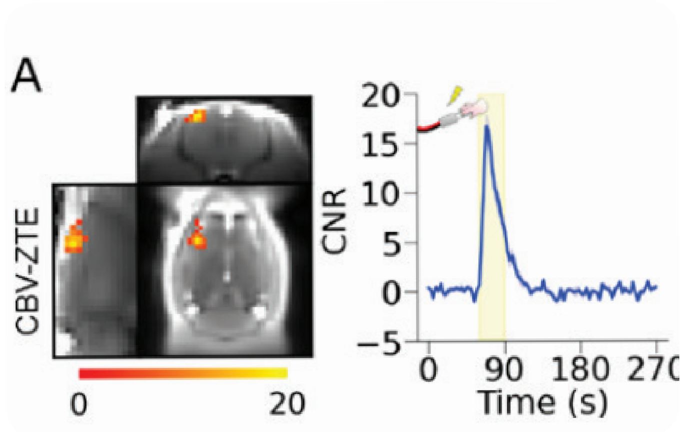

Towards silent and distortion-free fMRI with Zero Echo Time MRI

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Functional MRI, or fMRI, is a unique MRI technique which allows non-invasive mapping of brain activities (Ogawa,1990). By using fast imaging techniques capable of scanning large brain regions within short durations, continuous snapshots of a subject's brain are taken while an external stimulation, such as electrical forepaw stimulation in small rodents, is applied. Subsequent correlation of the stimulus with brain signal changes produces brain activity maps. Fast readouts are crucial for capturing the dynamic changes in fMRI studies. The most widely used fast imaging technique in fMRI studies is echo-planar imaging (EPI) (Bandettini,2012), but drawbacks of the sequence have led to the introduction of alternative methods such as zero echo time techniques.

EPI and Zero Echo Time fMRI

EPI was one of the earliest pulse sequence used in MRI (Mansfield,1977) and uses rapid switching of imaging gradients to acquire data after a single radio frequency (RF) excitation moving through k-pace with a zig-zag trajectory (Figure 1A). However, this technique has several well-known drawbacks such as loud acoustic noise, geometric distortion due to long echo time (TE) (Figure 1B) and magnetic inhomogeneity (especially in GRE EPI) (Jezzard,1995), and other image artifacts arising from motion (Cheng,2014) and eddy currents (Jezzard,1998).

Zero echo time MRI is one of the many fast imaging methods proposed as an alternative to EPI in fMRI studies. Zero echo time MRI refers to a group of MRI sequences characterized by virtually immediate radial center-out sampling of FIDs after RF excitation under the presence of imaging gradients (Weiger,2019) (Figure 1C). Major variants include ZTE (Zero Time Echo) which acquires signal immediately after a single short hard pulse (Weiger,2007) (Figure 1D) and SWIFT (Sweep Imaging with Fourier Transformation) which uses a series of gapped frequency swept chirp pulses interlaced with signal acquisitions (Idiyatullin,2006).

Zero echo time MRI addresses several critical issues of EPI for fMRI. The gradual switching of imaging gradients has two significant advantages. Firstly, the negligible eddy current artifacts lead to better image quality. Secondly, vibrations and acoustic noise are noise are minimized (Weiger,2007). The elimination of the loud acoustic noise is important in human fMRI experiments (Solana,2016). Although loud acoustic noise is less likely to affect the outcome of fMRI studies in anesthetized small animal fMRI, the growing interest in awake animal fMRI (Dopfel,2018) demands a reduced acoustic sound signature of the imaging sequence. Furthermore, due to the negligible TE, signal phase dispersal arising from magnetic susceptibility inhomogeneity is minimized and images with minimal geometric distortion or signal loss can

Figure 1

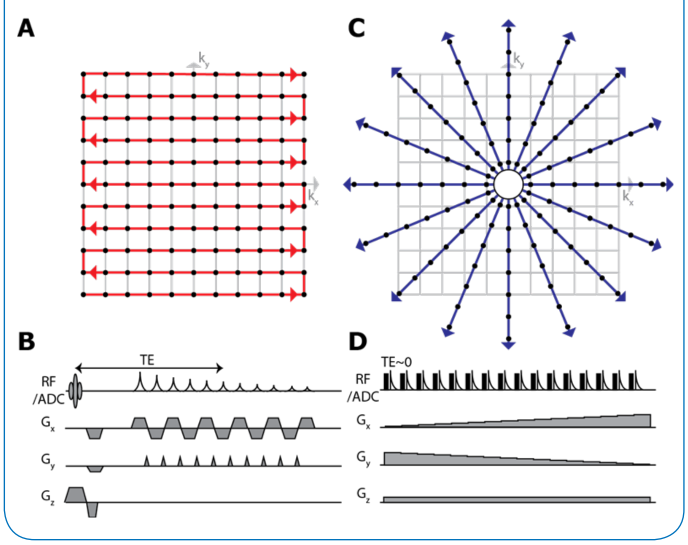

Figure 1. Schematics of EPI and ZTE. A) Zig-zag k-space trajectory of GRE EPI. B) Corresponding pulse sequence diagram of GRE EPI. TE is relatively long causing significant magnetic inhomogeneity induced signal loss and distortion. C) Radial k-space trajectory of ZTE.D) Corresponding Pulse sequence diagram of ZTE. TE is negligible due to sampling of FID.

easily be produced (Weiger2007). This allows brain regions close to air-tissue or implant interfaces to be studied with greater accuracy (Lehto,2017). The radial k-space sampling renders robustness against motion induced artifacts (Weiger,2007), thus reducing motion artefacts arising from respiratory or cardiac cycles even in highly secured anesthetized rodent heads and bulk voluntary motion in awake animal studies.

Contrast Origin in EPI and Zero Echo Time fMRI

Conventional blood oxygenation level dependent (BOLD) fMRI draws contrast from T2 and T2* changes related to deoxyhemoglobin. The relatively long TE in (GRE) EPI gives the method T2* sensitivity and hence its ability to detect BOLD contrast (Bandettini,2012). Zero echo time MRI, however, is a predominantly proton density weighted imaging sequence.

Interestingly, the first zero echo time fMRI experiment was performed to test the hypothesis that BOLD signal change reaches zero when data is acquired close to zero echo time (Mangia,2012). This implied that zero echo time imaging techniques should theoretically detect no brain activity induced changes. Using SWIFT imaging, Mangia et al. instead reported significant brain activation both in humans performing visual stimulation as well as in rats undergoing respiratory challenge. Mangia demonstrated that unlike BOLD contrast in which venous and arterial blood samples show strong contrast in gradient echo images, the lack of contrast between the two in SWIFT images indicates an alternative contrast mechanism. Mechanisms such as changes in transmembrane ion fluxes coupled with water exchange between cellular compartments as well as changes in local blood volume have been proposed to explain the observed changes.

There is interest in sensitizing zero echo time fMRI techniques to more conventional contrast associated with brain activity. Solana et al. (Solana,2016) added a T2 preparation module in front of a zero TE RUFIS readout to allow T2 weighting in zero echo time imaging to perform whole brain BOLD fMRI in humans. In another study, the same group introduced the Looping Star technique by adding a gradient refocusing mechanism to a traditional RUFIS readout to obtain T2* information (Dionisio-Parra,2020).

Positive contrast CBV-weighted fMRI with Zero Echo Time

Intravenous injection of superparamagnetic iron-oxide particles (SPIOs) has been used to sensitize EPI based fMRI techniques to cerebral blood volume (CBV) changes (Shih,2009) i.e. CBV-weighted EPI. During neuronal activation, regional increase in CBV leads to increased local concentration of SPIOs causing signal decrease in EPI images. Mackinnon et al. (MacKinnon,2020) extended this technique to ZTE fMRI. In contrast to CBV-weighted EPI, CBV-weighted ZTE has negligible TE and the increased concentration of SPIOs due to increased CBV causes a reduction in T1 relaxation time which increases ZTE signal in neuronally activated regions.

Figure 2

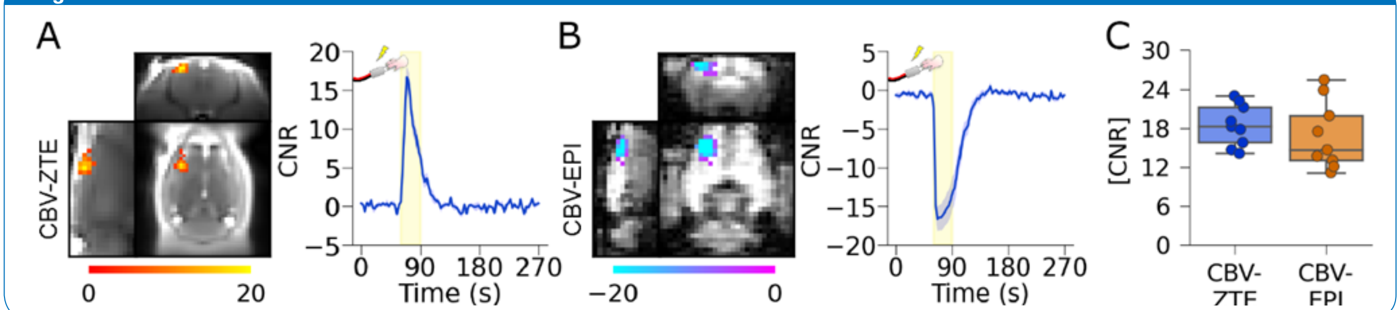

Figure 2. CBV-weighted ZTE and EPI functional responses during rat forepaw electrical stimulation at 3 s temporal resolution. A) CBV-weighted ZTE and B) CBV-weighted EPI functional responses (n=9 for each modality) to rat forepaw electrical stimulation C) The two methods do not have a significantly different CNR $t(16) = 0.79$, $P=0.44$. Figure provided by Martin John MacKinnon and Yen-Yu Ian Shih from University of North Carolina at Chapel Hill.

MacKinnon et al. (Figure 2, unpublished) compared CBV-weighted ZTE directly with CBV-weighted EPI using forepaw simulations in rats and reported similar activation regions as well as contrast-to-noise ratio(CNR). The main difference was that CBV-weighted ZTE displayed a positive response while CBV-weighted EPI showed a negative response. Importantly, ZTE images displayed minimal geometric distortion and signal drop-offs especially near high magnetic susceptibility regions.

Deep Brain Stimulation with Zero Echo Time fMRI

fMRI combined with deep brain stimulation (DBS) is an emerging field in fMRI which allows localized brain excitation via the use of an implanted electrode. However, depending on the materials' magnetic properties, DBS electrodes can induce significant susceptibility artifacts in EPI images thus rendering EPI based fMRI studies difficult if not impossible. Zero echo time fMRI, however, is well suited for such applications due to its robustness against susceptibility artefacts. Lehto et al. (Lehto,2017) showed that MB-SWIFT can reliably obtain distortion-free images and track brain activity changes in response to the DBS stimuli. Gröhn et al. showed (Figure 3, unpublished) that distortion-free DBS fMRI performed using MB-SWIFT (a modified SWIFT based zero echo time pulse sequence) (Figure 3B) can detect significant brain activation at the tip of the tungsten DBS electrode (Figure 3D). A corresponding SE-EPI based fMRI (Figure 3C) shows visible susceptibility-induced distortion artefacts and cannot detect significant brain activation (Figure 3E).

Figure 3

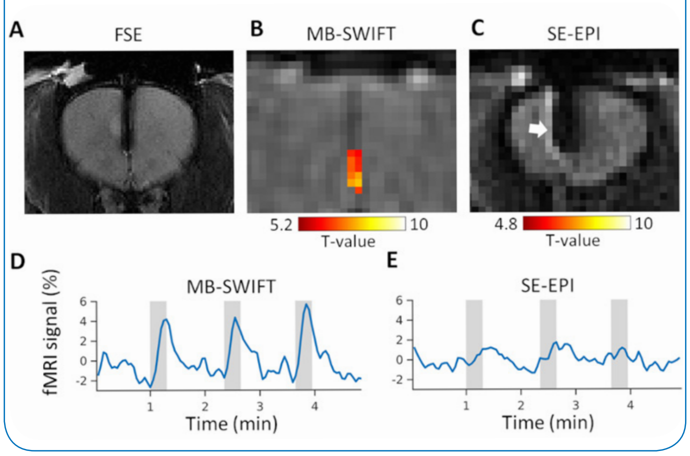

Figure 3. Functional response to deep brain stimulation (DBS) of the ventromedial prefrontal cortex, in rat brain. A lead with twisted set of three tungsten electrodes with 140 µm tip-contact diameter was used for stimulation. A) Anatomical T2-weighted fast spin-echo image at the electrode location. Activation maps obtained with B) MB-SWIFT overlaid on MB-SWIFT image, and with C) SE-EPI overlaid on SE-EPI image. Activated pixels shown have $p < 0.05$, family-wise error (FEW) corrected. Note, the magnetic susceptibility artefacts around the electrode (white arrow) in SE-EPI are hardly visible in MB SWIFT. Time series from ROIs at the tip of the electrode from D) MB-SWIFT and E) SE-EPI. Figure provided by Hanne Laakso and Olli Gröhn from University of Eastern Finland using data collected at Center for Magnetic Resonance Research, University of Minnesota by Lauri Lehto and Hanne Laakso.

Challenges of Zero Echo Time fMRI

The use of zero echo time techniques in fMRI has its own challenges. Being a 3D imaging technique, coverage of the FOV must include the entire coil-sensitive volume to prevent image aliasing. This inevitably limits the achievable spatial resolution when the emphasis lies on increasing scanning speed. Image acceleration techniques such as compressed sensing which have been extensively studied in radial MRI cardiac studies (Motaal,2014) will allow significant further improvement of the temporal resolution of zero echo time fMRI techniques.

Zero echo time fMRI is an attractive alternative to EPI fMRI that offers a quieter environment and less artifact-prone images. There is still much work to be done to better decipher the mechanism behind the functional contrast in zero echo time fMRI (Lehto,2017) in order to better relate it to existing BOLD fMRI contrast and it is hoped that both methods can complement each other to further understanding of fMRI detected brain activity.

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Abbreviations

BOLD – Blood Oxygenation Level Dependent

CBV – Cerebral Blood Volume

CNR – Contrast-to-Noise Ratio

DBS – Deep Brain Stimulation

fMRI – functional Magnetic Resonance Imaging

FOV – Field Of View

GRE – Gradient Echo

MB-SWIFT – Multiband Sweep Imaging with Fourier Transformation

MRI – Magnetic Resonance Imaging

RF – Radio Frequency

SE – Spin echo

SWIFT – Sweep Imaging with Fourier Transformation

TE – Echo Time

ZTE – Zero Echo Time

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