Functional imaging of the human mediotemporal lobe

A neuroscientist's guide to fMRI pulse sequence optimization

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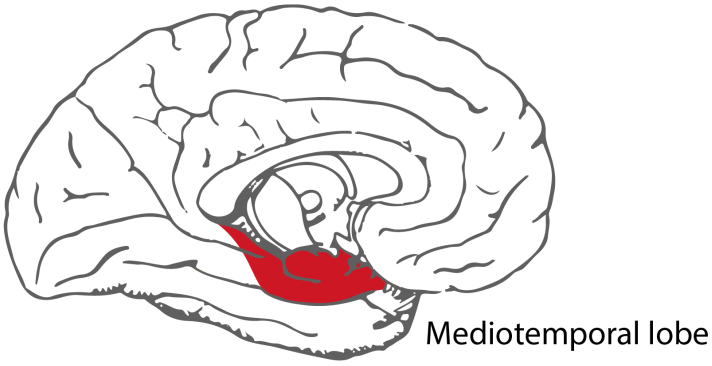

Contents

1 Why this guide and for whom is it?

Functional magnetic resonance imaging (fMRI) measures human brain activity non-invasively and has proven to be a 'workhorse' technique in cognitive neuroscience. One intensively studied region is the mediotemporal lobe (MTL). It comprises the hippocampus, the amygdala, the entorhinal cortex and the perirhinal cortex, and supports a wide range of perceptual and mnemonic functions. Unfortunately, it is also among the regions that are most difficult to image with fMRI. Its anterioventral parts are especially subject to strong distortions, signal loss and low temporal signal-to-noise ratios (tSNR). The MTL therefore requires some special dedication and care to get a good signal. Here, I compiled some tips and tricks about optimizing echo planar (EPI) sequences for studies of the human MTL and discuss how the individual sequence parameters affect the data quality. With this, I hope to help future generations of students to get the most of their precious scanning time, and that it triggers discussions from which I hope to learn myself. I simply wrote the guide I wished we had when setting up new EPI-sequences in the group of Christian F. Doeller (www.doellerlab.com).

I am not an MR-physicist, and this guide is not for MR-physicists, it is for those biology, psychology & medical students that are about to start a new fMRI-study, with only limited understanding of pulse sequences and data quality measures. The lessons learned here build on many hours of scanning, quality checks, online searches and reading. The most important conclusion is perhaps little surprising, but it is an important one: There is no free lunch! An 'all-round carefree' sequence does not exist and improving the data on one end, often affects it at another.

To give a simple example, if you want to study hippocampal subfields, a small voxel size is important. If you want to analyze the global connectivity of the amygdala, a big field of view (FOV) could help. Often you cannot have both and your choice influences other factors such as tSNR or artifacts. I am convinced that thinking about your requirements carefully before scanning, and understanding how your choice of sequence affects the data, will greatly benefit your study later on.

I plan to adapt and update this guide from time to time. If you have suggestions or comments, but especially if you disagree with anything, please approach me.

2 Background learning material

This guide assumes that you have a basic understanding of the key terms and parameters of an MRI pulse sequence. If the terms 'TR & TE', 'slice package' or 'multiband' do not mean anything to you, there are some great books [1] and online resources that will get you started. I highly recommend checking out the amazing online blogs that are around (e.g. practicalfmri.blogspot.com, mriquestions.com, technicalfmri.blogspot.com to mention a few). Also, Remi Gau made a great list of online learning material surrounding fMRI. You find it on his github page.

3 Why is the mediotemporal lobe so difficult to image?

There are at least three major problems in EPI-scanning that are not unique to, but often most severe in the MTL.

Distortions
MRI localizes voxels based on their resonance frequency. In an ideal world, the static B0-field of an MRI-scanner is the same for all voxels and does not affect this frequency. In reality, the B0-field is not perfectly homogeneous, and some voxels' B0 deviates from the one used to calibrate the RF-pulse exciting these voxels. If so, the voxels resonate at the 'wrong' frequency and will ultimately be mislocalized [2, 3]. This is called a susceptibility artifact and it gets more pronounced at the boundaries between air and tissue where the field is most inhomogeneous. Unfortunately, just below the MTL there are big air cavities, which make it very sensitive to distortions [4].

Signal loss
Another susceptibility artifact is 'drop out' or signal loss. If the B0-field is inhomogeneous, it varies not only across voxels, but also within a voxel, causing it to resonate at many frequencies. This can lead to phase-interference when reading the signal from that voxel, ultimately resulting in the signal being lost. Again due to its proximity to air cavities, the MTL is often strongly affected by such signal loss (along with the inferior temporal lobe) [4, 5].

Low temporal signal-to-noise ratio (tSNR)
The mean signal intensity of a voxel divided by its temporal standard deviation is *the* currency for any type of fMRI study. As discussed below, there are various ways of reducing distortions and signal loss, unfortunately many of them penalize tSNR (as well as the related contrast-to-noise ratio [6]). Sequences optimized for the MTL typically seek to reduce susceptibility artifacts, often leading to low tSNR values and lower statistical power.

4 Exploring EPI-sequence parameters

Let's look at the sequence parameters and some hardware options and how they affect the three problems introduced above. Please note that I refer to 3T-MRI by default.

Slice package
Three things are important here: field of view, spatial resolution and tilt. The bigger your field of view and the more voxels are in it, the longer it will take to acquire each volume. For whole-cerebrum (wc) coverage, not including the cerebellum, usually a slice package of at least 200×200×130 mm is necessary to accommodate most participants.

I typically aim at having relatively short TRs (∼1000 ms) to resolve fast events and to increase the number of volumes per event to get a good estimation of the hemodynamic response function (HRF) [7, 8]. Without multi-slice imaging (multiband (MB)/simultaneous multislice (SMS)) and with wc-coverage, this would require the voxels to be quite large (>3.5mm). MB/SMS reduces the TR drastically, allowing you to shrink the voxel size to around 2 mm and still get wc-coverage. To resolve hippocampal subfields, you want a voxel size no bigger than 1.5 mm isotropic (also see the 'in-plane resolution' section below). In that case, you will probably need to sacrifice coverage and focus your field of view on the MTL directly or have a long TR.

Once you defined your slice package, you need to choose its orientation relative to the participant's head. Importantly, distortions occur mostly along the phase-encoding direction. The slice tilt defines your phase-encoding direction relative to the head, which in turn affects susceptibility artifacts. Optimizing tilt can hence greatly affect your data quality [5, 9]. A positive slice tilt (Fig. 1), that is the anterior edge of the slice points towards the chest [5], aligns your slices parallel to the MTL (e.g. along the hippocampal long axis).

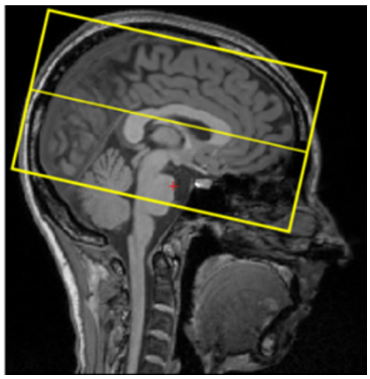

Figure 1: Positive slice tilt

If you choose a positive tilt (Fig. 1), use an anterior to posterior (A>>P) phase-encoding, as this has been shown to reduce susceptibility artifacts and improve MTL BOLD sensitivity (Fig. 2, [5], also see [9, 10]). Avoid the oral cavities here and do not tilt the slices more than ∼40°. Otherwise you will most likely cut off the nose and risk a strong phase wrapping artifact, meaning that the nose wraps around to the back of the head, potentially occluding parts of the

occipital or parietal lobe. For the same reason you generally do not want the object you are scanning to be larger than your field of view. Knowing this, do you see a problem in Fig.1?

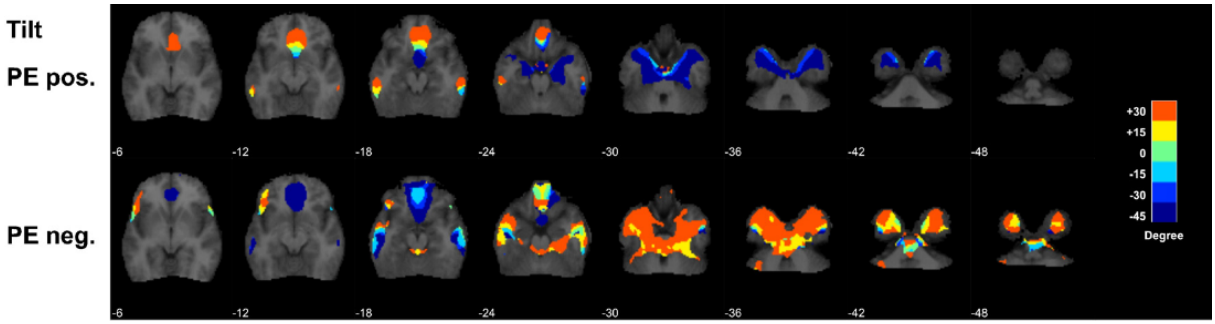

Figure 2: Optimal tilt and phase encoding direction at 3T. For the MTL, a positive tilt is best for anterior to posterior (A>>P) phase-encoding. PE pos. and PE neg. denotes positive (P>>A) and negative (A>>P) phase encoding direction. Figure adapted from [5].

By scanning only one pilot participant with several different slice tilts, you will learn a lot about your sequence. It is also a great example of how optimizing a simple parameter can improve your data substantially. Keep in mind however that optimizing tilt for the MTL can lead to a suboptimal tilt and hence stronger distortions in other areas such as the ventromedial prefrontal lobe (Fig. 2).

Echo time (TE)

Keep the TE short, but not too short. Typically, the longer your TE is, the stronger the susceptibility artifacts will be. To shorten the TE, you could increase the bandwidth (which penalizes tSNR), use parallel imaging such as GRAPPA or SENSE [10, 11] at moderate acceleration (~2-fold) [12], or do partial Fourier imaging. If the TE is too short however, i.e. the echo occurs earlier than ~15-20ms after excitation, the T2 signal did not have time to decay much before it is read out. This leads to a suboptimal signal amplitude and ultimately low tSNR. The sensitivity to BOLD is maximal when the TE equals the T2*-decay time constant, which differs across regions [14].

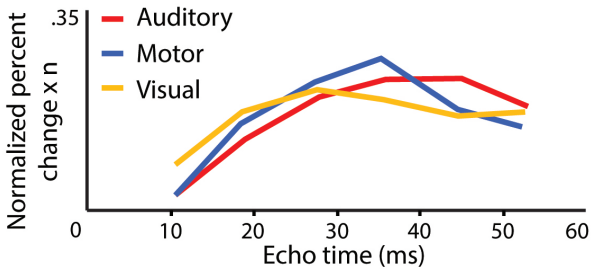

Figure 3: The effect of echo time (TE) on BOLD sensitivity. The optimal TE differs across regions (depicted are the auditory-, motor- and visual cortex). Data from [14].

The T2* decay is slower for cortical grey matter (∼66ms) than for deeper gray matter, such as the putamen (∼31ms) [13]. Others report the optimal TE to be 25-30 ms in visual cortex and 35-40 ms in auditory and motor cortices (Fig. 3) [14]. The optimal TE might also vary across the lifespan. If you scan infants for example, longer TE's are better [15].

To me, TE's of around 25 ms seem to be a good compromise between distortions and sensitivity for studies of the MTL. You might end up scanning a TE that does not maximize the tSNR fully, but your data will be less distorted. In many cases, this is still worth considering, simply because a region of interest (ROI) with lower tSNR is still better than an ROI that misses most voxels entirely due to distortions and drop-outs (also see chapter 'Quality assessment and artifacts'). If you do not see strong distortions in your data, you could afford taking a longer TE (∼30-35 ms). Side note: Always check your ROIs overlaid on the functional images, not on the structural T1 scan. If you use GRAPPA, be aware that it is quite sensitive to head motion occurring during the reference scan in the beginning. Generally, a super simple life-hack to reduce head movements is to attach medical tape on both sides of the head coil and across the participant's forehead after placing the cushioning but before putting on the front piece. This gives participants a gentle feedback about their own movements, many of which are not aware that they moved. It hence reduces movements during scanning to some degree at basically no cost (but not comparable to a head cast or bite bar solution).

Repetition time (TR) and multislice imaging

How much can you accelerate your sequence? As mentioned above, pulse sequences with short TR's produce more images, providing a better HRF-estimation, and often lead to higher statistical power [7, 8]. After testing many settings for the cmrr-multiband- and the Siemens SMS-package in combination with other factors such as GRAPPA acceleration and others, I recommend what Siemens and others had recommended anyway. Do not accelerate more than 6-fold overall! Keep in mind however that this might depend on the type of headcoil you use (I refer to the Siemens 32-channel head coil). With wc-coverage and a decent in-plane resolution this still gives you a TR of around 1000 ms. Notably, there are amazing fMRI studies with ultrashort TR's of below 100 ms, these however usually use only very few slices (e.g. [16]). Notably, multislice imaging can lead to an artifact called slice-leakage. Here, the signal of one slice leaks into the other simultaneously acquired slices (Fig. 4), leading to false positive activations across the brain [13,14]. This is critical because your nice cluster in hippocampus might actually originate somewhere else. To quantify this problem in your data, you can compute the 'L-factor', a metric that quantifies slice leakage [19].

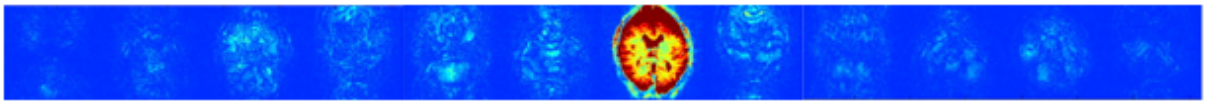

Figure 4: Slice leakage. Depicted are 12 simultaneously acquired slices (MB/SMS = 12). For very high multiband accelerations, you risk leakage of the signal of one slice into all other simultaneously acquired slices [20]. Color code depicts the L-factor, the fractional signal cross-contamination per slice. Figure adapted from [8].

Higher acceleration factors lead to more such false positive activations [18]. You can reduce this problem drastically by using the Split Slice-GRAPPA image reconstruction technique [17]. I did not yet compare these different reconstruction methods, but the benefit seems obvious (Fig. 5).

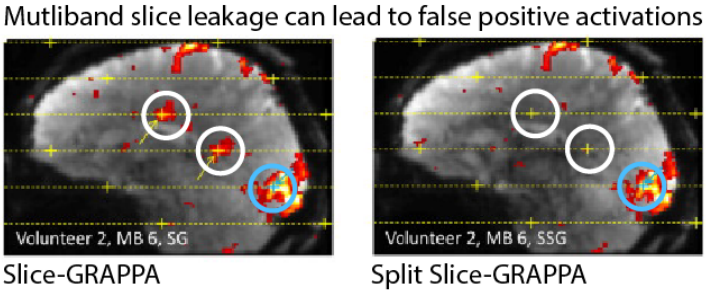

Figure 5: Mutlislice imaging (mutliband/SMS) can lead to false positive activations due to slice leakage. The signal of one slice (blue circle) leaks into other slices that were simultaneously acquired (yellow lines), leading to false positive activations (white circles). Split Slice-GRAPPA reconstruction reduces this problem [17]. Figure adapted from [18].

Generally, if you use MB/SMS with an interleaved acquisition, make sure the number of slices divided by the MB/SMS factor equals an odd number (Fig. 6). For example, 10 slices and SMS = 2 (10/2 = 5) is better than 12 slices and SMS = 2 (12/2 = 6). If it is an even number, the slice groups can interfere with each other and create artifacts.

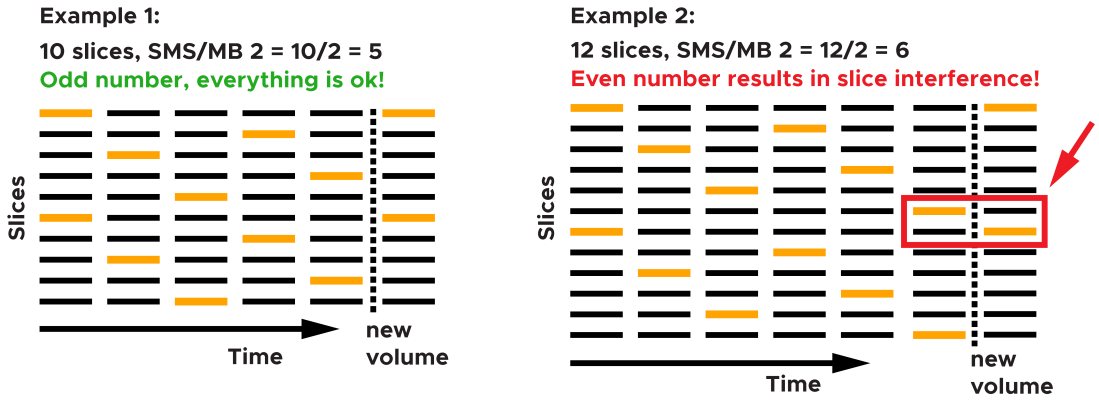

Figure 6: Number of slices divided by the MB/SMS factor must equal an odd number for interleaved acquisition.

Side note: when you adjust the TR of your sequence, do not forget to adjust the flip angle as well. You can calculate the optimal flip angle here: mritoolbox.com/ErnstAngle.

In-plane resolution

Increasing in-plane spatial resolution can decrease voxel-wise tSNR and increases the readout time. Longer readout time in turn leads to stronger distortions. If you require a voxel size smaller than ∼1.5mm at 3T, you will most likely have to sacrifice coverage/field of view to keep the readout time short. With 2-2.5mm voxels however you get enough voxels to perform multivariate analyses in areas such as the entorhinal cortex or hippocampus (>200 voxels), while still covering the entire cerebrum at a short TR. In theory, larger voxels should lead to higher tSNR because more signal is averaged and noise is reduced. This is true for most areas, specifically if the B0-field is homogenous. However, since drop out occurs due to inhomogeneity in the B0 within a voxel, increasing the voxel size can actually lead to more phase-interference in regions with B0-field inhomogeneity, resulting in stronger signal loss and hence lower average tSNR and amplitude in an ROI. In the MTL, larger voxels do not therefore automatically lead to higher tSNR. In fact, if you have strong signal loss in your data, reducing the voxel size (by increasing in-plane resolution or decreasing slice thickness), can help to recover the signal.

Bandwidth

While the term can mean two things, the transmitter bandwidth and the receiver bandwidth, by default it describes the latter. The receiver bandwidth refers to the range of frequencies that are read-out per pixel in the 2D-slice plane (e.g. 1500hz/pixel). It basically describes with how many 'bits' the signal is recorded. Increasing the bandwidth reduces distortions and drop out (even around metal parts) and allows for shorter TE's and TR's. It however also increases the amount of noise that is recorded, in turn leading to a decrease in tSNR. Therefore, keep the bandwidth low for the first pilot sequence and try to reduce susceptibility artifacts by other means (e.g. GRAPPA to shorten the TE, optimizing the slice tilt, unwarp your data...). If you are still not happy with the result, then start increasing the bandwidth. Side note: the transmitter-bandwidth defines the slice thickness (broader spectrum means more protons resonate). To find an excellent overview by J. Graessner about bandwidth [21] please click here.

Head coil

In addition to the sequence parameters discussed above, there are also hardware factors to be considered. An important one is your choice of head coil. The more coil elements in a head coil, the smaller each individual element is. The size of a coil element, determines its depth sensitivity, with larger coils receiving signals from deeper structures in the brain. The 32-channel head coil provides a good compromise between spatial resolution and tSNR in deep structures like the MTL. Notably, if a voxel size of >3 mm is sufficient for your study, it can be better to use a 20- or 12-channel head coil since the mean signal amplitude in deeper structures tends to be higher than with 32-channels [22]. However, only change to fewer channels if it does not cost you tSNR, which is typically higher on head coils with more channels [23](Fig. 7). This is true also for deep structures like the cerebellum, for which tSNR has been reported to increase by 40 percent on the 32- compared to the 12-channel head coil [22]. Since other factors such as e.g. voxel size play a more important role for tSNR (Fig. 7, [23]), I suggest to use the 32-channel head coil for your pilot scans and, once you have a favorite sequence, test it on the 12-, 20- or 64-channel head coil as well. Click here to find a nice blog-article related to this.

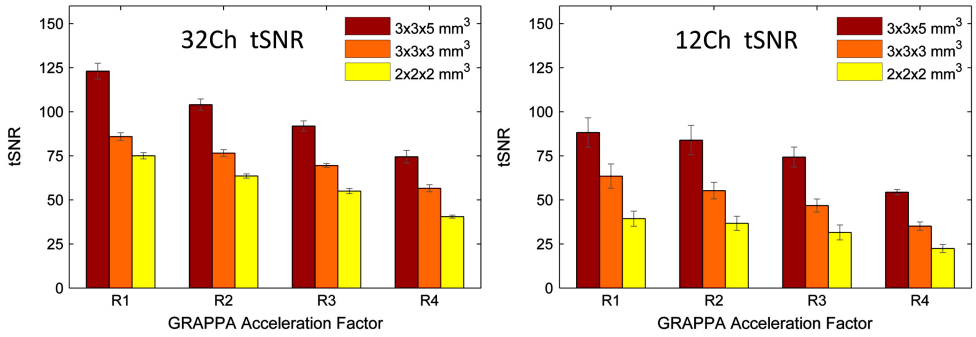

Figure 7: tSNR (average across several gray matter ROIs) as a function of head coil (12-channel vs. 32-channel), voxel size and GRAPPA acceleration factor. tSNR increases with voxel size and number of head coil channels, but decreases with increasing GRAPPA factor. Figure adapted from [23]

5 Quality assessment and MR-artifacts

Once you have a few different pilot sequences, you want to know how well they perform. Find below how to do a simple quality assessment. This does not replace proper control checks of the scanner by experts, but it will give you a quick idea of performance.

- Scan each of your sequence settings with the same pilot subject(s) for about 10 minutes (same duration, not the same number of TR's). Acquire a structural T1 scan. Ideally, you want a participant with a big head to be sure everybody else will fit too.
- Preprocess these data the same way you would preprocess your final data. At the very least, realign your images, create a meanEPI and tSNR image and coregister everything to the T1. Segment the T1 to get grey- and white matter masks as well as a global in-brain mask.
- Overlay your meanEPI on the T1 and/or the gray matter mask on the meanEPI (e.g. using itk-SNAP). Naturally, you want these images to overlap as much as possible. In reality, it will never be perfect. Search for mismatches between the meanEPI and the T1. If you find any, zoom in and double-check if there is grey matter still (but distorted) or if it is lost (drop out). Definitely zoom in on the MTL carefully. Distortions can be factored in on the ROI level, drop out cannot.
- Calculate the spatial signal-to-noise ratio (sSNR) for your ROIs using the meanEPI image. It is the average signal intensity of the ROI divided by the standard deviation in intensities across voxels. The higher sSNR, the better. By doing this, you can also identify areas that are partially affected by drop out (often those with very low sSNR).
- Coregister your favorite brain atlas to the T1 (e.g. the Juelich atlas) and compare the tSNR in a couple of regions across the brain as well as across sequences. The best sequence is the one for which the tSNR is highest and most similar across regions. The tSNR determines your minimal effect size and the minimal scan duration to detect it [24], so make sure your sequence and study design allow you to detect your expected effects (Fig. 8).
- Many software packages classify voxels using a voxel intensity cut-off and segment the brain based on the distribution of intensities across voxels. While tSNR is more critical than absolute amplitude for fMRI, make sure you do not lose voxels in the MTL only because they do not surpass the amplitude threshold of the software you plan to use (a common problem for entorhinal cortex for e.g. SPM defaults).
- Search through the meanEPI and the tSNR image and look for artifacts (Fig. 9). You will find a list of the common ones below, along with some tips on how to deal with them.

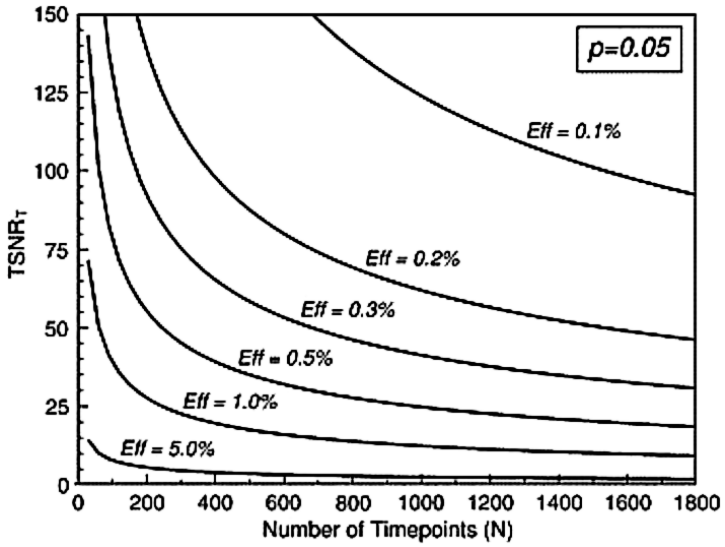

Figure 8: The tSNR and the scan duration determine the minimal effect size (Eff) you can expect to find. Depicted is the (theoretical) relationship between these factors for a liberal p-threshold (p = 0.05). Figure adapted from [24].

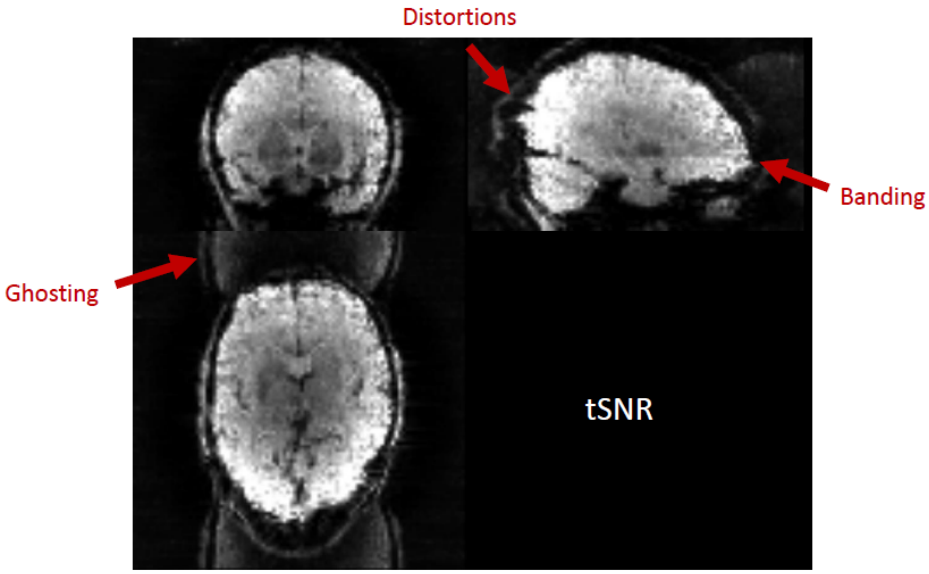

Figure 9: MR-artifacts. Depicted is the tSNR image of one participant for a poorly performing sequence, showing strong distortions, a strong Nyquist ghost and mutliband-banding

Distortions

Distortions and the influence of different sequence parameters are discussed throughout the guide. In short, to reduce distortions, try lowering the TE and/or the in-plane resolution and optimize the slice tilt first. Applying a moderate z-shim gradient pre-pulse can also recover tissue affected by distortions and drop out [5, 9].

Moreover, always try to correct distortions during the preprocessing, for example via the widely supported B0-field map correction. It requires you to perform an additional scan for each participant, but it is quick and all major fMRI software packages support it ('Unwarping' in SPM, 'FUGUE' in FSL...). Since distortions mainly follow the phase-encoding direction with a magnitude that depends on the TE, this method utilizes the voxel shift at two different TE's to reconstruct where the voxel must have been at a hypothetical TE = 0.

While the approach above is still the most widely used one, there are better options around. For example, rather scan a few extra volumes with your own functional sequence (∼1 minute) but reverse the phase-encoding direction (e.g. P>>A instead of A>>P) [25, 26]. In these extra images, the distortions will fall into the opposite direction compared to your functional images of interest. Create one meanEPI for your actual data and one for these extra scans. Then, use the FSL-function 'TOPUP' or CMTK to compute and correct the distortions. Such reverse-gradient correction techniques tend to work better than a classical field map (Fig. 10) [27].

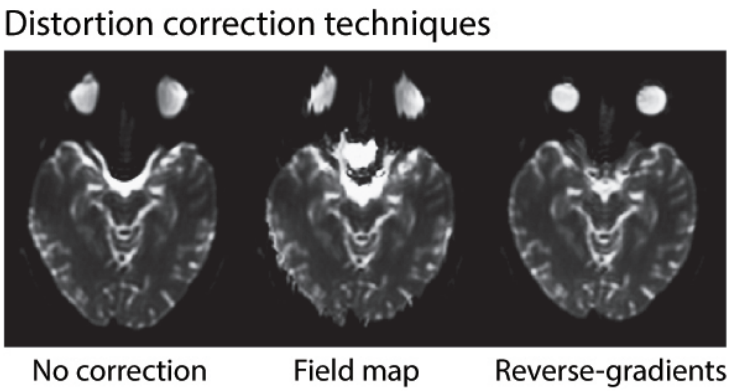

Figure 10: EPI-image distortions without correction (left), field map corrected (middle) and reverse-gradient corrected (right). Figure adapted from [27]

Nyquist ghost

In EPI, odd and even lines in k-space are sampled with opposite read gradients, making it necessary to reverse the direction of every other line before image reconstruction. Unfortunately, the two echoes with opposite gradient are sometimes not perfect mirror versions of each other and the timing of the switching gradients is not always perfect (because the machine is not). During image reconstruction, such timing differences can lead to errors in the estimated signal phase, ultimately resulting in a second image shifted/phase-offset relative to the main image [28, 29]. This is called the Nyquist- or N/2-ghost.

If you see ghosting in your meanEPI or the tSNR image, make sure it does not overlap with the brain. If so, this can severely confound your data, especially if participants move and the two overlaid images move relative to each other. As long as the ghost does not overlap with the brain, there are several methods to correct for it (e.g. [30] for recent work). Many of them require an additional calibration scan (for an overview and comparison see e.g. [31]). You can quantify the severity of ghosting using the ghost-to-signal ratio (GSR) and compare it across your epi-sequences. For each sequence, do the following steps.

- Mask 1: take the whole-brain mask (e.g. from the segmentation step).
- Mask 2: Circular-shift it by n/2-voxels along the phase encoding direction. Then, remove overlap with mask 1.
- Mask 3: Make an ROI for out-of-brain & out-of-ghost voxels
- Calculate mean intensities for these three masks across voxels and time
- GSR = (Mask 1 - Mask 3)/Mask 2 Ghosting often occurs when there are technical problems with the MR-scanner or the head coil. Ask your local support to double-check if the ghosting is severe.

Banding

Multiband/SMS imaging can lead to a surprisingly common artifact. It is visible as sudden intensity difference between slices and is often referred to as 'banding' (Fig. 9), see github-discussion here. In my experience, it is often times more pronounced in the tSNR image than in the meanEPI, so make sure to check those carefully. To reduce it, first try an 'ascending' or 'descending' slice order instead of 'interleaved'. If that does not help, increase the pulse duration (which will unfortunately lead to stronger drop out and longer TRs and TEs).

To be extended

6 One sequence to rule them all?

Many labs try to establish a standard sequence, which they trust and use for multiple studies. Having this sequence does make sense for similar study designs, if your task design or objectives differ, it clearly does not. Think about your own requirements carefully before scanning and adapt the sequence accordingly. This guide does not cover different task designs in detail, but as a start, it can help to see what sequence parameters other studies with similar designs have used. Below, you will find the T2*-EPI-sequence parameters of a few studies examining MTL activity, taken from the published articles. For quick overview, I indicated the objectives and analyses with simplified tags.

- **Baldassano et al., 2017** [32]: Hidden-Markov model, movie watching, event-segmentation.
  TR = 1500 ms, TE = 28 ms, voxel size 3×3×4mm, flip angle 64, 27 slices, FOV 192×192 mm.

- **Bellmund et al., 2018** [33]: Multivariate, pre-post design, picture viewing.
  TR = 2270 ms, TE = 24 ms, flip angle = 85°, voxel size = 1.5×1.5×1.5mm, 40 slices, FOV = 210×210mm.

- **Brunec et al., 2018** [34]: Temporal autocorrelation analysis, virtual navigation.
  TR = 2000 ms, TE = 30 ms, voxel size = 3.5×3.5×5.0mm flip angle = 70 degrees, FOV = 200 mm. Base resolution = 64×64, 30 axial slices.

- **Constantinescu et al., 2016** [35]: Univariate, movie stimulus-outcome judgement.
  TR = 3000 ms, TE = 30 ms, flip angle = 87°, voxel size = 3×3×3mm. 45 slices. FOV = 192mm.

- **de Voogd et al., 2018** [36]: Univariate, 2-back-task /w & /wo eye movements.
  TR = 2200 ms, TE = 9.4, 21, 33, 44 and 56 ms (multi-echo), iPAT/GRAPPA factor = 3; flip angle, 90°; slice matrix size, 64×64; slice thickness: 3.0 mm; slice gap: 0.51 mm; FOV: 212×212 mm; bandwidth: 2604 Hz/px; echo spacing: 0.49 ms, 35 axial slices, 1.5T.

- **Dimsdale-Zucker et al., 2018** [37]: Multivariate, object-recognition, HPC subfields.
  TR = 2010 ms, TE = 25 ms, multiband factor = 2, voxel size = 1.5×1.5×1.5mm. Field of view = 216 mm, image matrix = 144×152, flip angle = 79°, bandwidth = 1240 Hx/pixel, partial phase Fourier = 6/8, parallel imaging = GRAPPA factor 2 with 36 reference lines, 52 slices.

- **Garvert et al., 2017** [38]: Repetition suppression, stimulus detection & memory task.
  TR = 3010 ms, TE = 70ms, voxel size = 3×3×2mm, 1mm gap, 43 slices tilted by 30° relative to the rostro-caudal axis and a local z-shim with a moment of -0.4 mT/m ms was applied to the orbitofrontal cortex region.

- **Julian et al., 2018** [39]: Univariate, eye movements.
  TR = 1000 ms, TE = 25 ms; multiband factor = 4, voxel size = 2×2×2 mm; flip angle = 45°, FOV = 192°, matrix size = 96×96, 78 slices.

- **Kaplan and Friston, 2018** [40]: Univariate, memory-guided decision making.
  TR = 3360 ms, TE = 30 ms, voxel size 3×3×2mm, field of view, 64×72 mm, 48 slices tilted 45°.

- **Kim and Maguire, 2018** [41]: Repetition suppression, spatial & object memory task.
  TR = 3080 ms, TE = 30 ms, voxel size = 3×3×3mm, matrix size = 64×74, z-shim gradient moment of -0.4 mT/m ms, 44 transverse slices angled at -30°.

- **Kok and Turk-Browne, 2018** [42]: Inverted encoding, same-or-different detection task.
  TR = 1000 ms, TE = 32.6 ms, voxel size = 1.5×1.5×1.5 mm, multiband factor 6, flip angle = 55°, 60 slices, partial volume parallel to hippocampus.

- **Nau et al., 2018** [43]: Univariate, eye movements.
  TR = 1000 ms, TE = 34 ms, multiband factor = 6, voxel size = 2×2×2 mm, flip angle = 60°, FOV = 210×210 mm, 66 slices, base resolution 104×104.

- **Schuck and Niv, 2018** [44]: Multivariate/decoding, 1-back task /w rule-switching.
  TR = 3000 ms, TE = 27 ms, voxel size 2×2×2mm, flip angle = 80°, 53 slices, FOV = 192 mm, iPAT/GRAPPA factor = 3, positive tilt = 30°.

- **Stangl et al., 2018** [45]: Univariate, virtual navigation.
  TR = 1500 ms, TE = 30 ms, voxel size = 2×2×2mm, number of slices = 24, FOV = 216 mm, flip angle = 80°.

- **Zeithamova et al., 2018** [46]: Multivariate, reward encoding task.
  TR = 2000 ms, TE = 31 ms, multiband factor = 3, voxel size 1.7×1.7×1.7mm, flip angle = 73°, GRAPPA Factor = 2, base resolution: 128×128, 72 slices.

7 Conclusion

I hope this guide helped you to better understand some of the sequence parameters and that you feel more confident in testing the impact of some of them on your data yourself. If you do, test these parameters within the same pilot participants before you start your study. There is no perfect sequence that will always give you what you want and the choice of parameters very much depends on your study objectives. Having said this, if I had to put my recommendation into a nutshell, this would be it:

Top priorities are avoiding drop out and maximizing tSNR. Keep the TR as short as possible without inducing artifacts. Do not MB/SMS-accelerate more than 6-fold. Keep the TE at around 25 ms. Use a voxel size of 2 mm isotropic or less. Use a positive slice tilt. Use the 32-channel head coil. Keep the bandwidth low. Correct distortions with the reverse-gradient method. Always check for artifacts.

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8 References

[1] Scott A. Huettel, Allen W. Song, and Gregory McCarthy. Sunderland (2015) Functional Magnetic Resonance Imaging. Third Edition. Q. Rev. Biol. 90, 455-455

[2] Jezzard, P. and Clare, S. (1999) Sources of distortion in functional MRI data. Hum. Brain Mapp. 8, 80-85

[3] Farzaneh, F. et al. (1990) Analysis of T2 limitations and off-resonance effects on spatial resolution and artifacts in echo-planar imaging. Magn. Reson. Med. 14, 123-139

[4] Olman, C.A. et al. (2009) Distortion and Signal Loss in Medial Temporal Lobe. PLoS ONE 4, e8160

[5] Weiskopf, N. et al. (2006) Optimal EPI parameters for reduction of susceptibility-induced BOLD sensitivity losses: A whole-brain analysis at 3 T and 1.5 T. NeuroImage 33, 493-504

[6] Welvaert, M. and Rosseel, Y. (2013) On the Definition of Signal-To-Noise Ratio and Contrast-To-Noise Ratio for fMRI Data. PLoS ONE 8, e77089

[7] Feinberg, D.A. et al. (2010) Multiplexed Echo Planar Imaging for Sub-Second Whole Brain FMRI and Fast Diffusion Imaging. PLoS ONE 5, e15710

[8] Ugurbil, K. et al. (2013) Pushing spatial and temporal resolution for functional and diffusion MRI in the Human Connectome Project. NeuroImage 80, 80-104

[9] Deichmann, R. et al. (2003) Optimized EPI for fMRI studies of the orbitofrontal cortex. Neu-roImage 19, 430-441

[10] Tang H, Tabert MH, Albers M, Devanand DP, Wu EX, Brown TR. (2004) An optimized EPI pulse sequence using SENSE for fMRI studies of orbitofrontal and medial temporal brain areas. Proc. ISMRM

[11] Blaimer, M. et al. (2004) SMASH, SENSE, PILS, GRAPPA: how to choose the optimal method. Top. Magn. Reson. Imaging TMRI 15, 223-236

[12] Schmidt, C.F. et al. (2005) Sensitivity-encoded (SENSE) echo planar fMRI at 3T in the medial temporal lobe. NeuroImage 25, 625-641

[13] Peters, A.M. et al. (2007) T2* measurements in human brain at 1.5, 3 and 7 T. Magn. Reson. Imaging 25, 748-753

[14] Clare, S. et al. (2001) Single-shot T2(*) measurement to establish optimum echo time for fMRI: studies of the visual, motor, and auditory cortices at 3.0 T. Magn. Reson. Med. 45, 930-933

[15] Goksan, S. et al. (2017) Optimal echo time for functional MRI of the infant brain identified in response to noxious stimulation: Optimal TE for fMRI of the Infant Brain. Magn. Reson. Med. 78, 625-631

[16] Ekman, M. et al. (2017) Time-compressed preplay of anticipated events in human primary visual cortex. Nat. Commun. 8, 15276

[17] Cauley, S.F. et al. (2014) Interslice leakage artifact reduction technique for simultaneous mul-tislice acquisitions. Magn. Reson. Med. 72, 93-102

[18] Todd, N. et al. (2016) Evaluation of 2D multiband EPI imaging for high-resolution, whole-brain, task-based fMRI studies at 3T: Sensitivity and slice leakage artifacts. NeuroImage 124, 32-42

[19] Xu, J. et al. (2013) Evaluation of slice accelerations using multiband echo planar imaging at 3 T. NeuroImage 83, 991-1001

[20] Moeller S, Xu J, Auerbach EJ, Yacoub E, Ugurbil K (2012) Signal Leakage(L-factor) as a measure for parallel imaging performance among simultaneously multi-Slice (SMS) excited and acquired signals. Proc Int Soc Magn Reson Med

[21] Graessner J. (2013) Bandwidth in MRI? MAGNETOM Flash 22013

[22] Kaza, E. et al. (2011) Comparison of a 32-channel with a 12-channel head coil: Are there relevant improvements for functional imaging? J. Magn. Reson. Imaging 34, 173-183

[23] Triantafyllou, C. et al. (2011) Physiological noise and signal-to-noise ratio in fMRI with multi-channel array coils. NeuroImage 55, 597-606

[24] Murphy, K. et al. (2007) How long to scan? The relationship between fMRI temporal signal to noise ratio and necessary scan duration. NeuroImage 34, 565-574

[25] Andersson, J.L.R. et al. (2003) How to correct susceptibility distortions in spin-echo echo-planar images: application to diffusion tensor imaging. NeuroImage 20, 870-888

[26] Morgan, P.S. et al. (2004) Correction of spatial distortion in EPI due to inhomogeneous static magnetic fields using the reversed gradient method. J. Magn. Reson. Imaging 19, 499-507

[27] Holland, D. et al. (2010) Efficient correction of inhomogeneous static magnetic field-induced distortion in Echo Planar Imaging. NeuroImage 50, 175-183

[28] Bruder, H. et al. (1992) Image reconstruction for echo planar imaging with nonequidistantk-space sampling. Magn. Reson. Med. 23, 311-323

[29] Giannelli, M. et al. (2010) Characterization of Nyquist ghost in EPI-fMRI acquisition sequences implemented on two clinical 1.5 T MR scanner systems: effect of readout bandwidth and echo spacing. J. Appl. Clin. Med. Phys. 11, 170-180

[30] Ianni, J.D. et al. (2018) Ghost reduction in echo-planar imaging by joint reconstruction of images and line-to-line delays and phase errors: Joint Echo Planar Image, Delay and Phase Error Recon-struction. Magn. Reson. Med. 79, 3114-3121

[31] Clare S., Bowtell R., Morris P. (1998) Ghost artefact in fMRI: comparison of techniques for reducing the N/2 ghost. Proc. ISMRM

[32] Baldassano, C. et al. (2017) Discovering Event Structure in Continuous Narrative Perception and Memory. Neuron 95, 709-721.e5

[33] Bellmund, J.L.S. et al. (2018) Structuring Time in Human Lateral Entorhinal Cortex. bioRxiv. DOI: 10.1101/458133

[34] Brunec, I.K. et al. (2018) Multiple Scales of Representation along the Hippocampal Anteropos-terior Axis in Humans. Curr. Biol. 28, 2129-2135.e6

[35] Constantinescu, A.O. et al. (2016) Organizing conceptual knowledge in humans with a gridlike code. Science 352, 1464-1468

[36] de Voogd, L.D. et al. (2018) Eye-Movement Intervention Enhances Extinction via Amygdala Deactivation. J. Neurosci. 38, 8694-8706

[37] Dimsdale-Zucker, H.R. et al. (2018) CA1 and CA3 differentially support spontaneous retrieval of episodic contexts within human hippocampal subfields. Nat. Commun. 9, 294.

[38] Garvert, M.M. et al. (2017) A map of abstract relational knowledge in the human hippocampal-entorhinal cortex. eLife 6, e17086

[39] Julian, J.B. et al. (2018) Human entorhinal cortex represents visual space using a boundary-anchored grid. Nat. Neurosci. 21, 191-194

[40] Kaplan, R. and Friston, K.J. (2018) Hippocampal-entorhinal transformations in abstract frames of reference. bioRxiv. DOI: 10.1101/414524

[41] Kim, M. and Maguire, E.A. (2018) Hippocampus, Retrosplenial and Parahippocampal Cortices Encode Multicompartment 3D Space in a Hierarchical Manner. Cereb. Cortex 28, 1898-1909

[42] Kok, P. and Turk-Browne, N.B. (2018) Associative Prediction of Visual Shape in the Hippocampus. J. Neurosci. 38, 6888-6899

[43] Nau, M. et al. (2018) Hexadirectional coding of visual space in human entorhinal cortex. Nat. Neurosci. 21, 188-190

[44] Schuck, N.W. and Niv, Y. (2018) Sequential replay of non-spatial task states in the human hippocampus. bioRxiv. DOI: 10.1101/315978

[45] Stangl, M. et al. (2018) Compromised Grid-Cell-like Representations in Old Age as a Key Mechanism to Explain Age-Related Navigational Deficits. Curr. Biol. 28, 1108-1115.e6

[46] Zeithamova, D. et al. (2018) Abstract Representation of Prospective Reward in the Hippocampus. J. Neurosci. 38, 10093-10101