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Sub-Millimeter Isotropic MRI for Segmentation of Subcortical Brain Regions and Brain Visualization

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Abstract

Purpose—We evaluated a rapid sub-millimeter isotropic SPGR (non-selective SPGR) to facilitate the brain subcortical segmentation and the visualization of brain volume compared with the commonly-accepted SPGR-IR technique.

Materials and Methods—The feasibility of the non-selective SPGR was evaluated for two segmentation algorithms. FAST was used to segment the brain into constituent tissue classes (white matter, gray matter, CSF) and FreeSurfer was used to segment specific subcortical structures (hippocampus, caudate, putamen and thalamus). Localized apparent SNR and CNR values for non-selective SPGR and the SPGR-IR were compared for the studied subcortical regions. 3D volume rendering was generated to evaluate the non-selective SPGR and the SPGR-IR for brain visualization.

Results—In basal ganglia regions, non-selective SPGR allows for consistent segmentation results for both FAST and FreeSurfer. This sequence also better differentiated grey/white matter compared to SPGR-IR. An approximate two-fold improvement of image quality in apparent SNR and CNR was indicated for subcortical brain anatomical structures with non-selective SPGR versus SPGR-IR. The non-selective SPGR improved clarity and yielded a more realistic depiction of the brain surface for visualization compared with SPGR-IR.

Conclusion—Compared with SPGR-IR, non-selective SPGR allows for consistent segmentation results for basal ganglia regions and improved clarity for visualization of brain.

Keywords

Segmentation; Visualization; Subcortical Brain; High Resolution MRI; Isotropic MRI

INTRODUCTION

Three-dimensional (3D) high resolution structural images have become increasingly imperative for computer-assisted post-processing for brain segmentation and visualization.

Segmentation algorithms have been used to generate volumetric brain measurements for probing changes associated with neurological disorders in vivo. Segmentation-derived hippocampal volume measurements have shown promise for early diagnosis of Alzheimer's disease (1,2). Subcortical atrophy in diagnostic and prediagnostic Huntington's diseases have shown in segmentation results (3). Moreover, 3D brain rendering allows for visualization of fMRI activation maps and provides critical guidance for neurosurgery (4).

To obtain high resolution structural images for either brain segmentation or visualization, typically a T1-weighted 3D inversion recovery-prepared spoiled gradientecho (SPGR-IR) is used (e.g. SPGR-IR GE Healthcare, Milwaukee, WI or MP-RAGE, Siemens Medical systems, Erlangen, Germany). Normally, the anisotropic resolution prescribed with the through-plane resolution (1 ~ 1.2mm) exceeds the in-plane resolution (e.g. $0.9375 \times 0.9375 \text{ mm}^2$) such as in the widely adapted Alzheimer's Disease Neuroimaging Initiative (ADNI) protocol (5,6). Higher isotropic resolution could theoretically reduce partial volume artifacts, affording better precision/accuracy in deriving volumetric measurements and reducing systematic errors in registration (7). This is beneficial for detecting atrophic changes in small, anatomically eloquent subcortical brain structures (e.g. hippocampus) and for serial imaging studies (8,9).

An alternate approach for acquisition of high resolution structural images has been reported that utilizes a non-selective minimum phase hard pulse, which eliminates inversion recovery (10). This approach allows for isotropic, sub-millimeter resolution of the whole brain within 5 minutes. This is considerably shorter than the 7-10 minutes typically required with SPGR-IR. It has been suggested that the relative slice thickness that can be obtained with SPGR-IR within reasonable scan times could also be reduced with the non-selective SPGR (10). In this investigation, non-selective SPGR was further evaluated, with particular focus on the utility for brain visualization and segmentation of subcortical regions.

In this investigation non-selective SPGR was compared with the more commonly used SPGR-IR for brain segmentation and visualization. For the purpose of this comparison, SPGR-IR was also acquired with sub-millimeter, isotropic resolution, identical to that of the non-selective SPGR sequence. Localized apparent SNR and CNR values for the two sequences were compared in brain regions of interest in hippocampus and basal ganglia. To further evaluate the non-selective SPGR sequence for derivation of volumetric measurements, images acquired with the two different sequences were also submitted to segmentation algorithms. FAST (FMRIB's Automated Segmentation Tool) (Analysis Group, FMRIB, Oxford, UK.) was used to segment the brain into constituent tissue classes (white matter, gray matter, CSF) (11). FreeSurfer (Martinos Center for Biomedical Imaging, MA) was used to segment specific subcortical structures (hippocampus, caudate, putamen and thalamus) (12). Visualization results for both sequences are presented.

MATERIALS AND METHODS

Image acquisition

Whole brain images of nine healthy subjects (7 males, 2 females, mean age: 41.7, age range 17 – 56) were obtained using an 8-channel phased array coil (MRI Devices, Gainesville, FL) on a 3 Tesla General Electric (Waukesha, WI) HDx system. Two 3D image acquisitions, non-selective SPGR and SPGR-IR were performed on each subject. Standard SPGR-IR and SPGR sequences were used (13). To obtain non-selective SPGR, a spatially non-selective (“hard”) excitation was applied using an 800-microsecond RF pulse. Other parameters included repetition time (TR): 7.1 msec, echo time (TE): 3.0 msec using a full echo readout, 12 degree flip angle, sampling bandwidth of 31.25 kHz with 320 frequency samples; 320 phase-encoding lines, field of view: 22 cm $\times$ 18 cm, and slice thickness: 0.8

mm resulting in an isotropic voxel volume of $0.8 \text{ mm} \times 0.8 \text{ mm} \times 0.8 \text{ mm} = 0.51 \text{ mm}^3$ with 252 contiguous slices covering the whole brain. Half-Fourier analysis was applied in the phase-encoding direction resulting in scan time of 4 minutes 42 seconds. For the purpose of this comparison, SPGR-IR was acquired with sub-millimeter, isotropic resolution, identical to the non-selective SPGR sequence. Other parameters included: TR/TE/inversion time (TI)/bandwidth/flip angle: 7.9 msec/3.2 msec/450/31.25 kHz/12 degrees, also with half-Fourier analysis and 252 contiguous slices covering the whole brain. The scan time for this sequence was 6 minutes 17 seconds (approximately 33% longer than for non-selective SPGR). The study was approved by the Institutional Review Board.

Image analysis

Images were transferred offline to a Linux workstation for post processing. To evaluate the utility of the non-selective SPGR relative to the SPGR-IR, for segmentation of subcortical regions, FreeSurfer was implemented to segment hippocampus, caudate, putamen and thalamus. Another widely used segmentation algorithm, FAST, was used for global tissue segmentation to classify brain into gray matter, white matter and CSF. Volview 2.0 (Kitware, NY) was used for 3D volume rendering to examine the quality of images generated with non-selective SPGR vs. the SPGR-IR (14). A two-step pre-processing including BET- premask and BET were executed to automatically remove skull and extracranial tissues (15,16) prior to FAST segmentation, and before generating the 3D volume rendering.

Quantitative analyses

Segmentation generated with FreeSurfer was used to derive volumes of four subcortical brain structures including hippocampus, caudate, putamen and thalamus. The segmented brain structural masks generated with FreeSurfer were also used to derive volumes of interest (VOIs) for image quality assessment as follows: The segmentation masks were first registered to original gray scale images. After realignment, segmented masks were refined with 1 pixel erosion to eliminate possible partial volume artifacts and alignment error at edges. The mean signal intensity (SI) was then calculated for each of the studied subcortical brain structures by averaging the signal intensity of the voxels extracted from the original gray scale images based on the segmentation defined VOIs. It is difficult to perform exact signal-to-noise ratio (SNR) measurement in the setting of parallel imaging since noise is spatially heterogeneous and accurate estimation requires careful post-processing of the acquired complex k-space data. Apparent SNR estimates were calculated using signal measurements from similarly positioned regions, to eliminate any potential bias across sequences. Apparent signal-to-noise ratio (apparent SNR) and apparent gray matter-white matter contrast-to-noise ratio (apparent CNR) were determined according to standard equations: $\text{apparent SNR} = \text{Mean SI} / \text{SD noise}$ and $\text{apparent CNR} = (\text{Mean SI}_{\text{wm}} - \text{Mean SI}_{\text{gm}}) / \text{SD noise}$ (where SD_{noise} indicates standard deviation (SD) of noise in the air along the phase-encoding direction in extra-cranial space). The mean SI_{gm} was calculated for each of the bilateral subcortical gray matter regions (hippocampus, caudate, putamen and thalamus). The mean SI_{wm} were derived using white matter masks generated from the automated segmentation, the average signal was calculated for bilateral hemispheric white matter regions.

Statistical methods

Primary variables for analysis included the mean apparent SNR and CNR for each subcortical region for the different sequences. Statistical methods included repeated measures analysis of variance, t-tests and summary statistics. Intraclass correlation coefficients (ICC) were used to examine agreement between volumetric measurements

derived with non-selective SPGR and SPGR-IR. All statistical tests were 2-tailed and were executed in SAS 9.1 using a significance level of 0.05.

RESULTS

Quantitative evaluation

Means and standard deviations for apparent SNR and CNR values are presented in Table 1. Significantly higher values, indicative of greater image quality, were observed for the non-selective SPGR in all regions examined, including hippocampus (left (L): 38.5 vs. 22.8; right (R): 38.2 vs. 23.9), caudate (L: 43.5 vs. 24.0; R: 46.6 vs. 22.3), putamen (L: 45.4 vs. 25.4; R: 46.3 vs. 25.3) and thalamus (L: 46.1 vs. 29.0; R: 46.0 vs. 29.0), all $p < 0.0001$. A similar pattern was indicated for apparent CNR in all regions examined. Significantly higher values with $p < .001$ were obtained for non-selective SPGR in hippocampus (L: 21.3 vs. 8.3; R: 21.7 vs. 8.4), caudate (L: 16.2 vs. 7.1; R: 13.3 vs. 10.0), putamen (L: 14.3 vs. 5.7; R: 13.6 vs. 7.0) and thalamus (L: 13.7 vs. 2.1; R: 13.9 vs. 3.3).

Volumetric measurements derived with FreeSurfer based on non-selective SPGR showed a high degree of agreement with measurements based on SPGR-IR, with intra-class correlation coefficients ranging from 0.89 – 0.98 for the subcortical regions of interest. ICC values greater than 0.7 are generally considered to represent a high degree of correlation. Table 2 presents the mean volume difference between non-selective SPGR and SPGR-IR by location with 95% confidence limits and the intraclass correlation coefficient (ICC).

Visual inspection of segmentation results

FreeSurfer segmentation—Compared to SPGR-IR, non-selective SPGR produced more precise segmentation results for subcortical regions and generated more clearly defined boundaries at caudate nuclei and thalamus (Figure 1, left). SPGR-IR segmentation was associated with misclassifications at the edges of caudate and putamen (Figure 1, right, arrow heads) and misclassifications of lesions in normal white matter areas (Figure 1, right, small arrows). For the hippocampus, comparable segmentation results were observed for both SPGR methods (Figure 2).

FAST segmentation—Segmentation based on non-selective SPGR generated better-defined basal ganglia structures compared to SPGR-IR. The segmented putamen and caudate nuclei on non-selective SPGR images represented the original gray scale structural image accurately (Figure 3A1 and 3A2). Non-selective SPGR yielded more distinct border lines between gray matter (caudate nucleus, thalamus and putamen) and white matter (internal capsule, external capsule) tissues. Moreover, only segmentation based on the non-selective SPGR sequence depicted claustrum, a thin layer of gray matter between the extreme capsule and external capsule in the brain (Figure 3A3). FAST segmentation based on SPGR-IR failed to segment basal ganglia structures (particularly at the putamen and caudate) with misclassification of the two gray matter masses as white matter (Figure 3B1-3).

Volume rendering

Compared to volume rendering derived via SPGR-IR, the conspicuity of brain structures is substantially improved when non-selective SPGR is used (Figure 4). 3D volume rendering based on the non-selective SPGR showed realistic brain anatomy; the gyri, sulci and small veins are clearly represented, smooth and without distortion. Structural details are less prominent in the SPGR-IR rendering, in which many blurred areas obscure anatomical structures.

DISCUSSION

Brain segmentation is becoming increasingly important as a research and clinical diagnostic tool. This approach is the basis for tissue type extraction in quantitative image analysis and also for deriving volumetric measurements of atrophy in neurological disorders such as Alzheimer's disease (17). Generally, segmentation of subcortical brain structures relies on SPGR-IR, a method that produces reliable and reasonably clear images in approximately 7-10 minutes. However, inversion prepared acquisition has several detrimental features. First, the inversion pulse reduces the longitudinal magnetization of brain matter, which serves to reduce the signal-to-noise ratio during the imaging readout period. Second, a relatively high bandwidth is needed to facilitate an ultra short TR acquisition with the conventional inversion-prepared approach; this reduces signal-to-noise further. Third, the differential longitudinal relaxation of inversion-prepared tissues over the echo train during the conventional inversion-prepared acquisition introduces signal imperfections in the Fourier domain, which degrades the imaging point spread function. The non-selective acquisition reported in this manuscript does not have these limitations.

This investigation indicates that volumetric measurements of the hippocampus based on non-selective SPGR, acquired in less than 5 minutes, show close agreement with those of SPGR-IR. Importantly, in this comparative evaluation, the non-selective SPGR sequence demonstrated consistently and markedly higher apparent SNR and CNR than the SPGR-IR in subcortical structures. The markedly higher apparent SNR and CNR, may account for the enhanced quality and structural detail in segmentation of basal ganglia. Structural MR measures acquired with SPGR-IR often use a slice thickness of at least 1.2 mm (thicker than used in this investigation) for FAST and FreeSurfer segmentation. In this investigation, the spatial resolution of the SPGR-IR was made equivalent to that of the non-selective SPGR (sub-millimeter isotropic) to maintain consistency between the two methods. The sub-millimeter isotropic SPGR-IR provided poor apparent CNR and SNR in basal ganglia regions (See Table 1 and Figure 3), leading to the failure of FAST in segmenting the region. FreeSurfer (Figure 1) segmentation was able to depict most of the basal ganglia structures possibly because FreeSurfer utilizes *a priori* anatomical knowledge of brain atlas, which compensates for inadequate image quality in the sub-millimeter isotropic SPGR-IR. For the regions studied, T1 contrast/signal characteristics were more constant for non-selective SPGR than for SPGR-IR with reduced variability within studied regions. This advantage was also reflected in an image profile in basal ganglia regions; where non-selective SPGR showed more homogeneous signal in both gray matter and white matter and afforded better contrast between gray matter and white matter (Figure 5).

The basal ganglia are involved in cognitive (e.g. motor control, memory and learning) and affective functions. Injury to these nuclei figures prominently in Parkinson's Disease, Huntington's Disease and many other neurological conditions (18,19). The hippocampus is anatomically small but critical in the detection of early stage Alzheimer's disease. The high resolution, and high apparent SNR and CNR afforded by the non-selective SPGR sequence may benefit quantitative studies of these small, functionally eloquent brain regions. It should be noted that FreeSurfer resamples any voxel size to 1mm isotropic voxels including submillimeter voxels. However, it can be anticipated that the non-selective SPGR method will have potential benefit when segmentation technology can better accommodate processing of very high resolution images. Further studies could examine the utility of this method, specifically for clinical applications involving cortical parcellation.

The non-selective SPGR may also be useful for other important applications. In fMRI, 3D brain volume rendering is used for displaying activation maps. Acquisition of small, isotropic voxels eliminates magnetic susceptibility artifacts on the brain surface and

improves image-processing efficiencies relative to other methods (10). This is possible by enabling advanced 3D reconstruction in arbitrary orientations without interpretation blurring. Improved apparent SNR and CNR of non-selective SPGR produce realistic and accurate depictions of anatomic details, including pre-surgical visualization of small veins on the brain surface.

In conclusion, this investigation indicates that the non-selective SPGR sequence has excellent image quality and gray/white matter tissue contrast behavior for segmentation of subcortical structures and for advanced brain volume rendering for surgical preparation. The non-selective SPGR reduces scan time for whole brain coverage and can be integrated with currently available automated segmentation and visualization algorithms.

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Figure 1.

Segmentation results of non-selective SPGR (left) and SPGR-IR (right) using the automated segmentation program FreeSurfer. Non-selective SPGR produced clearer results than did SPGR-IR. In the SPGR-IR image, lesion misclassifications (black arrows), at caudate and putamen borders can be observed (black arrow heads), and in addition, cortical gray matter misclassifications (white arrow) are seen.

Figure 2.
The results of the FreeSurfer segmentation based on Non-selective SPGR (upper) and SPGR-IR (lower). The segmentation performances for hippocampus (arrows) are comparable.

Figure 3. Segmentation with FAST using non-selective SPGR (A1) and SPGR-IR. Representative regions magnified to illustrate details (A3 and B3, respectively). Non-selective SPGR segmentation (upper) delineates caudate (long arrow), putamen (short arrow), as well as the more diminutive claustrum (hollow arrow). Caudate and putamen are missing in the segmentation based on SPGR-IR (B2-B3).

Figure 4.

3D volume rendering of brain generated for non-selective SPGR (left) and SPGR-IR with isotropic sub millimeter. Anatomical details are best illustrated by non-selective SPGR compared to standard SPGR-IR sequences. Note even small veins on the brain surface are well-represented with non-selective SPGR. Blurring of brain gyri and sulci are evident for the SPGR-IR sequences.

Figure 5. Non-selective SPGR T1-weighting images (upper) and SPGR-IR (lower). For non-selective SPGR, the boundaries of caudate and putamen are conspicuous and the signal intensities are uniform within gray matter and white matter. For SPGR-IR, edges of caudate and putamen adjacent to the surrounding white matter are blurred, as reflected in the image intensity profile.

Table 1

Comparison of the Mean of non-selective SPGR and SPGR-IR

	Left				Right			
	Non-selective SPGR		SPGR-IR		Non-selective SPGR		SPGR-IR	
Region	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Hippocampus	38.45***	4.49	22.77	3.69	38.22***	4.82	23.87	3.66
Caudate	43.54***	4.93	23.98	3.39	46.57***	5.77	22.27	3.18
Putamen	45.41***	5.12	25.40	3.55	46.27***	5.57	25.29	4.09
Thalamus	46.08***	5.70	29.02	4.39	45.99***	6.04	29.04	4.40
White Matter	59.74***	6.06	31.12	4.10	59.89***	6.96	32.30	4.35
Hippocampus	21.29***	3.28	8.35	1.44	21.67***	2.70	8.43	1.19
Caudate	16.2***	2.02	7.15	0.84	13.33**	1.75	10.02	1.54
Putamen	14.33***	1.35	5.72	1.10	13.62***	1.98	7.01	1.08
Thalamus	13.66***	1.18	2.10	1.03	13.9***	1.38	3.26	0.97

p < 0.0001;**
p < 0.001.

Table 2

Volume difference (non-selective SPGR vs. SPGR-IR) by FreeSurfer segmentation

Location	mean diff.	95% CL	ICC
Left Caudate	-410.1	-696.2, -124.1	0.90
Left Hippocampus	-281.3	-407.9, -154.6	0.96
Left Putamen	-413.6	-645.8, -181.5	0.97
Left Thalamus Proper	-870.5	-1158, -582.8	0.98
Right Caudate	137.9	-68.36, 344.11	0.94
Right Hippocampus	-42.0	-250.1, 166.14	0.89
Right Putamen	-365.1	-666.2, -64.1	0.96
Right Thalamus Proper	-1488.0	-1737, -1240	0.97

Diff.: difference; CL: confidence limits; ICC: intraclass correlation coefficient