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Multi-echo acquisition

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Abstract

The rapid development of fMRI was paralleled early on by the adaptation of MR spectroscopic imaging (MRSI) methods to quantify water relaxation changes during brain activation. This review describes the evolution of multi-echo acquisition from high-speed MRSI to multi-echo EPI and beyond. It highlights milestones in the development of multi-echo acquisition methods, such as the discovery of considerable gains in fMRI sensitivity when combining echo images, advances in quantification of the BOLD effect using analytical biophysical modeling and interleaved multi-region shimming. The review conveys the insight gained from combining fMRI and MRSI methods and concludes with recent trends in ultra-fast fMRI, which will significantly increase temporal resolution of multi-echo acquisition.

Keywords

functional MRI; multi-echo acquisition; BOLD contrast; quantification; Z-shimming

INTRODUCTION

This review describes the development of fMRI from the point of view of a spectroscopist during a time period when imaging and spectroscopy were still considered very different disciplines. Spectroscopic imaging in humans was painfully slow and some researchers even ridiculed the low spatial resolution in metabolite maps in the human brain, contributing to the notion that the two fields had little in common. However, there was a growing curiosity about the biophysical mechanisms of BOLD contrast and the recognition early on that quantification of the fMRI signal changes might be challenging, yet critical to future acceptance of the new brain mapping technique, which inspired experiments to study water relaxation changes during brain activation. The echo time dependence of BOLD contrast in gradient echo and spin echo experiments were characterized within a few years after the initial discovery of the BOLD effect (Menon 1993, Bandettini 1994, Chen 1996, Gati 1997). Juergen Hennig from Freiburg introduced single voxel spectroscopy to characterize changes in water relaxation (T_2*) and initial signal intensity (I_0) during brain activation changes, which offered much greater sensitivity than conventional fMRI methods (Hennig 1994) and enabled clear detection of the initial dip (Ernst 1994). This demonstration of functional spectroscopy and the imaging based relaxation studies called for a merger of the two

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techniques that led to the development of functional MR spectroscopic imaging and multi-echo EPI. This development is continuing and recent advances in ultra-fast spatial encoding open up new perspectives for quantitative mapping of water relaxation changes with very high temporal resolution. The ultimate goal is to accomplish Hennig's experiment with single-shot 3D spatial encoding and millisecond temporal resolution in the relaxation time domain. Much has been learned about the BOLD effect and the many underlying contrast mechanisms using increasingly sophisticated measurement strategies and signal modeling approaches, yet the quest for quantifying the BOLD effect remains unchanged.

The early years: Transition from MR Spectroscopic Imaging to fMRI

My laboratory got into the field of fMRI rather late. I gathered my initial experience with fMRI in the early 90s as a postdoc at NIH using a 4 Tesla system, which could be interfaced either to a clinical console or to an experimental animal scanner console. To my dismay EPI was only available on the experimental console, which demanded great attention to manual shimming, and the image quality after time-consuming adjustments was marginal at best. Later on, I had the opportunity to participate in an fMRI experiment on a clinical scanner using conventional gradient echo imaging with rather long scan times, which unfortunately failed to show any convincing BOLD signal changes (not unexpectedly in retrospect). In the meantime, I focused my work at the Research Center Juelich in Germany on characterizing BOLD and metabolic signal changes during respiratory challenges and on the development of high-speed proton-echo-planar-spectroscopic-imaging (PEPSI), which matured to the point of high signal stability and excellent short echo time metabolite mapping in human brain. The initial reports from Ravi Menon et al in 1993 and from Peter Bandettini et al in 1994 using EPI at different echo times and from Juergen Hennig using single voxel PRESS spectroscopy (Hennig 1994), which characterized relaxation time changes during brain activation, inspired us to use the PEPSI method to map relaxation changes of the unsuppressed water signal during brain activation. Quantitative measurements of T_2* changes during brain activation using conventional fMRI methods were very time consuming and sensitive to variability in task execution during the many scan repetition at different echo times. It was clear to us that PRESS prelocalization was not optimal for MRSI, since the minimum echo time was rather long and it was sensitive to possible signal contamination from outside of the PRESS volume, in particular at short repetition time. Instead we used an FID version of the PEPSI sequence to achieve a minimum TE of 2 ms. We recognized that PEPSI in this implementation was similar to spectroscopic FLASH, which had been developed much earlier by Axel Haase (Haase 1990) and seemingly forgotten. Our earlier experience with conventional gradient echo imaging suggested that long repetition times were detrimental to functional sensitivity due to poor signal stability across large number of phase encoding steps, which was in part due to physiological fluctuations. Head movement was also a major concern as Hajnal's study had shown (Hajnal 1994). Our initial studies in visual cortex using LED stimulation were thus performed with rather limited spatial resolution of 0.36 cc. We subsequently found that reducing TR to 300 ms by sacrificing spectral resolution considerably improved functional sensitivity, as we had expected. We quantified the signal changes in the spectral domain and measured 4–6 % decreases in water line width in visual cortex during the activation condition, comparable to the magnitude of the positive BOLD effect observed with EPI, and less than 1 % change in peak area and peak frequency, which was reassuring (Posse 1997). We also noted slight changes in water line shape, but these were difficult to quantify in the frequency domain. In the time domain these signal characteristics were readily interpretable: The difference signals in the echo time domain showed the BOLD effect as a bell shaped curve with maximum close to T_2* of tissue (approximately 60–70 ms at 1.5 T), which had been described in previous studies. Interestingly, the BOLD effect extended over quite a large range of echo times (full width at half maximum: 60–120 ms depending on voxel location),

which did not fit with commonly used models of the BOLD effect that predicted faster fall-off towards longer echo times. Stefan Wiese in my lab confirmed this observation in a subsequent study using multi-echo EPI (Wiese 1999). Water signals from compartments with rather long T_2* values, such as CSF, contributed to the signal changes at long echo times, which was perhaps an effect of the large voxel size in our studies. Not surprisingly, this strongest effect size was mostly seen in a small region close to the sagital sinus, whereas EPI displayed a more widely distributed activation effect. We were also struck by the large contrast to noise ratio of the BOLD effect in the PEPSI measurement, which reached up to 50:1. This strong effect size and temporal extent of the BOLD effect in the echo time domain inspired us to consider faster multi-slice imaging methods to more fully sample the BOLD effect across a wide range of echo times with larger volume coverage. We then realized that the high sampling density in the echo time domain was unnecessary due to the smoothness of the signal relaxation and conjectured that additional spatial encoding in a second spatial dimension using gradient blips could be inserted between spectral acquisition points without much loss of relaxation information. At that point it became clear that insertion of an entire EPI readout module between spectral encoding points, albeit at low spatial resolution, was feasible. In my talk at the 1997 ISMRM meeting I hinted at this possibility by showing our first multi-echo EPI image with 8 echo times (Posse 1997). I named this MRSI approach Turbo-PEPSI, since I considered it an extension of the PEPSI method.

My students who made it a sport to come up with new acronyms also conceived an alternate name based on a competing soft drink. However, we finally decided to stay with the brand name. People often ask me as to whether PEPSI runs into trouble with PEPSICO Inc, but that’s not the case, since it is in a different product category. In fact, a Monte-Carlo generator in theoretical high-energy physics (http://arxiv.org/abs/hep-ph/9710381) and a spectrograph in large aperture telescopes (http://www.aip.de/pepsi/index.php?id=21) are also called PEPSI.

During these developments Valerij Kiselev, a gifted theoretical physicist, joined my lab and started looking at the biophysical mechanism of the BOLD effect with the aim of quantifying signal relaxation changes in different tissue compartments. He subsequently developed a theoretical framework for interpreting the relaxation changes by extending the analytical modeling of the static dephasing domain originally developed by Yablonski and Haacke (Yablonski and Haacke 1994) into the diffusion narrowing regime (Kiselev 1998, Kiselev 1999a), and demonstrated that his results were consistent with Monte Carlo simulations by Boxermann et al (Boxermann 1995). His simulations showed that the relaxation time courses of the initial FID and the spin echo contain a wealth of information about intra- and extra-vascular signal contributions originating from different tissue compartments and that the relaxation characteristics are dependent on vessel size. Markus Barth later demonstrated that large vessel contributions could be separated from small vessel contributions using high-resolution multi gradient echo fMRI and a fuzzy cluster analysis across echo times (Barth 1999a). Valerij’s simulations also showed that the relaxation behavior in the vicinity of large blood vessels could be quite complex and thus challenging to interpret. This further motivated me to explore the possibility of adding multiple spin echo acquisition modules to maximize information content for quantifying the gradient echo and spin echo BOLD signal. With his experience in modeling the signal relaxation in fMRI Valerij became closely involved in the development of multi-echo image analysis methods, and made key contributions to understanding the contrast behavior and to improving the quantification of the BOLD signal.

BOLD sensitivity enhancement

We soon started improving the performance of Turbo-PEPSI and conducted experiments with functional activation in visual and motor cortex on a conventional 1.5 Tesla clinical scanner. A key concern was that the signal might be dephased at long TE due to incomplete gradient refocusing as a result of eddy currents. In practice, the long-term eddy current effects were not quite as strong as expected and I reminded myself that when testing the signal refocusing during an echo-planar gradient train using the PEPSI sequence a couple of years earlier I measured coherent signal refocusing up to 512 ms after spin echo formation (Posse 1995). Interestingly, the readout duration in multi-echo EPI was similar to that of our PEPSI technique, but spectral resolution was much reduced due to the coarser sampling in the time domain. After much experimentation we were able to encode a 32x32 spatial matrix in 18.3 ms with up to 12 consecutive TEs and maximum TE of 212 ms, which led to unprecedented data rates and considerable challenges for data analysis. When fitting the relaxation time course data it became apparent that activation maps based on T_2* displayed higher sensitivity than those obtained with conventional EPI. We also found that the multi-echo acquisition at short TE in areas with magnetic field inhomogeneity, such as orbital-frontal cortex during olfactory stimulation, increased BOLD sensitivity compared to conventional EPI acquired at longer TE. Collecting data over a wide range of echo times thus ensured BOLD optimal contrast across the entire brain across regions with widely varying T_2* values (Posse 1998a).

After the submission of our 1998 ISMRM abstract we started looking at alternate means of combining the activation maps obtained at different TEs. It was apparent that significant BOLD contrast was detected in almost all of the echo images, following the bell-shaped curve we had previously seen in our PEPSI data. It was thus tempting to average the activation maps to reduce the random noise in individual maps. The initial analysis confirmed my assumption. It was a small step to perform the echo averaging within each TR. Valerij Kiselev developed an elegant theory comparing different preprocessing methods and demonstrated that the increase in temporal signal-to-noise and spatial extent of activation with TE averaging was comparable to averaging activation maps. Based on the BOLD contrast seen at different TEs it was clear that linear averaging was suboptimal and weighted averaging was thus adopted, initially using a global weight based on the average T_2* in the brain. This was later refined by using voxel specific weights obtained from T_2* mapping to optimize BOLD contrast across the entire brain across regions with widely varying T_2* values (Fig.1). We further determined that the increase in BOLD sensitivity plateaus when the echo train duration exceeds 3.22*T_2*, which enabled tradeoffs to be made between BOLD contrast and temporal resolution. I described our advances in maximizing BOLD contrast using weighted averaging in my talk at the 1998 ISMRM meeting (Posse 1998a) and at the 1998 HBM meeting (Posse 1998b).

Shortly thereafter Oliver Speck and Juergen Hennig published a paper describing mapping of I_0 and T_2* using multi-echo EPI on a 2T scanner with head gradient insert, which demonstrated the feasibility of monitoring localized changes in T_2* during fMRI (Speck and Hennig 1998). Subsequently, Markus Barth obtained similar results using a multi-echo spiral sequence (Barth 1999b). Since these results were similar to those obtained with our previous PEPSI experiments (Posse 1997) it seemed that fMRI and MRSI were merging in the context of multi-echo acquisition and a bright future opened up for improving quantification in fMRI.

New contrasts and compensation of magnetic field inhomogeneity

The BOLD contrast characteristics of multi-echo data acquisition offered considerable flexibility for increasing fMRI sensitivity and for exploring novel fMRI contrasts. Valerij Kiselev demonstrated that the BOLD contrast at different echo times enabled distinction of thermal noise and direct detection of BOLD signal changes without a-priori knowledge of the paradigm time course (Kiselev 1999b). We also sought to implement multi-echo acquisition into our real-time fMRI analysis pipeline to achieve maximum BOLD sensitivity in single trials. While spending a balmy winter in 1999 in beautiful Rome working with Gisela Hagberg we solved the problem of online T_2* mapping by developing a very fast NUMerical Algorithm for Real-time T_2* mapping (NUMART2*) using linear combination of the echo images (Hagberg 2002). With time, the performance of the reconstruction computers improved, correction for gradient heating related frequency drifts became available and eventually we were able to implement real-time reconstruction of the Turbo-PEPSI data on the scanner and perform real-time fMRI analysis of the multi-echo data with online T_2* fitting using our Functional-Imaging-in-REal-time (FIRE) software tool (Posse 2001a). Real-time fMRI studies at 1.5 and 4 Tesla confirmed that multiecho acquisition provided superior sensitivity, enabling detection of very brief episodes of activations in single non-averaged trials. A fascinating example, which I presented at the Society of Neuroscience meeting in 2004 was language activation in Broca's area when thinking of a single word (Fig. 2) (Posse 2004, Mayer 2006).

I had been keenly interested for quite some time in quantifying the BOLD contrast using absolute T_2* measurements. After our TurboPEPSI methodology was validated I sought the collaboration of Lars Kemna, a creative and resourceful young radiologist, and the PET group at the Research Center Juelich to compare TurboPEPSI and PET with arterial sampling, then and now still the gold standard for quantitative cerebral blood flow (CBF) measurements. We measured T_2* changes and corresponding CBF changes in the same subjects during manipulation of global CBF using respiratory challenges. Baseline T_2* values in gray matter and baseline CBF measured with PET showed a remarkably similar exponential increase with end-expiratory pCO_2 (Posse 2001b, Kemna 2001). Task induced T_2* and CBF changes showed distinct dependence on global CBF (Posse 2001b, Kemna 2001) and by combining the two measurements using Valerij Kiselev's theory it was possible to quantify $CMRO_2$ changes during brain activation as a function of global CBF (Kemna 2000).

Publications on single-shot multi-echo acquisition methods began to proliferate: Tomas Jonsson characterized motion correction in multi-echo EPI based on different echo images (Jonsson 1999), which was further developed by Oliver Speck using I_0 and T_2* maps (Speck 2001) and by Pieter Buur using linear regression based on the first echo time (Buur 2009). Gary Glover developed dual-echo spiral acquisition to reduce signal losses in frontal cortex and to increase sensitivity (Glover 2001). Nikolaus Weiskopf developed a new approach to correct geometrical image distortion in multi-echo EPI by measuring consecutive echo images with alternating phase encoding gradient directions and combining the images after deconvolution of the measured distortions (Weiskopf 2005). We and other groups using multi-echo EPI had seen that the signal relaxation in some brain regions was not necessarily mono-exponential, in particular in frontal areas and at the edges. To address this issue, Benedikt Poser developed a method to estimate optimal echo combination based on the contrast-to-noise ratio in resting state data acquired before the actual scan (Poser 2006). In his study he also proposed the use of parallel imaging to increase the number of acquired echo times to obtain finer sampling of the relaxation decay.

I now focused my attention on reducing signal losses in frontal and temporal areas, which is still a major limitation for fMRI compared to other brain imaging techniques. Z-shimming in frontal and temporal brain regions had been around for a while (Constable 1999), but the technique is very time consuming. I was curious whether Z-shimming (and by extension shimming along all three principal axes) in multiple regions could be interleaved into the Turbo-PEPSI sequence by applying brief shim gradients before the acquisition of each echo images. Local T_2* values in orbital frontal cortex and in particular in amygdala increased considerably with interleaved shimming, which created unique echo-time specific BOLD contrast. Weighted combination of these echo images required modification of the weights based on the measured T_2* values with interleaved shimming (Posse 2003). I used a CO_2 challenge paradigm to demonstrate that this gradient compensation method significantly enhances BOLD signal changes in amygdala as compared to conventional echo-planar imaging (EPI) and uncompensated TurboPEPSI. In later studies, we extended this approach using slice- and TE-specific interleaved shimming based on field mapping to increase the sensitivity gains (Posse 2005). We subsequently characterized the theoretical limits of interleaved linear shimming in different brain regions by mapping the local field gradient vectors across the brain and found that the amygdala is particularly suitable for interleaved shimming, since it exhibits more linear and uniformly oriented local gradients compared to other brain areas, such as the orbital-frontal cortex and the temporal lobe (Figs. 3–5) (Posse 2006). We also applied this approach to MRSI by interleaving a series of shim gradients with increasing moments into the echo-planar readout train of the PEPSI sequence to simultaneously shim two brain regions (Caprihan 2006).

The interest in using multi-echo EPI is still growing, in particular at high field where parallel imaging is now routinely used to minimize geometrical distortion. Multi-echo acquisition is advantageous when using parallel imaging, since it recovers the sensitivity lost by shortening the readout duration. In a recent study Benedikt Poser demonstrated considerable gains in sensitivity at 7 Tesla using multi-echo EPI with parallel imaging compared to conventional EPI (Poser 2009). However, the short T_2* values at 7 Tesla are a major challenge for multi-echo acquisition and even with parallel imaging the spatial resolution and number of echo times are limited.

Conclusions and Future Directions

Multi-echo acquisition has come long ways, starting with the initial studies using single voxel spectroscopy and high-speed MRSI this methodology has progressed to the development of real-time multi-echo EPI with parallel imaging and interleaved slice-specific shimming. It has become clear that relaxation time mapping, which is technically challenging and very time consuming with conventional fMRI methods, has the potential to take quantification of the BOLD effect to the next level. However, these advances come at the price of elongating TR or reducing volume coverage compared to conventional EPI, and may require sacrificing spatial resolution depending on the number of desired echo images. The optimal sampling duration decreases with increasing field strength as T_2* decreases. This enables higher temporal resolution, but gains in sensitivity decrease due to gradient performance limitations at high field strengths that limit the number of measurable echo images. These limitations persists to date and have prevented multi-echo EPI from entering mainstream fMRI, even though parallel imaging is beginning to alleviate these stringent requirements. Despite these limitations, multi-echo EPI is advantageous in selected applications where maximum sensitivity is required, such as real-time fMRI and when mapping functional activation in orbital-frontal cortex and amygdala. The recently introduced combination of parallel imaging with compressed sensing, which exploits the sparsity of the signal decay in the echo time domain (Feng 2011), has the potential to further

reduce encoding time, thus increasing spatial resolution and the number of echo times, and advancing the utility of multi-echo acquisition at high field.

A new generation of ultra-fast encoding techniques is poised to break down current barriers imposed by gradient encoding. Inverse imaging proposed by Fa-Hsuan Lin is almost instantaneous and can be combined with multi-echo readout as we have demonstrated for PEPSI (Lin 2008). Recent studies using multiplexed EPI (Feinberg 2010), MR encephalography (Zahneisen 2011) and echo-volumar imaging (Witzel 2011, Posse 2011) demonstrate that temporal resolution on the order of 100 ms or less significantly improves BOLD sensitivity not only for mapping stimulus correlated activation, but also for detecting resting state networks and for delineating physiological noise. Echo-volumar imaging, which can be performed in multi-slab fashion (Posse 2010, Posse 2011), can be extended to multi-echo acquisition to further maximize BOLD sensitivity. Further acceleration will be feasible by integrating compressed sensing (Lustig 2007) and superresolution reconstruction (Otazo 2009). The ultimate goal of quantitatively mapping water relaxation in 3 dimensions in a single shot with 100 ms temporal resolution may soon be within reach. This will bring us back to the goals of the early studies that measured BOLD signal relaxation using single voxel spectroscopy and MRSI. Quantification of signal contributions from different tissue compartments based on their relaxation and temporal correlation characteristics at both high spatial and high temporal resolution will be a key factor for improving the detection and the removal of physiological noise, whether it is due to vascular pulsation and autoregulation or due to uncontrolled thoughts, which ultimately limits fMRI sensitivity at high magnetic field strength. More importantly, this methodology will contribute to providing a deeper understanding of the BOLD contrast mechanisms and vascular regulation in human brain and enable new clinical application, including pharmacological fMRI and neurofeedback of single non-averaged trials using real-time fMRI.

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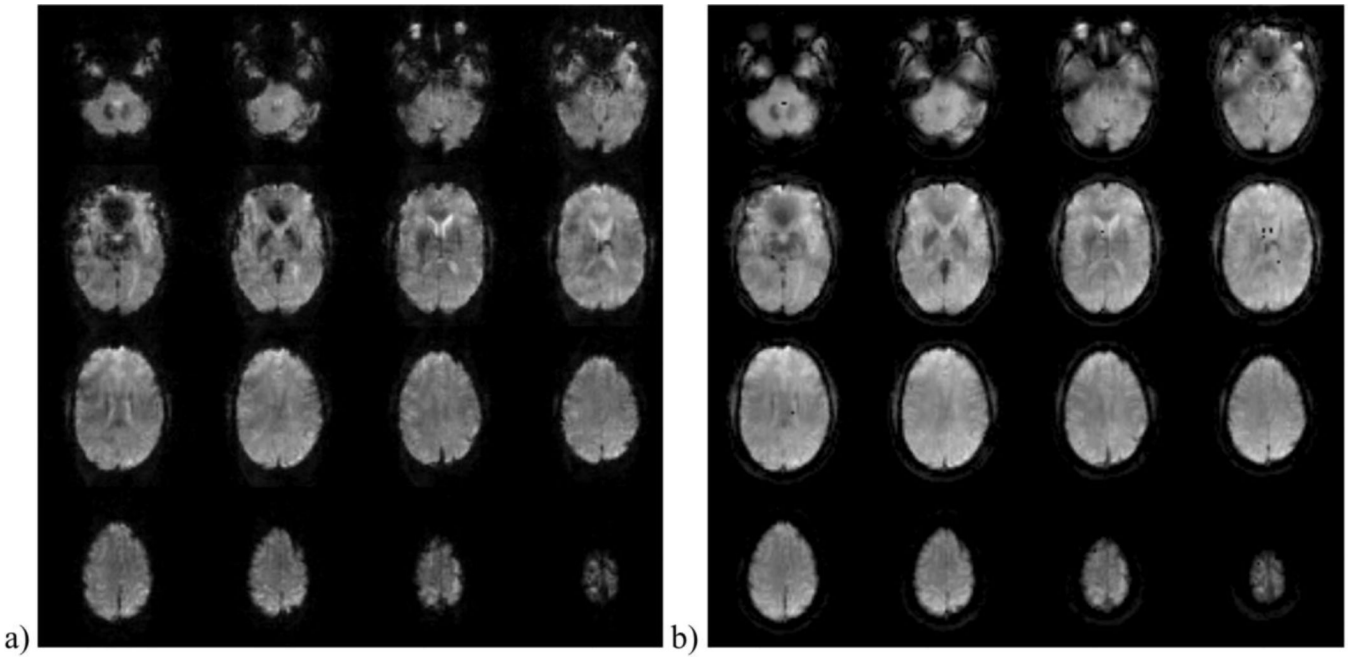

Figure 1.
(a) Conventional EPI at 4 Tesla measured with TE: 32ms suffers from significant signal dropouts in frontal and medial temporal areas. (b) Single-shot multi-echo EPI with weighted echo averaging shows considerably reduced signal losses and more uniform image contrast across frontal and medial temporal areas.

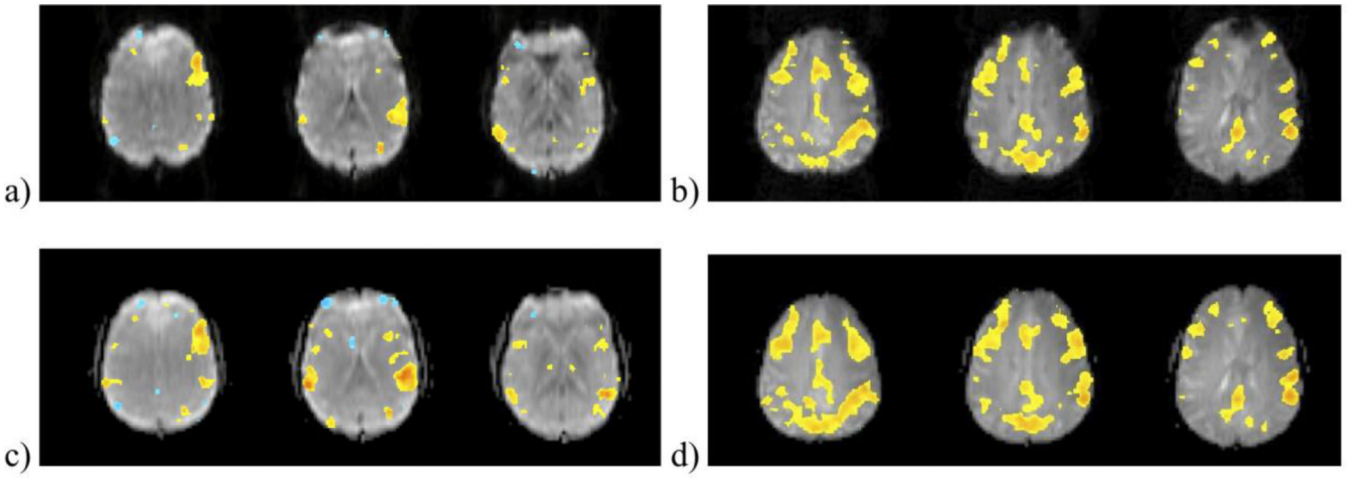

Figure 2.

Bilateral (left stronger than right) activation in Broca's area (BA 44 and 45) and Wernicke's area (BA 22) during single trial word generation at 1.5 (a,c) and 4 Tesla (b,d). Single-shot multi-echo EPI with weighted echo averaging (c,d) increases BOLD sensitivity at 1.5 (a,c) and at 4 Tesla (b,d) as compared to conventional EPI (a,b). The increase in BOLD sensitivity with weighted echo averaging is stronger at 1.5 Tesla as compared to 4 Tesla, due to the larger number of averaged echoes at 1.5 Tesla.

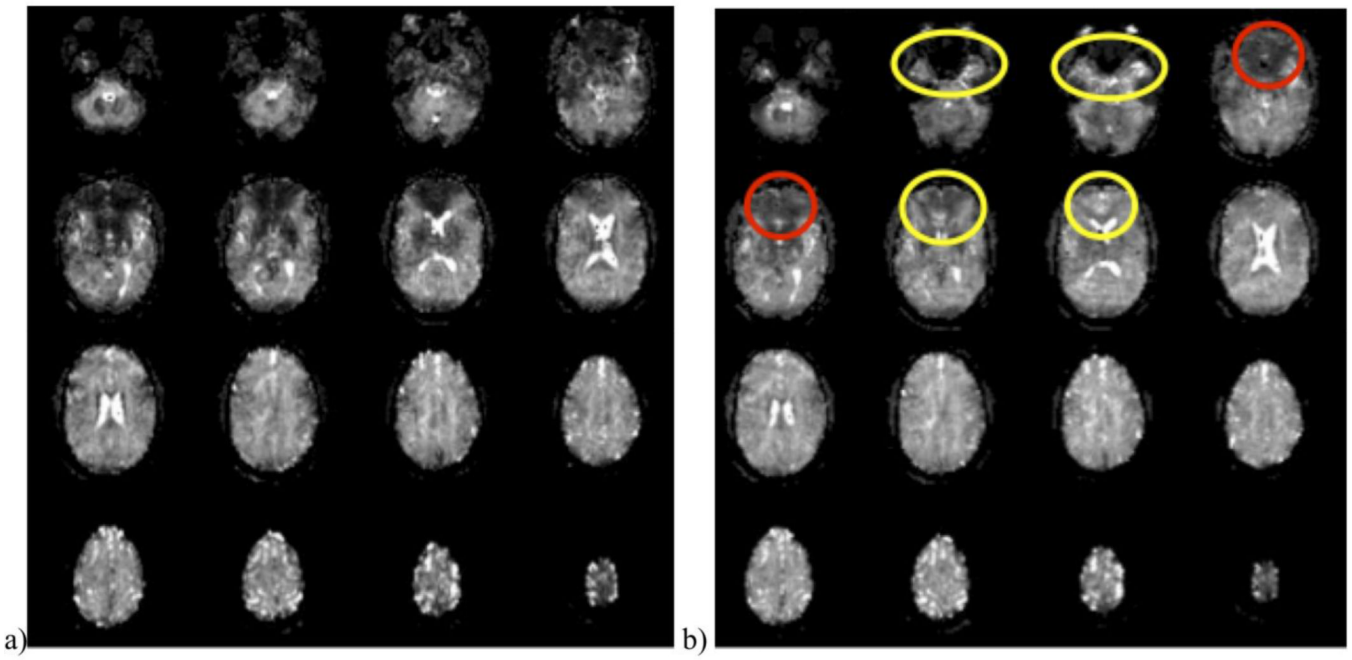

Figure 3.

T_2* maps at 4 Tesla using single-shot multi-echo EPI without (a) and with (b) slice-specific and TE-specific interleaved shimming display strong increases in T_2* in medial temporal lobe, which includes amygdala (20 ms with global shimming and 40 ms with interleaved shimming), and in dorsal prefrontal cortex (yellow circles). In contrast, T_2* increases in ventral prefrontal cortex are much smaller (red circles).

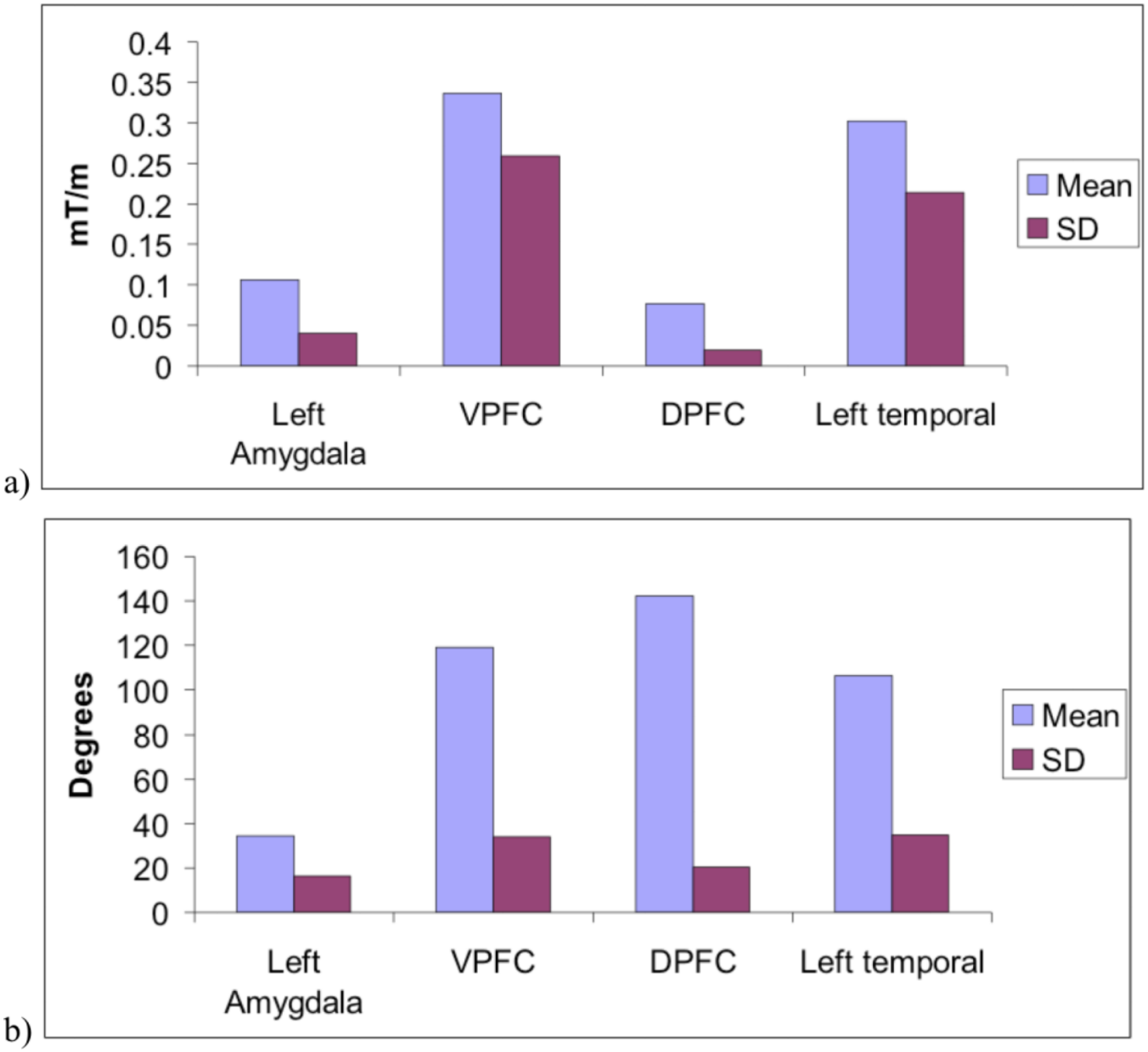

Figure 4.

(a) Amplitude distribution (mean and standard deviation) of local gradient vectors in four regions of interest (left amygdala, ventral prefrontal cortex (VPFC)), dorsal prefrontal cortex (DPFC) and left temporal cortex in the vicinity of the ear canal) measured in 9 healthy subjects using voxel-wise analysis of phase gradient vectors in high resolution field maps. (b) Corresponding inclination angle distribution with respect to the slice normal vector, which shows considerably larger standard deviation of local gradient amplitudes and vector orientations for VPFC and left temporal cortex compared to left amygdala and DPFC. These data show that amygdala and DPFC are more suitable for interleaved linear XYZ-shimming compared to VPFC and temporal cortex.

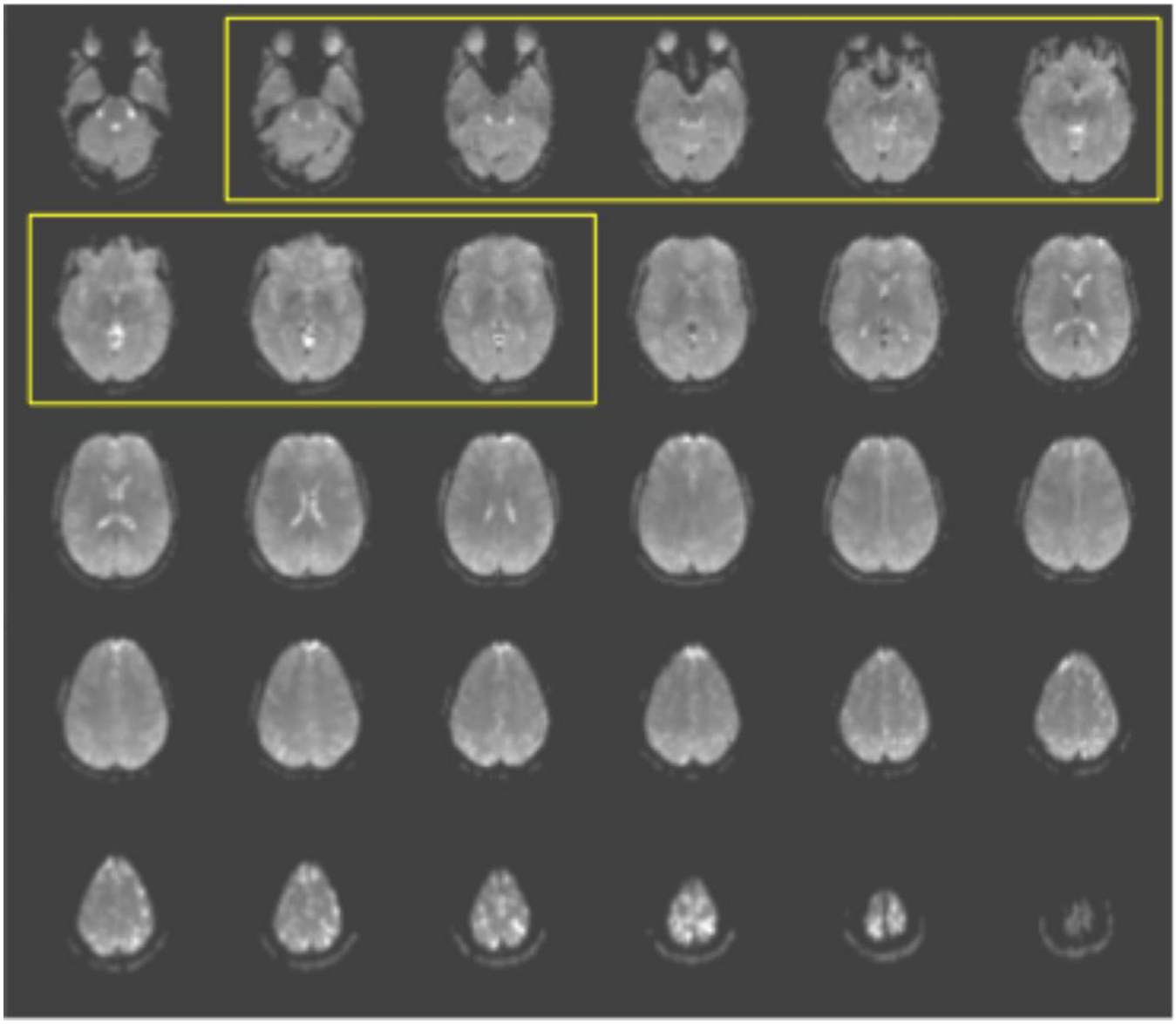

Figure 5.
Averaged single-shot multi-echo EPI at 4 Tesla acquired with 6 echo times ranging from 11 to 86 ms (which corresponds to approximately 2 * T_2*) and 64x64 spatial matrix using 2-fold GRAPPA acceleration. Echo-interleaved slice-specific shimming along all three gradient axes is applied to the slices enclosed by the yellow boxes. Echo combination is performed using weighted averaging with weights that are based on the measured increases in T_2* with interleaved shimming.