In vivo Two-photon Excitation Magnetic Resonance Imaging

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Technical Report No. UCB/EECS-2021-92
http://www2.eecs.berkeley.edu/Pubs/TechRpts/2021/EECS-2021-92.html

May 14, 2021

Acknowledgement

First, I would like to thank my advisor, Professor Chunlei Liu, for all his supports, advice and the opportunity for my master program. I would also like to thank Victor Han for his great mentorship and enormous resources and guidance. Additionally, a special thank you to Professor Michael Lustig for serving as the second reader for my report. Lastly, I have been fortunate to be part of Liu's group and it has been a pleasure to work with all the members in the group.

In vivo Two-photon Excitation Magnetic Resonance Imaging

by Jianshu Chi

Research Project

Submitted to the Department of Electrical Engineering and Computer Sciences, University of California at Berkeley, in partial satisfaction of the requirements for the degree of **Master of Science, Plan II**.

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1. Introduction

MRI is a widely used imaging technique to capture high-resolution contrast of soft tissues and functional information, and it has been used for many applications in the medical field, such as imaging lesions, brain activity and blood flow. It takes advantage of the net spin polarization of a large number of protons, which are present mostly in water in a biological tissue. In an MRI system, the net polarization of protons are initially aligned with the main magnetic field, called the B_0 field, then another magnetic field called the B_1 field is generated by a transverse RF pulse to make the polarization perpendicular to the B_0 field. When the RF pulse is turned off, the protons will return to the initial state. Due to the different tissue structures, the rate of relaxation will be different, and the receive coil will be able to capture the differences and show the contrast in the reconstructed images. In this process, since only a single transverse RF pulse of a single frequency is needed, we will refer to it as single-photon excitation imaging. On the other hand, two-photon excitation uses an additional frequency along with B_1 at the same time. The field generated at this additional frequency is called the B_{1z} field, and it is parallel with the B_0 field and perpendicular with the B_1 field. In this project, the goal is trying to implement this innovative two-photon excitation MRI method in vivo and evaluate its signal-noise-ratio (SNR) performance.

2. Phase I: In vivo Two-photon Magnetic Resonance Imaging of Human Hand at 1T

2.1 Overview

Multiphoton excitation has been used for many applications, especially in microscopy. In MRI, however, the concept is relatively unknown. Some, however, may know it as sideband excitation[1]. With a constant z-photon frequency, it turns out that slice selective *xy*-RF pulses (e.g. sincgauss pulses) simply act as scaled versions of their single-photon counterparts when the offset in frequency for the *xy*-pulse is set to meet the two-photon resonance condition[2]. In phantoms, we have shown elsewhere that if we take a standard pulse sequence and shift all of the transmit frequencies outside of the field of view and apply an extra z-axis RF at a frequency equal to that transmit frequency shift, we will get an image that looks almost identical to what we would get normally, if flip angle is calibrated for[2]. Here, we apply this idea to produce the first in vivo demonstration of two-photon MRI at 1T with no single-photon excitations. That is, there is no excitation at the Larmor frequency.

2.2 Implementation:

2.21 Scanner:

The scanner used for this phase is a 1 Tesla Wrist scanner from Aspect Imaging (Aspect Imaging, Shoham, Israel). Unlike a normal whole-body clinical scanner which uses a large superconducting magnet to generate a B_0 field, it uses a permanent 1 Tesla magnet. Its bore geometry is also unique because its B_0 field goes from left to right rather than the usual into the bore of the scanner. As a result, its B_1 field goes into the bore (Fig. 1).

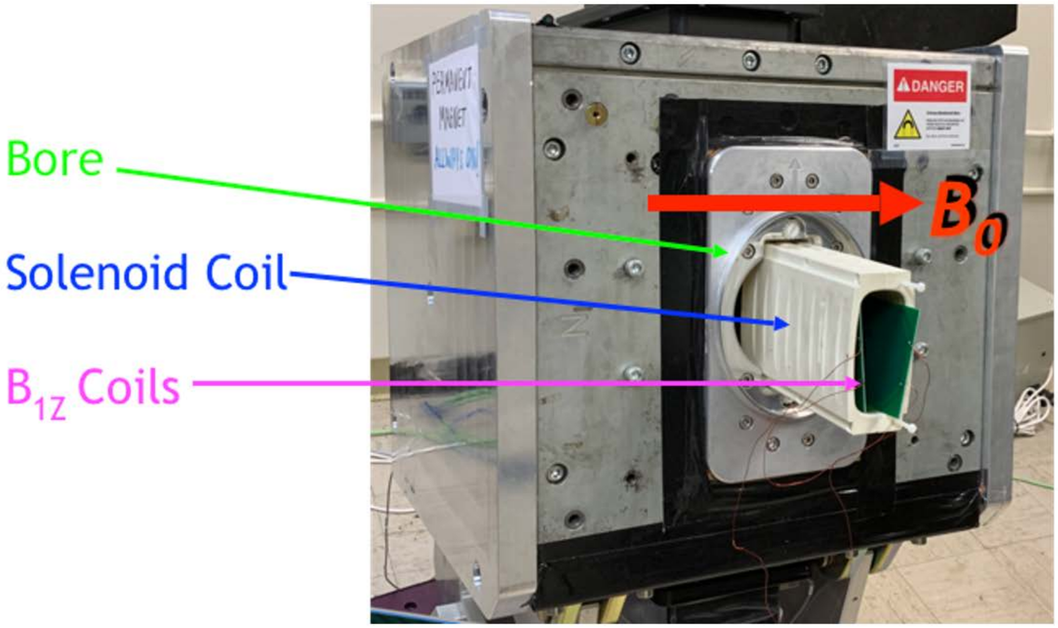

Fig. 1: The scanner setup with solenoid and B_{1z} Coil

2.22 B_{1z} Coils:

A pair of custom-built planar spiral coils was used to generate the extra low-frequency B_{1z} field. The planar structure was chosen due to the shape- and size- limitations of the solenoid T/R coil and the unique bore geometry of the Aspect scanner. Specifically, the B_0 field runs perpendicular to the bore of the scanner, so in order to keep the bore open, a standard solenoid could not be used to produce B_{1z}. It would block access to the bore, while a pair of planar coils placed on each side of the hand allows convenient access. Each planar coil has a dense spiral configuration to maximize the uniformity of the B_{1z} field; it has 68 turns, with 0.3 mm for trace width, and 0.2 mm spacing between traces (Fig. 2). Each planar spiral coil was fabricated on a 2-layer standard printed circuit board (PCB); the two layers have identical, but mirrored spirals with a via connection in the center. The mirroring was required to ensure that the magnetic fields of the two layers would constructively add. The total DC resistance is 20.2 ohms. The large number of turns increases the power- efficiency for low-frequency magnetic field production. Being a non-resonant coil designed for use at low frequencies, wavelength effects are not an issue, eliminating the need for tuning and matching.

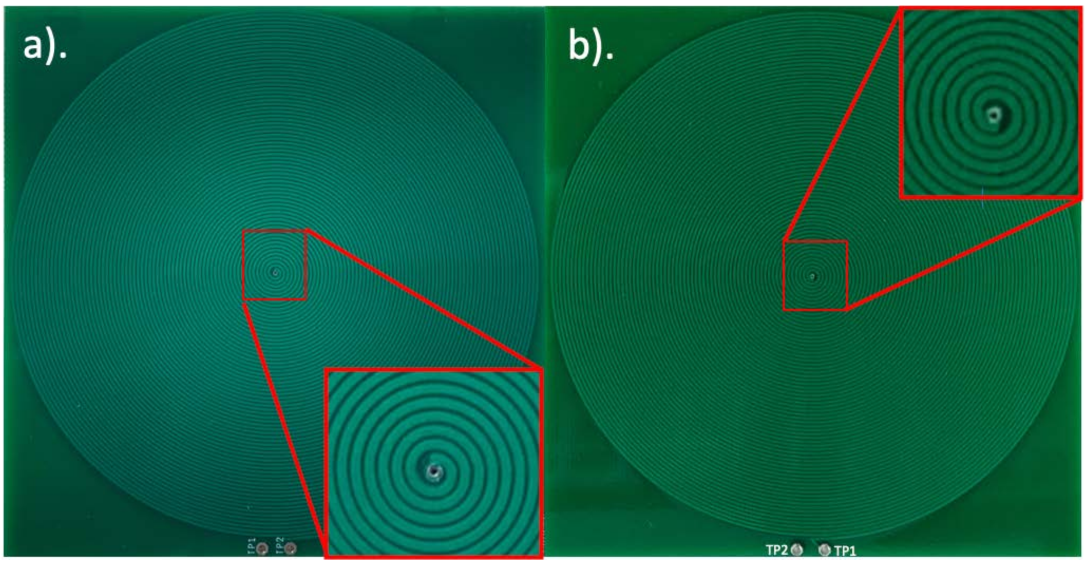

Fig. 2: Planar spiral coil. a) Top plate of spiral Coil. b) Bottom plate of spiral coil.

2.23 Set up:

We used a vendor-provided solenoid RF coil with an additional homebuilt low-frequency spiral coil (Fig. 3) to achieve multiphoton excitation by producing orthogonal RF fields B_{1xy} and B_{1z} respectively. By using two orthogonal fields with frequencies whose sum or difference equals the Larmor frequency, we are able to produce two-photon excitation. The B_{1z} coil is powered by a waveform generator (Keysight 33600A) at 20 kHz to produce a secondary excitation field. No external power amplifier was required. In order to reduce noise, an extra 10 nF capacitor was connected in parallel with the spiral coil to produce a lowpass filter (Fig. 3). In order to synchronize the waveform generator with the canner, the T/R switch circuit is need for this case.

We synchronized the waveform generator to the T/R switch of the scanner to turn off the low-frequency coil's signal during the receive period (Fig. 3). The whole setup is shown in Figure 4.

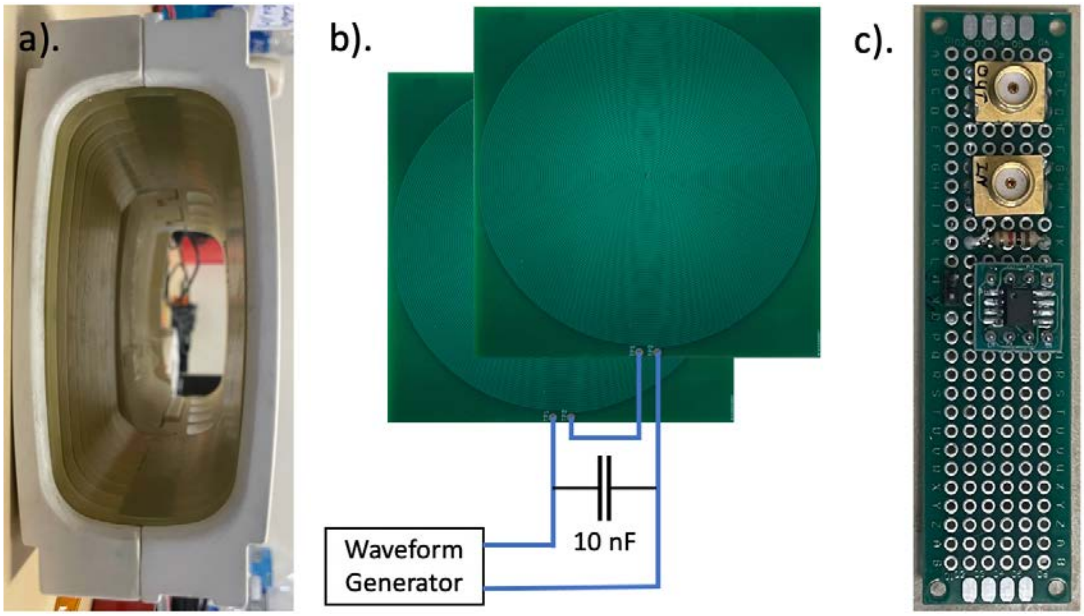

Fig. 3: a) Front view of vendor-provided solenoid RF coil b) Lowpass filter that was constructed with B_{1z} Coil and a 10 nF capacitor c) The T/R switch circuit to synchronize waveform generator and scanner

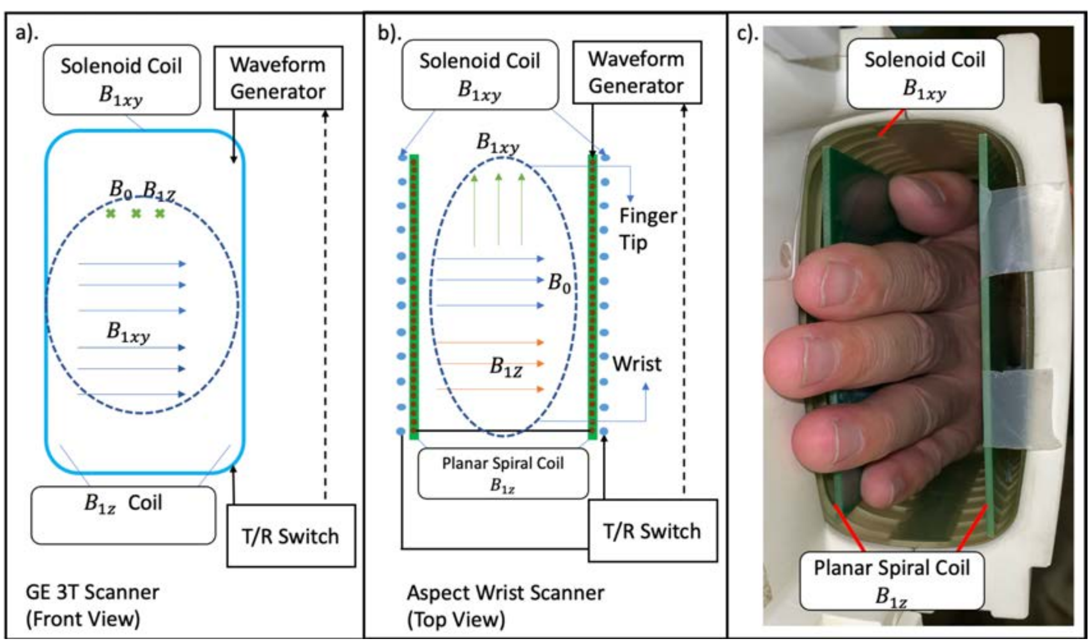

Fig. 4: Aspect Wrist Scanner setup with an additional pair of spiral coils for an extra B_{1z} field. a) Front view where a hand would go into the page through the dotted oval. b) Top view where a hand would enter the bore from the bottom. c) A photo of the physical set up (Back View).

2.24 Comparison:

To compare single-photon and two-photon images, we first acquired images using single-photon excitation by turning off the B_{1z} waveform generator using a standard 2D GRE pulse sequence (parameters listed in Table 1). We then turned on the B_{1z} waveform generator to produce the additional source of photons and shifted the frequency of B_{1xy} accordingly (Table 1). To transmit B_{1xy} at a frequency offset, we set the center slice position to be far outside of the field of view. The center slice position that produces 20 kHz offsets at a target location was calculated using the slice thickness and RF pulse bandwidth.

Parameters \ Fig. 3	a)	b)	c)	d)
TR/TE [ms]	250/6.8	250/6.8	250/6.8	250/6.8
$B1xy$ Flip Angle [$Degree$]	45	360	45	330
Resolution [mm^3]	1.25×0.63×2	1.25×0.63×2	1.25×0.63×2	1.25×0.63×2
Scan Time [s]	16.750	16.750	16.750	16.750
FOV [mm^2]	80× 80	80× 80	80× 80	80× 80
Pulse and Duration	Sincgause 10ms	Sincgause 10ms	Sincgause 10ms	Sincgause 10ms
Frequency offset [kHz]	0	20	0	20
Slice Bandwidth [Hz]	412	412	412	412
Readout Bandwidth [kHz]	40	40	40	40
Orientation	Axial	Axial	Coronal	Coronal
Waveform Generator Vpp	N/A	20	N/A	20
Waveform Generator mode	N/A	Hi-Z	N/A	Hi-Z

Table 1: Scan parameters corresponding to Fig. 5. Note that the B_{1xy} flip angle corresponds to only the B_{1xy} power, not the result of the final two-photon flip angle. For the two-photon case, the flip angle is proportional to B_{1xy} multiplied by B_{1z}.

2.3 Results

We successfully obtained hand images of a healthy volunteer using both single- and two-photon excitation (Fig. 5). The resulting images of both types of excitations have similar SNR with slight differences in contrast. This was because the flip angle was not too well calibrated, and the slice position was not perfectly matched. Furthermore, the two-photon images have inhomogeneous intensity towards the edges of the FOV due to the inhomogeneous B_{1z} field generated by the pair of spiral coils that has reduced field strength towards the edge of the coils.

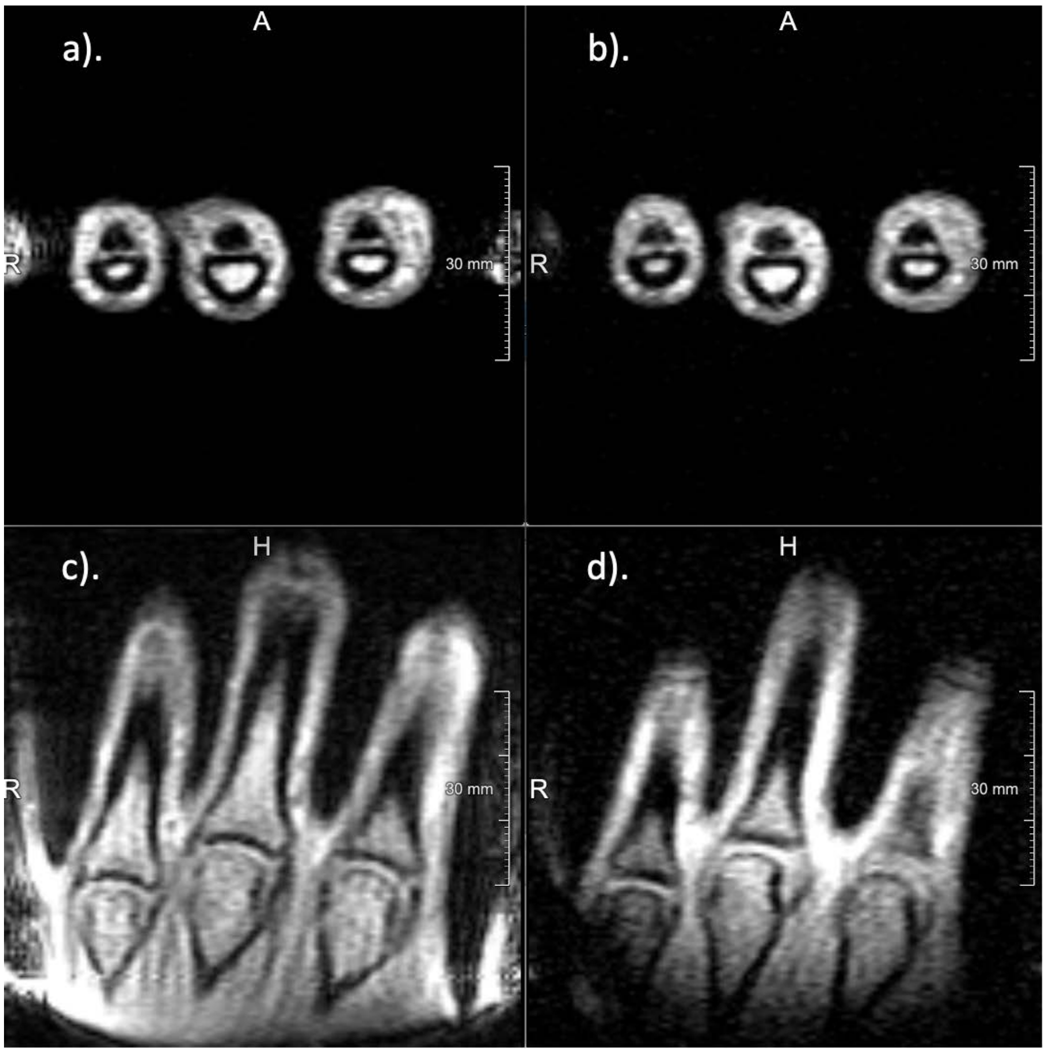

Fig. 5: Single-photon (left panel) vs. two-photon (right panel) GRE images of a hand. a) Single-photon excitation on transverse plane of fingers. b) Two- photon excitation on transverse plane of fingers. c) Single-photon excitation on coronal plane of hands. d) Two-photon excitation on coronal plane of hands. Note the slice locations are not perfectly matched.

2.4 Discussion

We have demonstrated that we can acquire images produced by two-photon excitation in vivo at 1T. However, we were not able to quantitatively compare image contrast due to the inhomogeneous B_{1z} field produced by our homebuilt spiral coil which generated spatially varying flip angles. To compare contrast more accurately, we plan to optimize our spiral coil winding to improve field homogeneity. In our case, SAR was not an issue as our offset frequency was relatively low and thus, despite the decreased efficiency of multiphoton excitation, the B_{1xy} increase needed to achieve similar flip angles did not produce significant SAR increase. If a larger offset frequency is desired, a greater B_{1z} is required to achieve the same flip angle with the same B_{1xy}. Since SAR is much less of a concern at lower frequencies, this should still be practical with larger power amplifiers for B_{1z}.

3. Phase II: In vivo Two-photon Magnetic Resonance Imaging of Human Brain at 3T

3.1 Overview:

Multiphoton excitation is an innovative MRI scanning technique. Despite using frequencies far from the Larmor frequency, spins can still be excited if conservation of energy and angular momentum are followed. In this Phase, we shifted the traditional *xy*-plane RF field from the Larmor frequency by 25.5 kHz and there was no excitation as expected. In contrast, when a z-direction RF field, called B_{1z}, parallel to the B_0 field, at 25.5 kHz is applied along with the 25.5 kHz-offset *xy*-plane RF field, called B_{1xy}, we were able to see two-photon excitation. One z-photon is absorbed together with one *xy*-photon to excite each spin. In imaging, it has been shown that we can use extra z-photons to turn slice selective *xy*-RF pulses (e.g., Sincgauss pulses) into scaled versions of their single-photon counterparts when the offset in frequency for the *xy*-pulse is set to meet the two-photon resonance condition[2]. Using an extra, uniform coil that produces a magnetic field in the z-direction, we can perform gradient echo scans with all single-photon excitations replaced by two-photon counterparts. This idea has been previously explored for the human hand in Phase I of this report, and it was found that two-photon images looked like their single photon counterparts[3]. However, there was still much to be desired in terms of SNR and B_{1z} field homogeneity due to the small-bore size. In this phase, we built a new version of the B_{1z} coil and associated setup for use on a clinical whole-body 3T scanner to resolve the imperfections of previous work. As result, we successfully acquired the first two-photon brain image[4].

3.2 Implementation:

3.21 B_{1z} Coils:

We designed and built a large size solenoid coil to produce a uniform B_{1z} field over the human brain, parallel to the B_0 field and perpendicular to the B_{1xy} field. For this coil we used a large PVC pipe with an 18-inch diameter and 20-inch length. Two parallel strands of 14 AWG wire were used to make a helix with 20 windings on the outer surface of pipe. We added another 20 windings on the inner surface of cylinder. The inner helix is mirrored with the outer helix and is joined at the bottom. Both windings meet at the top of the pipe and connect to the output of an amplifier. To stabilize the windings on the pipe, we applied epoxy on both inner and outer surfaces of the pipe. Lastly, we wrapped the coil with a UL94 V-0 rated flame-retardant sound-dampening mat for the safety of the human experiment (Fig. 6).

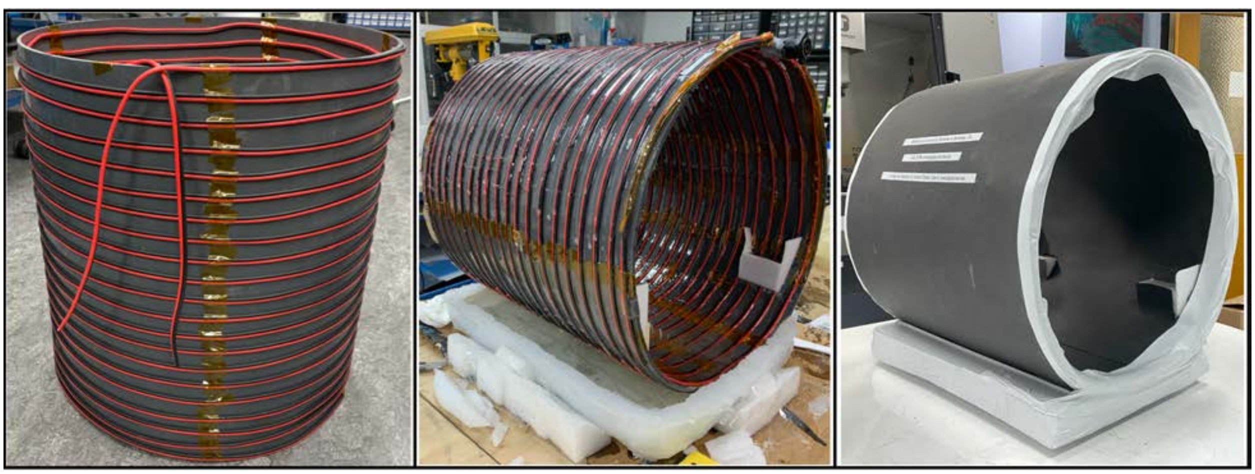

Figure 6: Left: Parallel wires winding inner and outer surface of PVC pipe. Middle: Epoxy applied to stabilize the wires and base being made for coil. Right: Coil with #ame-retardant sound-dampening mat.

3.22 Set up:

In this project, we targeted 25.5KHz for the frequency of the B_{1z} field. To achieve a large B_{1z} field strength, the coil was tuned and matched to 3 ohms for use with a 500W audio power amplifier. When scanning, the power amplifier amplifies a signal from a waveform generator in a gated burst mode, which is synchronized to the scanner with a Schmitt Trigger circuit to ensure that our B_{1z} field will be off during the receive period. For the cable that connects the coil to the amplifier, we added 15 baluns each separated by a Larmor frequency quarter wavelength to reduce the EMI effects of the long cable and improve the safety of the design (Fig. 7).

The setup was implemented on a GE 750W 3T scanner (GE Healthcare, Waukesha, WI). To compare single-photon (B_{1xy} at the Larmor frequency) and two-photon (B_{1xy} at 25.5 kHz away from the Larmor frequency) images, we calibrated the flip angles based on 1D projections of signal magnitude in manual pre-scans in gradient echo sequences. Signals were measured to ensure that single- and two-photon scans with proper B_{1xy} strengths produced similar amounts of signal and all other parameters were kept equivalent. We ensured that the frequency offset B_{1xy} fields did not produce any excitation without the B_{1z} fields.

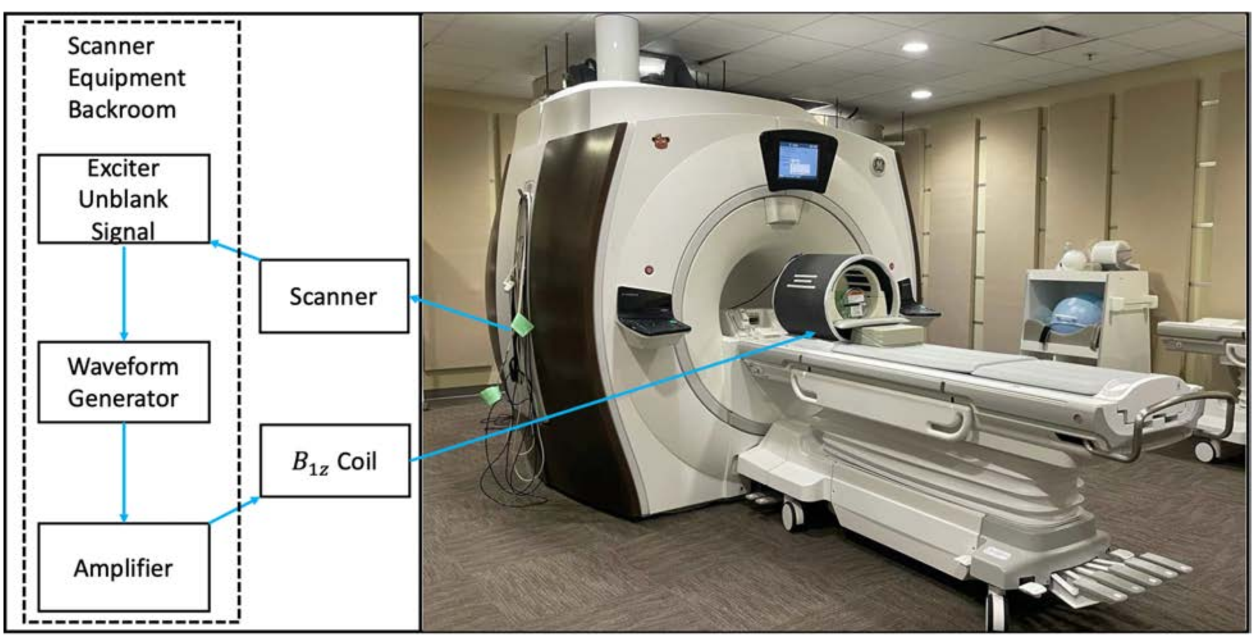

Figure 7: Left: equipment room set up. Right: B_{1z} coil in a 3T scanner.

3.23 Safety:

Since we will scan human subjects to further analyze our implementation, the safety for this phase is critical. There are several safety measurements needed in order to proceed. First is temperature. We measured the coil temperature after scan, the temperature of our coils remained at the room temperature. Furthermore, no appreciable vibration nor increased acoustic noise were observed.

3.3 Results:

We successfully obtained 2D GRE two-photon images with several TRs and FAs from a healthy volunteer. During scanning, no appreciable vibration nor increased acoustic noise were observed. Figure 8 shows the same slice with both single- and two-photon excitation. The overall SNR and image appearances appear to be comparable. Interestingly, the gray/white matter contrast of the two-photon image appears to be slightly enhanced compared to the single-photon image. In addition, we also explored various TRs while fixing flip angles (Fig. 9), and various flip angles while fixing the TR (Fig. 10). In all comparisons, the single- and two-photon images share overall similarities for the most part, but some small differences also exist throughout the brain.

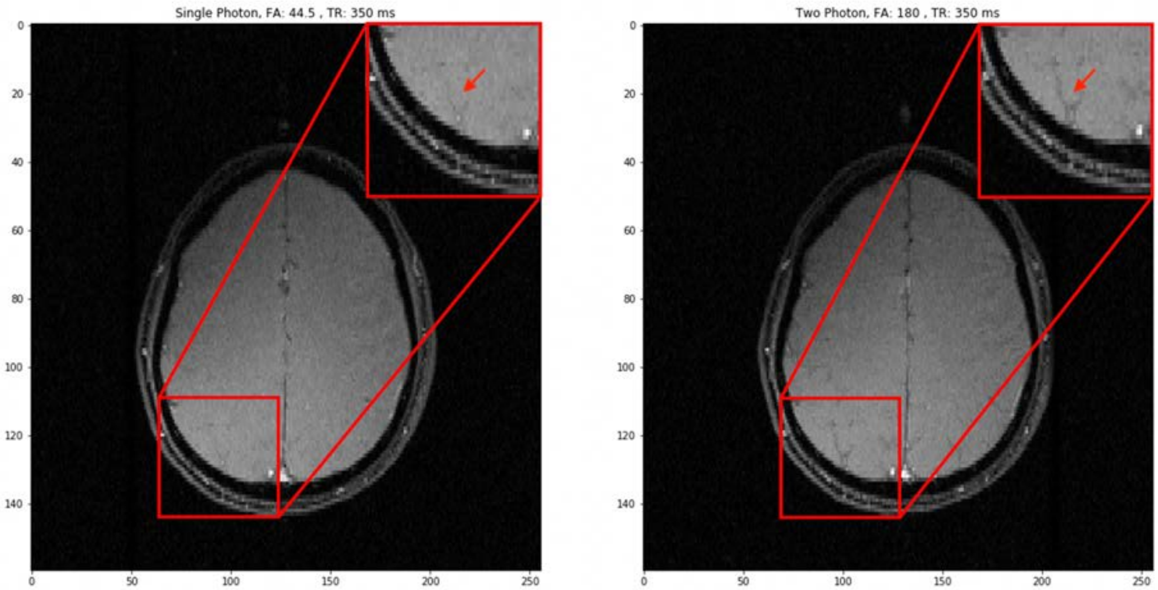

Figure 8: Single- and two-photon GRE brain images of a healthy volunteer. Left panel: Single-photon image with a flip angle of 44.5 degrees vs. a TR of 350 ms (Top) and a TR of 150 ms (Bottom). Right panel: Two-photon image with a B_{1xy} amplitude corresponding to an equivalent two-photon 44.5-degree flip vs. a TR of 350 ms (Top) and a TR of 150 ms (Bottom). Some brain structure contrast is seen to be enhanced. Other parameters: FOV 27.6 cm, slice thickness 3 mm, matrix 256x160, TE 10ms.

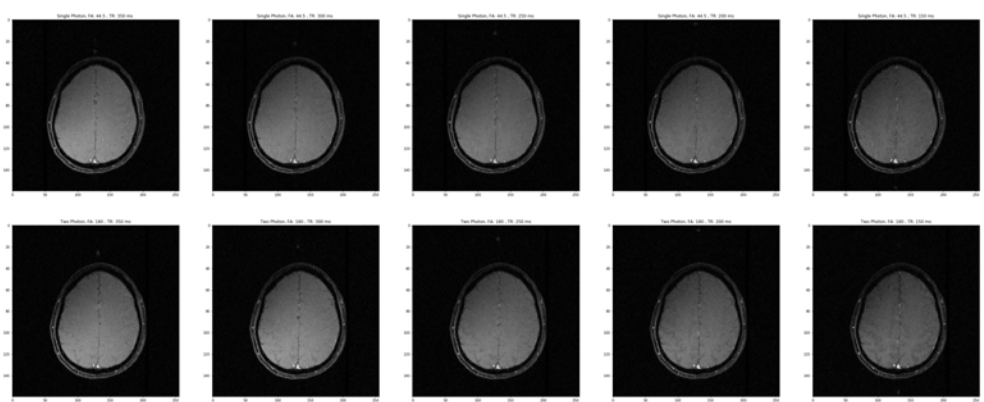

Figure 9: Single-photon (top row) vs. two-photon (bottom row) images of human brain with fixed flip angles (FA) and various TR. Each column is a pair of single- and two-photon images with matched equivalent flip angle. Parameters: FOV 27.6 cm, slice thickness 3 mm, matrix 256x160, TE 10ms, flip angle 44.5^{o}, TR (from 150 ms to 350 ms with step of 50 ms).

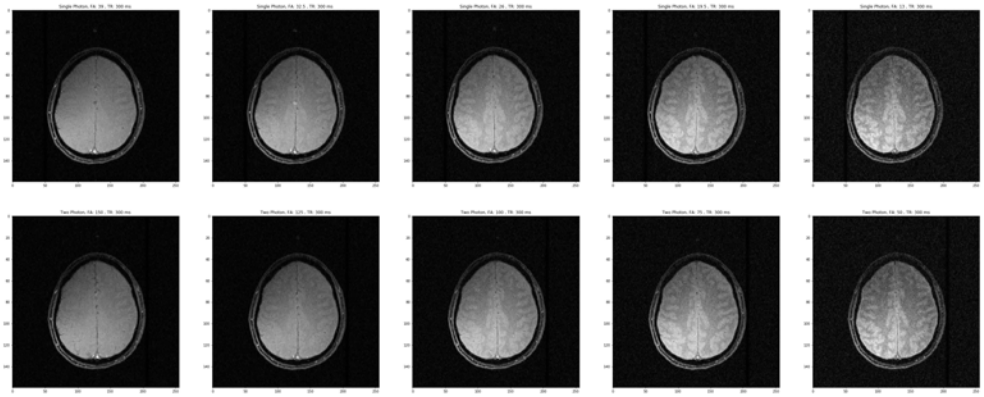

Figure 10: Single-photon (top row) vs. two-photon (bottom row) images of human brain with fixed TR and various FA. Each column is a pair of single- and two-photon images with matched equivalent flip angle. Parameters: FOV 27.6 cm, slice thickness 3 mm, matrix 256x160, TE 10ms, TR 300ms, flip angles (13, 19.5, 26, 32.5 and 39).

3.4 Discussion and Conclusion:

We have demonstrated that brain images can be obtained by using two-photon excitation on a clinical 3T scanner. The preliminary results suggest that two-photon excitation may provide some promise for creating different tissue contrasts. However, there are still many un-answered questions that need to be further explored, such as where these differences come from and what happens at different offset frequencies and B_{1z} amplitudes. To help answer these questions, we plan to improve the SNR by using arrays of surface coil receivers instead of the birdcage coil. Furthermore, more work needs to be done with pulse sequence and hardware design to streamline the process of setting up two-photon scans.

4. **Conclusion**

It is exciting to implement and discover the first in vivo two-photon excitation technique for MRI. Most importantly, we were able to build a safe and SNR-comparable two-photon excitation system, and we are confident that two-photon excitation is feasible in future clinical applications. However, the SNR needs further improvement because is still not optimal even though we have similar SNR for both techniques. We suspect that the head of birdcage transceiver coil we used was too close to the B_{1z} coil and thus was slightly detuned. We are verifying this and taking higher SNR scans by using arrays of surface coils instead. Furthermore, there are more improvements that need to be done, such as pulse sequence and hardware design to streamline the two-photon scanning process.

5. **References**

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