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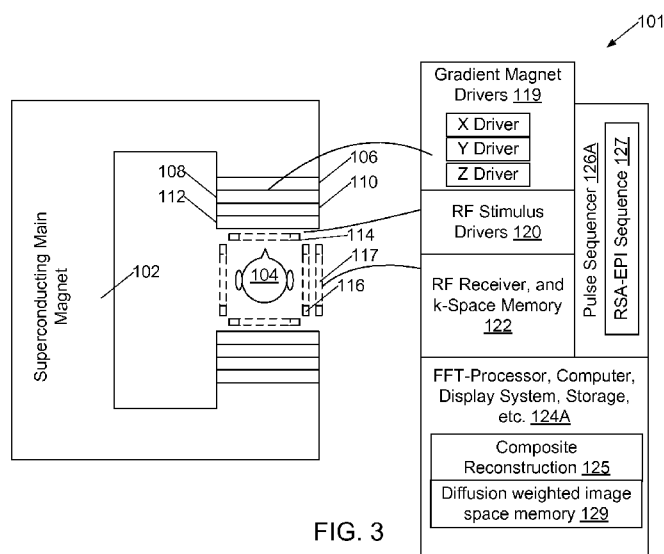
(54) **Title:** HIGH-RESOLUTION DIFFUSION-WEIGHTED MAGNETIC RESONANCE IMAGING

FIG. 3

(57) **Abstract:** A system and method of obtaining diffusion weighted images uses a magnetic-resonance imaging system and includes, for at least a first slice, exciting spins of the slice, then: applying a diffusion weighting gradient in i^{th} direction of N diffusion-weighted directions; sweeping a readout gradient across an EPI short-axis blade oriented at a first angle, pulsing phase-encoding gradient, recording spin-echo signal magnitudes in k -space memory for the short-axis blade; and simultaneously rotating the diffusion gradient direction to a next direction of the N directions and rotating the short axis blade to another angle. Storing spin-echo signals in k -space memory is repeated for a rotated short-axis blade with the rotated diffusion gradient. Composite reconstruction is done by "training" the i^{th} low-resolution image from Fourier transform of i^{th} k -space blade with the i^{th} high-resolution composite image from Fourier transform of collected k -space EPI blades of neighborhood diffusion directions.

High-Resolution Diffusion-Weighted Magnetic Resonance Imaging

FIELD

[0001] The present document relates to the field of pulse sequences for operation of a nuclear magnetic resonance imaging (MRI) system. In particular the document relates to pulse sequences for mapping not just composition of tissue, but also the orientation of neural tracts in the tissue; the method is particularly applicable to imaging of the brain.

CLAIM TO PRIORITY

[0002] The present application claims priority from U.S. Provisional Patent Application number 61/890,592 filed 14 October 2013.

GOVERNMENT INTEREST

[0003] This invention was made with government support under Grant number R21 NS075791 awarded by the National Institutes of Health. The Government has certain rights in the invention.

BACKGROUND

[0004] MRI systems 100, such as illustrated in Fig. 1 typically have a main magnet 102 that provides a magnetic field within which a subject 104 may be positioned. Poles of magnet 102 are equipped with trim magnets 106 that adjust the field for uniformity, as well as X 108, Y 110, and Z 112 gradient magnets. There are also typically RF field coils 114, 116, positioned to apply pulses of radio frequency (RF) electromagnetic radiation to subject 104. System 100 also has gradient magnet drivers 119 for driving the X, Y, and Z gradient magnets to generate rapid changes in magnetic field gradients at subject 104, and radio frequency drivers 120 coupled to provide pulses of RF energy to RF field coils 114, 116. System 100 also has a radio frequency receiver 122 coupled to receive RF spin echoes detected by a receiver coil 117 positioned to receive and record RF spin echoes radiated from subject 104. Receiver 122 provides signal amplitudes, and in some systems signal amplitudes over a distribution of frequencies, through an analog-to-digital converter into a k-space memory. The k-space

memory is coupled to a fast-Fourier-transform processor and computer 122 that is configured to compute fast Fourier transforms (FFTs) of k-space memory contents to generate memory and to process, display and store resulting images.

[0005] While trim magnets 106 and main magnet 102 provide a stable, uniform, magnetic field, gradient magnets 108, 110, and 112 change field rapidly and frequently while scanning each subject. Further, the radio frequency drivers 120 operate in a pulsed mode, and the k-space memory is configured by pulse sequencer 126 to receive data from the receiver at particular times relative to gradient field changes. The gradient magnet drivers 120, radio frequency drivers 120, receiver, and k-space memory 122 therefore operate under control of a pulse sequencer 126 that may be implemented in part in hardware timing and sequencing circuits, and in part in software in computer 124.

[0006] An MRI “pulse sequence” is a pattern, or sequence, of operations of the MRI machine, typically involving pulses provided by gradient drivers 119 to (a) enable and power gradient magnets 108, 110, and 112 and radio frequency drivers 120, (b) enable reception of data through radio frequency receivers 122 into k-space memory, and (c) control data acquisition in a particular order and with particular timing. The intent of many MRI pulse sequences is to gather information from at least a line of signal samples in the k-space, rather than an individual sample, with each “shot”, or set of radio frequency drive pulses followed by readout pulses, because of a relatively long relaxation time required between pulse sequences. Pulse sequences are repeated at a repetition interval known as TR.

[0007] The echo planar imaging (EPI) method is a fast acquisition method known in prior MRI, but with geometric distortions and limited spatial resolution. Typically, this EPI mode involves a pulse sequence, controlled by pulse sequencer 126, that:

- a) Operates magnet drivers to provide a magnetic field gradient to select a selected plane of voxels (stimulated plane) in the subject. Selection occurs because a frequency of nuclear spin resonance of atoms (usually hydrogen atom) in the subject is strongly dependent on the strength of applied magnetic field at that atom. Nuclear spins absorb energy and nutate or precess only where that resonant frequency matches the frequency of the radio frequency driver; the applied magnetic field gradient is determined such that the resonant frequency matches the driver frequency in the

selected plane, while in other nearby planes the resulting resonant frequency does not match the driver frequency.

- b) Stimulate nuclear spins along the selected plane by providing radio frequency energy through stimulus drivers 120 and coils 114, 116.
- c) Fill k-space memory by using the gradient drivers 119 and gradient coils to provide magnetic field gradients that select a readout plane, then stepping through lines of the readout plane with phase pulses in one axis of the plane, while maintaining a frequency shifting gradient in the other axis of the plane. At each line of the readout plane, k-space memory is filled by receiving spin-related radio frequency RF energy at each of multiple frequencies, recording received RF at each frequency in a location of a line of k-space memory, and
- d) Select additional readout planes and record received RF until RF has been measured from all voxels of the stimulated plane.
- e) Once filled, a 2-d Fourier transform of the RF intensity readings, as stored in k-space memory, is performed to generate pixel intensity information of an image.

[0008] The frequency of the RF energy used to stimulate nuclei of the stimulated plane is dependent on the particular type of nuclei used for imaging. While MRI can theoretically be performed using other nuclei having an odd proton count, virtually all medical imaging is performed on excited, spin-aligned, and nutating hydrogen such as the hydrogen associated with water or hydrocarbons in tissue.

[0009] Diffusion-weighted imaging is an MRI imaging technique that seeks to determine rates of diffusion, movement, or flow of excited, spin-aligned and nutating or precessing, hydrogen associated with water in tissues. This is done, in part, by using intense gradient fields-such that the stimulated plane is narrow--and observing a drift of nutating or precessing hydrogen nuclei out of the initial stimulated plane. Since nerve bundles include long, thin cells that allow diffusion and active flow of fluid along nerve fibers, but have membranes preventing movement from or across fibers, water molecules in tissue tends to spread along nerve fiber tracts more quickly than across those tracts, indicated as a lower apparent diffusion coefficient perpendicular to fibers than along the fibers.

[0010] Traditional tractography using diffusion weighted MRI often is done with diffusion tensor imaging (DTI) technique, which requires a series of magnetic field gradients in at least six different directions, and additional gradients that may improve accuracy for "off-diagonal" information; six directions is theoretically sufficient to measure single fiber tracts crossing voxels in uniform directions. While there are typically coils for directly providing magnetic field gradients in only three orthogonal directions or axes, gradients along additional directions are generated as vector sums of gradients along the orthogonal directions; for example, a gradient along an axis oriented at 45 degrees to both an X and a Y axis may be generated by energizing both an X gradient coil 108 and a Y gradient coil 110 simultaneously.

[0011] Each voxel of a human brain may, however, include fibers of more than one tract running at different angles, and it has been estimated that 30% of white-matter voxels may represent fibers running in more than one direction. Traditional DTI diffusion weighted MRI performed on these voxels can only measure a predominant direction, with directions of crossing fibers appearing as noise or an unexpectedly low anisotropy.

[0012] A method of determining which voxels have fibers running in multiple directions, known as HARDI (High-angular-resolution diffusion imaging) is known. In HARDI, instead of imaging each voxel with three gradients as required for basic imaging, or six gradients as required for basic diffusion-weighted imaging, each voxel is imaged with many (often 60 or more) gradients oriented along different directions. The system measures an effective diffusion along each directional gradient, measuring diffusion along each angle. A curve, with maxima and minima, of diffusion with respect to angle may be determined at each voxel from individual diffusion-weighted images at that voxel from the multiple angles.

[0013] If there is a single tract in a voxel, with HARDI there will be just two maxima in the curve of diffusion versus angle, these maxima point in opposite directions. If two tracts cross in the voxel, there will be two pairs of maxima, and so on.

[0014] The PROPELLER sequence for DWI (diffusion-weighted imaging) is a multishot pulse sequence called Periodically Rotated Overlapping Parallel Lines with Enhanced Reconstruction (PROPELLER) and is usually implemented with Fast Spin Echo techniques. The parallel lines 150 (Fig. 2) along which k-space is filled in PROPELLER are perpendicular to a magnetic field gradient established by the gradient

magnets, and are typically at an angle with respect to the X 154 and Y 152 axes of both k-space and the machine.

[0015] Unfortunately, obtaining full HARDI MRI diffusion-weighted image data is slow even with the conventional fast single-shot EPI sequence because of the many gradient orientations used. It is desirable to find faster ways of obtaining nerve-tract fiber-bundle information, including information regarding tracts that cross in particular voxels.

SUMMARY

[0016] In an embodiment, a method of operating a magnetic resonance imaging system to obtain diffusion weighted images in N diffusion-weighted directions uses an MRI system of the type having a magnet configured to provide a static magnetic field, X, Y, and Z-axis gradient coils configured to add gradients to the magnetic field, and magnet drivers coupled to drive the gradient magnets. The system has a radio frequency driver for stimulating nuclear spins in the magnetic field, a k-space memory coupled to an image processing computer, the image processing computer adapted to perform Fourier transforms of k-space memory contents and having machine readable code for performing the method, and radio-frequency receiver coupled to receive spin echoes from spins in the magnetic field and to provide spin echo magnitudes to the k-space memory, and a sequence controller coupled to sequence the magnetic drivers and the radio frequency driver, and to sequence capture of spin echo magnitudes into the k-space memory. The method includes, for at least a first slice, using at least one of the gradient coil and the radio frequency driver to select and excite spins of the slice. Then, for each integer i from one to N, using at least one of the gradient coils (X, Y, Z) to apply diffusion weighting gradient in the ith direction of the N diffusion-weighted directions; using at least one of the gradient coil(s) to sweep a readout gradient in trajectory across an EPI (echo planar imaging) short-axis blade oriented at a first angle, using at least one of the gradient coils to pulse a phase-encoding gradient, using the radio frequency receiver to record the spin-echo signals magnitudes and storing spin-echo magnitudes signals in the k-space memory for the short-axis blade; and simultaneously rotating the diffusion gradient direction to a next direction of the N directions and rotating the short axis blade to a second angle. The steps required to store spin-echo magnitude signals in the k-space memory are then repeated by using at least one of the gradient magnets coils to sweep a

readout gradient in trajectory across the short-axis blade, using at least one of the gradient coils to pulse a phase-encoding gradient, using the radio frequency receiver to record the determine spin-echo signals magnitudes and storing the signals as k-space data in the k-space memory for the short-axis blade. The method continues with performing a composite reconstruction by “training” the i 'th low-resolution image (from FT of the I 'th k-space EPI blade) with the i 'th high-resolution composite image (from FT of the collected k-space EPI blades of neighborhood diffusion directions).

[0017] In an embodiment, a system configured to obtain magnetic resonance diffusion weighted images in N diffusion-weighted directions, the system including a magnet configured to provide a static magnetic field, X, Y, and Z-axis gradient coils configured to add gradients to the magnetic field, and X, Y, and Z magnet drivers coupled to drive the X, Y, and Z-axis gradient magnets, at least one radio frequency driver coupled to a stimulus coil positioned to stimulate nuclear spins in the magnetic field, a sequence controller coupled to sequence the magnetic drivers and the radio frequency driver, and to sequence capture of spin echo magnitudes into the k-space memory, a k-space memory coupled to an image processing computer, the image processing computer having machine readable code stored in a memory for configuring the sequence controller for Rotating Short-Axis EPI (RSA-EPI) imaging and to perform composite reconstructions of k-space memory contents into diffusion-weighted images, and a radio-frequency receiver coupled to receive spin echoes from spins in the magnetic field and to provide spin echo magnitudes to the k-space memory. The machine readable code in the image processing computer includes code executable on the processor and adapted to: for at least a first slice of a sample, use at least one of the gradient coils and the radio frequency driver to select and excite spins of the slice; for a plurality of integers i , use at least one of the gradient coils to apply a diffusion weighting gradient in an i 'th unique direction; use at least one of the gradient coil(s) to sweep a readout gradient in trajectory across a short-axis EPI (echo-planar imaging) blade at a first angle, use at least one of the gradient coils to pulse a phase-encoding gradient, use the radio frequency receiver to record spin-echo signals and storing the signals in the k-space memory for the short-axis blade at a first angle; rotate the diffusion gradient direction to a next direction of the N directions and rotate the short axis blade to a second angle and repeat using at least one of the gradient coil to sweep a readout gradient in trajectory across the short-axis blade, using at least one of the gradient coils to pulse a phase-encoding gradient, using the radio

frequency receiver to record spin-echo signals and storing the signals as k-space data in the k-space memory for the short-axis blade oriented at the second angle; and perform a composite reconstruction to provide diffusion-weighted image data from k-space data obtained at a plurality of the blade angles.

BRIEF DESCRIPTION OF THE FIGURES

[0018] Fig. 1 illustrates an example Nuclear Magnetic Resonance Imaging machine on which conventional pulse sequences, may be executed.

[0019] Fig. 2 illustrates a long-axis “blade” of a PRIOR ART conventional “propeller” sequence, and how its parallel lines along a gradient are at an angle with respect to X and Y axes of k-space. The long-axis blade is defined as the frequency encoding direction is parallel to the long axis of the blade; thus, the k-space data within the blade is filled up with “long lines”.

[0020] Fig. 3 illustrates an example Nuclear Magnetic Resonance Imaging machine on which the RSA-EPI pulse sequence is executed

[0021] Fig. 3A illustrates an Archimedean curve of diffusion directions in 3-dimensional space for use with-HARDI.

[0022] Fig. 4A illustrates results from Diffusion Tensor Imaging.

[0023] Fig. 4B illustrates results from HARDI - High-angular-resolution diffusion imaging.

[0024] Fig. 5 is an example MRI of a brain showing an electrode placement, and its effects in MRI white matter tractography.

[0025] Fig. 6 is a composite figure having 7 sections, illustrating differences between RSA-EPI and SS-EPI scans. The upper row (a)-(c) shows the short-axis blade with the frequency encoding lines are parallel to the short axis of the blade; thus, the k-space data within the blade is filled up with multiple “short lines”.

[0026] Fig. 7 compares original EPI images (a) vs. computer simulated RSA-EPI images, where (b) to (e) are images of individual EPI blades, and (f) to (i) illustrate composite reconstructed RSA-EPI images.

[0027] Fig. 8 shows the RSA-EPI reconstructed fiber profiles (i.e., Orientation Distribution Function (ODF)) of three representative voxels that have single fiber orientation along x, y, and z axes at the corpus callosum, posterior corona radiata and

internal capsule, respectively; fiber directions vs. colors: L-R (x) in red, A-P(y) in green and S-I (z) in blue.

[0028] Fig. 9 shows the percentage of root mean squared error (RMSE) of apparent diffusion coefficient (ADC) between the RSA-EPI sequence and the SS-EPI sequence. Error bars denote the standard deviation across ~700 WM voxels highlighted in red in the bottom-right image.

[0029] Fig. 10 illustrates composite reconstruction of RSA-EPI image reconstruction algorithm. The k-space trajectory is a short-axis EPI blades displayed in the upper rows. The k-space composite is a collection of short-axis EPI blades from adjacent DW directions followed by a correction of sampling density.

[0030] Fig. 11 is a data flow diagram illustrating a simulation of RSA-EPI image acquisition using conventional HARDI imaging.

[0031] Fig. 12A a first portion (including particularly diffusion gradients and spin-echo preparation) of a pulse sequence diagram of RSA-EPI data acquisition.

[0032] Fig. 12B a second portion (short-axis EPI readout) of a pulse-sequence diagram of RSA-EPI data acquisition.

[0033] Fig. 13 is a flow diagram of RSA-EPI DW MRI data acquisition using the pulse sequence of Fig. 12A-B.

DETAILED DESCRIPTION OF THE EMBODIMENTS

[0034] A modified RSA-EPI pulse sequence is used for HARDI using rotating short-axis EPI blades (RSA-EPI). A short axis blade is a sweeping pattern involving a rotated rectangular zone, or blade, that sweeps gradients across the short dimension of the rectangular zone at a faster rate than gradients are swept along the long dimension of the rectangular zone. A diffusion-weighted image is reconstructed from gathered data using a novel image reconstruction algorithm, composite reconstruction. RSA-EPI samples only partial k-space to accelerate the scan time and uses composite images to restore signals. We evaluated the feasibility of RSA-EPI approach with different acceleration factors (AF) on estimating the directional measure, ODF at each pixel of the image.

[0035] We studied a system (Fig. 3) adapted to perform modified HARDI using an RSA-EPI (Rotating Short-Axis –Echo Planar Imaging) with short-axis “blades” as veering diffusion gradient directions with composite reconstruction (RSA-EPI) approach in which we sorted the DW (diffusion weighted) directions into a sequence that

was closest to an Archimedean spiral curve from $+z$ to $-z$, as illustrated in Fig. 3A. The system 101 differs from the system of Fig. 1 in that the pulse sequencer, pulse sequencer 126A, is configured to execute the RSA-EPI sequence 127, and the processor 124 is configured to perform the composite reconstruction 125. For each DW direction, a collected composite complete k-space from neighborhood diffusion weighting directions is used to “train” the diffusion image from the partial k-space at that particular DW direction. The ODF was reconstructed using the q-ball algorithm (integral of equator) on the diffusion-weighted data without any noise treatment, model assumption or spherical harmonic decomposition. Q-ball algorithm imaging is a method derived from that described in Neuron, Vol 40, No. 5, 4 December 2003, Pg 885–895 *Diffusion MRI of Complex Neural Architecture*, David S. Tuch, et al. (4 December 2003), DOI: 10.1016/S0896-6273(03)00758-X., the contents of which are incorporated herein by reference. Q-ball algorithm uses, for each direction, a computation of the integral over the corresponding perpendicular equator in k-space, and applying a Funk-Radon Transform (FRT) to compute the ODF for that direction.

[0036] This may simplify and help to appreciate direct effects of the RSA-EPI approach. Seven acceleration factors (AF) (1, 4, 5, 10, 20, 40, and 50) were simulated. The root mean square error (RMSE) of diffusion signals, the deviation angles and profiles of ODF were studied.

[0037] In a preliminary study, we showed that the modified HARDI using RSA-EPI is feasible. With some tolerance of error and angular uncertainty, the HARDI scan time may be reduced by a factor of 4 or maybe more from conventional HARDI. However, more studies are necessary to optimize AF and the number of directions.

SPECIFIC AIMS OF ONGOING WORK

[0038] Diffusion weighted imaging (DWI), a magnetic resonance imaging (MRI) based technology, allows visualization of white matter (WM) of the brain noninvasively. It can be used to assess the integrity of WM and to map the structural connectivity between brain regions using tractography. Conventionally, WM tractography uses diffusion tensor imaging (DTI), which reveals averaged WM microstructures within an imaged voxel. However, in cases of complex structures from crossing fibers and multiple diffusion compartments, DTI is limited due to its simplified mono-Gaussian model. This results in false negative tractography due to early termination of fiber tracts

and false positive tractography due to crossing fibers. In addition, new studies show that the prevalence of crossing fibers is higher than previously estimated.

[0039] To improve white matter imaging, researchers have focused on advanced diffusion imaging that imposes higher diffusion-weighting (DW) b-values (diffusion gradient strength) and substantially more DW directions than DTI. Such approaches, including High Angular Resolution Diffusion Imaging (HARDI), Diffusion Spectrum Imaging (DSI), Hybrid Diffusion Imaging (HYDI), and Composite Hindered and Restricted Model of Diffusion (CHARMED) estimate the probability of “all” possible fibers within a voxel and increase the accuracy of WM tractography. Advanced DWI has significant clinical potential, especially in certain neurosurgical procedures, such as deep brain stimulation (DBS), where mapping of fine white matter tracts is crucial for optimizing surgical placement of the DBS electrode. Unfortunately, such advanced approaches often require lengthy scan time that is prohibitive for most clinical applications.

[0040] The goal of this work is to develop a novel imaging technique for DWI that is faster than the single-shot EPI (SS-EPI) sequence commonly used in diffusion imaging. This will be done by Rotating Short- Axis EPI “blades” as veering diffusion gradient directions with composite reconstruction (RSA-EPI). In RSA-EPI, the scan time is less than SS-EPI because short-axis PROPELLER EPI (SAP-EPI) blades were split into individual DW directions and only partial k-space data is acquired while the image Signal to Noise Ratio (SNR) is compensated by shortened TE and composite reconstruction.

[0041] Unlike SS-EPI, the short-axis EPI blade is able to increase spatial resolution without aggravating geometric distortion. Once developed, such a pulse sequence would allow higher angular resolution diffusion data to be acquired in a short period of time, thereby greatly increasing the clinical potential of advanced diffusion imaging techniques. In addition, the RSA-EPI sequence could be combined with other fast imaging techniques such as parallel imaging, simultaneous multi-slice EPI, and compressed sensing. While RSA-EPI could be used in all DWI approaches including DTI, in this pilot proposal, we focus on combining RSA-EPI with a modified HARDI.

Aim 1. Computer Simulation

[0042] Aim 1a: Evaluate the image quality and effective resolution/SNR using Shepp-Logan and isotropic resolution phantoms: In addition to the Shepp-Logan phantom, we will develop resolution phantoms composed of different apertures with isotropic diffusion. The point-spread function (PSF) of the Shepp-Logan phantom will demonstrate effects of k-space sampling and the apertures FWHM of the resolution phantom will represent the effective imaging resolution.

[0043] Aim 1b: Develop a numerical white matter phantom: Because there is no in vivo gold standard for WM fiber tracts, we will design and use a numerical WM phantom as the gold standard. We will estimate the echotrain acceleration factor (ET AF) (i.e. k-space coverage) where RSA-EPI yields similar results compared to SS-EPI using a null hypothesis test. We will also permute the orientations of EPI blades with DW directions to measure the effects on the fiber orientation distribution function (ODF).

[0044] Aim 1c: Evaluate the image quality using post-processing computer simulation: HARDI using conventional SS-EPI with two opposite phase encoding directions and a fieldmap sequence will be performed on five human subjects. The geometric distortion will be first corrected and later reintroduced back to each short-axis EPI blade to evaluate its effects on the image quality as well as the ODF profiles.

[0045] Aim 2. MRI Pulse Sequence Development Aim 2a: MRI pulse sequence programming: We will develop the RSA-EPI pulse sequence by first decreasing the resolution of the SS-EPI frequency encoding direction to create a short-axis EPI blade. As an initial attempt, HARDI will be coded with RSA-EPI. The EPI “blade” will rotate as veering the DW directions of HARDI. The ET AF estimated in Aim1 will be hard-coded in the pulse sequence using the Philips pulse programming environment, PARADISE.

[0046] Aim 2b. MRI scans of human subjects and data processing: We will test the new HARDI RSA-EPI pulse sequence on 15 human subjects. We’ll also acquire two sets of SS-EPI diffusion data for each subject. One with matched DW directions of RSA-EPI but a significantly longer scan time will be processed as HARDI.

[0047] Another SS-EPI with a matched scan time as RSA-EPI but fewer DW directions will be processed as DTI. We will evaluate WM ODF profiles and tractography results for HARDI RSA-EPI (short scan time), HARDI SS-EPI (long scan time) and DTI SS-EPI (short scan time).

RESEARCH STRATEGY

A. Significance

Imaging the structural connectivity of the brain

[0048] Structural connectivity analyses are key to understanding the neural networks involved in neurological and psychiatric disorders. Measures of structural connectivity can be derived from white matter (WM) tractography approaches that estimate WM fiber orientation within a given WM voxel. Conventionally, WM tractography uses diffusion tensor imaging (DTI), which suffers from an inability to resolve multiple fibers (Figure 1 (a)). This limits its utility in areas of the brain with WM fiber bundles oriented in various directions such as the basal ganglia and ventral prefrontal cortex. To address this, advanced diffusion imaging methods have been developed that provide better resolution of crossing fibers and multiple diffusion compartments. These approaches, including High Angular Resolution Diffusion Imaging (HARDI), Diffusion Spectrum Imaging (DSI), Hybrid Diffusion Imaging (HYDI) and Composite Hindered and Restricted Model of Diffusion (CHARMED), estimate the probability of “all” possible fibers within a voxel and thereby increase the accuracy of WM tractography. An example comparison is in Figure 4A, where DTI predicts rounded profiles of fiber orientation function (ODF) and deviated fiber direction at the prefrontal WM while advanced diffusion imaging, e.g., HARDI in Figure 4B, yields crossing fibers and better angular resolution. DTI based tractography may result in false negative tracts by early termination of fiber tracts and false positive tracts due to partial voluming of crossing fibers. In addition, new studies show that the prevalence of crossing fibers is higher than previously estimated.

[0049] For advanced diffusion imaging, the scan time is linearly proportional to the number of acquired directions and also increases with diffusion-weighting (DW) b-values and spatial resolution. As such, acquiring a whole brain scan with high imaging spatial resolution and high resolution of fibers may take one to two hours. In addition, with currently available fast imaging sequences, e.g., single-shot EPI (SS-EPI), the geometric distortion increases with higher spatial resolution. Presently, scan time can be decreased by using fewer directions, fewer slices and/or larger voxel size. However, acquiring fewer directions reduces the ability to resolve crossing fibers, obtaining fewer slices leads to partial brain coverage, and having a larger voxel size (i.e. lower spatial

resolution) diminishes the ability to resolve smaller brain structures. Consequently advanced diffusion imaging offers the best potential method for white matter imaging to allow structural connectivity analyses, but a long scan time (vs. lower image quality) is the major obstacle to its clinical application.

Structural connectivity in clinical practice

[0050] Clinical applications of structural connectivity have flourished since the development of diffusion imaging with the majority using DTI. As above, structural connectivity based on advanced diffusion imaging such as HARDI is more accurate than DTI; furthermore, advanced diffusion imaging with multiple DW b-values can resolve multiple diffusion compartments as well as yield useful image biomarkers for studying WM integrity and estimating axonal density and diameter.

[0051] Unfortunately, advanced diffusion imaging is rarely used in the clinical or clinical research setting due to the long time needed to acquire an optimal scan.

[0052] An application of WM tractography that requires both high imaging resolution and high diffusion angular resolution is in deep brain stimulation (DBS) surgery for various neuropsychiatric disorders such as Parkinson's Disease, essential tremor, dystonia, epilepsy, obsessive-compulsive disorder, Tourette's Syndrome, and depression. DBS involves implanting a small electrode (e.g., approximately 1 mm wide and with four 1 mm contacts arranged in a 10-12 mm array) into a specific brain region using stereotactic neurosurgical techniques. For many DBS procedures, it is crucial to have higher imaging resolution (less than the currently used 2 mm³) and higher angular resolution to provide accurate imaging of WM tracts to guide targeting. For example, in Figure 5, electrodes located at N (204), a contact with positive effects as seen in positions on high resolution post-operative CT merged with pre-operative MRI 202 showing placement of a direct brain stimulation electrode in the subcallosal cingulate white matter in a patient with depression. The patient had a positive behavioral response whereas at N-1 (206), a shift of ~1 mm in position, had no behavioral response as seen in functional MRI (fMRI) images, 210. DTI-based tractography 208 shows differences in WM projections from N (green) 212 and N-1 (blue) 214.

[0053] The proposed project has the potential to significantly decrease the scan time of advanced diffusion imaging (e.g., HARDI) without sacrificing the SNR, slice number, angular resolution or imaging resolution. The goal is to reduce scan time,

allowing what would have been a one hour high quality scan (for more than 252 DW directions) to be completed within 10 minutes. The scan time would be less than 2 minutes if using the 60 DW directions often used with SS-EPI sequences – the minimum number for HARDI experiments. This shortened scan time would facilitate the clinical applications and real-time intra-operative room tractography for surgical planning or MRI guided operations. Shorter scan time would also increase the ability to scan subjects that may have difficulty remaining still for long periods of time such as children, patients with movement disorders, and the elderly. Beyond this, using current scan times (e.g., 30-60 minutes), a much higher resolution could be obtained allowing for exquisite detail of WM tracts. Thus this study could help revolutionize the use of high-resolution (both spatially and angularly) WM imaging in clinical and clinical research applications.

B. Innovation

RSA-EPI

[0054] Propeller was first proposed by Pipe in 1999 and was later improved for its SAR and long scan time issue using turboprop, X-prop, and turboprop+. Wang et al. proposed PROPELLER EPI to reduce the SAR issue in multishot fast spin-echo (FSE) based PROPELLER and later Skare et al. proposed short-axis PROPELLER EPI (SAP-EPI) to reduce geometric distortion in the PROPELLER EPI sequence. PROPELLER often provides high image quality, high imaging resolution, and motion correction for diffusion imaging; however, SS-EPI is still the fastest prior sequence despite the effects of undersampled k-space PROPELLER variations and X-prop.

[0055] Herein, we propose a PROPELLER-like sequence that is faster than SS-EPI for diffusion imaging and has advantages of PROPELLER blades - Rotating Short-Axis EPI “blades” as veering diffusion gradient directions with composite reconstruction (RSA-EPI). As shown in Figure 6 subfigures (a)-(c), only one EPI blade is acquired per DW direction in RSA-EPI. The scan time is less than the SS-EPI sequence (Figure 6 (e) - (g)) because of the reduced k-space coverage and resulting shortened echo time (TE) required to acquire each blade (i.e., less time needed to travel from peripheral k-space to the center of k-space). The echo-train acceleration-factor (ET AF) is defined as $dSSEPI / dRSA$. In addition, short-axis EPI blade reduces the geometric distortion compared to SS-EPI because of shorter echo spacing ($dRSA < dSS-EPI$), and is able to

increase the imaging resolution along the phase encoding direction (same echo spacing) without aggravating this artifact.

[0056] In RSA-EPI, the image SNR is compensated by shortened TE in an exponential rate and composite reconstruction (more in section C.5.1.2). The composite reconstruction first proposed by Mistretta et al. for Highly Constrained Back Projection for Time-Resolved MRI (HYPR) can compensate for the low SNR and the low resolution of the image (along the frequency encoding direction of the short-axis EPI blade). Two criteria for composite reconstruction are

1. sparsity of images and
2. slow changes of image intensity across temporal dynamics (i.e., DW directions in our case).

[0057] Advanced diffusion imaging methods including HARDI and other high b-value diffusion imaging are suitable for composite reconstruction for their sparse images where only WM is significantly visible and for their larger number of diffusion directions where the change of the image intensity is small in adjacent directions.

[0058] A somewhat similar idea of acquiring different diffusion direction with individual PROPELLER blades has been proposed by Cheryauka et al. in 2004. However, there are several fundamental differences between our proposed method and their Iterate Optimization Algorithm:

1. FSE based PROPELLER was used in their approach, which has higher SAR concern and longer scan time than EPI based PROPELLER blades.
2. Their approach worked only in two-dimensional (2D) space. Thus, it can only estimate 2D diffusion tensors.
3. Their image reconstruction algorithm can only estimate diffusion tensors whereas our approach is ready for arbitrary diffusion data processing algorithms after composite image reconstruction.
4. Only computer simulations of the two dimensional donut shape phantom were presented in their paper. The actual pulse sequence was not developed. Therefore, splitting PROPELLER EPI blades for three-dimensional (3D) advanced diffusion imaging combined with composite reconstruction is an innovative approach. In addition, the proposed project

intends to develop a real pulse sequence and perform rigorous tests of the new sequence on the human brain.

[0059] With respect to other fast imaging techniques, the fundamental time reduction mechanisms are different.

[0060] The parallel imaging requiring a multichannel receiver coil reduces sampling density along the phase encoding direction in the k-space. RSA-EPI, on the other hand, reduces k-space coverage. The simultaneous multi-slice technique takes advantages of multichannel receiver coils along the slice selection direction. The compressed sensing randomly samples k-space and/or q-space. Thus, the RSA-EPI approach is unique and is able to be combined with other fast image techniques.

C. Approach

C.1 Preliminary Studies

[0061] We have evaluated the feasibility of the RSA-EPI approach with HARDI using a post-processing computer simulation on human brain data. We compared the raw diffusion weighted images, directional measure, and the orientation distribution function (ODF) of WM fibers versus different echo-train acceleration factors (ET AF) of RSA EPI. Note that the simulation did not consider effects of geometric distortion of rotated short-axis EPI blades. Composite reconstructed RSA-EPI images in Figure 7(f) - (i) successfully restored SNR and image resolution compared to the subsampled short-axis EPI blade images (Figure 7(b) – (e)).

[0062] Figure 8 shows the RSA-EPI reconstructed fiber profiles (i.e., ODF) of three representative voxels that have single fiber orientation along x, y, and z axes at the corpus callosum, posterior corona radiata and internal capsule, respectively. When compared to conventional HARDI in Figure 4(b), the RSA-EPI approach for HARDI is feasible and looks promising in yielding a reasonable estimation of fiber orientations with an ET AF up to 12.8.

[0063] Figure 9 shows the percentage of root mean squared error (RMSE) of apparent diffusion coefficient (ADC) between the RSA-EPI sequence and the SS-EPI sequence. The ADC surface profile describes 3D diffusivities of water molecules and hence infers the fiber directions within the voxel. The overall RMSEs were less than 3% with a standard variation of ~1.2% across ~700 WM voxels.

[0064] The overall scan acceleration factor is a combination of ET AF and the shortened TE. For example, in the case of b -value = 1000 s/mm² (i.e., diffusion gradient duration (δ) = 13 msec, diffusion gradient separation (Δ) = 27 msec, and gradient strength = 55 mT/m) and imaging matrix size of 128x128 voxels, the RSA-EPI approach is able to reduce the EPI (without parallel imaging) ET from 84 to 6.6 msec with ET AF of 12.8, and reduce the TE from 113 to 47 msec. The overall scan time for one slice is reduced from 155 msec with SS-EPI to 50 msec with RSA-EPI. The SNR increases by a factor of ~2 when TE decreases from 113 to 47 msec; assuming T2 of WM is 87 msec. The timing numbers reported here were from the Philips pulse sequence simulator.

C.2 Estimate the optimum ET AF for RSA-EPI sequence

C.2.1 Evaluate image quality and effective spatial resolution/SNR

[0065] The Shepp-Loan phantom and its point-spread function (PSF) will be used to study the effects of k-space sampling and composite reconstruction at different ET AF (58). Resolution phantoms will be used to evaluate the effective spatial resolution/SNR for both SS-EPI and the RAS-EPI sequence at different ET AFs and SNR.

[0066] We will develop resolution phantoms with different apertures and with different isotropic diffusivities ranging from fast diffusion (e.g., GM and WM axial) to slow diffusion (e.g., WM radial). The FWHM of the apertures in the reconstructed image will indicate the effective resolution. Once the effective spatial resolution/SNR of RAS-EPI sequence is established, we could simulate a low-resolution full-sampled SS-EPI sequence, which has spatial resolution/SNR equal to the “effective” spatial resolution/SNR of RAS-EPI sequence. This low resolution full-sampled SS-EPI (denoted LR EPI) sequence will be subsequently used for comparison between high-resolution full-sampled SS-EPI (denoted HR EPI) sequence and subsampled RAS-EPI sequences in sections C.2.2 and C.2.3.

C.2.2 Develop a numerical WM phantom

[0067] Because there is no in vivo gold standard for WM fiber tracts, we will design a numerical phantom that has single/crossing fibers with different anisotropies with in vivo diffusion coefficients from prior studies. We have experience with designing numerical phantoms. For each voxel, the WM fibers will be modeled by the following

formula, a modified CHARMED model, that contains one hindered compartment and multiple restricted compartments (i.e., crossing fibers):

$$:E(\vec{q}, \Delta) = f_h \cdot E_h(\vec{q}, \Delta) + \sum_{j=1}^n f_r^j \cdot (E_r^j(\vec{q}, \Delta))$$

[0068] The hindered compartment represents the extracellular tortuosity diffusion. The intra-axonal diffusion will be modeled as a cylindrical Gaussian distribution in the restricted compartment. The k-space signal with added quadrature Gaussian noise will be sampled using SS-EPI sequences (including HR SS-EPI and LR SS-EPI) and RSA-EPI sequence of different ET AFs. After simple FT (for SS-EPI) and composite reconstruction (for RSA-EPI), the ODF will be computed and evaluated. The goal is to conclude a “minimum-required” ET AF where RSA-EPI yields similar estimates of fiber number and fiber orientation compared to SS-EPI using null hypothesis tests. The minimum requirement of ET AF is that, if higher, the errors in ODF estimation due to subsampling in the k-space start to outweigh the benefits from composite reconstruction. In an additional study, we will permute the orientations of EPI blades with DW directions to quantify the effects of the orientation of EPI blades on ODF profiles.

C.2.3 Post-processing computer simulation

[0069] In order to verify the RSA-EPI concept, we will acquire data from five human subjects with HARDI of 492 icosahedron directions using a SS-SE-EPI sequence 560 with both opposite phase encoding directions as well as a fieldmap sequence 562, as illustrated in Fig. 11. The images obtained using the SS-SE-EPI sequence will first be corrected for geometric distortion and re-Fourier transformed 564 into k-space data, before the k-space data is subsampled 566 with a different ET AF and regridded to provide simulated RSA-EPI blades 568. Although expected to be minimal in short-axis EPI blades, geometric distortion will be introduced back to the image using information from the fieldmap with matched rotation angle and echo spacing of short-axis EPI blades. In addition, Nyquist ghosts may also be introduced before the composite reconstruction. The goal of the post-processing computer simulation is to reassure the optimum ET AF estimated in C.2.2 with effects of EPI related artifacts in the brain data and compare the results to HR SS-EPI and LR SS-EPI sequences. We will consider many aspects including image SNR, effective resolution, imaging artifacts, accuracy of fiber orientation, estimation of fiber number and WM connectivity.

Simulate the RSA-EPI blades:

[0070] Once we have the RSA-EPI blade for each DW direction, we follow the reconstruction data flow of Fig. 10, as described above, for either real RSA-EPI acquired data or for simulated RSA-EPI data. Note the top half 513 of Fig. 10 represents data gathering operations, and bottom half 527 represents reconstruction operations, with operations FT (515, 515A) representing fast Fourier transforms performed by the image processing computer 124A (Fig. 3) on k-space data. The reconstruction dataflow results in converting raw intensity image data from k-space memory into diffusion-weighted image data in an image space memory 129 portion of memory of image processing computer 124A, where the diffusion weighted image data for each direction depends on raw intensity image data captured at more than one direction because the data captured at several angles (including the $i-1^{\text{th}}$ angle and the $i+1^{\text{th}}$ angle) around the i^{th} angle is a component of the composite I_c (521), and thus the reconstructed image I_{RSA} therefore is also a function of the data captured at several angles (including the $i-1^{\text{th}}$ angle and the $i+1^{\text{th}}$ angle) around the i^{th} angle.

C.3.1 Development of MR pulse sequence

[0071] After performing simulations as described above, we will develop the RSA-EPI sequence with HARDI q-space sampling scheme using the Philips pulse-programming environment for use on Philips MRI machines, as illustrated in the sequence diagram of Figs. 12A-12B and the flow diagram of Fig. 13. We will combine the Stejskel-Tanner diffusion-sensitizing, steep, pulsed, slice-selection gradients (Fig. 12A, 12B) with the short-axis EPI “blade”. The short-axis EPI blade has frequency encoding lines parallel to the short axis of the rotating rectangular blade; thus, the k-space data within the blade is filled up with multiple “short lines”. Note that the long-axis blade is defined as the frequency encoding direction parallel to the long axis of the blade; thus, the k-space data within the blade is filled up with “long lines”. A conventional EPI sequence does not have “blade”. The width and length of the EPI “blade” (i.e. ET AF) determined in Aim 1b will be coded in the pulse sequence.

[0072] K-space data acquisition occurs in three nested loops executed by the MRI pulse sequence controller 126. The outer loop 701 (Fig. 13) acquires data for the i^{th} direction of the (initially 492) DW gradient axis directions. The nested middle loop 704 acquires data for the j^{th} slice of the M slices required to properly image a human brain.

The nested inner loop 708 acquires data associated with the k^{th} blade angle of the total number of blade angles for which data is to be acquired. The outer loop 701 begins by providing 702 determining and setting the gradients 652 and RF pulse 656 for which data is to be taken for a particular slice.

[0073] With reference to Fig. 12A, 12B, and 13, each pulse sequence begins with determining gradients 702 to select a particular slice (j^{th} slice) prior to setting the diffusion gradients to be used for the i^{th} direction of diffusion-weighted imaging. This portion of the sequence includes a pulse 652 of slice-selection axis 602 gradient, a pulse 654 on any axis (in the example of Fig. 12A, 12B, on the readout selection axis 608) and a 90° radio frequency 656 pulse, shown on RF line 606. To create a spin echo signal for recoding in the k-space, a 180° radio frequency pulse 662 and corresponding slice selection gradient 660 are applied followed by the refocusing diffusion gradient (the second on in the pair).

[0074] Once the slice is selected, spins of the slice are stimulated 703 with a radio frequency pulse, and diffusion-weighting gradients are applied, readout begins 710 by sweeping the readout axis gradient 670 across the short axis of a current k^{th} blade, while pulsing 672 the phase-encoding axis 610 for creating a k-space trajectory. A sufficient number of readout sweeps 710 is performed to scan the entire length of the short-axis blade while recording the spin echo signal received from spins of the subject in k-space memory 122. The outer loop 701 is repeated with different slice selection gradients (increment in j), same diffusion-gradient settings and same k^{th} EPI read-out blade setting till all prescribed slices are finished. After finishing all prescribed slices, the dashed loop 702 restarts with the first slice, but with $i+1^{\text{th}}$ diffusion gradient direction and $k+1^{\text{th}}$ EPI blade, the diffusion gradient direction and EPI blade angle are changed simultaneously, without capturing data from multiple EPI blade angles for each diffusion gradient direction as in some prior procedures. Again the dashed loop 702 is repeated with different slice selection gradients (increment in j), same diffusion-gradient settings ($i+1^{\text{th}}$) and same $k+1^{\text{th}}$ EPI read-out blade setting till finished all prescribed slices. The whole process repeats till all diffusion gradients (e.g., 492 directions) are finished. While the diffusion gradient i increments continuously, the EPI blade rotates with increment of angle N_i with increment that completes a whole cycle of 360° before entering next cycle.

There may be several cycles until finishing the whole 492 diffusion-weighting directions used in this embodiment.

[0075] Rotating the DW direction to the next $i+1^{\text{th}}$ direction is by setting the relative strengths of X, Y, and Z gradients used to form gradients to appropriate values. 492 icosahedron directions with $\sim 10^\circ$ angular resolution will be used. Other numbers of DW directions may be considered in alternative embodiments. The k-space data of each slice contains only one EPI short-axis blade that is finished with one RF excitation 656. Thus, this sequence is a single-shot EPI sequence, which is faster than the convection short-axis PROPELLER EPI approach, a multi-shot EPI sequence. The k-space data is transferred 720 to a high-speed workstation computer component of processor 124, and the DW image will be reconstructed using the composite reconstruction algorithm described in section C.5.1 below.

[0076] In computing the DW images, the k-space data (one EPI blade per direction per slice) for each diffusion-weighting direction is reconstructed 722 by first phase-correcting 724, and performing 726 a Fourier transform to form a low resolution image 728. A composite reconstruction 730 is then performed using low resolution data from blades of the neighboring w diffusion-weighting directions 732 to form an i^{th} reconstructed diffusion-weighted image 734. This process is repeated 736 until k-space data from all diffusion directions for all slices has been processed in a manner similar to that performed on simulated data and described with reference to Fig. 10.

C.4 Scans of human subjects

C.4.1 Participants

[0077] We will perform MRI experiments on healthy subjects with both the conventional SS-SE-EPI sequences and the RSA-EPI sequences. The age range of participants will be 20-40 years old to decrease variability due to age. Subjects will have no clinically significant medical, neurological or psychiatric disorders. All methods of subject recruitment, informed consent, handling of personal information, and data sharing will follow the policies of the Dartmouth Committee for the Protection of Human Subjects. If assuming the effect size is 5% RMSE of ADC profiles between RSA-EPI and SS-EPI, given the maximum standard deviation of 1.2% from Figure 9, the sample size to reach significant p-values of 0.05 and 0.005 using a paired t-test is about 5 and 12 subjects, respectively. Therefore, we plan to recruit 5 subjects for the post-processing

computer simulation in Aim 1 and another 15 healthy subjects for the human experiments after pulse sequence development in Aim 2.

C.4.2 MR and diffusion imaging protocol

[0078] The MR imaging protocol will include anatomical T1W imaging, T2W imaging, fieldmap sequence with matched rotation angles, RSA-EPI sequence and two conventional SS-EPI sequences (both with and without parallel imaging). The first SS-EPI has matched DW directions of RSA-EPI but a significantly longer scan time and will be processed as HARDI. The second SS-EPI has matched scan time of RSA-EPI but with fewer DW directions and will be processed as DTI. We will evaluate WM ODF profiles and tractography results for HARDI RSA-EPI (short scan time), HARDI SS-EPI (long scan time) and DTI SS-EPI (short scan time) in section C.5.2 and C.5.3. The total experiment time will be about 2 hours including subject preparation and actual imaging time. The scans will be performed on a Philips 3.0T Achieva scanner. The b-value for DTI SS-EPI scan will be 1000 sec/mm² while HARDI scans will be around 3000 sec/mm². At 3000sec/mm², only WM still has significant signals and most of the GM signals are near noise floor. The sparse images of WM at higher b-value make HARDI suitable for composite reconstruction. To satisfy the second composite reconstruction criteria, it is important to “sort” the diffusion direction monotonically so that the angular change of consecutive DW directions is minimized and the DW signals change slowly across the sequence of DW direction to satisfy the second composite reconstruction criteria. We will use the Archimedean spiral curve to spirally “strip” the spherical surface and then sort the DW directions accordingly.

[0079] Thus, the angular changes between consecutive DW directions are minimized. The Archimedean sorting approach has the advantage of using arbitrary (in terms of number and generation algorithm) sets of DW directions instead of imposing analytic DW directions.

C.5 Data processing

C.5.1 Image reconstruction

C.5.1.1 Motion, phase and geometric distortion correction

[0080] Motion is a severe problem in diffusion imaging. In general, the motion artifact decreases as the scanning speed increases. The proposed RSA-EPI

sequence is robust to motion artifacts because of its fast scanning and its PROPELLER based reconstruction for retrospective motion correction. Motion artifacts arising between diffusion directions could be improved by correcting phase errors between EPI blades during the composite reconstruction. Short-Axis PROPELLER EPI is insensitive to geometric distortion and is able to increase imaging spatial resolution without the penalty of increasing the geometric distortion. Although not an essential step, a fieldmap sequence that matches the rotation angles of the RSA-EPI blade will be developed for retrospective correction. Alternatively, one could also operate the reverse phase encoding direction in the RSA-EPI sequence.

C.5.1.2 Composite reconstruction

[0081] After motion, phase, and any needed geometric distortion correction, of individual RSA-EPI blades, the k-space data associated with the blade will be first Fourier Transformed (FT) to the image space to form an initial low resolution and low SNR image of the i^{th} DW frame, I_i (right pathway 515 of Figure 10). In the left pathway 517 of Figure 10, the adjacent k-space blades 519 with the i^{th} frame in the middle of the sliding window are collected to fill-up a complete k-space composite with correction of sampling density. This is called a “moving composite” with a sliding-window width covering several closely-spaced DW directions. In this case, the window width is 8 from the $i-4^{\text{th}}$ to $i+3^{\text{th}}$ DW direction.

[0082] This paragraph defines the “training” process for reconstruction. The k-space composite then yields two composite images in the image space – one is I_C 521 and the other is I_C^i , 523 “re-sampled” from the k-space composite using the k-space data associated with i^{th} k-space blade. The final RSA-EPI image, I_{RSA} , is $I_{RSA} = I_C \cdot (F \otimes I_i) / F \otimes I_C^i$. Note that I_C^i normalizes the initial input I^i , and the convolution kernel, F , reduces image artifacts with a width that matches WM anatomy. The composite reconstruction compensates the SNR and restores the imaging resolution along the frequency encoding direction of the short-axis EPI blade in the final image 525, I_{RSA} . HARDI and other high b-value (high diffusion gradient) diffusion imaging techniques are suitable for composite reconstruction for their sparsity in images where only WM tracts are significantly visible. However, through a special “sparsifying” procedure, lower b-value DTI could be used for composite reconstruction as well. After composite reconstruction, the images are used for any diffusion processing algorithms.

C.5.2 Evaluation of WM ODF of HARDI for new RSA-EPI and SS-EPI sequence on human subjects

[0083] We will test the null hypotheses of the WM ODF between the RSA-EPI (reduced scan time) and SS-EPI (long scan time) sequence with HARDI. The paired t-test between RSA-EPI and SS-EPI will be voxel-based analysis (VBA) on the whole brain WM for all subjects. The fiber ODF may be estimated by Funk-Radon transform in q-ball imaging (QBI) or Bayesian technique. QBI-ODF processing is available in the Camino software package (<http://web4.cs.ucl.ac.uk/research/medic/camino/pmwiki/pmwiki.php>), and the Bayesian processing is available in Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Library (FSL) (http://www.fmrib.ox.ac.uk/fsl/fdt/fdt_bedpostx.html). In particular, fiber number and orientation will be extracted from ODF profiles and compared between RSA-EPI and SS-EPI sequences. We expect that the ODF profiles as well as the extracted fiber number and orientations are not significantly different between RSA-EPI (short scan time) and SS-EPI (long scan time).

C.5.3 Comparison of WM connectivity between DTI and two HARDI sequence

[0084] We will compare WM connectivity between DTI with the SS-EPI sequence (short scan time), HARDI with the SS-EPI sequence (long scan time), and HARDI with the RSA-EPI sequence (short scan time). We will initially assess tractography of the pyramidal tracts using the FSL software) and the Camino, an open-source software toolkit for diffusion MRI processing. However, other established WM tracts with potential clinical relevance (e.g., pathways in the prefrontal cortex, medial temporal lobe, visual and language areas), as determined by us will also be used for the comparison. The ROI of seed voxels and destination masks for the tractography will be determined using standard WM atlases available in FSL or Freesurfer, Freesurfer is available from Harvard(<http://surfer.nmr.mgh.harvard.edu/>). We will evaluate the WM tractography both qualitatively and quantitatively. The qualitative comparison of WM tractography in the subject space between DTI and two HARDI sequences will be performed by using the observation-rating scale followed by the McNemar test. A rater blinded study and a fair rating scale should be established. The quantitative comparison of

WM probability tractography will be done in the standard space using voxel-based analysis (VBA).

[0085] The term signal memory as used herein includes both k-space and q-space data memory.

CONCLUSION

[0086] We have implemented a new sequence that decreases EPI echo train and shortens TE for diffusion imaging. The sequence has minimal geometric distortion and is able to increase the imaging resolution without aggravating this EPI artifact. The sequence has potential for use with other diffusion imaging approaches and is able to be combined with existing fast imaging techniques. The immediate applications will be incorporating it with HARDI for higher image resolution and higher angular resolution in DBS procedures and clinical researches.

Combinations

[0087] The system and method herein described has features that can be combined in various ways. A few exemplary combinations of features include:

[0088] A method designated A of operating a magnetic resonance imaging system to obtain diffusion weighted images in N diffusion-weighted directions is described. The imaging system of the type including a magnet configured to provide a static magnetic field, X, Y, and Z-axis gradient coils configured to add gradients to the magnetic field, and X, Y, and Z magnet drivers coupled to drive the X, Y, and Z-axis gradient magnets, a radio frequency driver for stimulating nuclear spins in the magnetic field, and a signal memory coupled to an image processing computer. In the system, the image processing computer is adapted to perform Fourier transforms of signal memory contents and has machine readable code for performing the method, and the system also has a radio-frequency receiver coupled to receive spin echoes from spins in the magnetic field and to provide spin echo magnitudes to the signal memory, and a sequence controller coupled to sequence the magnetic drivers and the radio frequency driver, and to sequence capture of spin echo magnitudes into the signal memory. The method includes, for at least a first slice of a sample, using at least one of the gradient coil and the radio frequency driver to select and excite spins of the slice; and, for each integer i from one to N, using at least one of the gradient coils to apply diffusion weighting gradient in an i'th direction of N diffusion-weighted directions, using at least one of the gradient coils to

sweep a readout gradient in trajectory across a short-axis EPI (echo-planar imaging) blade at a first angle, using at least one of the gradient coils to pulse a phase-encoding gradient, using the radio frequency receiver to record spin-echo signals and storing the signals in the signal memory for the short-axis blade at a first angle, simultaneously rotating the diffusion gradient direction to a next direction of the N directions and rotating the short axis blade to a second angle and repeating using at least one of the gradient coil to sweep a readout gradient in trajectory across the short-axis blade, using at least one of the gradient coils to pulse a phase-encoding gradient, using the radio frequency receiver to record spin-echo signals and storing the signals as k-space data in the k-space memory for the short-axis blade oriented at the second angle, and performing a composite reconstruction to provide diffusion-weighted image data from signal memory data captured from several blade angles.

[0089] A method designated AA including the method designated A wherein only k-space data for only one short axis blade is stored as signal data in the signal memory for each diffusion gradient direction for each slice.

[0090] A method designated AB including the method designated A or AA wherein the composite reconstruction is performed by “training” an *i*th low-resolution image from Fourier Transform of the *i*th signal memory EPI blade with the *i*th high-resolution composite image from Fourier Transform of the collected signal memory EPI blades of neighborhood in a plurality of diffusion directions.

[0091] A method designated AC including the method designated A, AB, or AA, wherein the sample comprises a human brain.

[0092] A system designated B and adapted to obtain magnetic resonance diffusion weighted images in N diffusion-weighted directions, the system including a magnet configured to provide a static magnetic field, X, Y, and Z-axis gradient coils configured to add gradients to the magnetic field, and X, Y, and Z magnet drivers coupled to drive the X, Y, and Z-axis gradient magnets, at least one radio frequency driver coupled to a stimulus coil positioned to stimulate nuclear spins in the magnetic field, a sequence controller coupled to sequence the magnetic drivers and the radio frequency driver, and to sequence capture of spin echo magnitudes into the k-space memory, a k-space memory coupled to an image processing computer, the image processing computer having machine readable code stored in a memory for configuring the sequence controller for RSA-EPI imaging and to perform composite reconstructions of k-space memory

contents into diffusion-weighted images, and a radio-frequency receiver coupled to receive spin echoes from spins in the magnetic field and to provide spin echo magnitudes to the k-space memory. The machine readable code in the image processing computer includes code executable on the processor and adapted to: for at least a first slice of a sample, use at least one of the gradient coils and the radio frequency driver to select and excite spins of the slice; for a plurality of integers i , use at least one of the gradient coils to apply a diffusion weighting gradient in an i 'th unique direction; use at least one of the gradient coil(s) to sweep a readout gradient in trajectory across a short-axis EPI (echo-planar imaging) blade at a first angle, use at least one of the gradient coils to pulse a phase-encoding gradient, use the radio frequency receiver to record spin-echo signals and storing the signals in the k-space memory for the short-axis blade at a first angle; rotate the diffusion gradient direction to a next direction of the N directions and rotate the short axis blade to a second angle and repeat using at least one of the gradient coil to sweep a readout gradient in trajectory across the short-axis blade, using at least one of the gradient coils to pulse a phase-encoding gradient, using the radio frequency receiver to record spin-echo signals and storing the signals as k-space data in the k-space memory for the short-axis blade oriented at the second angle; and perform a composite reconstruction to provide diffusion-weighted image data from k-space data obtained at a plurality of the blade angles.

[0093] A system designated BA including the system designated B wherein only k-space data for only one short axis blade is stored as k-space data in the k-space memory for each diffusion gradient direction for each slice.

[0094] A system designated B or BA wherein the composite reconstruction is performed by "training" an i th low-resolution image from Fourier Transform of the i th k-space EPI blade with the i th high-resolution composite image from Fourier Transform of the collected k-space EPI blades of a plurality of neighboring diffusion directions.

[0095] A method designated C including selecting, using a magnetic field, and exciting, using a radio-frequency field, nuclear spins of at least a first slice of a sample; for a plurality of integers i , applying diffusion weighting magnetic field gradient in an i 'th unique direction to the first slice; sweeping a readout magnetic field gradient in a trajectory across a short-axis EPI (echo-planar imaging) blade at an i th angle, pulsing a phase-encoding magnetic field gradient, receiving spin-echo signals and storing at least received signal magnitudes in a signal memory associated with the short-axis EPI blade

oriented at an i 'th angle; simultaneously rotating the i 'th direction to a next $i+1$ th direction of a plurality of diffusion-weighted directions and rotating the short axis blade to an $i+1$ th angle near the first angle, and repeating sweeping a readout magnetic field gradient in trajectory across the short-axis blade, pulsing a phase-encoding magnetic field gradient, receiving spin-echo signals and storing at least received signal magnitude data in the signal memory associated with the short-axis blade oriented at the $i+1$ th angle. Once data is gathered in the signal memory for the blade and diffusion weighted gradients, the method continues with performing a reconstruction of the signal memory data into diffusion-weighted image data wherein reported data at the i th direction is derived from both signal memory data recorded at the i th and at the $i+1$ th diffusion-weighted direction.

[0096] A method designated CA including the method designated C wherein only recorded data for one short axis blade is stored in the signal memory data in the signal memory for each diffusion gradient direction for each slice.

[0097] A method designated CB including the method designated C or CA wherein the composite reconstruction is performed by "training" an i th low-resolution image from Fourier Transform of the i th k-space EPI blade with the i th high-resolution composite image from Fourier Transform of the collected k-space EPI blades of a plurality of neighboring diffusion directions.

Conclusion

[0098] It should be noted that the matter contained in the above description or shown in the accompanying drawings should be interpreted as illustrative and not in a limiting sense. The following claims are intended to cover generic and specific features described herein, as well as all statements of the scope of the present method and system.

CLAIMS

What is claimed is:

1. A method comprising:
selecting, using a magnetic field, and exciting, using a radio-frequency field,
nuclear spins of at least a first slice of a sample;
for a plurality of integers i ,
applying diffusion weighting magnetic field gradient in an i 'th unique direction to
the first slice;
sweeping a readout magnetic field gradient in a trajectory across a short-axis EPI
(echo-planar imaging) blade at an i th angle, pulsing a phase-encoding
magnetic field gradient, receiving spin-echo signals and storing at least
received signal magnitudes in a signal memory for the short-axis EPI blade
oriented at an i 'th angle;
simultaneously rotating the i 'th direction to a next $i+1$ th direction of a plurality of
diffusion-weighted directions and rotating the short axis blade to an $i+1$ th
angle near the first angle, and repeating sweeping a readout magnetic field
gradient in trajectory across the short-axis EPI blade, pulsing a phase-
encoding magnetic field gradient, receiving spin-echo signals and storing
at least received signal magnitude data in signal memory for the short-axis
blade oriented at the $i+1$ th angle; and
performing a reconstruction of the signal memory data into diffusion-weighted
image data wherein reported data at the i th direction is derived from both
signal memory data recorded at the i th and $i+1$ th diffusion-weighted
direction.
2. The method of claim 1 wherein only recorded data for one short-axis EPI
blade is stored in the signal memory data in the signal memory for each diffusion gradient
direction for each slice.
3. The method of claim 1 or 2 wherein the composite reconstruction is
performed by "training" an i th low-resolution image from Fourier Transform of the i th k -
space EPI blade with the i th high-resolution composite image from Fourier Transform of
the collected k -space EPI blades of a plurality of neighboring diffusion directions.

4. A method of operating a magnetic resonance imaging system to obtain diffusion weighted images in N diffusion-weighted directions, the system comprising:

- a magnet configured to provide a static magnetic field,
- X, Y, and Z-axis gradient coils configured to add magnetic field adients to the static magnetic field, and X, Y, and Z magnet drivers coupled to drive the X, Y, and Z-axis gradient coils,
- a radio frequency driver for stimulating nuclear spins in the magnetic field,
- a signal memory coupled to an image processing computer, the image processing computer adapted to perform Fourier transforms of signal memory contents and having machine readable code for performing the method,
- a radio-frequency receiver coupled to receive spin echoes from the nuclear spins and to provide associated spin echo magnitudes to the signal memory, and
- a sequence controller coupled to sequence the magnetic drivers and the radio frequency driver, and to sequence capture of the spin echo magnitudes into the signal memory;

the method comprising:

- for at least a first slice of a sample,
- using at least one of the gradient coils and the radio frequency driver to select and excite nuclear spins of the slice;
- for each integer i from one to N,
- using at least one of the gradient coils to apply diffusion weighting gradient in an i'th direction of N diffusion-weighted directions;
- using at least one of the gradient coils to sweep a readout gradient in trajectory across a short-axis EPI (echo-planar imaging) blade at a first angle, using at least one of the gradient coils to pulse a phase-encoding gradient, using the radio frequency receiver to record spin-echo signals and storing the signals in the signal memory for the short-axis EPI blade at a first angle;
- simultaneously rotating the i'th direction to a next direction of the N diffusion-weighted directions and rotating the short axis blade to a second angle and repeating using at least one of the gradient coils to sweep a readout gradient in trajectory across the short-axis EPI blade, using at least one of the gradient coils to pulse a phase-

encoding gradient, using the radio frequency receiver to record spin-echo signals and storing the signals in the signal memory for the short-axis EPI blade oriented at the second angle; and performing a composite reconstruction on the signal memory data to provide diffusion-weighted image, where reconstructed diffusion weighted data for each reported diffusion angle is derived from signal memory data captured at a plurality of diffusion-weighted directions in a window around the reported diffusion-weighted direction.

5. The method of claim 4 wherein only k-space data for only one short axis blade is stored as k-space data in the k-space memory for each diffusion gradient direction for each slice.

6. The method of claim 4 or 5 wherein the composite reconstruction is performed by “training” an i^{th} low-resolution image from Fourier Transform of the i^{th} k-space EPI blade with the i^{th} high-resolution composite image from Fourier Transform of the collected EPI blades of a plurality of neighboring diffusion directions.

7. The method of claim 4 wherein the sample comprises a human brain.

8. A system adapted to obtain magnetic resonance diffusion weighted images in N diffusion-weighted directions, the system comprising:

a magnet configured to provide a static magnetic field,

X, Y, and Z-axis gradient coils configured to add gradients to the static magnetic field, and X, Y, and Z magnet drivers coupled to drive the X, Y, and Z-axis gradient coils,

At least one radio frequency driver coupled to a stimulus coil positioned to stimulate nuclear spins in the magnetic field,

a signal memory;

a sequence controller coupled to sequence the magnetic drivers and the radio frequency driver, and to sequence capture of spin echo magnitudes into signal memory,

an image processing computer coupled to the signal memory, the image

processing computer having machine readable code stored in a memory for

configuring the sequence controller for RSA-EPI imaging and to perform composite reconstructions of signal memory contents into diffusion-weighted images,

a radio-frequency receiver coupled to receive spin echoes from the nuclear spins and to provide spin echo magnitudes to the signal memory; and

the machine readable code comprising code executable on the processor and adapted to:

for at least a first slice of a sample, use at least one of the gradient coils and the radio frequency driver to select and excite spins of the slice;

for a plurality of integers i ,

use at least one of the gradient coils to apply a diffusion weighting gradient in an i 'th unique direction;

use at least one of the gradient coil(s) to sweep a readout gradient in trajectory across a short-axis EPI (echo-planar imaging) blade at a first angle, use at least one of the gradient coils to pulse a phase-encoding gradient, use the radio frequency receiver to record spin-echo signals and storing the signals in the signal memory for the short-axis blade at a first angle;

rotate the diffusion gradient direction to a next direction of the N directions and rotate the short axis blade to a second angle and repeat using at least one of the gradient coil to sweep a readout gradient in trajectory across the short-axis blade, using at least one of the gradient coils to pulse a phase-encoding gradient, using the radio frequency receiver to record spin-echo signals and storing the signals as signal data in the signal memory for the short-axis blade oriented at the second angle;

perform a composite reconstruction to provide diffusion-weighted image data for each diffusion weighted direction from k-space data obtained at a plurality of the blade angles.

9. The system of claim 8 wherein only signal data for only one short axis blade is stored as signal data in the signal memory for each diffusion gradient direction for each slice.

10. The system of claim 8 or 9 wherein the composite reconstruction is performed by "training" an i th low-resolution image from Fourier Transform of the i th

signal EPI blade with the i th high-resolution composite image from Fourier Transform of the collected signal EPI blades of a plurality of neighboring diffusion directions.

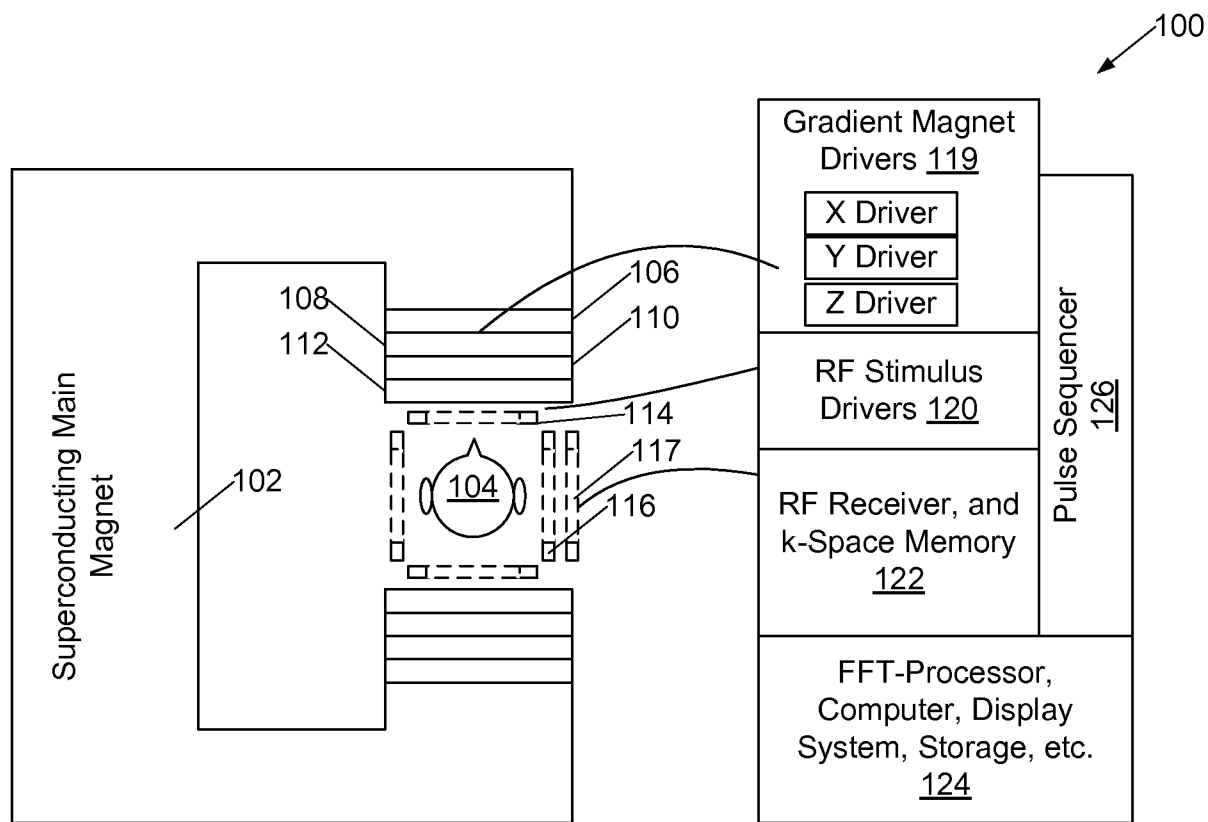
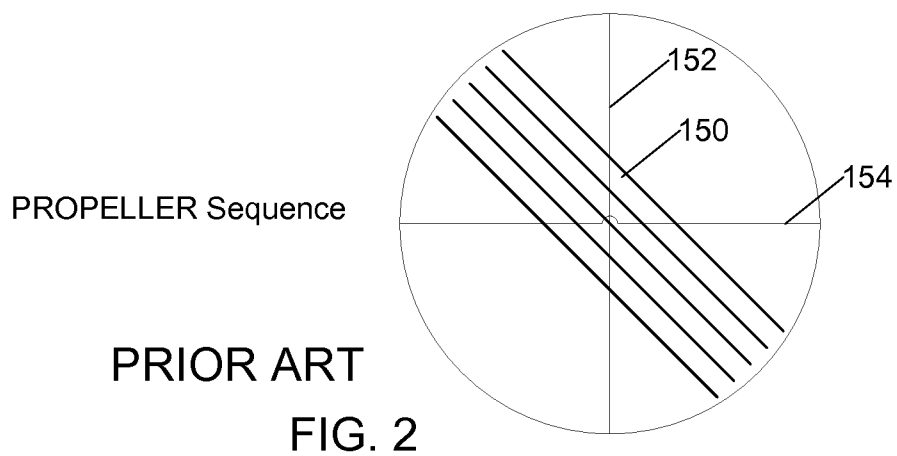


FIG. 1



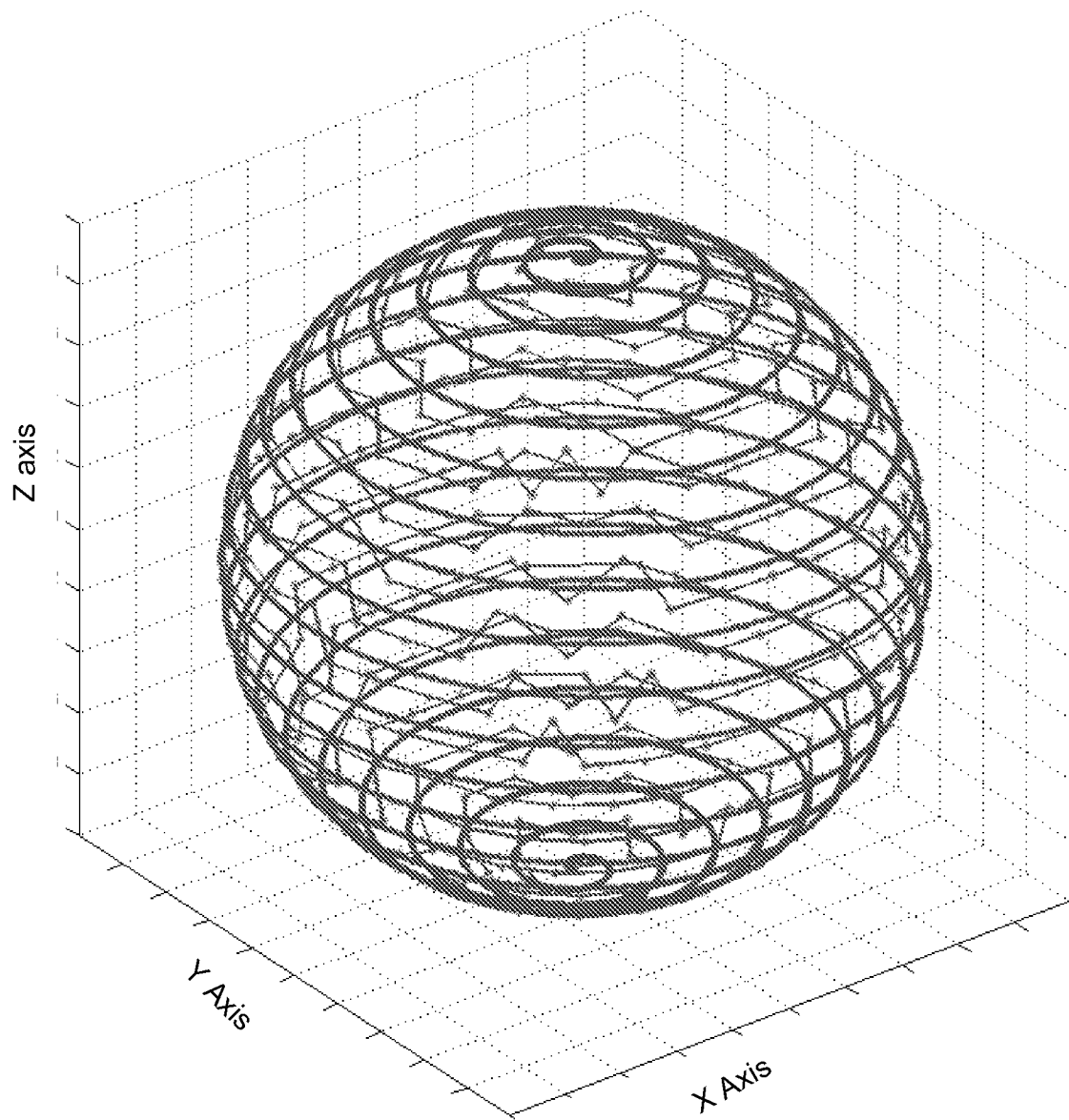
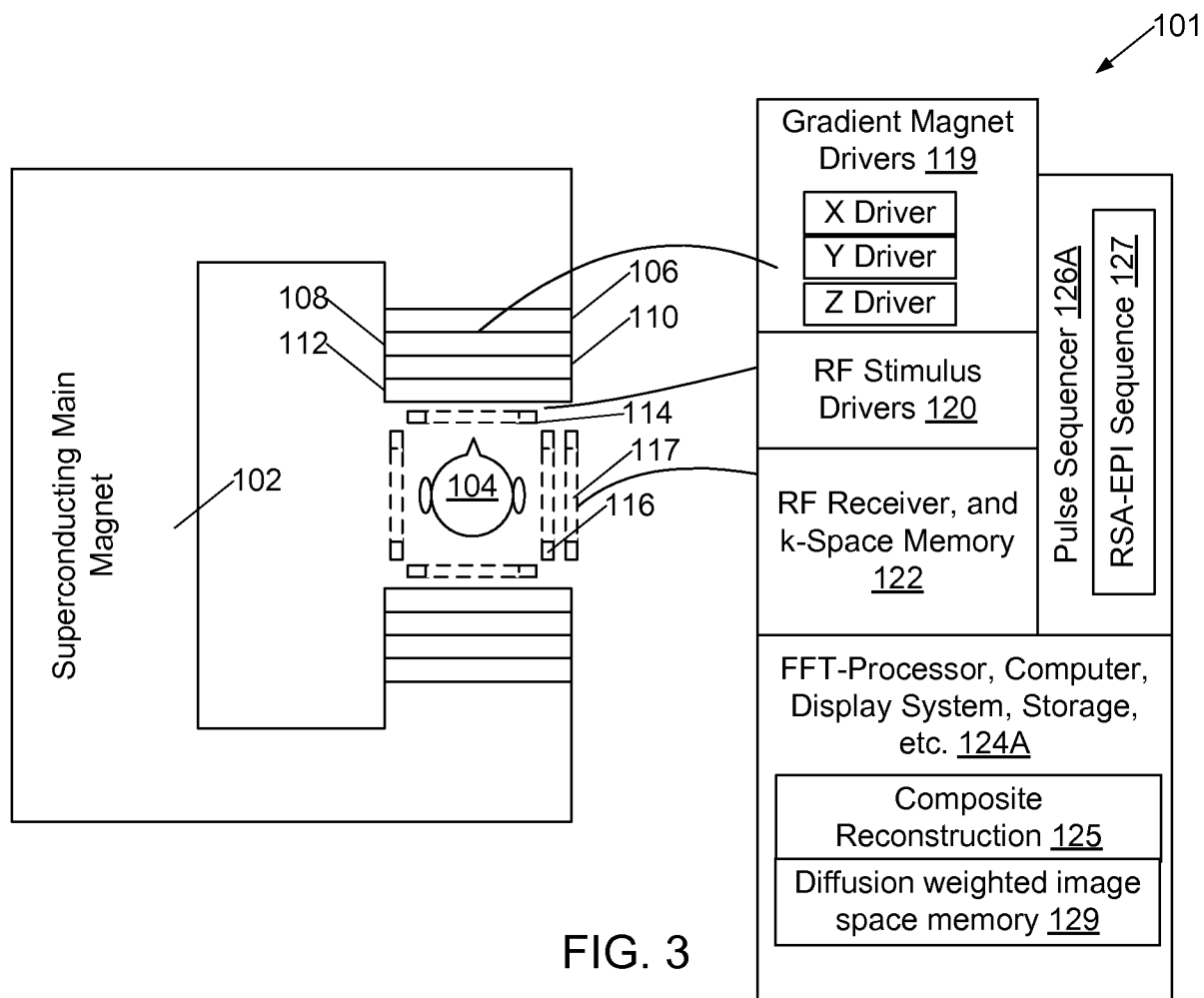


FIG. 3A



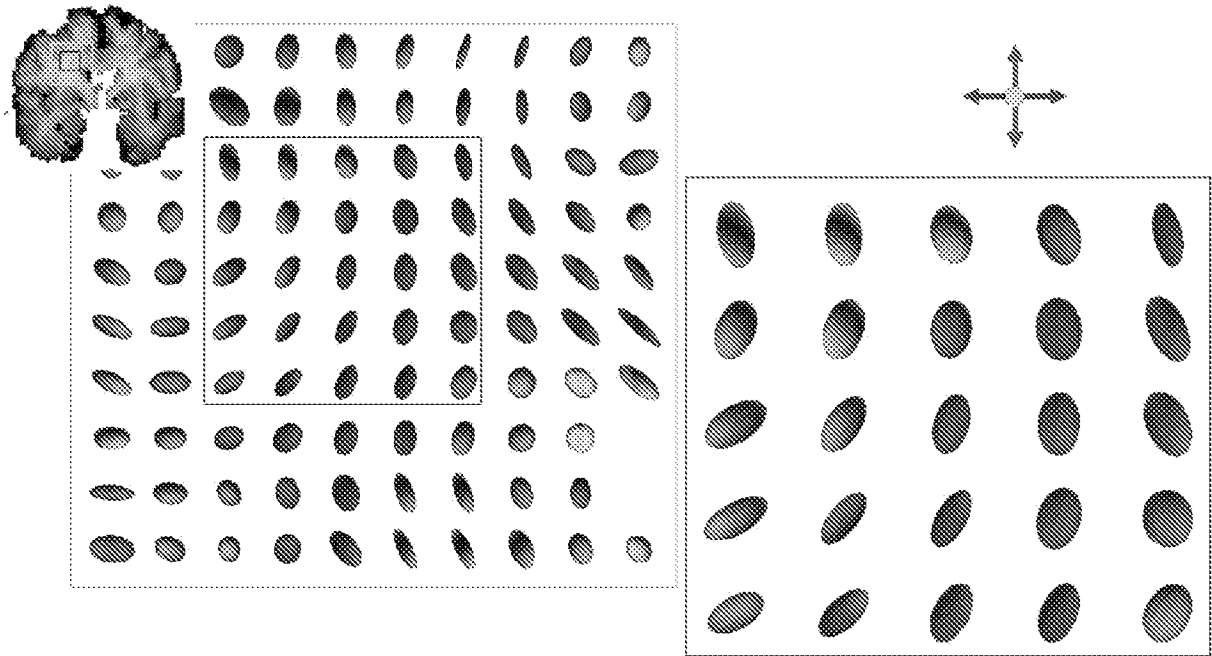


FIG. 4A

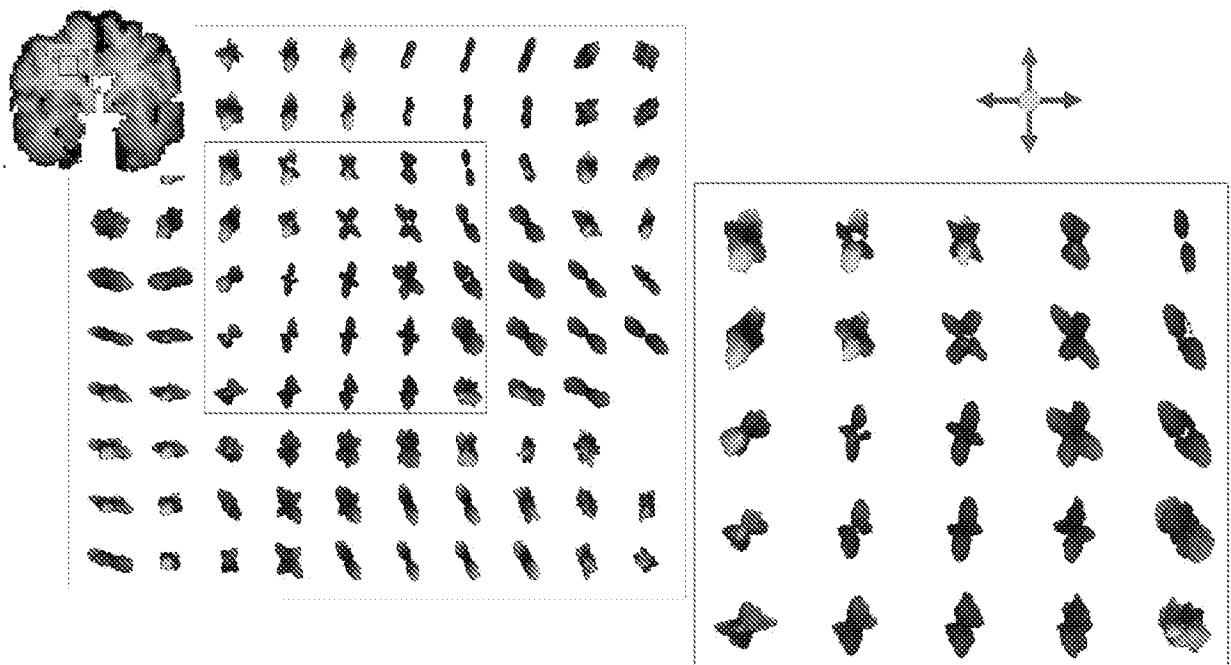


FIG. 4B

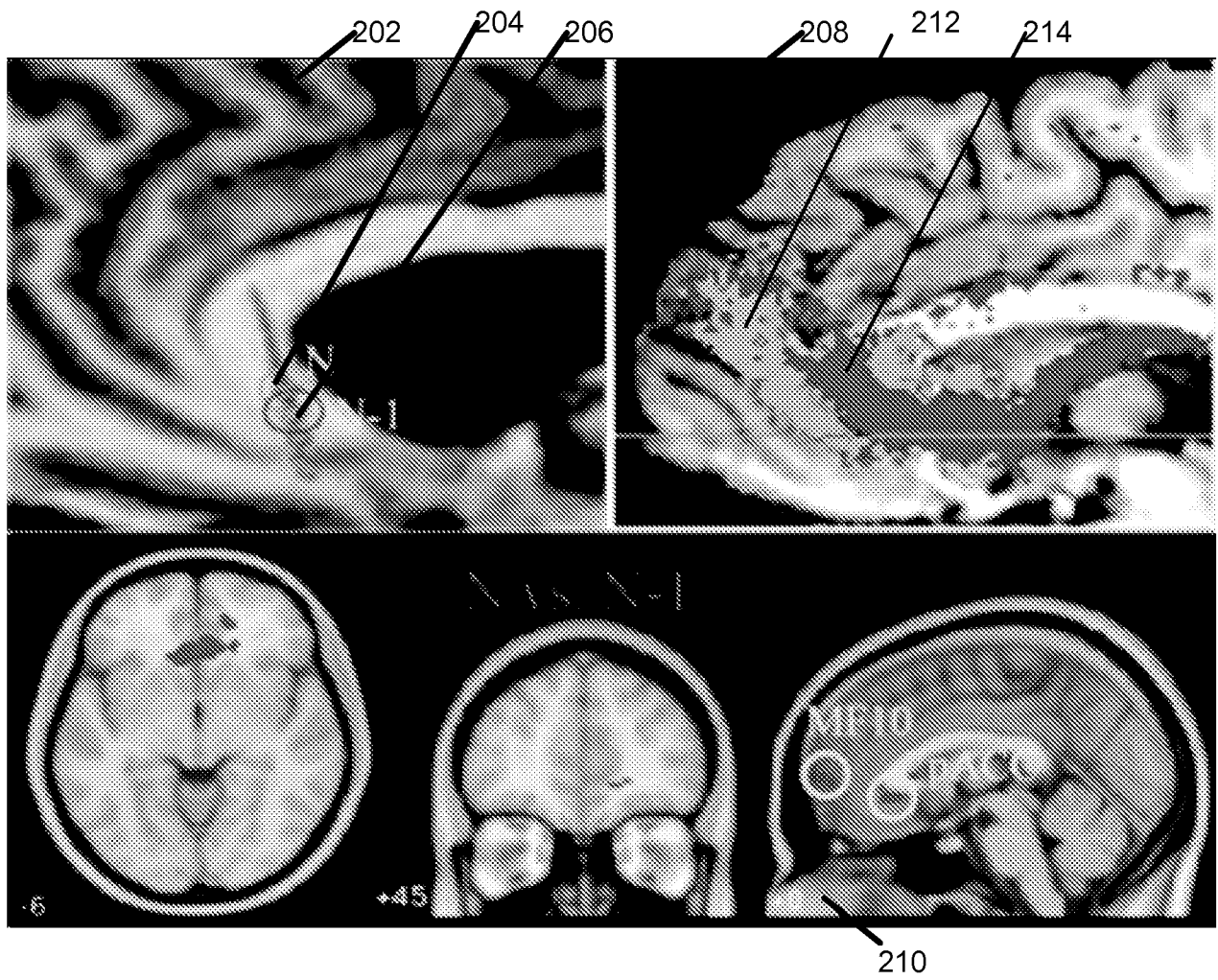


Fig. 5

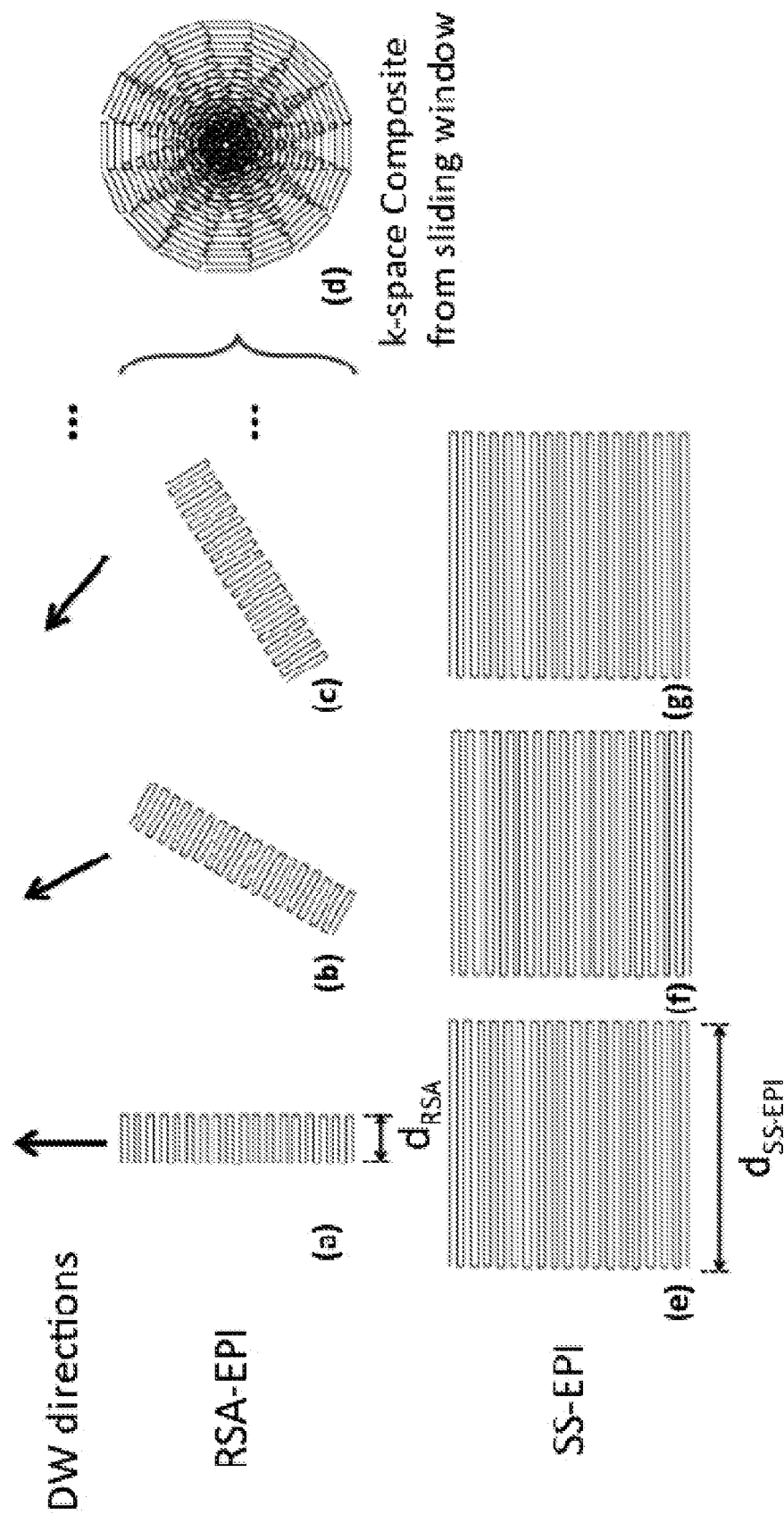


Fig. 6

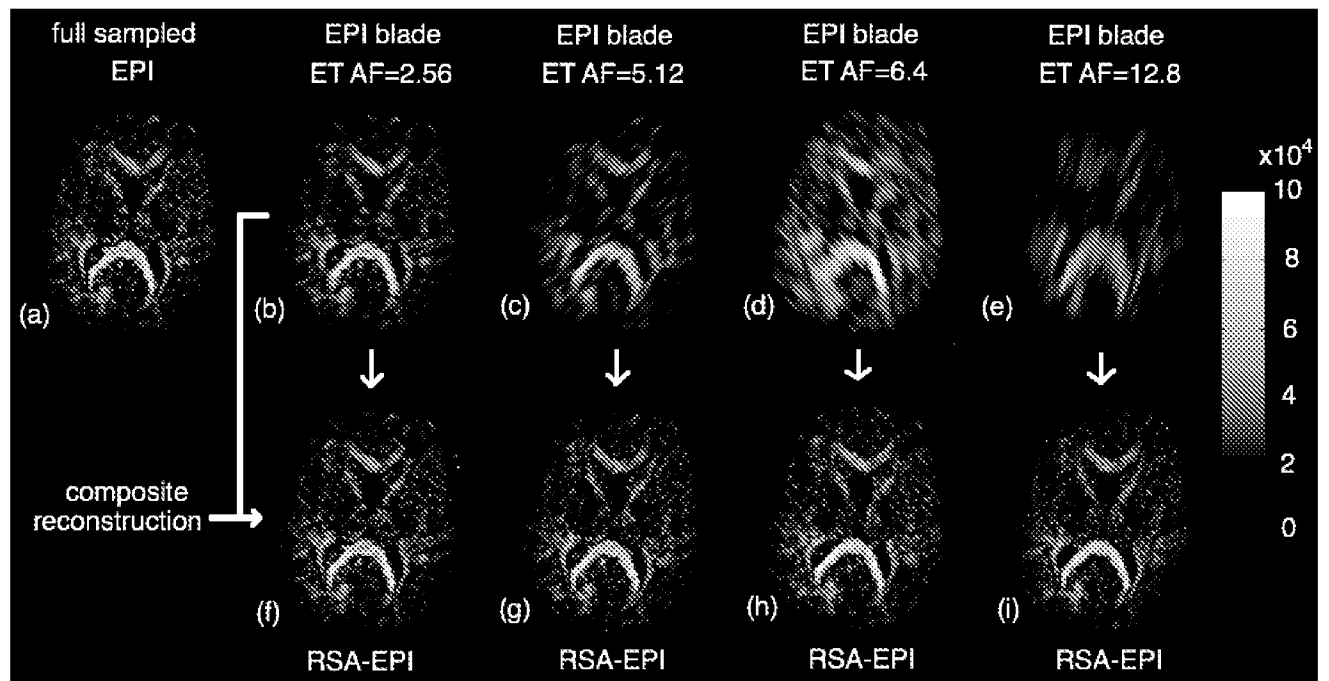


Fig. 7

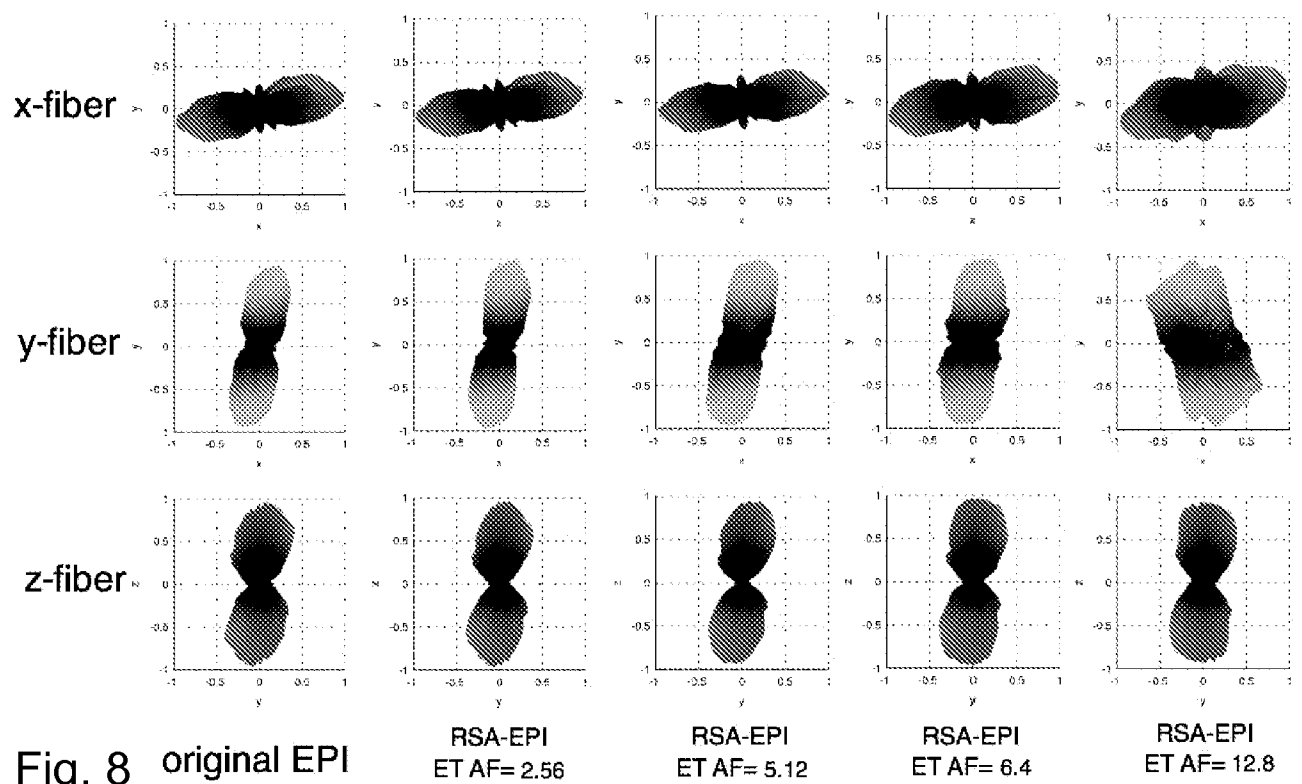


Fig. 8 original EPI

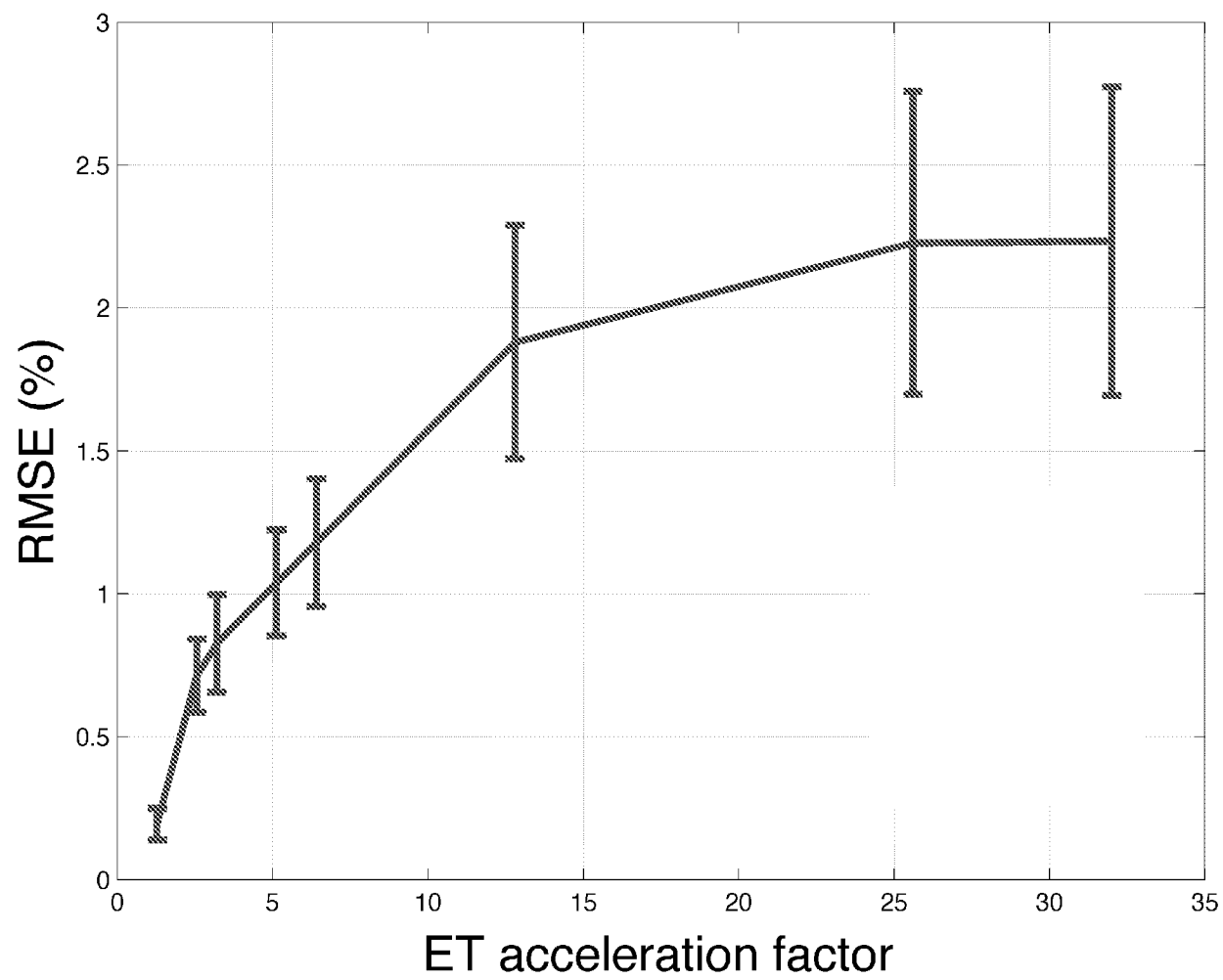


Fig. 9

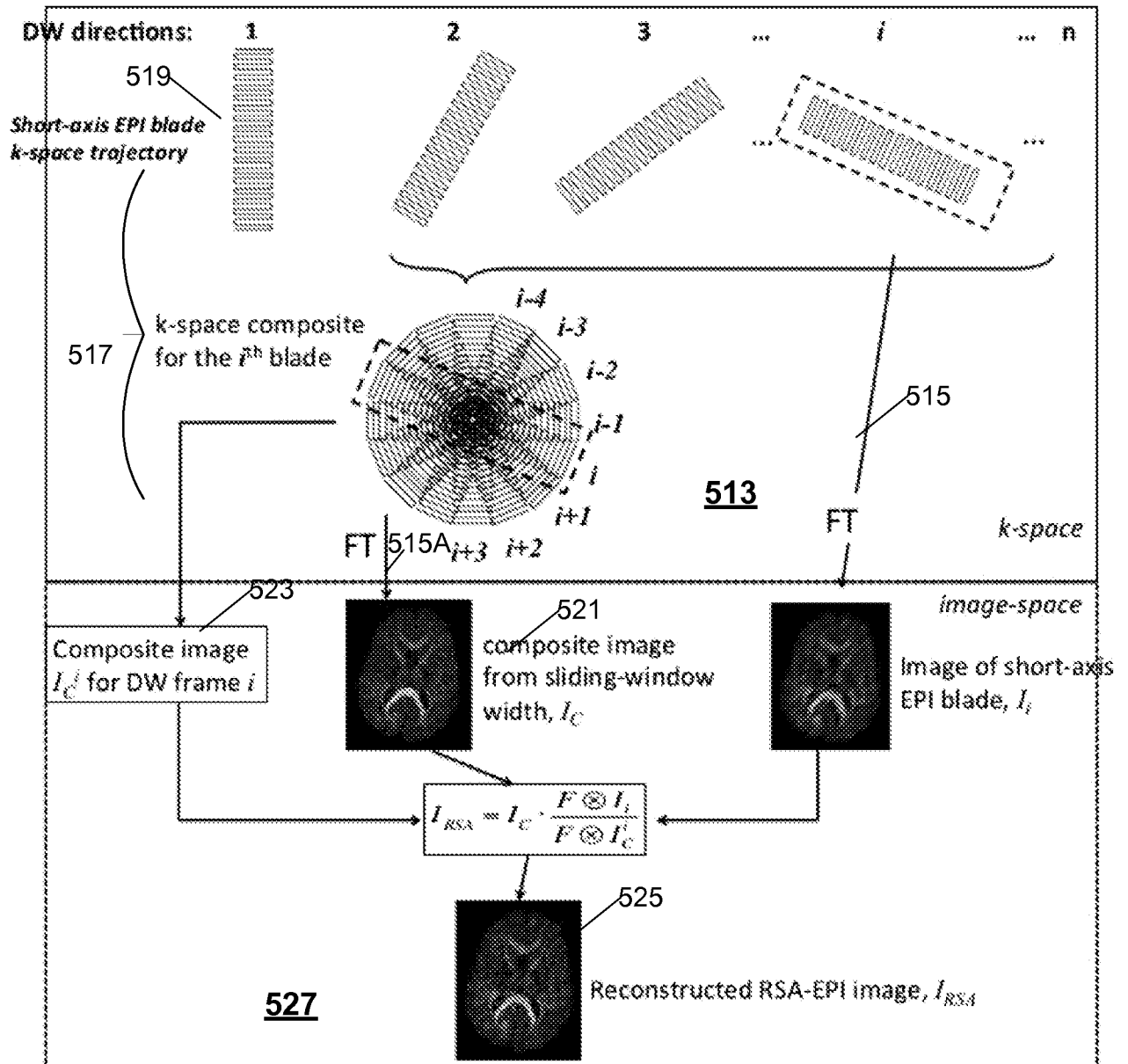


Fig. 10

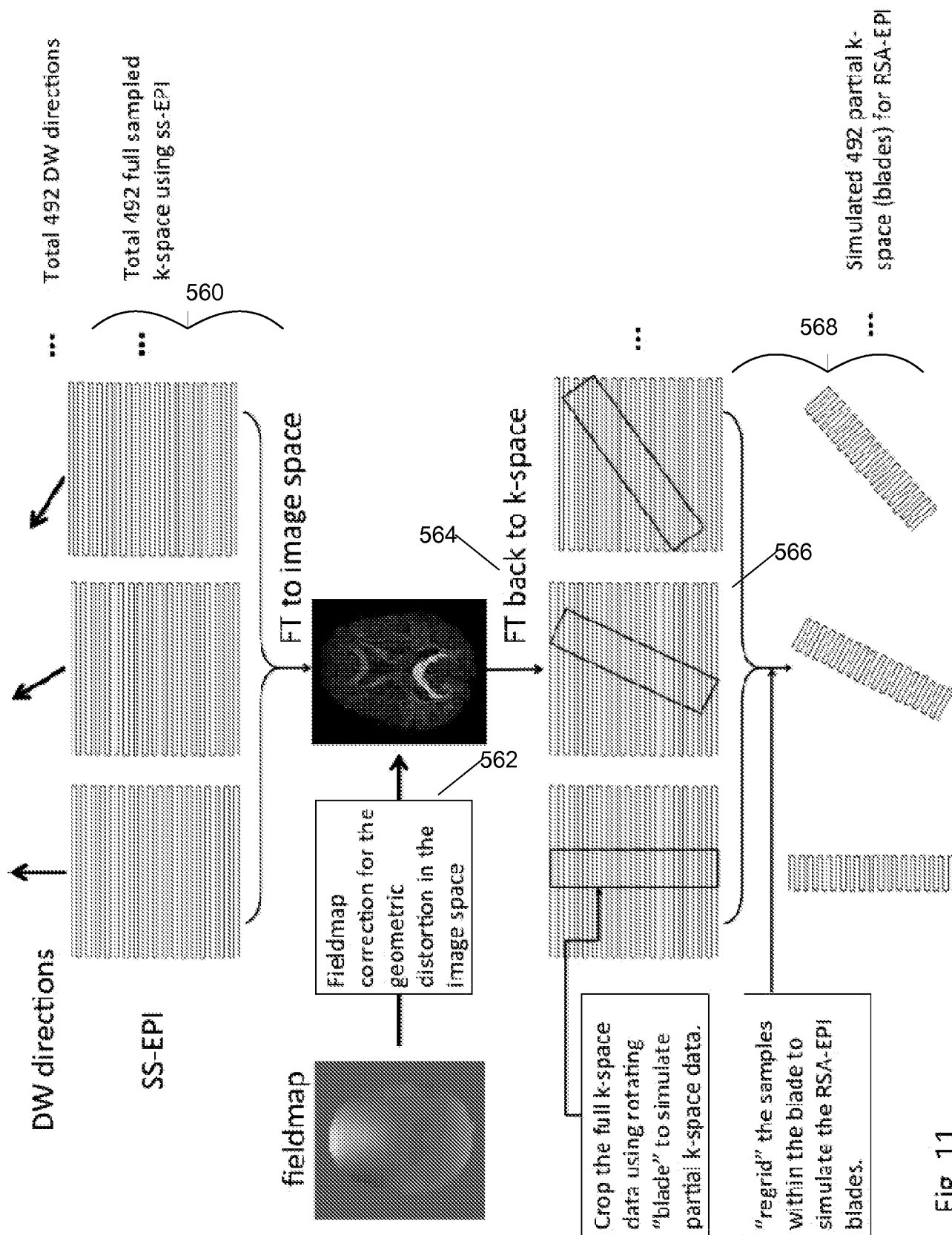


Fig. 11

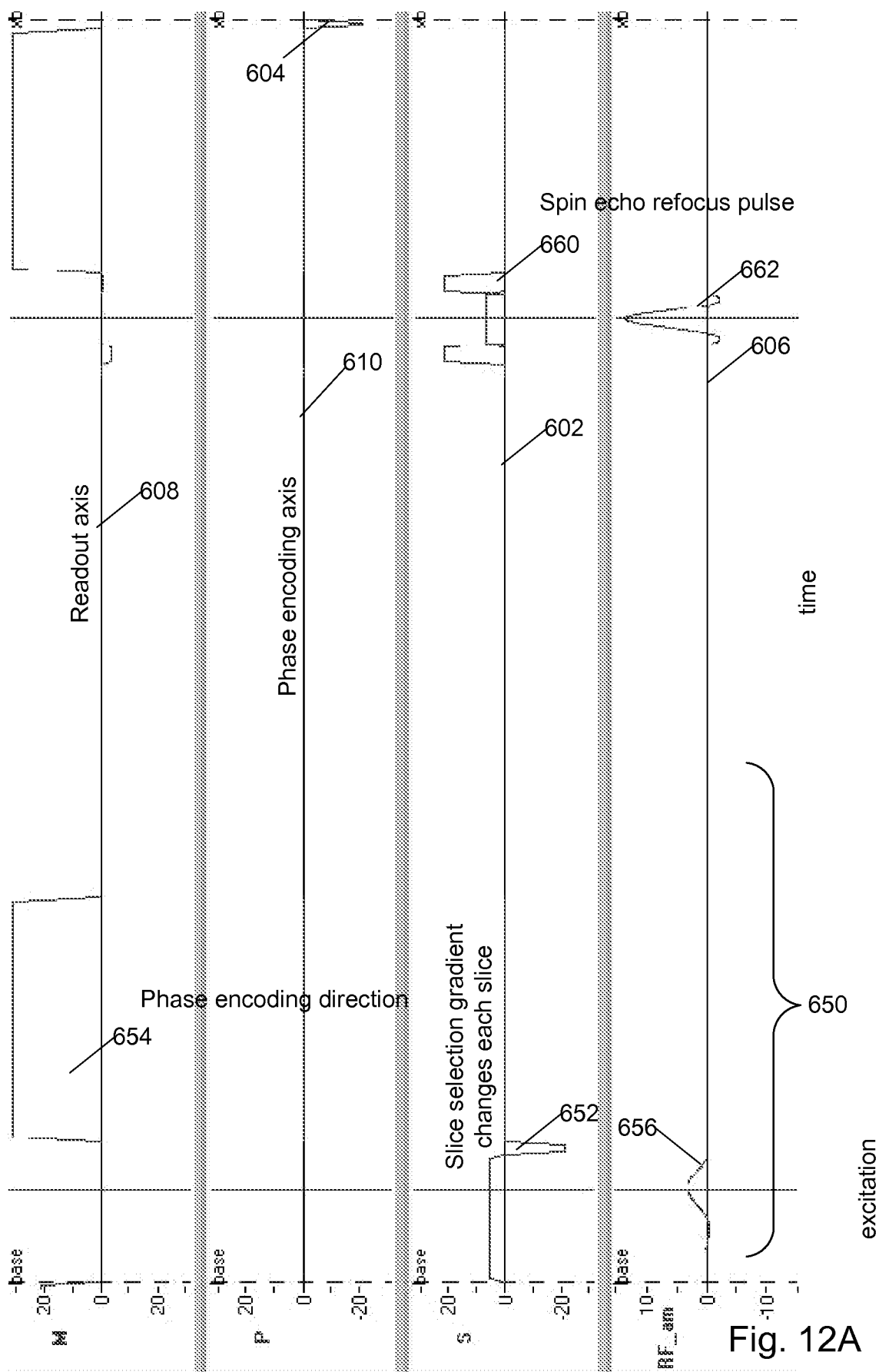


Fig. 12A

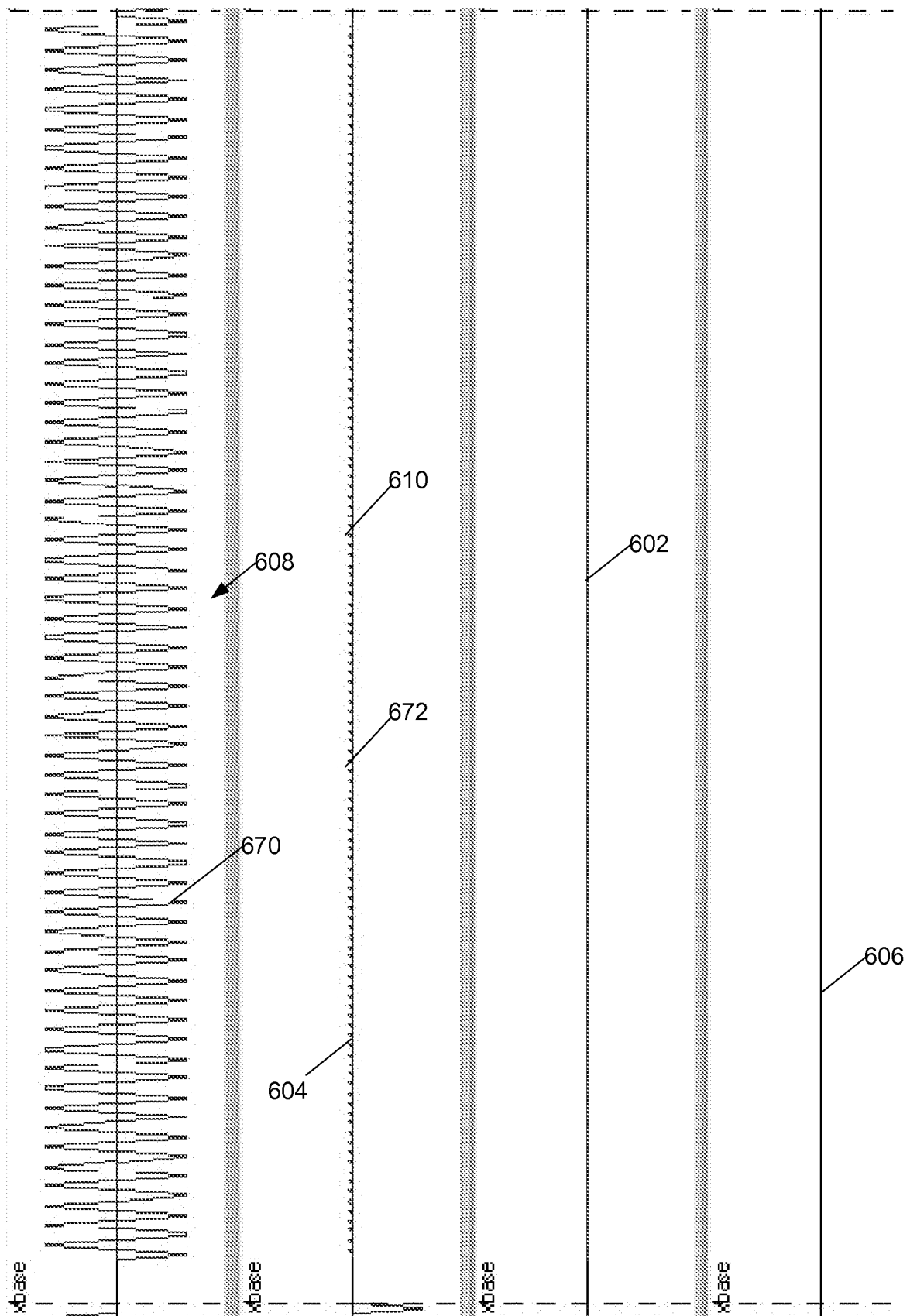
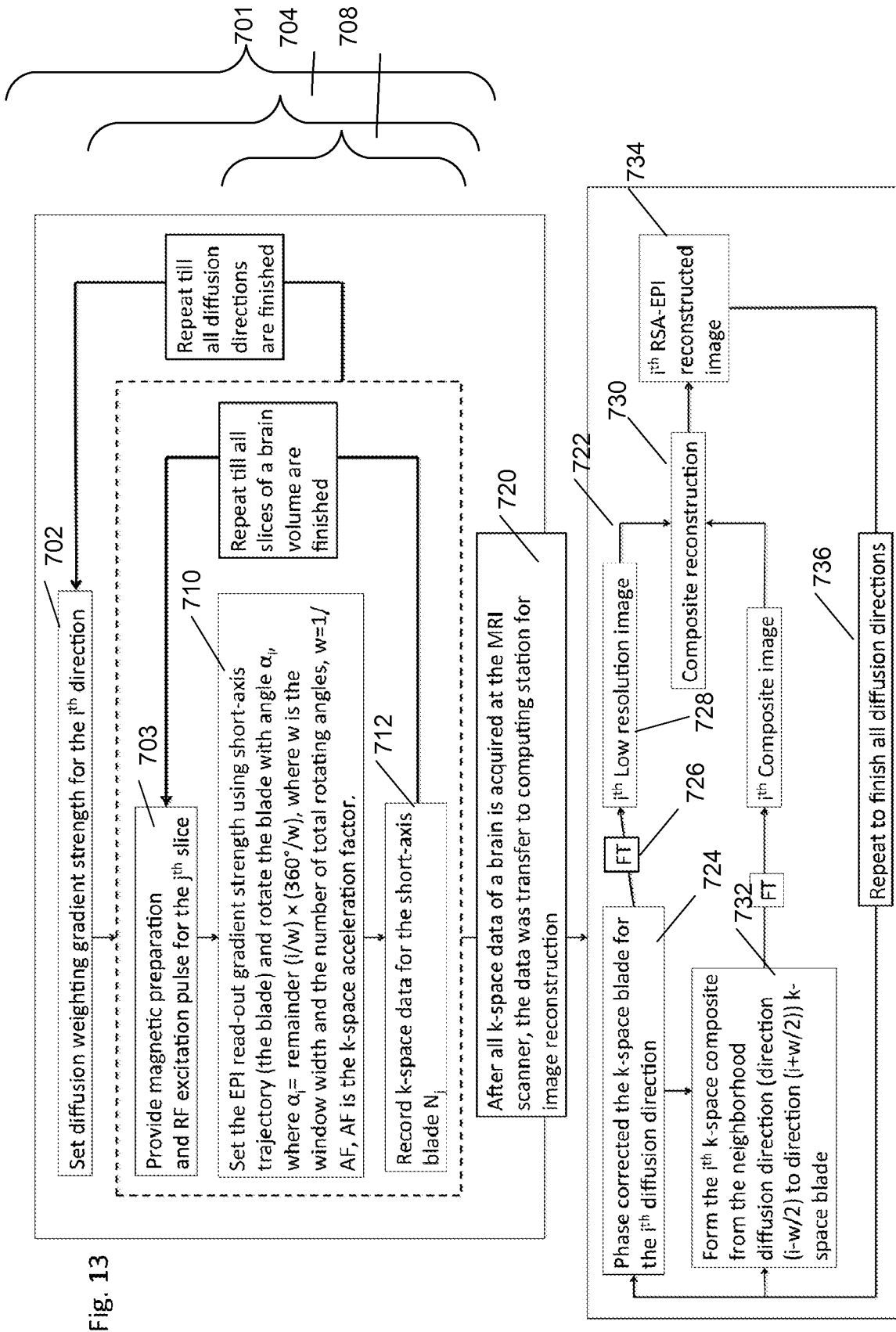


Fig. 12B



INTERNATIONAL SEARCH REPORT

International application no.

PCT/US14/60541

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - G01R 33/48, 33/54, 33/56 (2014.01)

CPC - G01R 33/48, 33/54, 33/56

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC(8): G01R 33/20, 33/44, 33/48, 33/54, 33/56, 33/561, 33/565; G01V 3/00, 3/12, 3/14 (2014.01); CPC: G01R 33/20, 33/44, 33/48, 33/54, 33/56, 33/561, 33/565; G01V 3/00, 3/12, 3/14; USPC: 324/300, 307, 309, 312, 313

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

PatSeer (US, EP, WO, JP, DE, GB, CN, FR, KR, ES, AU, IN, CA, INPADOC Data); Google; Google Scholar; ProQuest; KEYWORDS: magnetic field RF system gradient coil with i+1th direction sample slice nuclear spin short-axis EPI blade spin-echo signal composite image signal memory k-space fourier transform

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2011/0199084 A1 (HASAN, K.) August 18, 2011; figures 1, 20; paragraphs [0026, 0067-0069, 0074-0076]	1-10
A	FIELD, A. et al. Diffusion Tensor Eigenvector Directional Color Imaging Patterns in the Evaluation of Cerebral White Matter Tracts Altered by Tumor. Journal Of Magnetic Resonance Imaging, Vol. 20, No. 4, 2004, pp. 555-562 [online], [retrieved on 2014-12-23]. Retrieved from the Internet <URL: http://haxbylab.dartmouth.edu/publications/FAW+04.pdf >	1-10
A	WU, Y. et al. Hybrid diffusion imaging. NeuroImage, Vol. 36, No. 3, 24 March 2007, pp. 617-629 [online], [retrieved 2014-12-23]. Retrieved from the Internet <URL: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2428345/ >	1-10

☐ Further documents are listed in the continuation of Box C.

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

23 December 2014 (23.12.2014)

Date of mailing of the international search report

09 JAN 2015

Name and mailing address of the ISA/US

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