Phantom MRI experiments:

Phantoms of different concentrations of the two contrast agents (i.e. Gd-DTPA and the Gd-Chelate GadoSpin™ P) were prepared and their T1s were calculated at 37^{o} C. GadoSpin™ P was prepared according to the manufacturer's instruction; and to reconstitute the lyophilizate, 1cc sterile 0.9% NaCl was injected into each vial containing 33mg GadoSpin™ P, yielding a 0.165 mM solution. Magnevist® injection is a 0.5M solution of 1-deoxy-1(methylamino)D-glucitol dihydrogen [N,N-bis[2-[bis(carboxymethyl)amino]ethyl] glycinato (5-)]gadolinite(2-)(2:1); and 0.01ml of this solution was diluted with 0.23ml of 0.9% sterile NaCl yielding a 20.8mM Gd-DTPA solution.The undiluted, reconstituted GadoSpin™ P and 20.8mM Gd-DTPA represented the initial solutions from which the phantoms of different concentrations were made. Thus, Gd-DTPA phantoms were prepared by serially diluting 20.8mM Gd-DTPA with sterile 0.9% NaCl to obtain 1:10, 1:20, 1:40, 1:80, 1:160,1:320, 1:640 and 1:1280 volume ratios. Similarly, from the reconstituted GadoSpin™ P solution, phantoms were prepared using the same volume ratios (1:9~1:1279) as for Gd-DTPA. Each phantom (0.5ml of a given dilution) was scanned at 37°C using identical MR parameters as the animal study: 2D single slice FLASH sequence, (TR=15msec, TE=3.8ms, NA =5), and 26 flip angles (2°~80°). T1 was calculated by a standard spoiled gradient echo sequence (FLASH) expressed as:

$$S(\theta, TE) = S_0 \frac{(1 - e^{-TR/T1})\sin\theta}{(1 - e^{-TR/T1}\cos\theta)} e^{-TE/T_2^*}$$

where S_0, TR, TE, $T2^*$, $T1$, θ denote proton density, repetition time, echo time, transverse relaxation time, longitudinal relaxation time, and flip angle, respectively. Nelder-Mead simplex algorithm built into MATLAB 7.1 was employed in the fitting procedure. **Figure 1S** (volume ratio of 1:20) depicts detected signal changes over the range of flip angles for the two contrast agents. In **Figure 2S**, calculated T1s are plotted as a function of paramagnetic contrast

concentrations ranging from 0.1 (1:10 ratio) and 0.01 (1:100 ratio). As can be seen from Figure 2S, the T1's of the two different contrast agents are comparable over a wide range of decreasing concentrations. Based on these experiments it was assumed that 0.165mM GadoSpin and 20.8mM Gd-DTPA would yield near-equivalent T1 effects at the start of the experiment (initiation of intra-thecal infusion).

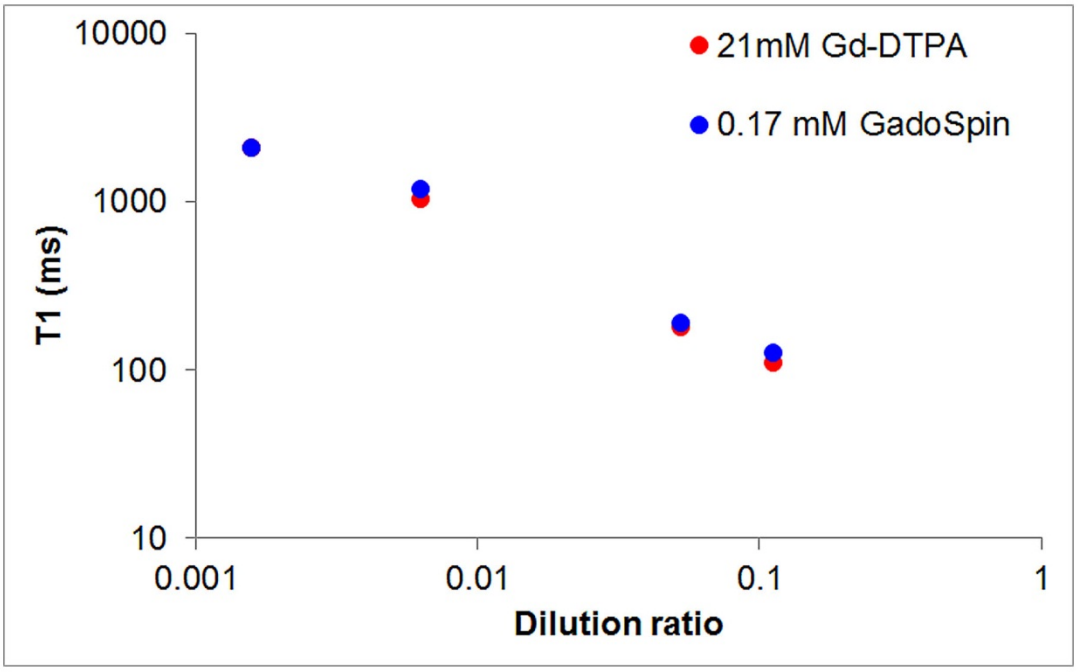


Figure 1S: Longitudinal relaxation times (T1) are plotted as a function of dilution ratios, defined by volume ratio between 0.9% NaCl and paramagnetic contrast agents, in logarithmic scales taken at 37 degrees celcius.

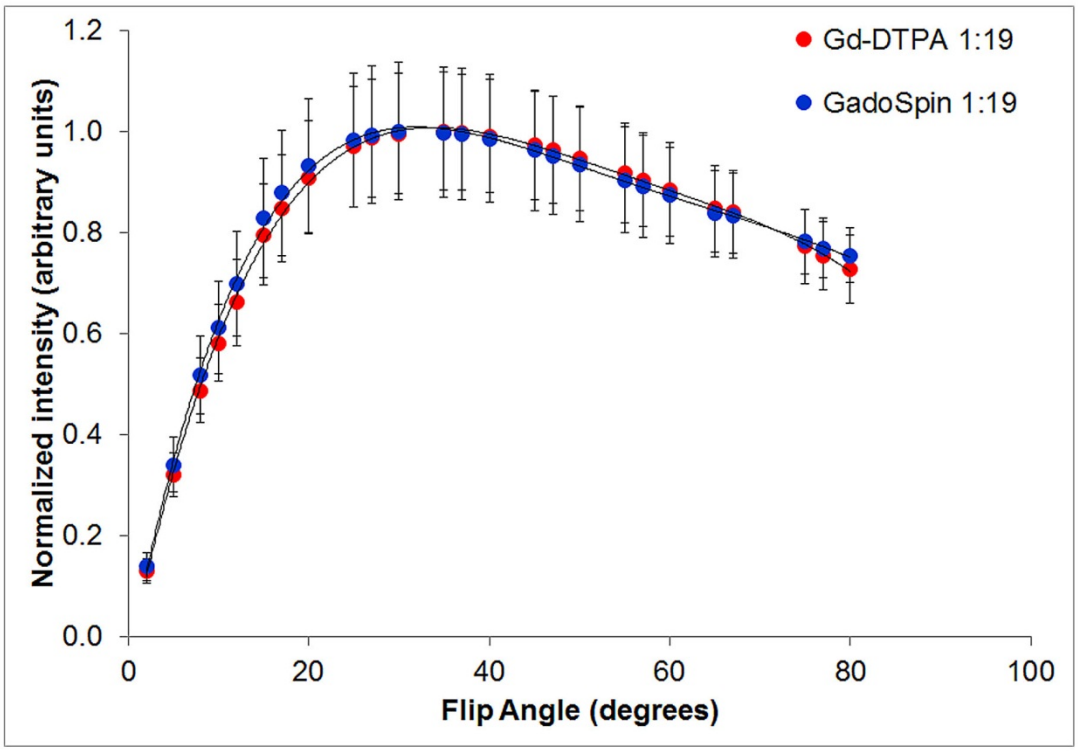
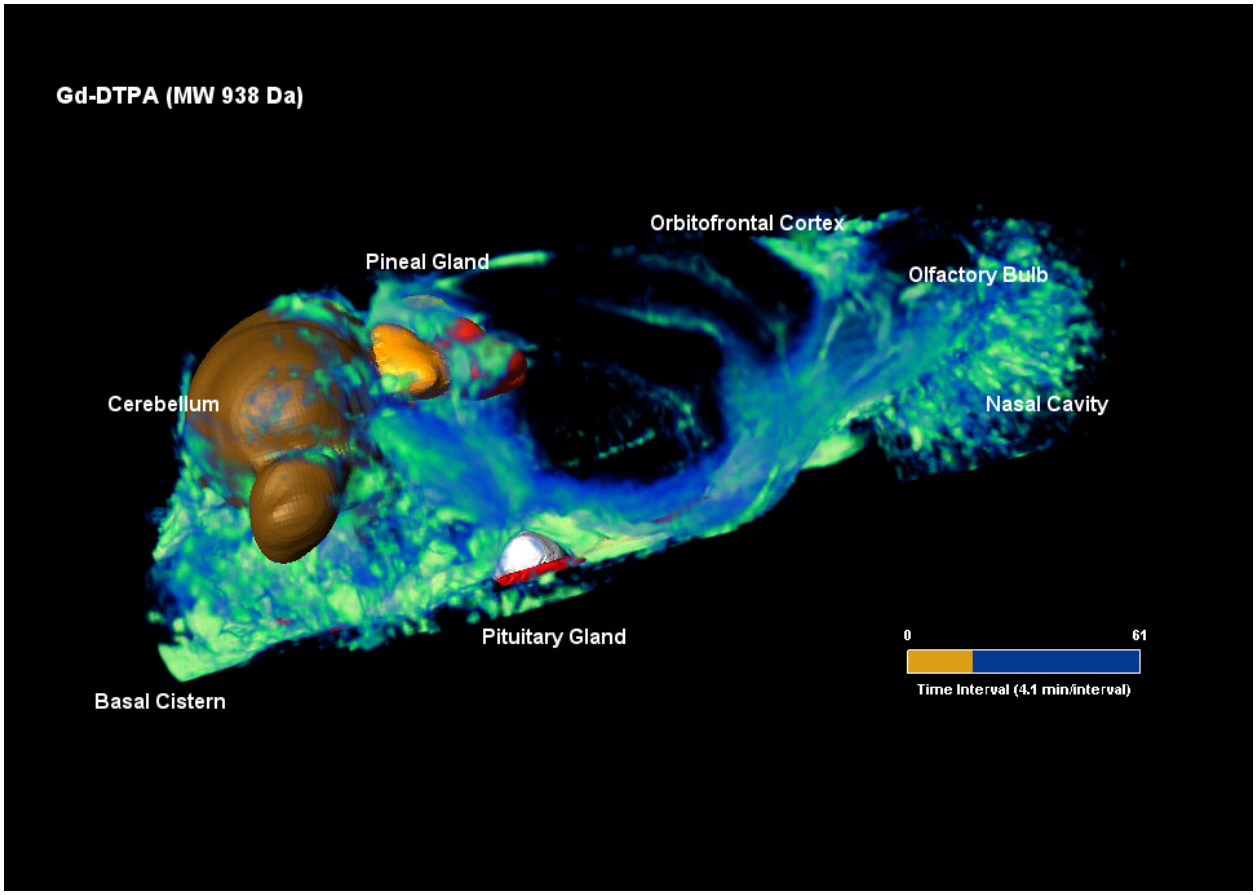
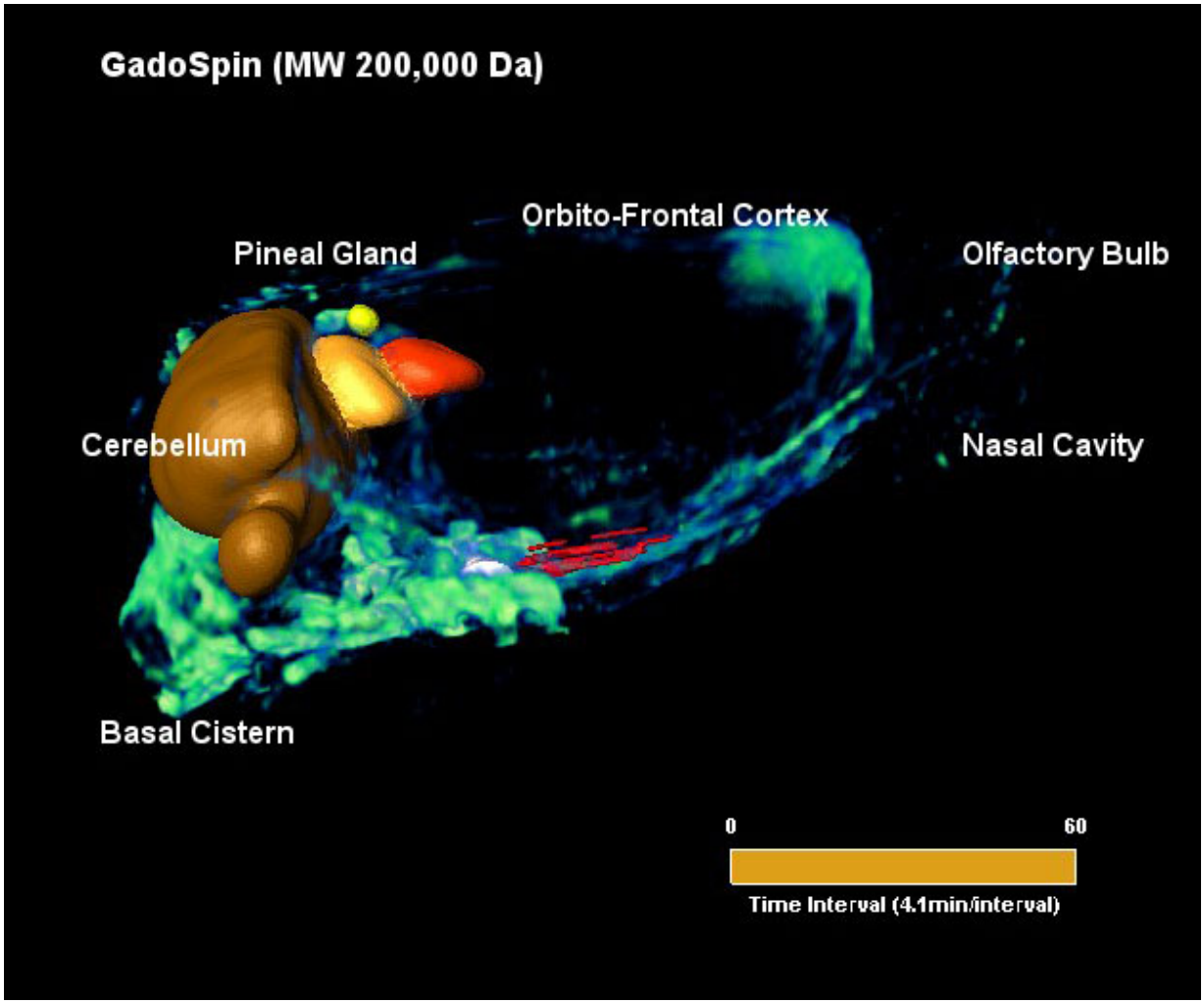


Figure 2S: Normalized signal intensities (mean +-SD) are plotted as a function of flip angles in FLASH MRI sequence taken at dilution ratio of 1:19, defined by volume ratio between paramagnetic contrast agents (21mM GD-DTPA and 0.17mM GadoSpin) and 0.9% NaCl, taken at 37 degrees celcius. Normalization is achieved by dividing intensity by its maximal value across the flip angles.



Movie S1 (still): Dynamic display of Gd-DTPA administered into the basal cistern and moving through the 'glymphatic' pathway'. Gd-DTPA paramagnetic contrast is represented by green/blue color and each time-frame represent 4.1/min. Key anatomical structures of the rat brain has been displayed in 3D including the cerebellum (brown), pineal gland (yellow) superior colliculus (orange), inferior colliculus (red), pituitary gland (white) and large basal arteries (red). As can be observed from the dynamic time-series, Gd-DTPA moves from the basal cistern along para-vascular pathways associated with the large vessels and then enter the brain parenchyma and also exit from the brain and into the nasal cavity via the cribriform plate. The movement of Gd-DTPA is captured over ~4 hrs, and the contrast has still not cleared and is evident at the pineal recess, olfactory bulb and at the basal cistern at the end of the 4 hour period.



Movie S2 (still): Dynamic display of GadoSpin administered into the basal cistern and moving through the 'glymphatic' pathway'. GadoSpin paramagnetic contrast is represented by green/blue color and each time-frame represent 4.1/min. Key anatomical structures of the rat brain has been displayed in 3D including the cerebellum (brown), pineal gland (yellow) superior colliculus (orange), inferior colliculus (red), pituitary gland (white) and large basal arteries (red). Similar to Gd-DTPA, GadoSpin also enters the most proximal part of the glymphatic pathway along para-vascular conduits, however, in contrast to the smaller contrast molecule Gd-DTPA (MW 938 Da) which more easily gains access to the brain interstitial space, the larger GadoSpin molecule (MW 200,000 Da), preferentially remains in the paravascular compartment (compare Movie S2 to Movie S1).