Microangiography of the primate brain at 7 Tesla using USPIO particles

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Introduction

It is well known that variations in the structure of microvasculature are frequently correlated to the advance of cerebral diseases such as stroke, aneurysm or brain tumor [1]. Consequently, over the last decades, the *in vivo* study of cerebral microvasculature in humans has appeared to be challenging. Despite the high capability of magnetic resonance imaging (MRI), the detection of the microvasculature in humans using this technique is limited by the low size of blood micro vessels and their low natural contrast. In this context, blood contrast agents for MRI, such as Utrasmall SuperParamagnetic Iron Oxide particles (USPIO), have recently been developed [2,3]. In parallel, the development of high field MRI has allowed increasing the accessible image resolution. In this context, the aim of this study was to evaluate the potentiality of USPIO for microangiography in the primate brain on a clinical 7 Tesla, as a first step in the use of this technique for humans' clinical studies.

Materials & Methods

Animal preparation and NMR system The experiments were performed on 2 healthy monkeys (*macaca fascicularis*; body weight ~6.5 kg) and all work was conducted according to local experimental approvals. For MR experiments, animals were anesthetized using an intravenous (i.v.) infusion of propofol (~200 µg/kg/min), intubated, ventilated and placed in the Sphinx position using a stereotaxic frame. Physiological parameters (temperature, cardiac and respiratory frequencies) were kept in normal ranges during the acquisition. MR experiments were performed on a 7T human scanner equipped with a head gradient set (Siemens, Erlangen, Germany) and a home made surface coil (^{1}H, Ø~7cm) placed on top of the monkey head.

Injection protocol and NMR acquisitions Given the fact that the half-life time of USPIO is more than 350 minutes in the monkey brain [REF], the injected doses were considered as cumulative in time during the experiment (~ 100 minutes). As a consequence, the injection protocol was designed as followed: 4 i.v. injections of a USPIO agent (Sinerem®, Guerbet, France) were performed; the injected doses were 5/10/30/90µmol/kg, leading to cumulated doses of 5/15/45/135µmol/kg. Note that, although 45µmol/kg was shown to be the clinical dose, for monkey [4], the authors chose to achieve 3 times this dose at the end of the protocol to visualize the possible effects of susceptibility variations on MRI images. After a localizer scan, a set of 16 pre-injection gradient echo images were acquired with a coronal slice orientation in an area around the anterior commisure. Imaging parameters were TE 25ms, TR 815ms, TA 16 min, flip angle 25°, slice thickness 1mm, FOV 124x124mm, matrix 576x576, 2 averages. Then the same acquisition was repeated after each USPIO i.v. injection. For robustness, the experiment was repeated once on another monkey.

Results

The experiments were found to be reproducible on the two monkeys and Figure 1 presents the images acquired in one animal. On control images of the cingular cortex (1), few blood vessels perpendicular to the brain surface are visible in the grey matter. As the dose is increased, the number of visible blood vessels becomes larger and the hyposignal of these structures becomes stronger. It is important to notice that there is a dose/effect relationship with the USPIO. At low doses (5 and 15 µmol/kg), the effect of this contrast agent exists and allows identifying some blood vessels of the grey matter. At 45µmol/kg, many vessels can be distinguished without any effect on the image quality. However, at 135µmol/kg, susceptibility effects seem to appear in the cingulate sulcus and in the ventricles, probably due to the accumulation of USPIO agent in these structures. At and above the clinical dose (45µmol/kg) of USPIO, blood vessels in the white matter become clearly distinguishable. The second set of images (2) shows the precentral gyrus situated on top of the postcentral gyrus and how the blood vessels alimenting the postcentral gyrus are unambiguously revealed with the contrast agent while invisible without. Furthermore, with increasing dose, susceptibility effects reduce the signal to noise ratio leading to an overall degradation in image quality.

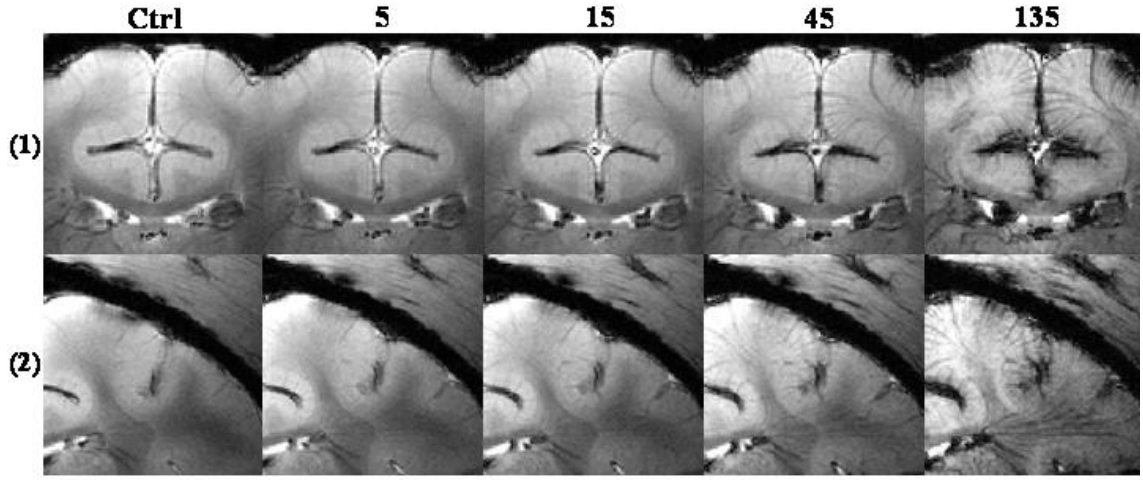

Figure 1 – Gradient echo images of the same monkey brain, zoom on (1) the cingulate cortex and (2) the radiations of corpus callosum. The cumulated doses (µmol/kg) are given on the top.

Conclusion & Perspectives

This study presents a direct validation of the interest of the USPIO contrast agent to do microangiography of the primate brain at 7T. Combining high field and contrast agent allows the identification of the main microvasculature in the brain, making it possible to detect anomalies such as variations of the form of vessels (aneurysm…) or increase in the number of vessels (angiogenesis in tumor…). As a consequence, the use of USPIO associated with high field NMR system should prove a useful tool for clinical studies in humans, allowing a better and earlier diagnostic of brain disease affecting the microvasculature.

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