In vivo detection of a hyperpolarized xenon magnetic resonance imaging contrast agent

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Supplementary Information

Control Images

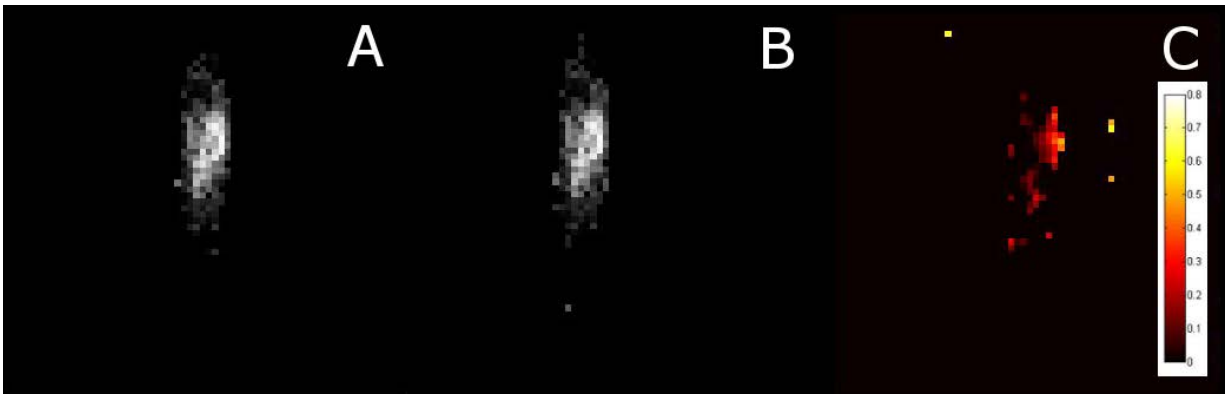


Figure S1. Xe MR control images (NSA=3) of a Sprague-Dawley rat brain absent any cage molecule. A) A 2D gradient echo (GE) Xe MR image of the brain following the application of an off-resonance pre-pulse (+260 ppm). B) Same as A) but following an on-resonance HyperCEST saturation pre-pulse at the chemical shift of the CB6 cage molecule (which was absent) (+123.4). C) A saturation map constructed by subtracting, pixel-by-pixel, the on-resonance HyperCEST image from the off-resonance control image, and dividing by the off-resonance control image as explained in the methods section. Notice the absence of a HyperCEST effect compared to Figures 3 and S2, which is expected because there is no cage molecule present.

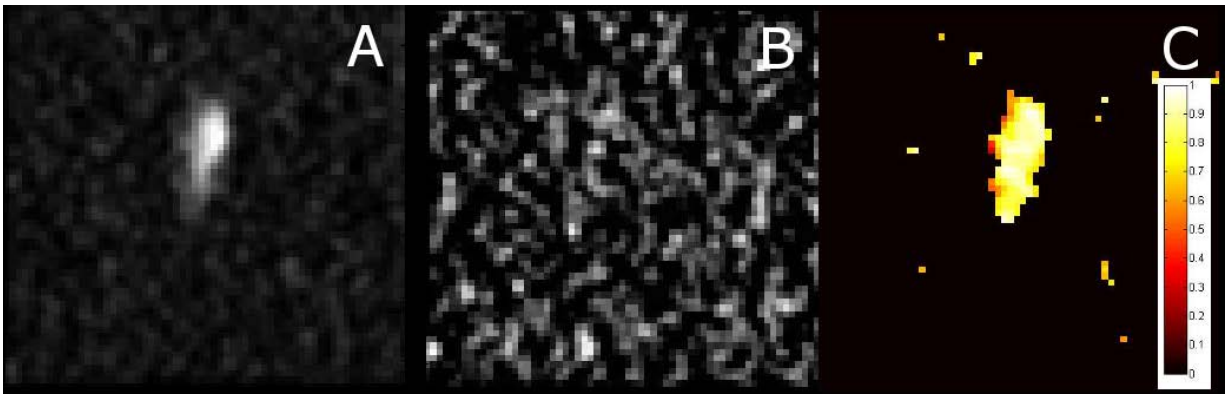
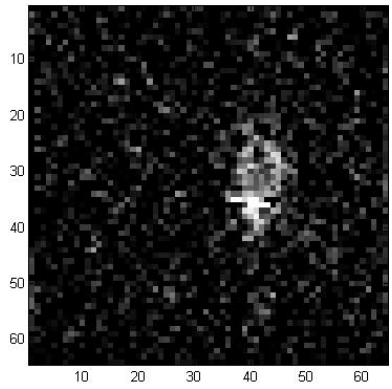
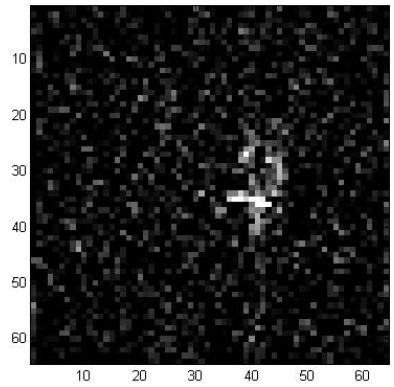
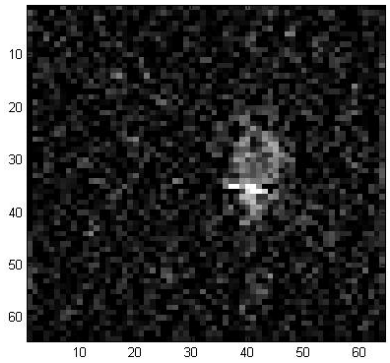
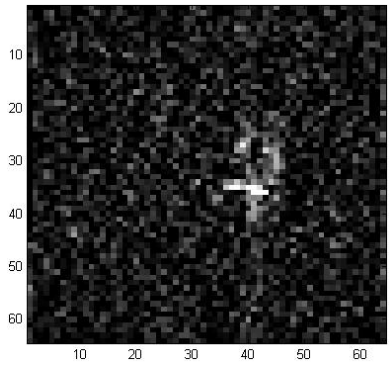
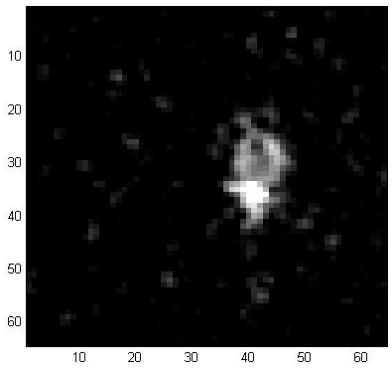
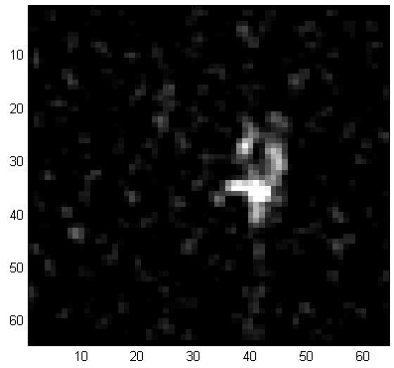


Figure S2. Xe MR control images of a Sprague-Dawley rat brain. A) A 2D gradient echo (GE) Xe MR image of the brain following the application of an off-resonance pre-pulse (+260 ppm). B) Same as A) but following an on-resonance HyperCEST saturation pre-pulse at the chemical shift of xenon dissolved in brain matter (+191.4 ppm). The polarization of the xenon is completely destroyed. C) A saturation map constructed by subtracting, pixel-by-pixel, the on-resonance HyperCEST image from the off-resonance control image, and dividing by the off-resonance control image as explained in the methods section. Compared to Figures 3 and S1 notice a high saturation signal indicating a compete depolarization of the xenon dissolved in brain matter.

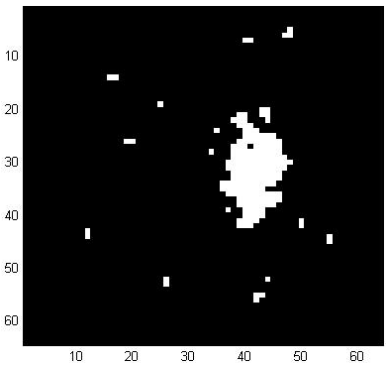
Image Post Processing Methodology

MR Image with Off Resonance Saturation Pulse (Control)	MR Image with On Resonance Saturation Pulse (HyperCEST)
A matrix of the MR image is exported from Philips MR scanner to Matlab for processing.	
$\begin{bmatrix} 0 & 0 & 0 & 0 & 0 & 2 \\ 45 & 21 & 0 & 0 & 35 & 2 \\ 19 & 5 & 0 & 17 & 10 & 5 \\ 17 & 26 & 0 & 0 & 0 & 23 \\ 39 & 21 & 23 & 4 & 0 & 1 \\ 5 & 0 & 2 & 33 & 15 & \dots \end{bmatrix}$	$\begin{bmatrix} 0 & 0 & 0 & 0 & 0 & 0 \\ 20 & 0 & 0 & 26 & 39 & 0 \\ 11 & 1 & 0 & 17 & 29 & 0 \\ 15 & 22 & 6 & 3 & 22 & 16 \\ 31 & 23 & 4 & 0 & 0 & 0 \\ 13 & 7 & 0 & 0 & 0 & \dots \end{bmatrix}$
The matricies are converted to MR images using the Matlab script below.	
	
The MR images are normalized with respect to noise by sampling a representative noise area, in this case, the first 10x10 voxels. Each pixel is divided by the standard deviation of the noise to obtain an SNR map.	
	
The SNR maps are smoothed by convoluting the SNR matrix by a 3x3 Gaussian convolution matrix.	





A mask of the off-resonance image is taken to remove background noise. This is necessary because during the creation of the HyperCEST saturation map [1]. Masking is necessary because noise subtracted from noise and divided by noise results in an image where the noise is indistinguishable from the object.



The smoothed on Resonance SNR Map is subtracted is subtracted from the off resonance SNR map and divided by the off-resonance SNR map and multiplied by the mask to create a HyperCEST saturation map as seen in figure 3F of the manuscript. The color map is changed to “hot”.

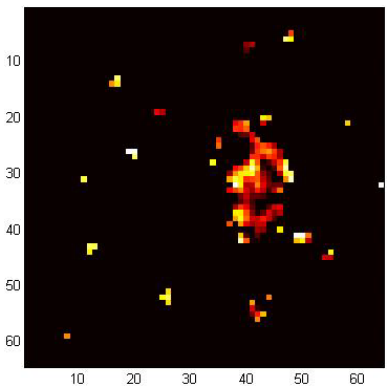


Table S1

Matlab Image Processing Script

```
% INSTRUCTIONS
% This Script subtracts an on-resonance HyperCEST image from an off-resonance control image and %
divides by the off-resonance image.
% At the first file select box, select the Off-resonance image, at the second file select box, select the on-
resonance image.
%
%% *Sample script for viewing images*

%% *Prepare workspace*
clear all;
close all;
clc;

%% *Select .PAR file*
path = 'C:\Users\Peter\Documents\Philips 3T Data';

%% Select Off-Resonance Image
[filename,pathname] = uigetfile('*.PAR','Select *.PAR file');
OffResonanceparfile = [pathname filename];
[OffResonanceSignal,parms,dims] = GetData_parrec(OffResonanceparfile,'FP','info'); % call function
% which converts MR data to Matlab useable matrix

% Create Off-Resonance SNR map
dataSelected=OffResonanceSignal([1:20],[1:20])
Noise=std(reshape(dataSelected,400,1))
OffResonanceSNRMap = OffResonanceSignal/Noise;

% Select On-Resonance Image
[filename,pathname] = uigetfile('*.PAR','Select *.PAR file');
OnResonanceparfile = [pathname filename];
[OnResonanceSignal,parms,dims] = GetData_parrec(OnResonanceparfile,'FP','info');

% Create On-Resonance SNR map
dataSelected=OnResonanceSignal([1:10],[1:10]);
Noise=std(reshape(dataSelected,100,1));
OnResonanceSNRMap = OnResonanceSignal/Noise;

% Smooth both Images
ConvKern = [1 2 1; 2 4 2; 1 2 1];
SmoothOffResonanceImage = conv2(OffResonanceSNRMap,ConvKern,'same');
SmoothOnResonanceImage = conv2(OnResonanceSNRMap,ConvKern,'same');

% Create mask of Off Resonance Control Image
MaskThreshold=35; % set threshold to select more or less noise
MatrixSize=size(SmoothOffResonanceImage);
mask = zeros(MatrixSize(1),MatrixSize(2));
for i = 1:MatrixSize(1)
   for j = 1:MatrixSize(2)
      if SmoothOffResonanceImage(i,j) < MaskThreshold
         mask(i,j) = 0;
      else mask(i,j) = 1;
      end
```

```
   end
end

% Create a saturation map & Apply Mask
SaturationMap = (SmoothOffResonanceImage-SmoothOnResonanceImage)./SmoothOffResonanceImage;
SaturationMapMasked=SaturationMap.*mask; % Use only data from within mask
imagesc(SaturationMapMasked);

% apply image parameters
colormap hot;
axis square;
caxis([0 0.8]);
colorbar;
```

References

1. Witte, C. *et al.* Live-cell MRI with Xenon Hyper-CEST Biosensors Targeted to Metabolically Labeled Cell-Surface Glycans. *Angew. Chemie (International Ed.* **54,** 2806–2810 (2015).