (CBF) changes measured with arterial spin labelling (ASL) (Williams et al 1992; Detre et al 1994; Kim 1995), a measure recently used to address the origin of the BOLD response (Goense et al 2012; Mullinger et al 2013; Mullinger et al 2014); and magnetic resonance spectroscopy (MRS) to directly assess metabolite changes (Mangia et al 2006; Schaller et al 2014).

This article describes the different contrast mechanisms used in fMRI studies. BOLD contrast based on gradient-echo (GE) and spin-echo (SE) measures and perfusion contrast obtained with ASL are reviewed, with an emphasis on high and ultra-high field (UHF) imaging. Both task induced functional changes and functional connectivity measures are discussed.
2. Bold fMRI

Functional MRI based on BOLD contrast is now widely used to map brain function. BOLD contrast arises from the change in oxygenation resulting from changes in CBF, CBV and the cerebral metabolic rate of oxygen (CMRO$_2$). In response to a local increase in neural activation, the vasculature responds by increasing CBF (accompanied by an increase in CBV) to the active brain region in order to satisfy the increase in the rate of oxygen (CMRO$_2$) and glucose (CMR$_{glu}$) metabolism. In practice, the increase in local CBF exceeds the demand for increased CMRO$_2$ in the active brain region, an effect first observed using PET (Fox and Raichle 1986), increasing the blood oxygenation in downstream capillaries and veins. The reason for this mismatch between CBF and neuronal activity remains to be completely understood and has been the subject of extensive research (Buxton et al 2004; Uludag et al 2004), as reviewed in (Kim and Ogawa 2012). Experimental studies comparing electrophysiological measurements with BOLD have shown that the BOLD effect is linearly correlated with local field potentials (Logothetis et al 2001) and evoked potentials (Arthurs and Boniface 2003), with a recent study addressing the coupling of EEG with underlying BOLD and CBF changes (Mullinger et al 2013). Current research suggests that neuronal activity is coupled to local blood flow changes through an intermediary, the astrocytes (for a review see (Petzold and Murthy 2011)).

The origin of BOLD contrast itself arises from the change in blood oxygenation on activation, since deoxygenated haemoglobin is paramagnetic whilst oxygenated haemoglobin is diamagnetic (Pauling and Coryell 1936). At baseline, T$_2^*$-weighted MR images show a darkening in the vicinity of deoxygenated red blood cells due to the loss of signal caused by the difference in susceptibility between the paramagnetic deoxyhaemoglobin and surrounding tissue. On activation the oxygenation in capillaries and veins is increased to active brain region, reducing the concentration of deoxyhaemoglobin, resulting in an increase in the BOLD signal (Thulborn et al 1982). This change in the BOLD signal can be observed by acquiring a series of T$_2^*$-weighted images (typically with a 2D-EPI acquisition) while a subject performs a task or experiences some form of stimulation. The BOLD contrast depends on both intravascular (IV) and extravascular (EV) signal changes. As field strength is increased, the EV contribution dominates over the IV effects, and the percentage change in BOLD signal due to EV effects increases. Further, the EV BOLD signal originates more strongly from the dephasing around small vessels (microvasculature) compared to large vessels (macrovasculature) (Boxerman et al 1995). This has led to a rapidly growing interest in moving from high (> 3 T) to ultra-high field (> 7 T) MR scanners for fMRI.

3. Limitations

The vascular origin of the BOLD response imposes constraints on the temporal and spatial resolution of BOLD fMRI studies. Although neuronal changes to stimulation occur on the order of milliseconds, fMRI signal changes are temporally blurred in the vascular domain, resulting in haemodynamic changes being delayed by several seconds with respect to the neuronal activity. The BOLD signal response can be considered as a convolution of the neuronal activity with a haemodynamic response function (HRF) (figure 2). The HRF peaks a few seconds after the onset of the stimulation, depending on the size of the vessels from which the signal is originating (de Zwart et al 2005). The positive component of the HRF is very robust and routinely used to produce maps of functional activity. The HRF is also proposed to display an initial decrease in signal intensity approximately two seconds after stimulus onset (Duong et al 2000; Yacoub et al 2001b), termed the ‘initial dip’, reflecting an increase in
oxygen consumption prior to the onset of increased blood flow. The existence of the initial dip has remained controversial (Hu and Yacoub 2012), but a recent study has highlighted the use of trial-by-trial variability to reveal a reliable initial dip (Watanabe et al. 2013). After stimulus cessation, the BOLD signal decreases to a level below the initial baseline, from which it then recovers slowly to return to baseline, this is termed the ‘post-stimulus undershoot’. Even for a brief stimulus, the time from onset to the return of the signal intensity to baseline may be as long as 30 s. To model the underlying haemodynamics, it is possible to approximate the HRF to a summation of gamma variate functions whose parameters are optimized experimentally to form a canonical HRF (Friston et al. 1998).

In an fMRI experiment, a dynamic scan consisting of a set of slices through the brain is acquired in a typical measurement period, TR, of a few seconds. However, high temporal resolution (<1 s) is important in fMRI experiments for optimal modelling of the haemodynamic function and is especially important in identifying functional connectivity between brain areas. Until recently, temporal resolution for whole brain coverage at a reasonable spatial resolution has been poor, but recent technical advances have overcome this, as highlighted in the Human Connectome Project (Ugurbil et al. 2013).

The spatial resolution of fMRI is intrinsically limited by the volume over which haemodynamic regulation occurs. Oxygenation changes due to increased neuronal activity are initiated in the capillary bed and propagate down the vasculature to large draining pial veins. Degradation of the specificity of the BOLD response can arise from the signals originating...
from these draining veins, which may lead to mis-localization of the source of activation by as much as a few millimetres from the site of elevated neuronal activity (Turner 2002). This problem has been largely ignored in standard fMRI studies, where image resolution is relatively coarse (~3 mm isotropic voxels) compared with such spatial errors caused by draining veins, particularly in group studies where spatial smoothing is applied prior to normalizing subjects’ brains to a common MNI template. However, as high spatial resolution single-subject data becomes feasible and more popular, methods to suppress the contribution from draining veins are required. The identification of draining veins based on the phase of the MR signal (Menon 2002) or co-registration of fMRI data with a high resolution T2*-weighted scan on which veins are discernable (Hall et al 2002) has been used to remove draining vein contributions. Alternatively, differential fMRI paradigm designs can be used to eliminate non-specific venous activation common to two or more task conditions (Menon et al 1997) yielding higher spatial resolution maps of activation, with spatial specificity on the millimetre to sub-millimetre scale (Duong et al 2000; Yacoub et al 2001b). Spatial specificity can also be improved using spin echo rather than gradient echo based BOLD contrast, or by directly assessing CBF using ASL imaging techniques, as discussed later.

3.1. Improving the spatial resolution with ultra-high field

fMRI is limited in its spatial resolution by the available BOLD contrast-to-noise ratio (CNR), this is principally determined by the strength of the magnetic field. As magnetic field strength increases, BOLD signal changes increase (Gati et al 1997; Yacoub et al 2001a; van der Zwaag et al 2009). BOLD contrast depends on the ratio of the change in the transverse tissue relaxation rate on activation (ΔR2*) relative to the resting relaxation rate R2* (equal to 1/T2*) and is optimal when the echo time (TE) used matches the relaxation time T2* of grey matter. A study comparing the BOLD signal change to a simple motor task across three field strengths (1.5, 3 and 7 T) (van der Zwaag et al 2009) showed a linear increase in ΔR2*/R2* with field strength, and an increase in ΔR2*/R2*, resulting in a substantial increase in the BOLD signal at ultra-high field (figure 3). This increase in BOLD contrast, in conjunction with the increased intrinsic SNR, yields an increase in BOLD CNR which can be exploited to improve the spatial resolution and/or decrease the number of repeats required to demonstrate robust activation in functional mapping. However, physiological noise, fluctuations associated with the cardiac cycle and respiration, has been shown to increase with magnetic field strength (Triantafyllou et al 2005; Kruger and Glover 2001). Nevertheless, at high spatial resolution (<1.5 mm isotropic) the physiological noise contribution at 7 T is significantly reduced to a level where fluctuations are thermal noise dominated (Triantafyllou et al 2005), and the benefit of UHF can be most fully realized. Furthermore, as the magnetic field strength increases, BOLD signal changes are more strongly weighted to the microvasculature signal from the capillary bed relative to signal from macrovasculature (Duong et al 2003); the EV BOLD signal from the capillaries increases with the square of the magnetic field strength whilst large veins show a linear increase (Thulborn et al 1982; Gati et al 1997; Duong et al 2003). UHF also offers intrinsically improved spatial specificity when using echo times (TE) optimized for grey matter, since the IV signal is diminished due to the disproportional shortening of blood T2 compared to tissue T2 or T2* (Thulborn et al 1982; Gati et al 1997; Duong et al 2003). The width of the cortical point spread function (PSF) of the gradient-echo signal in grey matter ranges from 3.9 mm at 3 T (Parkes et al 2005) to less than 2 mm at 7 T (Shmuel et al 2007) and 1.6 mm at 9.4 T (Park et al 2004), reducing as contributions from large draining veins are removed. Recent studies of layer-specific activation using gradient-echo BOLD (Harel...
et al 2006; Ress et al 2007; Koopmans et al 2010; Polimeni et al 2010) suggest that the intrinsic spatial resolution is at the sub-millimetre level if contributions from pial veins are excluded. The use of GE-BOLD fMRI at high field in combination with differential fMRI paradigms has allowed the mapping of ocular dominance columns in humans with sub-millimetre accuracy (Menon et al 1997; Cheng et al 2001).

3.2. Spin-echo BOLD

fMRI signal changes can also be observed using spin echo (SE) EPI T₂-weighted BOLD contrast. A spin echo refocuses the static dephasing induced by field inhomogeneities around large vessels, thus reducing the functional contrast compared to gradient-echo BOLD contrast by eliminating the EV contribution from large vessels to the BOLD effect. However, as a consequence, SE-BOLD contrast is sensitive to signal changes around small venules and capillaries (Kiselev and Posse 1999; Duong et al 2003; Yacoub et al 2003), offering a gain in spatial accuracy (Jochimsen et al 2004; Jochimsen and Moller 2008), with a sharper PSF of SE-BOLD compared to GE-BOLD (Olman et al 2004). The improvement in spatial accuracy is best realized at ultra-high field due to the accompanying reduction of the IV contribution to the BOLD signal. Improvements in the spatial specificity of the SE BOLD response with respect to GE BOLD contrast have been demonstrated in human visual cortex (Duong et al 2002; Duong et al 2003; Yacoub et al 2003), and motor cortex at 7 T (Harmer et al 2012) (figure 4) and 9.4 T (Budde et al 2014), and across the depth of the cortex (Siero et al 2013). The increased specificity of SE-BOLD at 7T has been exploited to reveal robust and reproducible

![Figure 3. Gradient echo BOLD time-course of a motor task at field strengths of 1.5, 3 and 7T. Image adapted from van der Zwaag et al (2009) with permission. Copyright 2009 by Elsevier.](image-url)
maps of ocular dominance (Yacoub et al 2007) and orientation columns (Yacoub et al 2008) in the human visual cortex, as well as layer specific activity (Olman et al 2012).

3.3. Technical challenges at ultra-high field

Despite the clear advances of UHF for fMRI studies, this is accompanied by technical challenges related to the decrease in $T_2/T_2^*$ relaxation times, increased $B_0$ and $B_1$ inhomogeneity, and increased specific absorption rate (SAR) as a consequence of a quadratic increase in RF power.

At UHF, the acquisition of high spatial resolution fMRI can be limited by the need for a short echo time (imposed by a grey matter $T_2^*$ of ~ 25 ms) and increased vulnerability to susceptibility-induced geometric distortions and signal loss in EPI acquisitions. Parallel imaging techniques such as sensitivity encoding (SENSE) imaging (Pruessmann et al 1999) which uses multiple receive coils, can alleviate this problem, as the echo train length of EPI images is shortened thus reducing image distortion.

Magnetic field inhomogeneity can be minimized by using improved shimming capability (using higher order shim coils) and improved shimming methods. For example, image-based shimming requires the acquisition of a field map which is used to characterize field inhomogeneity ($\Delta B_0$) and to determine the shim coil currents needed to minimize $\Delta B_0$ over the region of interest. Use of local image-based shimming (Wilson et al 2002; Poole and Bowtell 2008) has been shown to restrict geometric distortions to less than one voxel (1 mm) in GE-EPI data at 7T (Sanchez-Panchuelo et al 2010). $B_1$ inhomogeneity increases at UHF as the RF wavelength

Figure 4. Activation maps overlaid on corresponding echo planar images for GE and SE data and fMRI time series showing the BOLD percentage signal change for GE and SE data. Image adapted from Harmer et al (2012) with permission. Copyright 2011 by Wiley.
is short compared to the dimensions of the head, causing an inhomogeneous flip angle and central brightening in the images. Various methods have been proposed to reduce these strong transmit $B_1$ inhomogeneities, such as multichannel parallel transmit for $B_1$ shimming techniques (Adriany et al 2005; Adriany et al 2008; De Martino et al 2012) and the use of spatially targeted RF pulses with amplitude and phase modulation (Setsompop et al 2008; Zelinski et al 2008). High permittivity dielectric pads have also been shown to increase image quality at 7T in regions of low radiofrequency transmit efficiency (Teeuwisse et al 2012), whilst tailored RF pulses, such as the optimized TR-FOCI (Hurley et al 2010), can be employed to improve the image quality for sequences that use inversion pulses, such as magnetization prepared rapid acquisition gradient echo structural scans and arterial spin labelling schemes.

SAR can become limiting at UHF, particularly when using a SE-EPI acquisition for fMRI. A multi-slice SE-EPI acquisition with fat suppression can be severely restricted in number of slices that can be acquired in a given repetition time compared to a multi-slice GE-EPI fMRI acquisition. To overcome this Slice Selective Gradient Reversal (SSGR) (Gomori et al 1988; Harmer et al 2012), in which the fat signal is sufficiently shifted relative to the excited water signal in the imaging slice, can be used. Standard 2D GE-EPI can also approach the SAR limit when a large number of slices are acquired. 3D GE-EPI, which uses a lower flip angle provides an attractive alternative, particularly at high spatial resolution for a large number of slices, as the SNR of 3D GE-EPI is superior to 2D GE-EPI acquisitions, and parallel imaging allows acceleration in two spatial dimensions, significantly reducing the total volume acquisition time (Barry et al 2012; van der Zwaag et al 2012).

### 3.4. Applications

The majority of fMRI studies at high field to date have collected data with a spatial resolution of a few millimetres, and performed a group analysis across subjects to increase the statistical power. In group analysis, individual subjects’ data is spatially normalized to a template brain (typically the MNI template), having first applied spatial smoothing of typically twice the voxel size to account for differences in brain morphology between subjects, limiting the spatial resolution to about 8–10mm. However, as the need for clinical fMRI increases, the goal is to interpret the fMRI results on an individual subject basis.

The improvements in sensitivity and spatial specificity at UHF have improved the resolving power of fMRI to sub-millimetre isotropic resolution. Figure 5 illustrates 0.75 mm isotropic 3D GE-EPI data acquired at 7T with a 32 channel receiver coil and SENSE acquisition factor of 2, showing excellent quality EP images which also reflect good structural detail. In such state-of-the-art data, the functional contrast-to-noise of the BOLD images is sufficiently high that spatial smoothing is not necessary or advisable. In fact, for such fMRI applications it is often crucial to not spatially smooth, to retain the high spatial resolution by reducing the partial volume effect of averaging voxels together.

The advantage of UHF fMRI has largely been exploited in targeted studies of partial coverage of the brain. The development of ‘travelling wave’ or ‘phase-encoding’ paradigm designs, which allow the identification of cortical mappings with respect to continuously varying parameters, has advanced precision of fMRI measures (Engel et al 1994; Engel 2012). This has been demonstrated in high resolution functional (retinotopic) and structural (linked to myelination) parcellation of primary visual cortex V1 (Sanchez-Panchuelo et al 2012b), topographic mapping of the human tonotopic organization in the auditory cortex (Formisano et al 2003; Talavage et al 2004) and inferior colliculus (De Martino et al 2013a), and the somatotopic mapping of the digits of the hand (Sanchez-Panchuelo et al 2010) and fine scale within-finger somatotopic organization in the primary somatotopy
cortex (Sanchez-Panchuelo et al 2012a). In addition to cortical topographic maps, finger somatotopy has been mapped in the cerebellum (van der Zwaag et al 2013) and retinotopy has been mapped in the Lateral Geniculate Nucleus (LGN) (Chen et al 1999). Submillimetre columnar architectures, such as ocular dominance columns (Cheng et al 2001; Yacoub et al 2007) and orientation columns (Yacoub et al 2008) in the visual cortex have also recently been revealed with fMRI and laminar specific activations across the width of the cortical layer resolved (Koopmans et al 2010). fMRI of cortical layer activity is now possible (De Martino et al 2013b), using different conditions to preferentially activate input and output layers of the cortex, providing the possibility to study the brain at a level which so far remains relatively unexplored.

These high spatial resolution studies have, until recently, been confined to a small region of the brain. However, multiplex techniques where multiple slices are simultaneously excited and sampled, have recently been developed (Moeller et al 2010; Feinberg et al 2010), providing whole brain coverage while maintaining high spatial resolution and short acquisition times. These method have facilitated high spatial and temporal investigations of functional connectivity networks (De Martino et al 2011), as outlined further below.

Recent developments have also been shown in fMRI analysis, such as the use of multivariate pattern analysis (MVPA) to decode brain activity patterns (Norman et al 2006; Spiers and Maguire 2007). MVPA algorithms applied to relatively coarse spatial resolution 3T fMRI data were shown to decode visual stimuli functionally segregated at the submillimetre resolution (Haxby et al 2001; Haynes and Rees 2005; Kamitani and Tong 2006), and reveal voxels that demonstrate preferential activation corresponding to a unique cortical column (such as an ocular dominance, orientation or direction of motion specific column, known to have dimensions of ~1 mm). It has been shown that high spatial resolution fMRI further improves the classification performance obtained with MVPA (Swisher et al 2010; Beckett et al 2012).

**Figure 5.** Statistical activation maps to vibrotactile stimulation of the left hand digits overlaid on 0.75 mm isotropic 3D GE-EPI data acquired at 7T. The effect of spatial smoothing with a FWHM of 1.5 and 3 mm is also shown; the unsmoothed activation map is closely matched to the cortical ribbon, whilst for smoothed data the activated region extends into adjacent white matter.
4. Phase based fMRI measures

Conventionally, BOLD fMRI is measured from the magnitude MR images. Only a few studies have investigated BOLD contrast using phase images (Menon 2002; Rowe et al 2007; Tomasi and Caparelli 2007; Hagberg et al 2008; Hahn et al 2009; Petridou et al 2009; Arja et al 2010; Hagberg et al 2012; Bianciardi et al 2014; Chen et al 2013). At the spatial resolution allowed by conventional magnetic fields, the BOLD phase effect is averaged out due to the orientation dependence of microscopic field perturbation effects, hence substantial phase contrast can only be found near large veins of diameter comparable to the voxel dimensions. At high spatial resolution, the phase of the fMRI time-series have been used to identify the dominant non-local BOLD effects due to large veins and to remove their contribution from BOLD statistical maps (Menon 2002). The introduction of quantitative susceptibility maps (QSM) (Li and Leigh 2004; de Rochefort et al 2008; Shmueli et al 2009; Liu et al 2009; Wharton and Bowtell 2010; Schiwes er et al 2011) has opened up new possibilities to use phase images for fMRI studies. Bianciardi et al (2014) generated QSM for each volume in the phase time-series of 2.5 mm isotropic fMRI data acquired at 7 T in order to compute activation related susceptibility change maps. They showed that functional, task related magnitude and phase changes can be detected with comparable sensitivity, and that these changes have the same BOLD origins. Balla et al (2014) used single orientation (SO) and multiple orientation (MO) experiments to assess the potential of functional QSM relative to standard magnitude BOLD fMRI data at 7 T.

5. Direct CBF fMRI measures

The direct change in CBF due to increased neuronal activation can be measured using arterial spin labelling (ASL) fMRI (Williams et al 1992). ASL uses labelled inflowing arterial blood as an endogenous tracer, allowing the non-invasive quantification of regional brain tissue perfusion (CBF). In ASL, the arterial blood upstream from the area of interest is magnetically labelled by applying a single radiofrequency pulse (pulsed ASL) (Edelman et al 1994; Kim 1995; Kwong et al 1995), or a train of pulses (continuous or pseudocontinuous ASL (Wu et al 2007)) to invert the blood water magnetization. After a period of time—the post-label delay—to allow labelled spins to flow into the imaging plane, an image (label) is acquired. A second image (control) is acquired without labelling of inflowing arterial blood. Label images are then subtracted from control images to yield a perfusion weighted image that can be quantified in terms of cerebral blood flow in ml/100 g/min (Buxton et al 1998). The temporal resolution of perfusion based fMRI is lower than BOLD fMRI due to the time required to collect both a label and control pair, and the CNR of perfusion-based functional maps is lower than BOLD. However, as field strength increases the T1 of arterial blood increases, giving rise to an increase in the perfusion weighted difference signal and so perfusion CNR, which peaks at longer post-label delay. The feasibility, and advantages, of UHF ASL measurements have been demonstrated in pulsed ASL based fMRI studies conducted in the human brain at 7 T (Pfeuffer et al 2002; Gardener et al 2009), and the introduction of 3D image acquisition strategies may provide improved resolution and coverage of perfusion images for functional studies. Figure 6 shows an example of BOLD and perfusion weighted statistical maps acquired at 7 T in response to a finger tapping task. ASL fMRI is more spatially localized to the active tissue than BOLD fMRI (Silva et al 1999; Duong et al 2000), since the perfusion signal changes originate from the small arterioles and the parenchyma. Perfusion based fMRI has been shown to yield high-quality functional maps of orientation columns in the cat visual cortex (Duong et al 2001) at high field strength (4.7 T),
demonstrating the potential of this technique for high resolution mapping of sub-millimetre functional organization in humans.

Unlike BOLD, ASL permits measurements of baseline levels of CBF as well as activation dependent changes in CBF. Since BOLD contrast reflects a complex interaction between haemodynamic changes in CBF, CBV, blood oxygenation and also depends on the baseline physiological state, this can make it difficult to interpret BOLD signal changes. Goense et al (Goense et al 2012) have used high resolution fMRI at 4.7 T in monkeys to study layer-specific fMRI signals, and shown that regions with positive BOLD responses have parallel increases in CBV and CBF, whereas areas with negative BOLD responses show a decrease in CBF but an increase in CBV, suggesting different mechanisms for neurovascular coupling for BOLD increases and decreases. Further, baseline CBF measures from ASL can be used to study physiological factors (e.g. breathing CO2 (Cohen et al 2002)) and pharmacological interventions, and how this is altered by vascular and neuronal diseases.

ASL is typically limited to a few brain slices and yields lower contrast-to-noise ratio than BOLD. However, more efficient labeling approaches are being developed to improve SNR while reducing RF power at ultra-high field, together with technical improvements such as 3D acquisitions, background suppression and multiplex excitation, this will allow whole brain coverage with increasing resolution. ASL offers the advantage of producing a quantifiable signal that is more directly related to neural activity, and may eventually replace BOLD as the technique of choice in certain applications, particularly in longitudinal studies and pharmacological fMRI.

6. Functional connectivity using resting state fMRI

Until relatively recently, most fMRI studies had studied the response to a task or stimulus. However, brain activity continues in the absence of goal-directed neuronal action, and in recent years the importance of measuring connectivity between spatially separate but functionally related brain areas when at rest has become of considerable interest. This intrinsic neuronal activity manifests as spontaneous fluctuations in the fMRI time series (Gusnard and Raichle 2001), with this being suggested to be dominated by low frequency fluctuations (<0.1 Hz) and more recently by spontaneous events (Petridou et al 2013). Functional MRI can be applied to...
identify functional connectivity (fc) between brain regions by measuring these spontaneous fluctuations. When spontaneous activity is strongly temporally correlated across two or more spatially segregated brain regions, these regions are assumed to be functionally connected. In resting state functional connectivity experiments, subjects are typically instructed to lie still in the scanner with their eyes closed (or opened while fixating on a cross) while fMRI data is collected (Fox et al. 2005; Damoiseaux et al. 2006).

There are a number of methods to study connectivity between brain regions and thus identify functional networks; seed-based correlation, where a seed voxel is pre-specified to determine brain areas which correlate temporally with this seed, or independent component analysis methods which allow identification of resting state networks based on spatial or temporal independence (Beckmann and Smith 2004) are commonly used. The first functional connectivity study was performed by Biswal et al. (Biswal et al. 1995), who demonstrated that under resting conditions the BOLD fMRI time series of a voxel in the sensorimotor cortex was strongly correlated with the time-series of other voxels in the contralateral sensorimotor cortex, suggesting functional communication between these regions during rest. Several groups have since employed resting-state fMRI to identify other resting state functional networks (such as the visual network (Lowe et al. 1998; Cordes et al. 2000), auditory network (Cordes et al. 2000), and default mode network (Gusnard et al. 2001; Raichle et al. 2001; Greicius et al. 2003).

Resting state fMRI has become increasingly popular to study alterations in networks in the clinical setting. It offers several advantages for clinical use over task-related fMRI, given that

Figure 7. Functional connectivity maps (Pearson correlation coefficient images) for sensorimotor and default mode networks overlaid onto a standard MNI brain. The seed is located in right sensorimotor cortex and posterior cingulate cortex for SMN and DMN connectivity analysis respectively. Low spatial resolution (3 mm isotropic) 3T data and high spatial resolution 3T and 7T data (1.5 × 1.5 × 3 mm³) shown for different spatial smoothing kernels (FWHM of 3, 4 and 5 mm) prior to correlation computation. Image adapted from Hale et al. (2010) with permission. Copyright 2010 by Springer.
it does not require patients to perform a task nor hardware for stimulus presentation. Thus, resting state fMRI is very suitable to study patient populations who cannot accurately perform tasks due to physical impairment or cognitive dysfunction, eliminating confounds of differences in the level of task performance. Resting state fMRI measures have been correlated to clinical variables in patient populations and controls, with applications in neurodegenerative brain diseases (Li et al., 2002; Lowe et al., 2002; Greicius et al., 2004; Wang et al., 2007; Rocca et al., 2010; Bonavita et al., 2011), and neuropsychiatric disorders (Cherkassky et al., 2006; Calhoun et al., 2009; Church et al., 2009).

Recent studies at 7 T (Hale et al., 2010; Newton et al., 2012) have shown that, despite the lower signal-to-noise ratio of smaller voxels, the detectability of functional connectivity within the sensory-motor system increases as the spatial resolution increases, possibly due to decreased partial volume effects, demonstrating the potential benefits of UHF for detecting and analyzing functional connectivity. Figure 7 shows the increased detectability of functional networks at 7 T compared to 3 T. Further, 7 T has allowed the study of resting state connectivity at both a fine and large scale within and across visual areas V1, V2 and V3 (Raemaekers et al., 2014).

7. Summary

In summary, the field of fMRI has rapidly grown, with applications in basic sensory processing and cognitive neuroscience, as well as clinical applications. The recent advent of ultra-high field scanners, has lead to significant advantages in terms of both the increase in the contrast to noise ratio (CNR) and the spatial specificity of functional MRI studies. This is an area which will continue to expand with improvements in hardware and analysis techniques, allowing functional measures of the human brain with even greater sensitivity and detailed specificity, to approach whole brain sub-millimetre spatial resolution acquisitions in future studies.

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