Since its introduction 20 years ago (1,2), functional magnetic resonance imaging (fMRI) has evolved into the most commonly used methodology for mapping brain function, particularly in humans. The ability to non-invasively monitor processes related to brain function with high degrees of spatial and temporal precision has proven to be an invaluable tool for neuroscience. Further, the spatial and temporal resolvability limits of fMRI continue to expand making many more neuroscience questions within reach. Manipulation of acquisition strategies (i.e. magnetic field strength, pulse sequences, parallel imaging, etc.) can significantly affect observed fMRI signals in terms of vascular specificity as well as functional sensitivity and acquisition efficiency. Blood oxygen level dependent (BOLD) (1,3) based imaging is the most widely used methodology for fMRI, especially in human applications. Although there are in principle several fMRI techniques that could potentially be used for functional mapping at either low or high magnetic fields, because of its ease of implementation and relatively high contrast to noise ratio (CNR), BOLD based techniques are typical always used. The use of higher magnetic fields has only enhanced the preference for using BOLD imaging, as significant gains have been demonstrated in both spatial specificity and in the CNR of BOLD based fMRI images (4,5). Further, since the vast majority of fMRI studies ask supra-millimeter resolution neuroscience questions, the specificity of gradient echo (GE) or T2* weighted BOLD fMRI is generally sufficient and the preferred sequence choice due to its high CNR. However, a significant component of the GE BOLD response does originate from large vessels, which can be several millimeters away from the neural activity and can also contaminate tissue signals. While the specificity of GE- BOLD signals on the whole is generally poor (i.e. several mm), it is extremely heterogeneous, and it does carry highly specific information (6-8). On the other hand, if high spatial precision is desired, spin echo (SE) based (T2 weighted) BOLD imaging (5,9,10) can provide significant improvements at high fields, albeit at the cost of sensitivity and efficiency.

The BOLD signal measures the hemodynamic response to neural activity by exploiting the magnetic properties of blood water. BOLD fMRI is sensitive to any changes in oxygen metabolism (CMRO2), cerebral blood flow (CBF) or volume (CBV), all of which alter the relative amount of deoxyhemoglobin, and thus the local magnetic field in the brain. The paramagnetic properties of deoxyhemoglobin lead to increases in the transverse relaxation times which can be observed on either GE (T2* weighted) or SE based (T2 weighted) contrast. The total deoxyhemoglobin concentration following neural activity decreases due to large increases in CBF and CBV without commensurate changes in CMRO2. The end result of this is an increase in local signal intensity on T2/T2* weighted MR images in brain regions involved in a task relative to a basal state. This increase in signal intensity can result from different mechanisms and can arise as either extravascular or intravascular effects. One mechanism occurs when spins located around blood vessels (extravascular) give rise to a dynamic averaging effect, which is the result of diffusion during a given echo time (TE) in the blood vessel generated magnetic field gradients outside the vessels (3,11,12). The diffusion distance within a typical TE is small and, because of this, dynamic averaging is a dominating mechanism for small blood vessels only. This averaging due to diffusive processes will lead to an apparent change in the T2 relaxation constant, which is evident on both GE and SE BOLD images. For larger blood vessels, the effect of dynamic averaging seen around small vessels is negligible, and static averaging is the governing mechanism unless SE refocusing pulses are used. In the case of extravascular BOLD signals, the response from GE vs SE contrast is quite different. In GE BOLD, the static effects from large vessels and the dynamic effects from smaller vessels are both typically seen. Whether or not extravascular effects from larger vessels are prominent in GE BOLD images depends on 1) the blood volume in a given voxel, 2) the magnitude of the susceptibility change caused by the local activation, and 3) the extent of pooling of blood from the activated site with blood from regions that remain in their basal state of activity as blood flows away from the active site. For SE BOLD images, where the large vessel static effects are refocused with 180 degree refocusing pulses, only dynamically averaged diffusion effects contribute to the extravascular BOLD contrast at any field, provided that T2* contamination in SE images is not significant. While relatively small at low fields, when going to higher fields, the extravascular component becomes increasingly more important for both large and small vessels for GE images and for small vessels only in SE images. The small vessel (dynamic averaging) component increases with the square of the magnetic field (3), while the large vessel (static averaging) contribution goes linearly. The other means by which BOLD signal changes can arise is through intravascular or blood effects. Inside the blood, the susceptibility effect of deoxyhemoglobin is dynamically averaged and shortens the T2 of blood water. Ultimately, the effect of the intravascular (blood) signal on the image contrast will be dependent on the TE used and the blood T2. At TEs comparable to the T2 of tissue, the
blood signal is greatly diminished at high fields and is expected to contribute negligibly in contrast to low fields (13-15). Irrespective of the total blood contribution, it should be similar for GE and SE BOLD data, provided the TEs used are comparable. In summary, GE and SE BOLD fMRI at low fields are subject to a dominating (similar) intravascular blood effect that cannot be suppressed by longer echo times because of the long blood T2. As the intravascular effect is diminished at high fields, the extravascular effect becomes dominant, and, what is left is a BOLD signal that reflects extravascular effects around large and small vessels for GE and more favorable to smaller vessels in SE BOLD.

The neuroscience advantages of using SE (T2 weighted) contrast have been demonstrated for high resolution applications of fMRI (8,10); however, unless such spatial resolution and specificity is required, for many applications, such as resting state or event related fMRI, the tradeoffs in coverage, efficiency, and CNR do not justify its use over GE-based methods. In SE based imaging, because a 180 degree RF pulse(s) is needed, transmit field inhomogeneities and power deposition (SAR) limits are problematic, especially at high fields, making large volume coverage extremely inefficient. As such, the vast majority of studies at any field rely on GE BOLD. Further, field inhomogeneities and SAR limits are problematic, especially at high fields, making large volume coverage extremely inefficient. As such, the vast majority of studies at any field rely on GE BOLD. Further, high resolution GE-fMRI applications have successfully demonstrated sufficient functional specificity at the sub-millimeter (columnar) level, albeit relying on the explicit avoidance and/or removal of large non-specific signals (6,8,16). For mapping studies, such avoidance, depending on the location in the brain, is not always achievable in the human. In addition to columnar organizations, neuronal interactions and computational processes are distributed across the cortical lamina or within a cortical column. fMRI studies have looked to exploit these processes by characterizing activation according to cortical depth location. Such information could provide invaluable insight into basic neuronal inter-connections. GE and SE based methods (17-23) have shown the ability to resolve cortical depth dependent information, however, the extent to which surface vessel related effects can be minimized is unclear, especially in GE methods, complicating the interpretation of layer specific fMRI signals.

Alternatives to BOLD, such as arterial spin tagging (ASL), blood volume based contrast (CBV), or the use of contrast agents, could potentially improve the spatial specificity of the signals (24). ASL is based on the fact that the magnetization and relaxation characteristics of tissue water are affected by the inflow of blood water, and it benefits from the increased T1 encountered at higher magnetic fields. The tissue specificity of ASL improves (24) because of the fact that tagged spins require a finite amount of time to reach the capillaries and exchange with tissue water. Non-invasive CBV based methods, such as VASO (25), may also provide improved specificity over BOLD techniques. However, to realize the advantages of higher specificity, higher resolution images are required and since the intrinsic signal to noise ratio (SNR) and temporal efficiency of CBV and ASL methods are much lower, this realization can be challenging. Thus, BOLD alternatives in human studies are not often used. These techniques can, however, provide valuable information about hemodynamic processes associated with brain function (26).

In addition to the different contrast mechanisms, there are also many different pulse sequences that can be used in fMRI. However, the vast majority of applications use single shot multi-slice (2D) echo planar imaging (EPI)(27) or spiral imaging (28,29) because of their temporal efficiency. While most fMRI studies cannot afford reduced efficiency, cases can and have been made to utilize non-EPI acquisitions for applications which require reduced distortions, motion artifacts, or susceptibility effects. There are also, however, numerous ways to mitigate these issues in EPI. Additionally, non-EPI based imaging for SE contrast has also been successfully applied, resulting in a more pure T2 weighting (30-33) and images free of T2* contamination. However, the penalty in efficiency for these methods is even greater due to limitations from the many more refocusing pulses needed.

3D sequences are often used in fMRI and have the advantage of higher SNR, however, the acquisition time for a given slice is convolved over the volume acquisition time (2-3s), making it highly sensitive to motion and physiological noise. Historically, this has resulted in the use of 2D techniques for most applications. However, 3D approaches can be ideal for high resolution applications, which require a large number of thin slices, problematic for 2D acquisitions because of slice profile issues, and when SNR is limiting. Both 2D and 3D acquisitions can capitalize on accelerated acquisitions (made possible by parallel imaging technology) using phase encode reductions. Since 3D utilizes 2 phase encode directions, accelerations along two dimensions can be achieved, reducing even more the acquisition times and allowing for much more efficient 3D acquisitions (Poser et al., 2010). Recently (34-36), simultaneous 2D slice excitation was introduced for fMRI, reducing the volume TR in 2D acquisitions several fold, without losses due to undersampling, as is incurred with conventional phase encode accelerations. This recent development has made 2D-EPI extremely efficient, allowing for unprecedented combinations of spatial and temporal resolution, while still achieving whole brain coverage. Continued improvement in the efficiency and quality of 2D techniques has allowed 2D fMRI techniques to remain the most attractive to
neuroscientists, allowing for unprecedented combinations of spatial and temporal resolution, whereby permitting many more unique neuroscience investigations.

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