# Acquisition Methods for fMRI at 7 Tesla

Peter J. Koopmans, Nuffield department for clinical neurosciences, University of Oxford, UK

- fMRI at 7 Tesla is mostly used in the context of high spatial resolution
- Resolution in part limited by $T_2^*$ effects in EPI readout
- Other limitations come from vascular organisation, impact depends on application
- High resolution is probably best used as a method to flexibly shape regions of interest, rather than trying to compare groups of subject based on a volume of 1 $mm^3$ or smaller.

Goal: to give the reader some insight in the effects under consideration when choosing a method for high-resolution fMRI (the main application of high field fMRI).

## FMRI and high field, which application?

For most imaging applications the benefit of 7+ Tesla scanners is quite obvious: there is more signal which can be used to improve SNR-starved images or, in case of an SNR surplus, it can be invested in shorter acquisitions without compromised image quality. In the typical BOLD fMRI experiment (2-3 mm isotropic spatial resolution, volume TR of 2-3 seconds) there is plenty image SNR. Tryantafyllou et al.[1] showed that in most experimental conditions, the unwanted temporal fluctuations are dominated by physiological noise sources that scale with the signal strength hence increasing $B_0$ is not particularly useful. One could try and use the SNR surplus to obtain shorter acquisition times but the fixed echo time for optimal BOLD contrast and the fact that fMRI scan times are often limited by the time it takes the subject to perform enough instances of a task both reduce the impact of high field scanners on fMRI.

Another way to invest the signal boost is to increase the spatial resolution without losing too much SNR. The question to ask then is if increasing the spatial resolution of fMRI data is useful. Conventional multi-subject fMRI studies use large amounts of smoothing in order to be able to look at group effects. People's brains are simply too different to compare at scales <~1cm even after 'normalisation'. From that perspective it does not make sense at all to invest in high-resolution fMRI. Of course, this does not mean that there are no interesting processes happening in the brain at scales smaller than 1 cm, it only requires a different analysis philosophy: instead of trying to pool all data into a single average brain, we need to look at the smallest scales in individual subjects first, come up with a summarising measure, and only then compare those measures across subjects. In some applications this can be quite a hurdle when effects are hard to determine in just a single subject.

One important point to realise is that the focus of the analysis seldom is to analyse a single location of say $1mm^3$. More often multiple very specific voxels are chosen and combined into a very specific ROI. Laminar fMRI studies are a good example, where many small voxels are combined that all are located in a single layer (e.g. layer 4) of a particular brain area (e.g. V1). Another example would be the study of cortical columns where the behaviour of groups of cortical columns is described by averaging many columns (each 1 voxel wide and only a couple of voxels high).

## Resolution and sequence contrast choice:

For spatial resolution in fMRI there are a two main points to consider:

- The BOLD signal is a mix of various contrast effects that each have an intrinsic spatial resolution
- The obtained voxel size is not identical to the nominal resolution of the sequence (i.e. what was entered on the console)

The BOLD effect consists of four contrast mechanisms

1) Extravascular static dephasing (the deoxyhaemoglobin in the big veins elicits a magnetic field inhomogeneity outside the vessel that is large w.r.t. the path length that free diffusing spins travel between excitation and the echo time).
2) Extravascular dynamic dephasing, similar to (1) but this time in the capillaries. The extent of the field now is rather small, meaning that free diffusing spins tissue experience a wide range of fields instead of an approximately constant one as was the case in (1). Therefore, static dephasing can be refocused with a spin-echo, dynamic dephasing cannot.
3) A frequency difference between the blood signal and its surrounding tissue, causing the entire vessel to dephase w.r.t. grey matter. This can be refocused with a spin-echo.
4) Intravascular $T_2$-effect. There are two competing explanations which are hard to verify: intravascular dynamic dephasing may occur or there could be a rapid exchange of protons between sites that have different magnetic susceptibility.

Two of these contrasts effects can be refocused meaning they will not contribute in a spin-echo experiment. This reduces the BOLD sensitivity of spin-echo (which is one of the reasons that spin-echo is not used much in neuroimaging studies). On the other hand, one of the refocused effects (nr 3) is located in the draining veins, rather remote from the site of activation. This means that the intrinsic spatial resolution of gradient-echo based fMRI should be inferior compared to that of spin-echo. This poses a bit of a dilemma: ideally one would want a spin-echo experiment but in submillimetre applications (i.e. layers and columns) there may not be enough CNR to be able to afford the loss of two contrast mechanisms.

It must be said that the above strictly holds for a pure spin-echo experiment, which is rather time inefficient. In reality one would always use SE-EPI where the EPI kernel adds a significant amount of $T_2^*$ weighting, equalising the GE and SE experiments to some degree[2].

Another downside of having to use (long) EPI readout trains is the fact that $T_2^*$ decay over the course of the entire readout has a smoothing effect: consider the exponential decay as a multiplicative filter function in k-space. Fourier theory states that the multiplication in k-space equates to a convolution in image space of the original image with a kernel that is the Fourier transform of the decay filter function (see figure 1). The fact that k-space is band-limited (we scan up to a certain spatial frequency, higher ones are set to zero) can be similarly described as a filtering function with a smoothing effect in image space through convolution with a sinc function in this case. It should be noted that the smoothing effect of the $T_2^*$ decay is less strong in spin-echo EPI as the decay function is centred around the centre of the readout, whereas in the gradient-echo case it decays monotonically from the start.

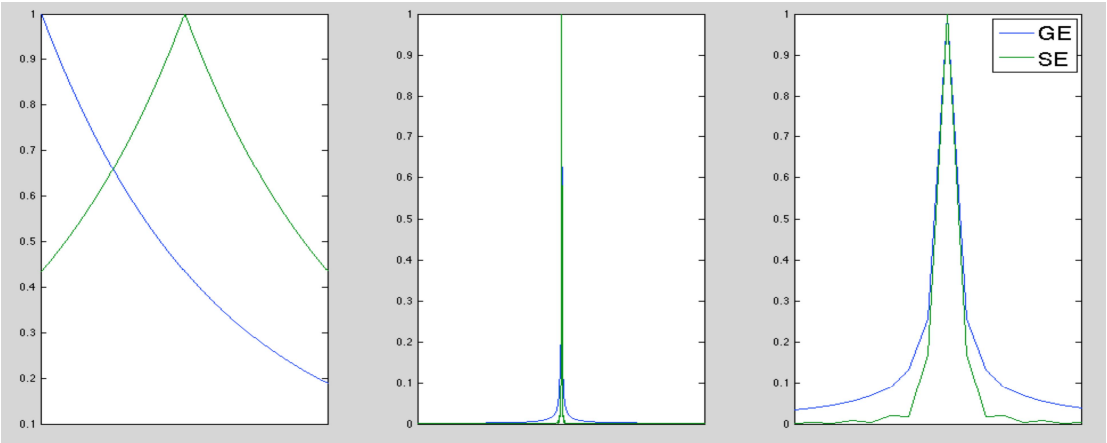


*Figure 1: $T_2^*$ k-space filter functions (left) for gradient-echo (blue) and spin-echo (green) and their Fourier transforms. These curves assume a long EPI kernel duration of 50 ms (to be interpreted as worst case scenario) with a $T_2^*$ of 30 ms (~grey matter at 7T). From the zoomed image on the right it is clearly seen that the gradient-echo kernel is wider at the bottom and hence the images will be more smooth in the phase encode direction compared to spin-echo.*

Finally, the impact of the $T_2^*$ weighting in gradient-echo (and spin-echo EPI) should be put into context of what the goal of the experiment is. The large draining veins are located on the surface of the cortex. Most of the impact could be avoided by simply excluding the surface voxels from the analysis. This will fix most problems in columnar analyses (as shown by Polimeni et al.[3]). In cortical layer analyses, things that happen on the surface are completely irrelevant by definition. There is a caveat here however in the sense that extravascular effects of the big surface vessels can show up in superficial layers. Using a very slow non-EPI sequence Koopmans et al.[4,5] showed that gradient-echo is able to show specific laminar profiles where grey matter layers do not simply mimic what happens at the surface.

**Sequences:**

With respect to specific sequences there is not very much choice. From a time-efficiency standpoint EPI is all but obligatory. In order to reduce the in-plane blurring effect described above, segmented EPI could be considered. The downside is that (phase) inconsistencies between segments can increase temporal fluctuations by quite a lot. Navigators can be used to counter it and very convincing resolution recovery has been shown in the form of RESOLVE by Porter and Heidemann[6] (see for example figure 5 in that text). Navigators do require taking another hit in time efficiency however meaning five-fold segmentation slows the acquisition by quite a lot more than just a factor of five.

Another way of reducing the $T_2^*$ blurring is to reduce the FOV. Using outer volume suppression pulses or inner volume selection (spin-echoes only) small sections of the brain can be scanned with high resolution and a small matrix (i.e. short readout) without the rest of the brain folding in because it does not produce signal [e.g. ZOOPPA[7]].

Overall, one could state that the choice in work-horse sequences is similarly limited as always has been the case in conventional resolution fMRI. Some groups have used SE-EPI, GE-EPI and 3D-GRASE (which is a hybrid of the two), all suffer from blurring artefacts of their readout trains, and they each have $T_2^*$ contributions to a certain degree, but all have the capacity to cover reasonable volumes relatively quick. More exotic methods include VASO (CBV-weighted, mostly in animals with contrast agents) and a line-scanning method where laminar projection images of a very small patch of cortex were made with very high temporal resolution[8].

**Comment on slice resolution:**

Both 2D-EPI as 3D-EPI have been used for high-resolution fMRI. The 3D method uses secondary phase encoding for slices rather than RF slice selection. The reason this can be useful in high-resolution fMRI is that thin slices are hard to produce with RF pulses because strong gradients and low bandwidth pulses are required. The latter results in low bandwidth-timeproducts however, which can be interpreted as a measure for slice profile quality. Phase encoding is not ideal either of course as the k-space truncation effect discussed earlier shows up here too. 3D-EPI has the slight advantage that it is easier to use parallel imaging to accelerate in the slice direction due to the secondary phase encoding property. Recently, the advent of multiband imaging, a technique where multiple slices are excited at the same time, has made slice acceleration possible for 2D too, but this can be very SAR intensive, especially if thin slices are desired.

**Experiments:**

Cortical columns have not been studied much yet with fMRI. Yacoub et al. were one of the first to convincingly show ocular dominance and orientation column results in humans with fMRI[9,10], but since then there has not been much follow up. This may in part be explained that, in contrast to layer studies (see below), it is hard to get an independent measure to select voxels belonging to a certain group of columns. For layers one can simply take the voxel's cortical depth coordinate, i.e. a structural measure, but for columns there are no anatomical landmarks available in MRI. Pattern classifiers have been used to try and find voxels that match in behaviour, but if those classifiers truly point out columns or some other underlying structure or that they even simply reflect the vascular organisation instead is still under debate[11].

Layer studies have been performed but to date have been mostly about method validation in primary sensory areas rather than answering neuroscience questions. Early studies mostly reported on relatively strong activation in layer 4 of primary visual cortex but effects outside layer 4 slowly start to filter through. Unfortunately, the first gradient-echo experiments confirmed that indeed a very large fraction of the signal change originates from the surface vessels. This means that it will likely be quite hard to 're-examine' some neuroscience findings at higher resolution in cases where effect sizes were already quite small.

**References:**


1 Triantafyllou, C., Hoge, R. D. & Wald, L. L. Effect of spatial smoothing on physiological noise in high-resolution fMRI. *NeuroImage* **32**, 551-557, doi:10.1016/j.neuroimage.2006.04.182 (2006).

2 Goense, J. B. & Logothetis, N. K. Laminar specificity in monkey V1 using high-resolution SE-fMRI. *Magnetic resonance imaging* **24**, 381-392, doi:10.1016/j.mri.2005.12.032 (2006).

3 Polimeni, J. R., Fischl, B., Greve, D. N. & Wald, L. L. Laminar analysis of 7T BOLD using an imposed spatial activation pattern in human V1. *NeuroImage* **52**, 1334-1346, doi:10.1016/j.neuroimage.2010.05.005 (2010).

4 Koopmans, P. J., Barth, M. & Norris, D. G. Layer-specific BOLD activation in human V1. *Human brain mapping* **31**, 1297-1304, doi:10.1002/hbm.20936 (2010).

5 Koopmans, P. J., Barth, M., Orzada, S. & Norris, D. G. Multi-echo fMRI of the cortical laminae in humans at 7 T. *NeuroImage* **56**, 1276-1285, doi:10.1016/j.neuroimage.2011.02.042 (2011).

6 Porter, D. A. & Heidemann, R. M. High resolution diffusion-weighted imaging using readout-segmented echo-planar imaging, parallel imaging and a two-dimensional navigator-based reacquisition. *Magnetic resonance in medicine : official journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine* **62**, 468-475, doi:10.1002/mrm.22024 (2009).

7 Heidemann, R. M. *et al.* Isotropic submillimeter fMRI in the human brain at 7 T: combining reduced field-of-view imaging and partially parallel acquisitions. *Magnetic resonance in medicine : official journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine* **68**, 1506-1516, doi:10.1002/mrm.24156 (2012).

8 Yu, X., Qian, C., Chen, D. Y., Dodd, S. J. & Koretsky, A. P. Deciphering laminar-specific neural inputs with line-scanning fMRI. *Nature methods*, doi:10.1038/nmeth.2730 (2013).

9 Yacoub, E., Shmuel, A., Logothetis, N. & Ugurbil, K. Robust detection of ocular dominance columns in humans using Hahn Spin Echo BOLD functional MRI at 7 Tesla. *NeuroImage* **37**, 1161-1177, doi:10.1016/j.neuroimage.2007.05.020 (2007).

10 Yacoub, E., Harel, N. & Ugurbil, K. High-field fMRI unveils orientation columns in humans. *Proceedings of the National Academy of Sciences of the United States of America* **105**, 10607-10612, doi:10.1073/pnas.0804110105 (2008).

11 Beckett, A., Peirce, J. W., Sanchez-Panchuelo, R. M., Francis, S. & Schluppeck, D. Contribution of large scale biases in decoding of direction-of-motion from high-resolution fMRI data in human early visual cortex. *NeuroImage* **63**, 1623-1632, doi:10.1016/j.neuroimage.2012.07.066 (2012).