Brief Report

Whole body MRI of the non-human primate using a clinical 3T scanner: initial experiences

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Abstract: With the advent of parallel imaging MRI techniques, whole-body MRI is being increasingly used in clinical diagnosis. However, its application in preclinical research using large animals remains very limited. In the present study, the whole-body MRI techniques for adult macaque monkeys were explored using a conventional clinic 3T scanner. The T1, T2 anatomical images, and MR angiography of adult macaque whole bodies were illustrated. The preliminary results suggest whole-body MRI can be a robust tool to examine multiple organs of non-human primate (NHP) models from head to toe non-invasively and simultaneously using a conventional clinical setting. As NHPs are intensely used in biomedical research such as HIV/AIDS and vaccine discovery, whole body MRI techniques can have a wide range of applications in translational research using NHPs.

Keywords: Whole-body MRI; macaque monkey; anatomical image; high field magnet; parallel imaging

Submitted Mar 24, 2017. Accepted for publication Apr 07, 2017.
doi: 10.21037/qims.2017.04.03
View this article at: http://dx.doi.org/10.21037/qims.2017.04.03

Introduction

Whole-body MRI allows for scanning the entire body head to toe within one scanning session, providing high-resolution multi-modality MR images such as T1 and T2 anatomical images, angiography, diffusion-weighted images of different organ systems without exposing the subject to ionizing radiation. Its clinical usage in full-body examination for disease in patients was limited previously because of the long scanning duration and poor image quality. With the advent in high field MRI and parallel imaging techniques, the image quality and scanning duration have been improved substantially (1-4), allowing for better spatial resolution and diagnostic accuracy compared to traditional PET/CT (5).

Whole body MRI techniques have been explored generally to examine the anatomical structures of multiple organs (such as neck, chest, abdomen, spine, pelvis, and extremities) and disease conditions including bleeding, edema, lymphoma, skeletal metastases in patients (6-11), whole body inflammation (12), diabetes (13), or virtual autopsy (14). Also, it has been applied for evaluating the distribution of extensive local lesions and that of multi-organ systemic disease and lipodystrophy and fat distribution in HIV patients (15,16), and to identify inflammation and structural damages in patients with rheumatoid arthritis in order to assess the staging and treatment response during medical treatment (17). In particular, whole-body MRI and FDG PET/CT showed excellent agreement in detection of skeletal metastases of pediatric patients (18).

Non-human primates (NHPs) are our closest biological relatives and resemble most aspects of human including anatomical structures and vascular anatomy, physiology, neurology, immunology (19). NHPs are widely used in neuroscience research like stroke (20-22), aging (23,24), hippocampal lesion (25), Huntington's disease (26), drug addiction (27), developmental dysfunction (28), and infection diseases including HIV (29-35), Ebola (36) and

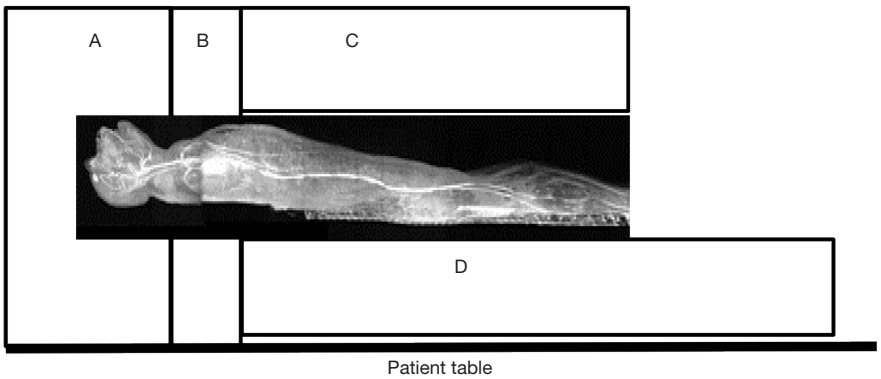

Figure 1 Schematic drawing of the experimental settings for RF coils and a monkey in a clinical 3T MRI scanner. (A) 12-ch head coil; (B) 2-ch neck coil; (C) 4-ch FLEX coil; (D) 8-ch spinal matrix coil.

Zika virus infection (37), and vaccine discovery research (38). As seen in the studies of infectious diseases or tumors, multiple organs in the animal body can be affected during the disease evolution, and the extent and distribution of the multifocal diseases can be assessed with whole body MRI (3). However, to our knowledge, whole body MRI has not been generally utilized in large animals like NHPs. In the present study, we explored the whole-body MRI techniques for imaging the entire body of adult macaque monkeys from head to toe by using a clinical 3T MRI scanner. The preliminary results were illustrated and discussed for application in biomedical research using NHPs.

Methods

Adult female rhesus monkeys (n=4, 7–11 years old, 8.5–10.5 kg) were initially anesthetized with Telazol (5 mg/kg, i.m.), and then switched to ~1% isoflurane mixed with 100% oxygen using an isoflurane vaporizer (Patterson Veterinary, Devens, MA, USA). The anesthetized animals were immobilized with a home-made head holder and placed in the "supine" position during MRI scan. The arms and legs were secured with belts and tapes in the scanner. Animals breathed spontaneously. Respiration rate, isoflurane concentration (end-tidal) and Et-CO_2 were continuously monitored with a PROCARE Monitor B40 anesthesia machine (GE Healthcare, Milwaukee, WI, USA), heart rate and O_2 saturation with a Nonin pulse oximeter (Nonin medical, Plymouth, MN, USA), blood pressure by a Surgivet V6000 (Smiths Medical PM, Waukesha, WI,USA), and body temperature with a Digi-Sense Temperature controller (Cole-Parmer, IL, USA), respectively. Lactated ringer's solution was administered intravenously to prevent dehydration during scanning. The physiological parameters were recorded and maintained in normal ranges (39).

The MRI scans were performed on a Siemens 3T TIM Trio whole body scanner (Siemens Medical Solutions USA, Medical, PA, USA) by using multiple receive-only RF array coils (12-ch head matrix coil, 2-ch neck matrix coil, 8-ch spinal matrix coil, and 4-ch FLEX large coil). The length of the body (from head to toe) of an adult macaque monkey is about 100 cm. As seen in *Figure 1*, the head and chest of the animal were covered by the head coil and neck coil. The abdomen was covered partially by the neck coil and mostly by the spinal coil under the body and the FLEX coil above the body. The legs were placed on the anterior part of the spine coil. All these coils were iPAT (integrated Parallel Acquisition Techniques) -compatible and allowed to be combined with each other to image different body parts.

The T2- weighted images (*Figure 2*) were acquired with turbo spin-echo pulse sequences and scanning parameters: TR =7,880 ms, TE =114 ms, data matrix =288×384 and FOV =203 mm × 905 mm, slice thickness =4.0 mm (composed images). The T1-weighted images (*Figure 3*) were acquired using turbo spin-echo sequence with TR =260 ms, TE =2.5 ms, BW =268 Hz, data matrix =160×256, FOV =195 mm × 250 mm, slice thickness =4.0 mm. 3D time-of-flight (TOF) MR angiogram (MRA) pulse sequence (flip angle =18°; TE =3.6 ms; TR =20 ms) was used to acquire the vascular images, spatial resolution: 0.25×0.25×2.00 mm^3 for head and neck (*Figure 4A*,*B*), 0.51×0.51×4.40 mm^3 for lower part of the body (*Figure 4C*,*D*), The composing software (Siemens) was utilized for composing of MR images from different table positions in order to create whole body anatomy images. All images were processed with a Siemens work station installed with

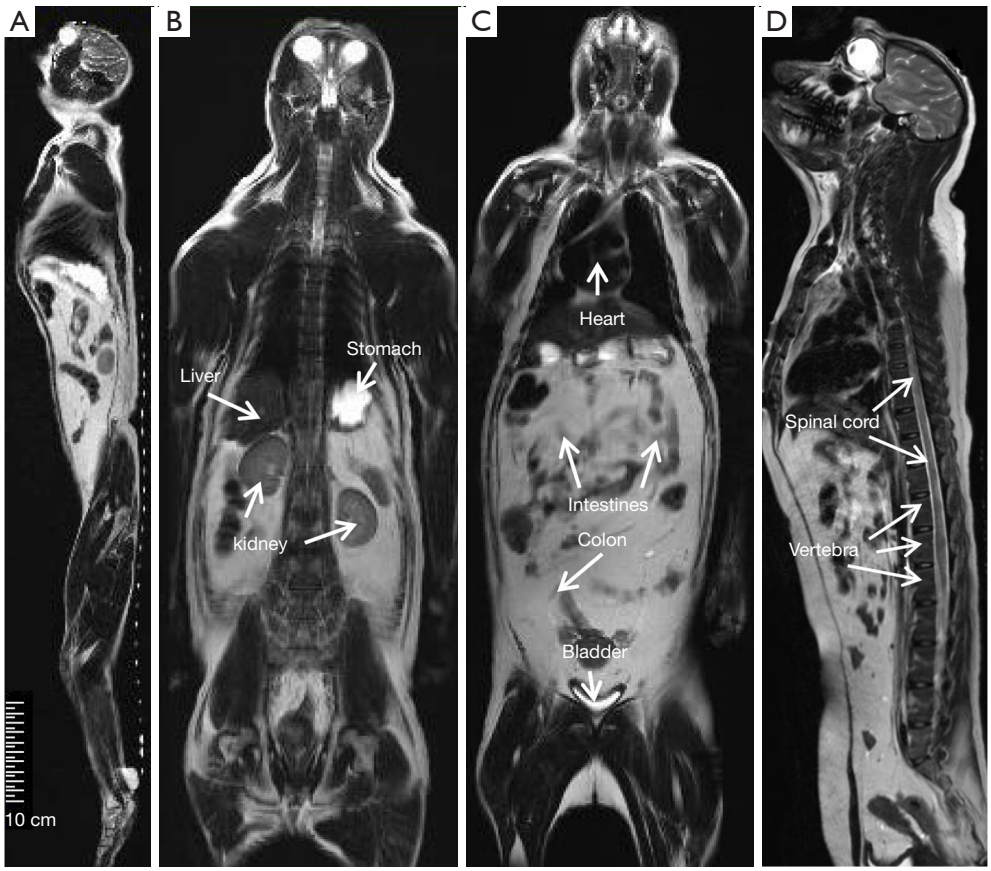

Figure 2 Composed T2-weighted anatomical images of an adult macaque. (A) Sagittal image, from head to toe; (B,C,D) body images to show important organs such as liver, kidney, stomach (coronal, B); heart, intestines, colon and bladder (coronal, C); and spine (sagittal, D). Artifacts in (A) are from heating pad.

Siemens Sygno MRI data processing software.

All procedures followed the protocols approved by the Institutional Animal Care and Use Committee (IACUC) of Emory University in accordance with the NIH Guide for Care and Use of Laboratory Animals.

Results

The T2-weighted anatomical images of the entire body of adult macaques were acquired. One sagittal slice of the body from head to toe is shown in *Figure 2A*, in which the anatomical images of brain, chest, abdomen, muscle, knee, and toe are demonstrated with one composed image. Also, important organs such as liver, kidney, bladder, heart, intestines and colon and spine are specifically illustrated (*Figure 2B*,*C*,*D*). The T1-weighted anatomical images (sagittal and axial) of a macaque monkey abdomen are illustrated in *Figure 3*. MR Angiographies of the whole body head to toe, specific regions for brain and neck are also shown (*Figure 4*). As seen in the illustrated images, the brain and neck angiography, structural anatomy of liver, kidneys, spine cord, and intestine of an adult monkey can be clearly identified with whole body MRI using a conventional clinical setting.

Discussion

These preliminary results indicate the whole-body MRI techniques can be a robust approach to simultaneously examine multiple organs of the entire body of adult macaque monkeys non-invasively by using the conventional clinical settings. In addition, multiple modalities including T1 and T2 weighted imaging, MRA, and other techniques like DWI, can be conducted in the same subject and in the same scanning session to provide complementary information for screening or evaluation of the disease staging and treatment

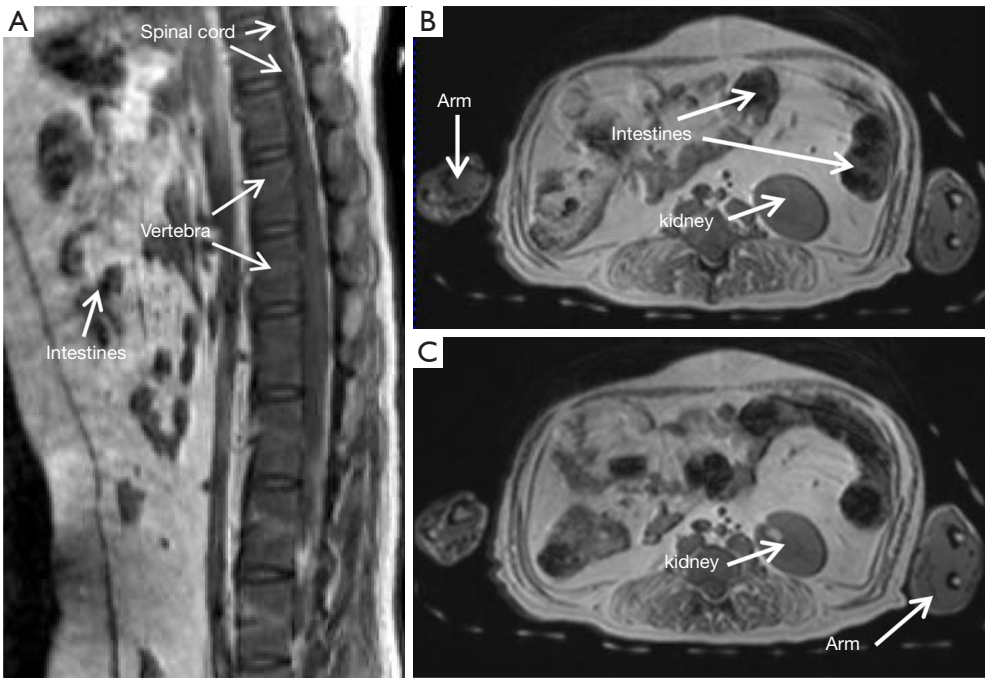

Figure 3 T1-weighted anatomical images of an adult macaque abdomen to show important organs such as spine, intestines (sagittal A); kidney, intestines, arms (coronal, B and C).

response. In particular, as NHPs are anesthetized during scanning, the scan duration can be extended for several hours to allow for specific and detailed examination from whole body screening to region-specific imaging of multiple organs, which cannot be conducted readily in clinical patients. Therefore, NHP models can be further exploited to assess and optimize the clinical protocols in whole-body MRI examinations of pediatric patients.

Compared to other species, NHPs resemble most aspects of human, and are excellent animal models in biomedical research including infection diseases such as HIV/AIDS (38). Antiretroviral therapy (ART) is generally used for HIV patients. However, there is no cure for HIV disease (40), and HIV/AIDS is still spreading worldwide. Currently, NHP models are intensively used for finding a safe and effective cure for HIV/AIDS patients (41).

HIV infects the cells of the immune system, resulting in an immune-deficient state and severe pathology across multiple organ systems in the body. CD4+ T cells are a primary target of HIV and CD4 cell depletion is a major factor in the pathogenesis of HIV infection (42). Also, CD8+ T cells play a critical role in controlling HIV viremia and reducing overall numbers of HIV-infected cells in approaches to eradicate HIV(43,44). Due to their roles in the process of the adaptive immune system, tracking these T cells *in vivo* will play a critical role in drug discovery and modern vaccine development (45,46).

In vivo molecular imaging has emerged as a promising means for immune cell tracking to study immune cell proliferation, apoptosis and interaction at the microscopic and macroscopic level with living subjects (47). Currently there are two different labeling strategies for immune cell tracking: (I) direct labeling by using probes that are internalized by immune cells; (II) indirect labeling with genetic modification. Among the several imaging techniques including CT, PET, SPECT, MRI, optical imaging, and ultrasound, MRI can provide high spatial and temporal resolution with the use of iron oxide- particles and ^{19}F-based probes for image-guided immune cell delivery and visualization of immune cell homing and engraftment, inflammation, cell physiology and gene expression (48). Available MRI techniques include using Gadolinium-based T1 contrast agent, superparamagnetic iron oxide nanoparticles (SPIONs) based T2 contrast agent, and molecular probes containing ^{19}F or inducing chemical exchange saturation transfer (CEST) signals. Cell tracking

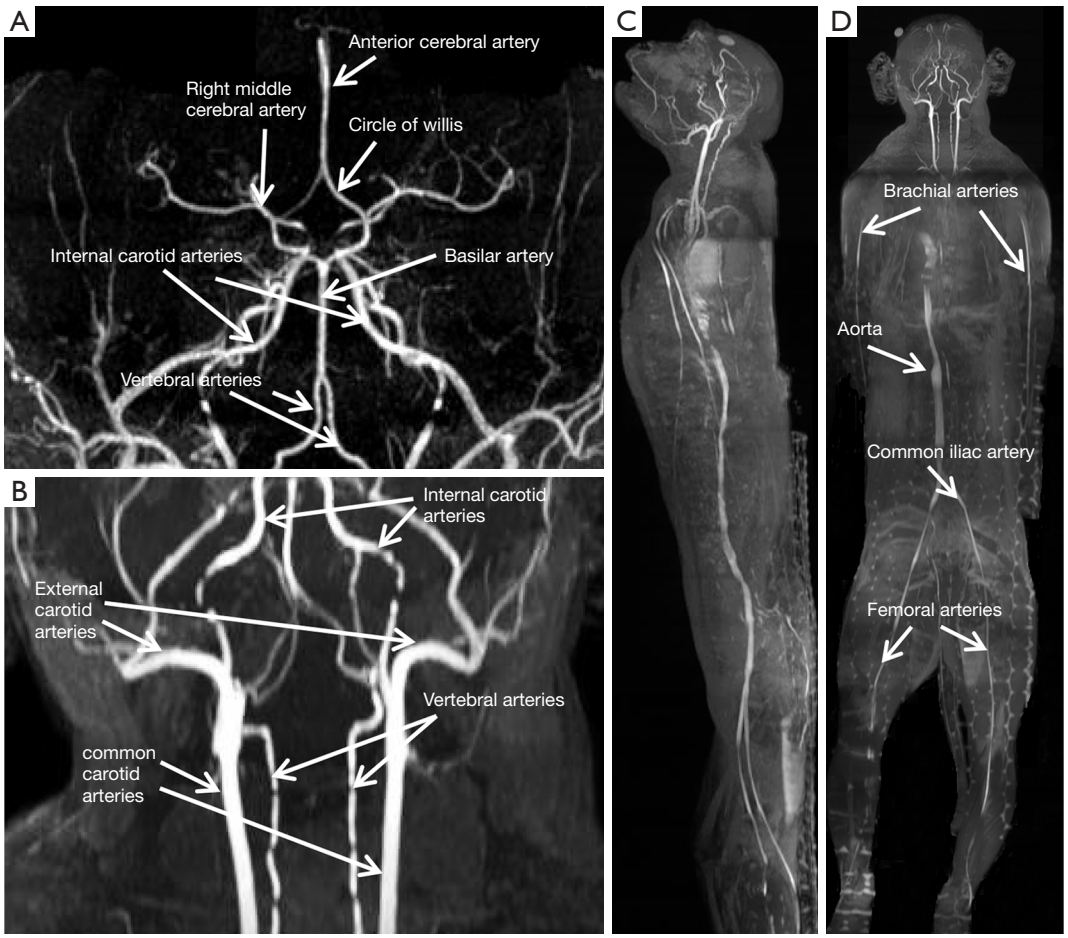

Figure 4 Regional MR angiography images (A: brain, B: neck) and composed vascular images of sagittal (C) and coronal (D) planes of an adult macaque from head to toe.

with SPIONs has been used in cell-based therapy (49,50). It has been explored previously to image immune cell (such as CD4 T+ cells, CD8 T+ cells, and Mac1+ cells) location and homing in the central nervous system of mice with superparamagnetic antibodies (51).

Molecular imaging has been successfully applied to visualize simian immunodeficiency virus (SIV)-infected cells in the body of rodent models of HIV (52). Like human, lymph nodes are located throughout the whole body of a macaque monkey. Therefore, we believe the whole body MRI based molecular imaging can be exploited as an effective tool in disease diagnosis and evaluation of brain and other organs of macaque models of HIV/AIDS.

The site and source of virus replication cannot be identified by using traditional examinations with blood, CSF, and biopsies. Recently, an *in vivo* viral imaging method has shown its effectiveness in detecting whole-body SIV replication by using ^{64}Cu-labeled SIV Gp120-specific antibody with whole-body PET (53). The signals are detected in the gastrointestinal, respiratory tract, lymphoid tissues and reproductive organs of viremic monkeys, demonstrating its wide application in HIV/AIDS research and drug and vaccine development. As a technical limitation, the signal cannot be seen in brain. It is very important to identify the sites and sources of virus replication in the entire body in approaches to eradicate HIV as they may serve as viral reservoirs. Nanoparticles have very small size and can go anywhere in the body. Therefore, the molecular imaging with whole body MRI can provide complementary information about the infection progress in the whole body including brain and other organs.

Whole-body MRI has emerged to be a promising

means for the screening, diagnosis, staging and response assessment in pediatric cancer patients due to its superior contrast resolution and tissue characterization (7,54). However, MRI in young children is usually performed under sedation or general anesthesia for motion control in clinic (55,56). Preclinical studies suggest anesthetics may have neurotoxic effects on the developing brain (57). There is a strong concern to sedate young children during MRI scanning. NHPs are important models in cancer therapy (58-61). Therefore, whole body MRI techniques can be intensively explored with the NHP models to optimize and improve its detection capacity in pediatric oncology.

Certainly, the whole body MR imaging approaches are not limited to what we discussed above and can be further facilitated with the advent of new techniques and are capable to be translated into other research fields such as pharmaceutical and neuroscience studies using NHP models. Also, this study is aimed to demonstrate the potential and capacities for imaging the entire body of large animals from head to toe using different modalities on a conventional clinic scanner. As a limitation, the spatial resolution and image contrast of the demonstrated whole body images in this study were not fully-optimized. but the imaging quality in the entire body or specific regions or organs can be further improved when experimental parameters are specifically optimized or using customer-built coils and/or performing more averages with respiratory-gating for anesthetized monkeys.

Conclusions

The preliminary results suggest the whole-body MRI techniques can be a robust approach to examine the brain and other multiple body organs of macaque monkeys non-invasively and simultaneously. In particular, its application in HIV/AIDS research can be further exploited using immune celling tracking techniques to examine the whole body including brain and other organs. Furthermore, whole body MRI of NHPs can be intensively explored for other preclinical studies such as cancer research and imaging protocol development and optimization in clinical diagnosis of pediatric oncology.

Acknowledgements

The authors are grateful to Sudeep Patel, Ruth Connelly, and Doty Kempf (DVM) for assistance in data acquisition and animal handling, and technical support from Siemens.

Funding: The project was funded by the National Center for Research Resources (P51RR000165) and is currently supported by the Office of Research Infrastructure Programs (OD P51OD011132).

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Li CX, Zhang X. Whole body MRI of the non-human primate using a clinical 3T scanner: initial experiences. Quant Imaging Med Surg 17;7(2):267-275. doi: 10.21037/qims.2017.04.03

