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Quantitative vascular neuroimaging of the rat brain using superparamagnetic nanoparticles: New insights on vascular organization and brain function

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ABSTRACT

A method called Quantitative Ultra-Short Time-to-Echo Contrast Enhanced (QUTE-CE) Magnetic Resonance Imaging (MRI) which utilizes superparamagnetic iron oxide nanoparticles (SPIONs) as a contrast agent to yield positive contrast angiograms with high clarity and definition is applied to the whole live rat brain. QUTE-CE MRI intensity data are particularly well suited for measuring quantitative cerebral blood volume (qCBV). A global map of qCBV in the awake resting-state with unprecedented detail was created via application of a 3D MRI rat brain atlas with 173 segmented and annotated brain areas. From this map we identified two distributed, integrated neural circuits showing the highest capillary densities in the brain. One is the neural circuitry involved with the primary senses of smell, hearing and vision and the other is the neural circuitry of memory. Under isoflurane anesthesia, these same circuits showed significant decreases in qCBV suggesting a role in consciousness. Neural circuits in the brainstem associated with the reticular activating system and the maintenance of respiration, body temperature and cardiovascular function showed an increase in qCBV with anesthesia. During awake CO_2 challenge, 84 regions showed significant increases relative to an awake baseline state. This CO_2 response provides a measure of cerebral vascular reactivity and regional perfusion reserve with the highest response measured in the somatosensory cortex. These results demonstrate the utility of QUTE-CE MRI for qCBV analysis and offer a new perspective on brain function and vascular organization.

1. Introduction

The mammalian brain has evolved an exceptional ability to autoregulate regional blood supply to specific anatomical regions in response to changes in function or state. While the underlying neurovascular architecture is fixed by evolutionary and developmental needs, the blood supply is highly dynamic and changes with metabolic demand. Magnetic resonance imaging (MRI) is the most common clinical imaging modality for investigating neural blood flow and vascular structure. An approach to absolutely measure and map quantitative cerebral blood volume (qCBV) would provide a proxy to measure capillary density and enable identification of brain areas critical to the evolution of function and survival. Further, deviations in this global map of capillary densities and the changes in blood volume to these areas following physiological or traumatic perturbations would greatly enhance our understanding of the distributed, integrated neural circuits underlying brain function.

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Conventional MRI techniques cannot absolutely and quantitatively measure qCBV at the level of the microvasculature across the entire brain. Generally, MRI techniques rely on qualitative image assessment, relative signal changes or have high degrees of error which limit accurate quantification. Quantitative MRI measurements are hampered by susceptibility-induced spin dephasing, field inhomogeneity, spin dephasing and motion/flow artifacts. Imaging techniques that employ a time-to-echo (TE) of half a millisecond or more are particularly vulnerable to these complications (Bernstein et al., 2006; Farrar et al., 2009). Dynamic susceptibility contrast (DSC) MRI is most commonly used for measuring CBV values (Sourbron et al., 2009; Barbier et al., 2001) but fundamentally requires accurate determination of the arterial input function (AIF) (Rempp, 1994), or contrast concentration versus time curve (Yankeelov and Gore, 2009), which are typically 15–30% inaccurate (Walker-Samuel et al., 2007; Schabel and Parker, 2008). The typically employed echo-planar imaging (EPI) sequences are prone to image distortions such as warping and signal dropout due to spin dephasing. Related dynamic contrast enhanced, DCE-MRI, techniques employ TEs greater than half a millisecond and report similar error when applied to CBV (Sourbron et al., 2009). Other techniques for measuring the CBV, such as steady-state gradient echo (SSGRE) susceptibility contrast mapping, steady state CBV (SSCBV), and ΔR2 all utilize T_2 and T_2^* effects, which are prone to susceptibility-induced intravoxular dephasing as well as flow artifacts which necessitate a reduction in resolution to compensate for partial volume effects (Stuber et al., 2007; Troprès et al., 2001).

We have previously introduced Quantitative Ultra-short Time-to-Echo Contrast-Enhanced (QUTE-CE) MRI, a method utilizing Ultrashort-Time-to-Echo (UTE) sequences with SPIONs that produces angiographic images with positive T_1 contrast (Zhao et al., 2011; Hoelscher et al., 2012), high clarity, high definition and the low error of quantification (Gharagouzloo et al., 2014). We utilize ferumoxytol, an FDA-approved SPION formulation already used off-label for human MRI. SPIONs have been recognized to be an alternative to nephrotoxic gadolinium-based contrast agents (CAs) (Neuwelt et al., 2009; Turkbey et al., 2015), but their use has been greatly limited clinically by the commonly employed T_2-weighted imaging techniques which produce negative contrast.

Here we apply the QUTE-CE MRI method to find absolute measurements of qCBV across the entire awake rat brain. From these measurements, a global map of qCBV in 173 regions was created and regions of homogeneous microvasculature were identified. Next, we demonstrate that regional alterations to this qCBV can be measured during steady-state changes, here due to hypercapnia (elevated blood CO_2) and inhaled isoflurane anesthesia. Inferences about brain function and vascular organization are drawn from the spatial mapping of regional changes between these functional states.

2. Methods

2.1. Animal model and state changes

All animal experiments were conducted in accordance with the Northeastern University Division of Laboratory Animal Medicine and Institutional Animal Care and Use Committee. Sound- and restraint-acclimated (Ferris et al., 2015) Sprague Dawley (SD) rats (~300 g, n = 11) were anesthetized with isoflurane (1–3%), mechanically restrained, and fit with a tail vein catheter containing heparinized saline. Animals were imaged in the anesthetized state then injected with an i.v. bolus of 6 mg/ml Fe of Ferumoxytol. The injected volume was tailored for each rat (assuming 7% blood by body weight) to produce a starting blood concentration of 200 μg/ml Fe (2× the clinical dose approved for use in humans). Rats were allowed to awaken for 25 min and then 5% CO_2 was delivered via mask for 2 min to induce hypercapnia before commencing another scan. The CO_2 was next replaced with air at the same flow-rate, and the next scan commenced after 2 min to measure a standard resting steady-state. Finally, 3% isoflurane was added to the air and this concentration was used until respiration decreased to 30–40 breaths/minute, indicating anesthetization. Isoflurane percent was adjusted manually throughout the scan to maintain a steady breathing rate.

2.2. QUTE-CE image acquisition

In the underlying theory of QUTE-CE MRI, the intensity magnitude I_M of each voxel is a function of standard MRI parameters governed by the Spoiled Gradient Echo (SPGR) equation (Schabel and Parker, 2008; Gharagouzloo et al., 2014),

$$I_M = K\rho \cdot e^{(-\mathrm{TE}/T_2)} \cdot \sin(\mathrm{FA}) \frac{1 - e^{(-\mathrm{TR}/T_1)}}{1 - e^{(-\mathrm{TR}/T_1)} \cdot \cos(\mathrm{FA})} \quad (1)$$

where TE is the time-to-echo, TR is the repetition time, and FA is the flip-angle. TE, TR, and FA are user-defined image acquisition parameters and their optimization is a vital component of technique. T_1 and T_2 are relaxation time constants dependent on the local environment of each voxel, which is mutable via contrast agents, and dependent on the magnetic field strength. K is a constant determined by the properties of the receive coil and ρ is the proton density of the medium.

User-defined QUTE-CE MRI image acquisition parameters available for optimization included the TE, TR and FA. TE is chosen to be (<100 μs) to eliminate eliminate susceptibility-induced signal modifications. The choice of a very low TR (<5 ms) in a 3D volume excitation pulse minimizes effects from the extravascular water exchange (Kim et al., 2002) and eliminates signal enhancement from blood flow within the cranial space. Setting the FA at the Ernst angle maximizes the T_1-enhanced signal and minimizes sensitivity to small perturbations. Here, QUTE-CE MRI images were obtained at ambient temperature (~ 25° C) using a Bruker Biospec 7.0 T/20 cm USR horizontal magnet (Bruker, Billerica, Massachusetts, USA) equipped with a 20-G/cm magnetic field gradient insert (ID = 12 cm, Bruker) and a custom built 30 mm diameter 300 MHz quadrature volume coil (Animal Imaging Research, Holden, MA). The coil apparatus was equipped with restraints to hold the rat head fixed and centered during both asleep and awake imaging. Optimized acquisition parameters of TE = 13 μs, TR = 4 ms, and FA = 20° were utilized with a high RF pulse bandwidth of 200 kHz. Therefore, the pulse duration was short (6.4*μs)* compared to the T_2 of the approximate ferumoxytol concentration (4.58 ms for 3.58 mM, i.e. 200 μg/ml(Gharagouzloo et al., 2014) to minimize signal blur and reduce the probability for a curved trajectory of the magnetization vector M_z (Tyler et al., 2007). A 3 × 3 × 3 cm^3 field-of-view was used with a matrix mesh size of 200 × 200 × 200 to produce 150 μm isotropic resolution. Images were averaged over 2 scans.

2.3. Rat brain atlas

A 173-region rat brain atlas was developed using high resolution (85 μm × 85 μm) T2-weighted anatomical MRI images acquired using a Bruker 7.0T scanner. A 2D multi-slice Turbo-RARE sequence with fat suppression was used with following parameters: TE_{eff} = 48 ms, TR = 5000 ms, RARE factor = 16, FA = 90°, averages = 15. Anatomical and functional regions were drawn on 65 contiguous axial slices of 400 μm thickness, producing 173 regions of interest. General segmentation and specific annotation were adopted from Paxinos and Watson (The Rat Brain, 6th Edition). This MRI atlas was developed to overcome the many shortcomings of existing commercial and public-domain atlases (Ekam Solutions, Boston, MA USA). The atlas more accurately reflects living structures because, unlike the histology images traditionally used in atlas development, there is no shrinkage due to preparation of the reference tissues. This greater biological accuracy improves registration and segmentation quality. Note that, while the atlas includes a region for the ventricle (#155), this was excluded from all CBV analysis.

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