Title: **Smart MRI Agents Sensing Extracellular Calcium Fluctuations**

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Functional Magnetic Resonance Imaging (fMRI) is currently the main tool used for the study of function and dysfunction of the human brain. The current mainstay of fMRI, the so-called Blood-Oxygen-Level-Dependent (BOLD) contrast, capitalizes on the detection of changes in cerebral blood flow, volume and oxygenation, but cannot directly report neural activity, as it suffers from poor spatiotemporal resolution and specificity compared to the actual neural events. An alternative methodology could be that relying on the responsive, 'smart' contrast agents whose relaxivity depends on the concentration of substances directly related to neuronal activity. Ca^{2+} is an excellent marker closely linked to brain activation and is preferred target for various imaging methods. We report two Gd^{3+} chelates linked to a modified EGTA moiety that have a relaxivity response to extracellular Ca^{2+} fluctuations in the brain. The proton relaxivity of both Gd^{3+} complexes is sensitive to the variation of Ca^{2+} concentration. They are selective to Ca^{2+} with respect to the main competitor cation Mg^{2+}. Upon interaction with Ca^{2+}, the complexes exhibit high and reversible relaxivity changes; the relaxivity response of one complex upon addition of Ca^{2+} exceeds 80%. Moreover, the relaxivity changes remain remarkable (>50%) even in the medium mimicking the brain extracellular fluid, exhibiting a ~10% relaxivity change in the physiologically relevant Ca^{2+} concentration range (changes induced during the neural activity).
These agents have great potential to be applied as functional MR markers and be used for the visualization of the neural processes. They can substantially increase the specificity and spatial resolution of the MR-detected signals and open new perspectives in fMRI.