Superparamagnetic iron oxide nanoparticle magnetic resonance (MR) contrast agents are gaining use in the central nervous system (CNS) for monitoring trafficking of particles and cells, and visualizing intracerebral tumors and inflammatory lesions. We performed MR imaging and histological studies of iron oxide nanoparticles in animal models of CNS delivery, brain tumors, and stroke using ferumoxides (Feridex, SPIO), ferumoxtran-10 (Combidex, USPIO), and ferumoxytol (USPIO). After intracerebral convection-enhanced delivery in normal rat brain, signal changes were detected even at 3 months with high concentrations of nanoparticles, with no evidence of neuropathology. After transvascular delivery with osmotic blood-brain barrier disruption., ferumoxtran-10 or ferumoxytol induced transient (3 day) T1-MR enhancement throughout the disrupted hemisphere while ferumoxides caused long term (28 days) signal drop out on GRET2* scans. In a stroke model using temporary middle cerebral artery occlusion, ferumoxtran-10 enhanced the ischemic brain if given immediately after the stroke, but not if delayed until 6 hours after stroke. Ferumoxtran-10 enhanced one lung carcinoma intracerebral xenograft tumor model within 30 min, with maximal enhancement at 6-24 h and return to baseline by 7 days. Ferumoxytol was less effective than ferumoxtran-10 and ferumoxides did not enhance at all in this brain tumor model. No ferumoxtran-10 enhancement was seen in another lung metastasis model or a glioma model. MR enhancement correlated with iron staining in cells with macrophage morphology at the tumor margin. We conclude that the clinical iron oxide nanoparticle formulations ferumoxtran-10, ferumoxytol, and ferumoxides were easily detected the CNS in multiple animal models by MR imaging and histochemistry. Enhancement of a rat stroke model was dependent on time of administration, while enhancement in brain tumor models was dependent on tumor type and size, and on the type of nanoparticle. The safety and efficacy data suggest that clinical trials of CNS lesions are warranted.