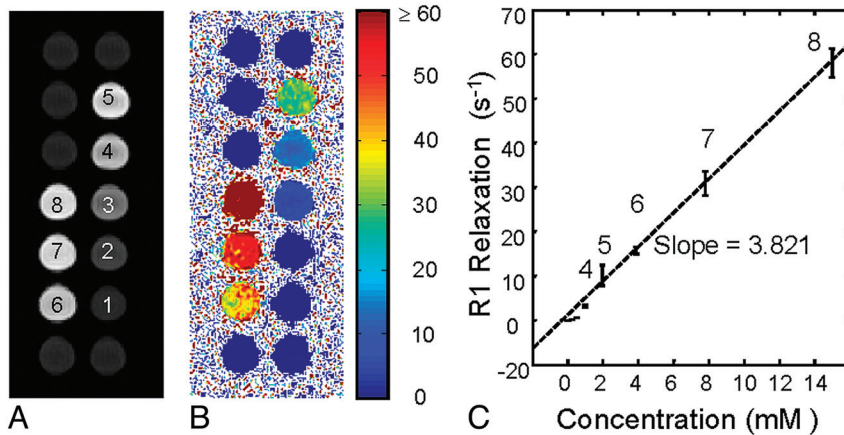
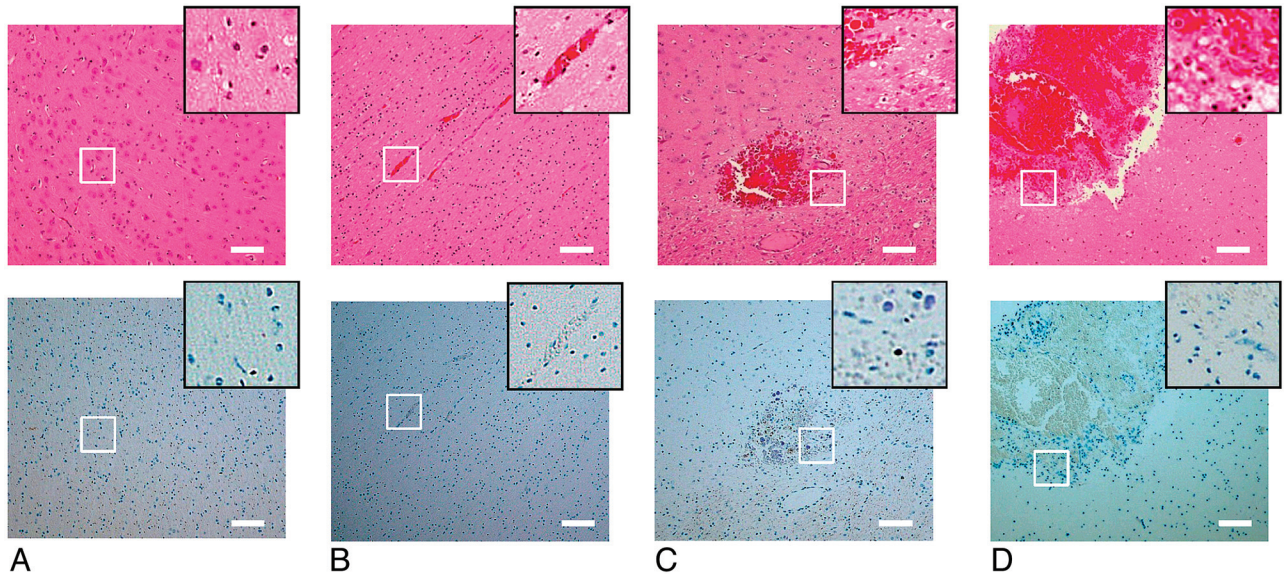


On-line Fig 1. *A*, Experimental setup showing the neuronavigation system registration of the focal point position of the FUS transducer on the neuronavigation system. M1/M2 indicate markers providing spatial reference for the neuronavigation system; T indicates FUS transducer. *B*, Images from the neuronavigation screens showing interactive positional changes of the FUS focal beam (red) to the planned target position (yellow). *C* and *D*, Free-field measured and transcranially measured pressure distributions of the applied FUS along the transducer's axis (left) and along the cross-sectional direction (right). The pressure decay (calculated as the fractional loss of pressure measured before and after skull insertion) was found to be approximately 30% after FUS energy penetrated through the swine skull; however, no focal beam shift was observed along the cross-sectional direction.



On-line Fig 2. MR in vitro relaxometry of Gd-DTPA for imaging-concentration correlation. *A*, T1-weighted images of the samples; *B*, R1 mapping of the samples; *C*, relationship of longitudinal relaxation (R_1 , in seconds⁻¹) versus Gd-DTPA concentration (in mM). Linear fit was obtained between the gadolinium ion concentration and R_1 . A R_1 relaxivity of 3.821 was estimated. Gd-DTPA concentration in numbered wells in panel *A*: (1): 0 mmol/L (2); 0.24 mmol/L (3); 0.49 mmol/L (4); 0.97 mmol/L (5); 1.96 mmol/L (6); 3.9 mmol/L (7); 7.8 mmol/L (8); 15 mmol/L. The other wells of the cell-culture dish were filled with degassed water.



On-line Fig 3. H&E-stained (*upper panel*) and TUNEL-stained (*lower panel*) brain sections characterized as different hemorrhagic damage levels. *A*, grade 0: no damage; grade I: no damage but with temporal vasodilations (*B*); grade II: small groupings of erythrocyte extravasations (*C*); grade III: extensive erythrocyte extravasations or perivascular hemorrhages (*D*). Bar = 100 μ m.

On-line Table 1. Summary of animal experiments

| Group | Pressure (MPa) | Single/Multiple ^a | Animal No. | Sonication No. | Histology No. | First MRI (before FUS) | Second MRI (after FUS) |
|-------|----------------|------------------------------|------------|----------------------|---------------|------------------------|------------------------|
| 1 | 0.26 | Single | 5 | 8 ^b | 4 | T1 | T1/T2/SWI/R1 |
| 2 | 0.43 | Single | 9 | 12 (2 ^c) | 8 | T1 | T1/T2/SWI/R1 |
| 3 | 0.56 | Single | 9 | 16 | 8 | T1 | T1/T2/SWI/R1 |
| 4 | 0.43 | Multiple | 6 | 6 ^b | 4 | T1 | T1/T2/SWI/R1 |
| Total | | | 29 | 42 | 24 | | |

^a Single-point FUS sonication (single) or 3 × 3 points FUS sonication (multiple).

^b The positional discrepancy between the actual BBB-opened location and the target position was not measured for 0.26-MPa FUS exposures.

^c Two of the 12 animals were sacrificed immediately after the diagnostic MRI session for Gd-DTPA quantification via ICP-OES assay.

On-line Table 2. Summary of histologic examination

| Pressure (MPa) | Single/Multiple ^a | Grade Occurrence ^b | | | | Sample No. (Animal No.) |
|----------------|------------------------------|-------------------------------|-----------|----------|---------|-------------------------|
| | | 0 | 1 | 2 | 3 | |
| 0.26 | Single | 182/82.7% | 36/16.4% | 2/0.9% | 0/0.0% | 220 (4) |
| 0.43 | Single | 268/60.9% | 134/30.5% | 38/8.6% | 0/0.0% | 440 (8) |
| 0.56 | Single | 391/60.1% | 174/26.8% | 65/10.0% | 20/3.1% | 650 (8) |
| 0.43 | Multiple | 125/40.3% | 105/33.9% | 60/19.4% | 20/6.4% | 410 (4) |
| Total | | 966/56.1% | 449/26.1% | 165/9.5% | 40/2.3% | 1720 (24) |

^a Single-point FUS sonication (single) or 3 × 3 points FUS sonication (multiple).

^b Grade 0 = no histologic changes compared with normal tissues; grade 1 = no damage, some capillary vasodilations observed; grade 2 = capillary vasodilations accompanied with few erythrocyte extravasations; grade 3 = larger degree of erythrocyte extravasations.