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Review

Spin-echo fMRI: The poor relation?

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ABSTRACT

Spin-echo fMRI offers a potentially better intrinsic functional spatial resolution than its gradient echo counterpart, as well as the elimination of signal dropouts in the image. This comes at the price of a significant loss in sensitivity. In this article the main methods for measuring spin-echo fMRI are presented: HASTE, SSFP, RASER and most importantly spin-echo EPI. Their relative merits and limitations are discussed. The BOLD contrast mechanisms responsible for spin echo fMRI are summarised, and the spatial origin of the signal within the neocortex discussed. The major publications concerning the use of spin echo fMRI are examined. At present the most promising application for this methodology would appear to be in the examination of cortical layers and columns. The balance of experimental and theoretical evidence accumulated to date leads the author to propose that: (i) There is little point in conducting spin-echo fMRI at main magnetic field strengths of 3 T and below; (ii) There are fundamental limitations to acquiring spin-echo BOLD data at 7 T and above; (iii) Whole brain coverage with SE-BOLD at very high static magnetic field strengths could prove valuable; and (iv) SE-BOLD is probably better suited to study cortical columns than cortical layers. Recently gradient-echo approaches for high spatial resolution fMRI have been demonstrated that employ special techniques to avoid the effects of larger post capillary vessels. The coming years will show whether spin-echo techniques can remain the method of choice for high spatial resolution studies, and whether they can extend their range of application at 7 T and above.

Contents

Introduction

The history of MRI can be viewed provocatively as an ongoing struggle between the spin and the gradient echo. In the earliest days there were troubles producing slice selective 180° pulses, and gradient echo sequences were commonly used. Then the spin echo and the multi-slice, multi-echo approach reigned supreme in the early eighties, only for the advent of FLASH and related sequences to swing the pendulum back in favour of the gradient echo, owing to their shorter acquisition times and higher sensitivity. However, the advent of phase coherent synthesisers in the late 1980s made it possible to implement RARE, now more commonly known as FSE/TSE in clinical practice, and since then spin-echo based sequences have taken a central place in clinical routine, while gradient echo sequences retain an important position.

In the history of fMRI the above development has not been paralleled: the overwhelming majority of fMRI experiments are performed using gradient echo EPI while spin-echo measurements remain something of a rarity. For the advocates of spin-echo fMRI, this technique offers a superior localisation of functional signal changes to the capillary bed. For reasons that will be given below this superior localisation manifests itself more clearly at higher static magnetic field strengths. Furthermore the use of a spin-echo eliminates the signal voids that plague gradient echo sequences, and, as there is little variation in the T2 of grey matter through the brain (unlike the considerable variation in T2*) a single echo time should yield optimal sensitivity. For the sceptic, spin-echo fMRI will always remain the poor relation of the mighty gradient-echo approaches with their

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compact measurement sequences and maximum BOLD sensitivity. For the neutral observer spin-echo fMRI offers tantalising glimpses of a better future, but one that seems to remain just out of reach. In this article I shall describe the development of spin-echo fMRI, and the controversies surrounding its use. I shall attempt to precis the major papers on the subject, and chart the development of my own views on the topic.

Measurement techniques

Gradient-echo EPI is an ideal technique for the measurement of the T2*-weighted BOLD signal. The TE can generally easily be matched to the average grey matter T2* giving a sensitive sequence with data acquisition rates well in excess of ten slices per second. The experimenter wishing to measure the T2-weighted BOLD signal immediately faces considerable experimental difficulties, which enforce some degree of compromise: First, as indicated in the Introduction, the use of T2-weighted BOLD is generally justified by the expectation of a narrower spatial point spread function (PSF) in the BOLD response and hence a requirement for better in-plane spatial resolution and thinner slices in the acquisition. Furthermore, the optimal TE should be matched to the T2 of grey matter giving a TE of 70–80 ms at static magnetic field strengths of 1.5 and 3 T, and 60 ms or less at 7 T or higher. The combination of this relatively long TE together with the desire for a high spatial resolution often makes it difficult to obtain whole brain coverage with a sufficient temporal resolution for event-related fMRI studies. Second, the general requirement to have at least one refocusing radio frequency pulse in the sequence can mean that even if data could be acquired at a sufficient rate, the experiment may be limited by radio frequency power limits (SAR), particularly at the high static magnetic field strengths where spin-echo sequences are expected to be most advantageous.

Pure spin-echo fMRI was introduced in the form of a segmented FSE acquisition at 1.5 T (Constable et al., 1994). The advent of parallel imaging techniques combined with partial Fourier acquisition made it possible to accelerate single shot FSE sequences so that about 8 slices a second could be acquired at 3 T (Poser and Norris, 2007). The pulse sequence used is shown in Fig. 1. Despite the attractions of this sequence, whole brain coverage with this approach is currently not possible at a sufficiently short TR for event-related fMRI. At higher field strengths than the 3 T used by Poser and Norris (2007) the rate of data acquisition has hitherto been limited by SAR considerations. Using some of the SAR reduction techniques described at the end of this section a zoomed single-slice approach with a high spatial resolution would probably still be possible at 7 T.

Given that the power deposition associated with a pure spin-echo sequence will hinder implementation at ultra high field strengths of 7 T and higher, two alternative strategies have hence been developed. One of these is to employ the S2 signal of a SSFP sequence (Barth et al., 2010), shown in Fig. 2. This sequence has a low radiofrequency power deposition while retaining the benefits of no signal drop-out and negligible distortion. This comes at the expense of a very slight additional T2* weighting, but a similar sensitivity to that of spin-echo EPI at 7 T could

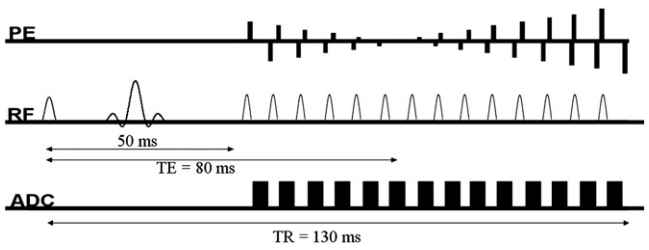

Fig. 1. Single shot HASTE pulse sequence. This consists of a preparatory spin-echo experiment to allow the functional contrast to develop followed by a HASTE readout accelerated by the use of parallel imaging, and the use of a partial Fourier acquisition. Figure taken by kind permission from Poser and Norris (2007).

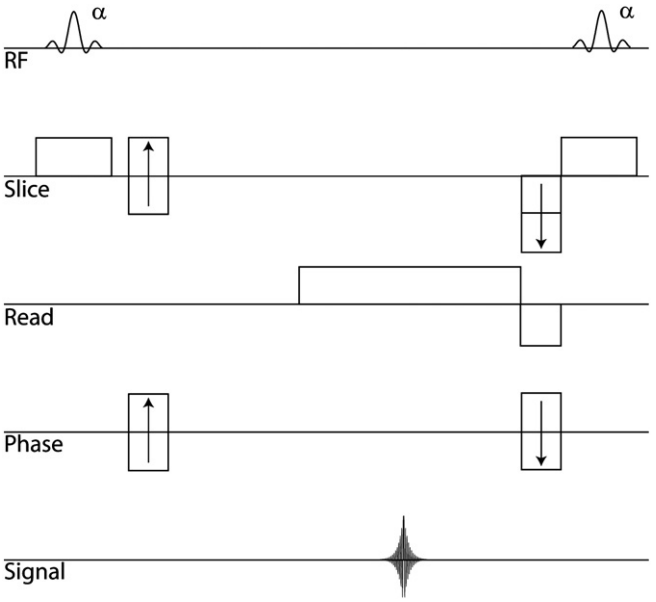

Fig. 2. 3D SSFP sequence to read out the S2 signal. The diagram is not to scale. In practice the time between the echo and the subsequent RF pulse will be minimised to reduce the T2* contamination, and the TR will be set to roughly half the TE used in a normal spin-echo sequence for SE_BOLD.

be demonstrated Barth et al. (2010). Although the initial study used a standard 3D SSFP sequence, acquisition could in theory be speeded up using a combination of SSFP with EPI (Miller et al., 2006). The resulting sequence would then have similar characteristics to the spin-echo EPI sequence discussed below, but considerably reduced SAR.

The second alternative goes under the acronym RASER (rapid acquisition by sequential excitation and refocusing, shown in Fig. 3), and essentially exploits the quadratic phase of a frequency-swept chirp pulse to produce a string of spin-echoes all having equal echo times (Chamberlain et al., 2007). There is hence neither distortion nor signal dropout present with this sequence. The use of a chirp pulse together with two 180° refocusing pulses will however lead to a high SAR, with the main contribution coming from the chirp pulse. RASER is essentially a line-scanning technique, with the data for each image line being acquired sequentially, and no phase-encoding or Fourier transform being applied along the second spatial axis. This will reduce the SNR of the sequence as compared to EPI, although this is not critical for fMRI studies at higher main magnetic field strengths, where physiological noise can be expected to dominate. Similar time course SNR values have been recorded for GE-EPI, SE-EPI and RASER (Goerke et al., 2011).

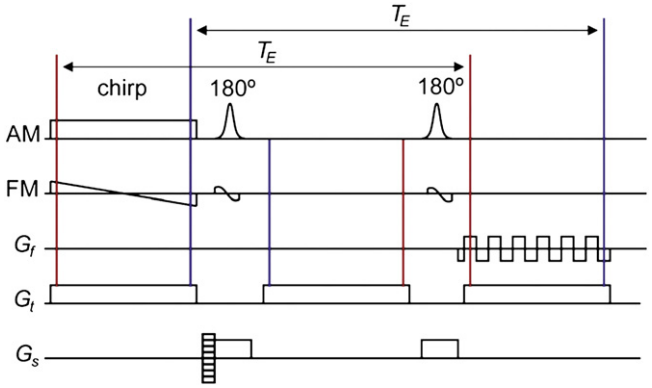

Fig. 3. Principle of RASER acquisition. The chirp excitation pulse is refocused to give an echo as long as the pulse itself, hence each echo has the same echo time. The dimensions encoded by G_f and G_t are encoded in a single shot. In the multi-shot 3D version grey shaded phase-encoding gradients are used to phase-encode the third dimension. Taken by kind permission from Goerke et al. (2011).

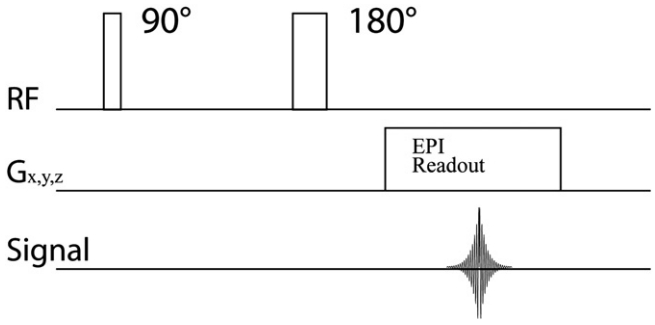

Fig. 4. Schematic of spin-echo EPI sequence. For SE-BOLD the TE must be sufficient to let the functional contrast develop, typically about 80 ms at 1.5 or 3 T and 60 ms at 7 T. The EPI readout should be kept short to minimise the contribution of T2* to the signal.

If used to obtain a single 2D image, then acquisition will be limited to a single slice by the necessity to apply the chirp and refocusing pulses along orthogonal axes, hence a 3D acquisition may be preferred in practice at the expense of the single shot capability. The spatial resolution along the second axis in a 2D acquisition is determined by the quadratic phase profile of the chirp pulse, which may be a limitation for applications requiring a higher spatial resolution.

Currently the most popular choice of pulse sequence for T2-weighted BOLD is spin-echo EPI, which was originally introduced as an alternative to gradient echo EPI at 1.5 T (Bandettini et al., 1994), and illustrated in Fig. 4. If this sequence is used then there is the possibility of image distortion (which may be corrected using distortion correction techniques), and simultaneously of a significant T2*-weighting for the higher spatial frequencies in the image, which may be relevant for high spatial resolution studies of intra-cortical structures such as layers or columns. At ultra-high field strengths of 7 T and above the ability to cover extended regions may still be limited by SAR, whereas at lower field strengths it is generally possible to obtain whole brain coverage at moderate spatial resolution within a TR of 3 s. These considerations mean that spin-echo fMRI at 7 T and above is often restricted to a limited region of the brain, and that the acquisition is frequently segmented, in order to reduce the effects of distortion and T2*-contamination while permitting a high spatial resolution. By multiply refocusing the EPI readout using a string of spin-echoes it is possible to generate a 3D-EPI sequence (Song et al., 1994), that can also be seen as a form of 3D-GRASE sequence, and which can potentially be used to obtain single shot 3D T2-weighted images. A high spatial resolution can also be obtained using this technique by combining it with a zoomed acquisition (Feinberg et al., 2008).

Future methodological development for all spin-echo fMRI techniques will primarily be concerned with SAR reduction techniques in order to allow greater volume coverage, particularly at 7 T and above. The SAR in FSE based sequences can be reduced by using both GRASE (Feinberg and Oshio, 1991; Oshio and Feinberg, 1991) and TRAPS (Hennig et al., 2003). The SER approach (Feinberg et al., 2002) makes it possible to refocus the signal from multiple slices excited in rapid succession by a series of 90° pulses using a single 180° pulse: the resultant signals are interleaved in an EPI readout train. This multiplexing technique can considerably reduce the number of refocusing pulses required but by lengthening the readout train distortion increases. Slice multiplexing (Feinberg et al., 2010; Larkman et al., 2001; Moeller et al., 2010) which simultaneously excites and receives the signal from a number of slices, in combination with radio frequency pulses where the power is independent of the number of slices (PINS, Norris et al., 2011), potentially offers considerable reduction in SAR and a significant increase in speed for both spin-echo EPI and FSE type sequences.

The origins of the spin-echo fMRI signal

One of the key arguments for spin-echo fMRI, and indeed for the move to very high static magnetic field strengths was given by Ogawa and colleagues, who were the first to show that the BOLD extravascular signal change could be separated into a static dephasing regime, and a dynamic averaging regime (Ogawa et al., 1993). Both of these would contribute to a T2*-weighted experiment, but only the latter to a T2-weighted one. Of course it is the presence of the static dephasing components that makes T2*-weighted fMRI considerably more sensitive than the T2-weighted experiment. The two components left in the T2-weighted signal from both intra- and extravascular compartments are the extravascular dynamic averaging and the intravascular T2-like changes. The main attractive property of the extravascular dynamic averaging component, is that the signal changes should be localised to the smaller vessels, primarily in the capillary bed. Even when both compartments contribute to the signal, it is predicted that the spin-echo fMRI signal should be better localised to the neuronal activity than gradient-echo (Boxerman et al., 1995). Ogawa et al. (1993) showed that the strength of this contribution increases with the square of the strength of the static magnetic field. This provided one of the main motivations to move to high static magnetic field strengths for functional imaging. A second argument for improved spatial specificity with increasing static magnetic field strength is the dramatic reduction in venous T2 that occurs with increasing magnetic field. Thus at very high static magnetic fields (7 T and above) the spin-echo fMRI signal is expected to be dominated by the extravascular dynamic averaging component, because of the virtual disappearance of the intravascular contribution (Lee et al., 1999; Ugurbil et al., 2000; Yacoub et al., 2003). Simulation predicts that the spin-echo fMRI signal without a change in blood volume will rise, up to a main field strength of about 7 T and then flatten off (Uludag et al., 2009).

The addition of a small degree of diffusion-weighting to a spin-echo sequence is known to suppress the intravascular component. Using this technique the relative contributions of the two contrast mechanisms that contribute to SE-EPI can be assessed as a function of static magnetic field strength. These experiments have shown that there is a small (Jones et al., 1998) or negligible (Oja et al., 1999) extravascular contribution at 1.5 T, which rises to about 50% at 3 T (Jochimsen et al., 2004; Norris et al., 2002). Duong et al. (2003) investigated the intravascular contribution at both 4 and 7 T and found that in both cases the signal change is dominated by the extravascular compartment, with a larger intravascular contribution at 4 T. These results are in general agreement with recent simulations (Uludag et al., 2009) that predict a steady fall in the relative intravascular contribution with increasing static magnetic field strength, but notably still predict an intravascular contribution of about 25% at 7 T.

The distribution of blood vessels of various diameters is not uniform throughout the grey matter, and has a different structure than that associated with the histological divisions. The grey matter in the brain has six histological layers but only four vascular ones. These are illustrated in Fig. 5. Given that there is a greater capillary density in vascular layer 3 than in any of the other vascular layers it is to be expected that the T2-weighted BOLD response will have the largest contribution from this vascular layer, which subsumes histological layer IV, which is generally the layer at which neuronal input to a region occurs, as well as parts of layers III and V. In general the blood supply to grey matter is provided on the arterial side by vessels running into the grey matter from the pial surface, and on the venous side by drainage in the opposite direction, *i.e.* the dominant venous flow direction is from the deeper to the more superficial layers. There are hence a far greater number of larger vessels, and indeed a greater blood volume at the pial surface than within the grey matter itself.

On measurement and interpretation

At 1.5 T the assumption can be made that the entire T2-weighted signal change is of intravascular origin, which permitted the development of a theoretical construction showing how spin-echo based fMRI signal changes can be used to calculate absolute blood volume

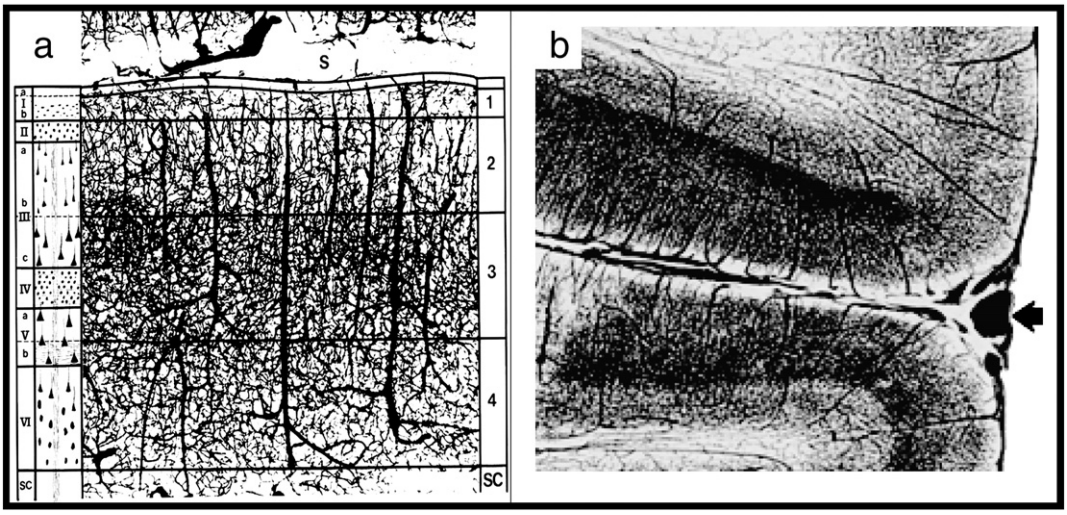

Fig. 5. (a), Vascular and histological layers of the human cortex. The six histological layers are numbered in roman numerals and sketched on the left, the depiction of the vasculature takes the bulk of the diagram, with vascular layers numbered using the Arabic system on the right. Taken with kind permission from Fig. 255 Duvernoy and Bourgouin (1999). (b), Vascular density in human primary visual cortex: the sparsity of vessels in layer 4 and the dominance of layer 3 are clearly visible. Taken with kind permission from Duvernoy et al. (1981).

(van Zijl et al., 1998). However, the initial studies at 1.5 T showed that the sensitivity of SE based fMRI is much lower than that of GE, and that its use is probably confined to the primary cortices (Bandettini et al., 1994; Constable et al., 1994; Jones et al., 1998; Oja et al., 1999). This has also been the general experience at 3 T (Lowe et al., 2000; Schafer et al., 2008; Thulborn et al., 1997), although one publication did look at whole brain activation in a colour word matching Stroop task (Norris et al., 2002). The conclusions reached: that Z-scores are reduced by a factor of about three with respect to a comparable GE sequence; and that the localisation of signal would not be much better than in GE acquisitions because about 50% of the signal contribution is intravascular, has probably dissuaded other investigators from the use of SE at 3 T, even though the elimination of signal dropout made it possible to detect some activation that was invisible with gradient echo. At 7 T there are remarkably few (if any) truly cognitive studies using SE fMRI outside the primary cortices, though this is probably in large part caused by the experimental difficulties discussed above. One recent publication (Goerke et al., 2011) has compared gradient-echo EPI, spin-echo EPI and RASER at 7 T for both the Stroop colour word matching task and activation in visual cortex. In strongly distorted regions the performance of RASER was superior to that of the EPI-based sequences, though the intrinsic contrast as measured in primary visual cortex was lowest.

For standard fMRI experiments the spatial PSF has not shown the improvement expected with increasing static magnetic field strength (c.f. Table 2 in Norris, 2006) when measured using retinotopy in humans (Engel et al., 1997). Although it is conceivable that this has something to do with the nature of the retinotopy experiment, in which waves of activation propagate along primary visual cortex, as other experiments have indicated a superior PSF to that found in retinotopic mapping (Yacoub et al., 2003). Comparisons between SE-BOLD at 3 and 4 T with 7 T have shown an increase in sensitivity, even though the intravascular contribution is expected to diminish at 7 T (Duong et al., 2002; Duong et al., 2003; Schafer et al., 2008; Yacoub et al., 2003). If the intravascular contribution is eliminated by diffusion weighting, then the increase in sensitivity between 4 and 7 T follows a near quadratic relationship (Yacoub et al., 2003). Although SE-BOLD will always be less sensitive than GE-BOLD in terms of the magnitude of the signal change, the use of spin echoes will eliminate many sources of signal fluctuation, and hence lead to better temporal noise characteristics than for GE-BOLD. In summary, given the difficulties in acquiring high spatial resolution SE-BOLD data from extended regions of the brain, and the intrinsically lower sensitivity compared to GE, SE-BOLD has to date primarily been employed at high static magnetic field strengths to examine the layers and columns of the brain.

A number of studies have investigated layer specific activation in the primary cortices of mammals ranging from rats to humans. There is a general consistency through the spin-echo literature showing that there is a peak of activation at a depth corresponding to that of layer IV, the input layer (Goense and Logothetis, 2006; Harel et al., 2006; Zhao et al., 2006), although Jin and Kim (2008b) failed to find an SE-BOLD peak at layer IV. The peak at layer IV is also consistent with investigations using CBF (Zappe et al., 2008) and CBV (Harel et al., 2006; Jin and Kim, 2008a) as contrast parameters.

Ocular dominance columns (ODCs) have been mapped in humans using both GE-BOLD (Cheng et al., 2001; Dechent and Frahm, 2000; Goodyear and Menon, 2001; Menon et al., 1997; Yacoub et al., 2007; Zhang et al., 2010) and SE-BOLD techniques (Yacoub et al., 2007). Yacoub et al. (2007) performed a direct comparison and found SE-BOLD to be superior for the mapping of ODCs. However, the use of a 3 mm slice thickness in this study meant that pial contributions to the GE signal could not be removed on the basis of position. Following on from this result the same group used SE-BOLD to investigate the orientation columns in human visual cortex, which are at a considerably finer spatial scale than the ODCs (Yacoub et al., 2008). An example of the convincing results obtained is shown in Fig. 6.

The SE-BOLD investigations of both cortical layers and columns used without exception some form of segmented spin-echo EPI acquisition to obtain sufficient spatial resolution and to reduce the T2* contamination. In this context the study of Goense and Logothetis (2006) is particularly valuable, as it shows the effect that increasing the EPI readout train length has on the laminar excitation profile. Figure four of Goense and Logothetis (2006) shows that at a readout train length of 7.7 ms there is negligible T2* contamination, but that this is already significant at a readout train length of 15.4 ms. These results were obtained at 4.7 T, but equivalent readout train lengths at other field strengths can be obtained by using equation 6 of Uludag et al. (2009). As all the studies at 7 T and higher cited here have used readout trains of 20 ms or more the conclusion can safely be drawn that a significant degree of T2*-weighting is present. No equivalent experiment to that of Goense and Logothetis (2006) has been performed for cortical columns, and it is hence unclear how an increase in the echo train length will affect such measurements. However, given that the columns represent a quasi-periodic distribution of point activations on a folded surface it would seem plausible that

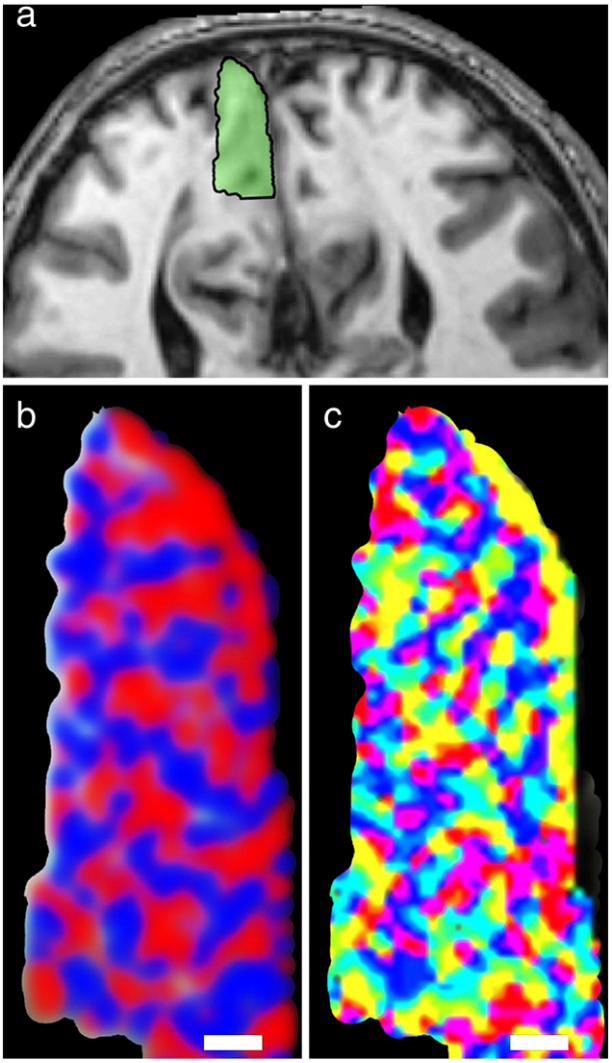

Fig. 6. Ocular dominance columns and orientation columns. Slice selection and functional domains in human visual cortex. (a) Depicts the optimal region of flat grey matter in primary visual cortex (parallel to the calcarine sulcus) in one subject from which columnar level fMRI maps of ODC (b) and orientation preference (c) are generated and characterised. The functional maps in (b) and (c) are zoomed views of the ROI in (a). The red and blue colours in (b) indicate preferences to right or left eye stimulation, whereas the colour distribution in (c) represents a given voxel's fMRI time course phase, which is indicative of its preferred stimulus orientation. (Scale bar: 1.0 mm.). Taken by kind permission from Yacoub et al. (2008).

higher spatial frequency components are present. This remains to be investigated experimentally.

Personal conclusions

This article has not been written along the lines of a traditional review, and has attempted to give a fair appraisal of the current literature, while stimulating debate. In this spirit the article concludes with a series of proposals based on the foregoing text and supported by a short rationale:

1. *There is little point in conducting spin-echo fMRI at main magnetic field strengths of 3 T and below.* There may be some limited applications for SE in regions where GE approaches show signal dropout (Norris et al., 2002; Schwarzbauer et al., 2010), but in general the loss in sensitivity is too great, and the gain in spatial specificity too little (Parkes et al., 2005). In the light of this conclusion the remaining points will be discussed in the context of applications at 7 T or higher.
2. *There are fundamental limitations to acquiring spin-echo BOLD data at 7 T and above.* The ideal sequence to use would be a string of pure spin echoes such as the HASTE approach of (Poser and Norris, 2007). This approach will generally be limited by power deposition, even if the refocusing pulses later in the echo train are reduced using TRAPS (Hennig et al., 2003). If the degree of T2* weighting is to be kept negligible, then the results of (Goense and Logothetis, 2006) imply that the number of gradient echoes that can be recalled between successive refocusing pulses will be severely curtailed. The use of slice multiplexing combined with PINS (Norris et al., 2011) could bring the speed of data acquisition to a competitive level for whole brain coverage at moderate spatial resolution, but slice multiplexing will be of little use for high spatial resolution applications requiring near contiguous slices. Pure SSFP sequences represent a low SAR alternative for whole brain studies, but the contrast of SSFP may not be exactly equivalent to that of a spin-echo. RASER offers pure T2-contrast but at the cost of: high SAR, either single slice or segmented acquisition, and a limited spatial resolution. In conclusion, very high spatial resolution with whole brain coverage, an acceptable acquisition time and a pure spin-echo contrast is a Utopian goal. Hence the only realistic approach currently available is to use spin-echo EPI. This may be valuable for conducting whole-brain studies for regions affected by dropout, in which case the readout train length should be minimised by the use of parallel imaging, and PINS multiplexing will be necessary to ensure whole brain coverage at short TR. For high resolution studies a combination of zooming and segmentation is required, as has already been successfully applied (Yacoub et al., 2007, 2008). The acquisition of contiguous volumes at high spatial resolution will probably require the use of zoomed 3D-EPI/GRASE sequence (Feinberg et al., 2008).
3. *Whole brain coverage with SE-BOLD at very high static magnetic field strengths could prove valuable.* Any spin-echo based pulse sequence will by definition have no signal dropouts and distortion can be limited by the use of parallel imaging techniques. The optimum TE will not vary strongly throughout the brain, unlike the T2* variation, which is a disadvantage for GE sequences. Furthermore if the degree of T2* contamination is insignificant, then the signal will be largely localised to vascular layer 3 of the parenchyma, which should improve the spatial localisation in comparison to a GE sequence of the same nominal resolution, and may also simplify the interpretation of the data, on the basis that the signal can only be arising from histological layers III–V. The time course noise of such a signal can also be expected to be lower than that of a corresponding GE sequence. This approach could offer an improvement in spatial resolution to the neuroscience community at an intermediate level between current spatial resolutions and refined studies of layers and columns. Data would need to be analysed at the single subject level prior to averaging to avoid the extensive data smoothing currently employed in group analyses.
4. *SE-BOLD is probably better suited to study cortical columns than cortical layers.* The variation in density of the microvasculature through the cortex (c.f. Fig. 5) means that there will be a strong variation in the sensitivity of measurement in the different laminae. Vascular layer 3 can be expected to give the strongest response. The columns of course run through all the layers, and hence a robust total SE-BOLD response can be expected when integrated over the whole column, albeit weighted by the differing sensitivity of the laminae. This is the situation that will pertain if a spin-echo experiment is performed with a relatively thick slice, with the slice orientation perpendicular to the cortical surface (Yacoub et al., 2008). In the study of layers, vascular layer 4 (which contains the whole of cortical layer VI) has a low capillary density which may make it difficult or impossible to detect activation with SE-BOLD, and layers 1 and 2 have a far lower capillary density, which may make the detection of activation in the corresponding histological layers (I–II) difficult.

In recent years there has been an increase in discussion regarding the relative merits of SE-BOLD and GE-BOLD for the performance of high resolution fMRI. The original argument for SE-BOLD that it was exclusively sensitive to the parenchyma has been countered by arguments that at high spatial resolution the pial layer can be excluded from analysis and venules radial to the cortex identified and removed (Barth and Norris, 2007; Koopmans et al., 2010; Polimeni et al., 2010). Variations in the laminar activation profile obtained with GE-BOLD have been explained in terms of layer specific variations in T2* (Koopmans et al., 2011), and it has been shown that the spatial PSF of GE-BOLD improves with increasing laminar depth (Polimeni et al., 2010). It will also be necessary to determine the radial PSF for GE-BOLD, as activation originating in deeper cortical layers may contaminate the signal from more superficial ones, a problem that is less likely to be of significance for SE-BOLD. Furthermore activation in the superficial layers will be difficult to measure in GE_BOLD, and any SE-BOLD signal with significant T2*-weighting, because of the close proximity to the pial surface. GE-BOLD has still to demonstrate that it is capable of high resolution columnar studies such as those examining orientation columns. On the other hand, it would be advantageous for SE-BOLD if convincing activation could be shown outside of vascular layer 3.

An interesting corollary of the result that within grey matter, contamination with T2*-weighted signal is not incompatible with resolving cortical layers, is that a higher degree of contamination can be tolerated for SE-BOLD at high spatial resolution. Indeed the use of asymmetrical spin-echo (Boxerman et al., 1995), originally proposed in the early days of fMRI, could be considered in order to improve the sensitivity, particularly for cortical layers with a low capillary density.

As a general conclusion, spin-echo fMRI has a number of attractive characteristics. Rapid developments in our understanding of the origin of BOLD signal changes, and in our ability to conduct spin-echo fMRI studies, mean that the coming years will show whether spin-echo fMRI remains a niche application or indeed assumes a more central role in fMRI.

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