Use of Magnetic Resonance Imaging to Quantitatively Assess Inflammation and Blood Labyrinth Barrier Integrity in Inner Ear Disease

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INTRODUCTION

- Cochlear injury or disease is the major cause of hearing loss [1,2]. There is evidence that inflammation and disruption of the Blood-Labyrinth Barrier (BLB) contributes to cochlear injury, for example after cochlear implantation [3].
- As yet no approach is available to identify inflammatory changes in the intact, living inner ear of humans.
- Recent developments in Magnetic Resonance Imaging (MRI), using Dynamic Contrast Enhanced-MRI (DCE-MRI) offer opportunities to study structure, function and metabolism of the intact, living cochlea.
- The large amount of MRI data can be automatically analysed with image registration to produce accurate spatial and temporal results.

STUDY OBJECTIVES

1. Develop and apply DCE-MRI to quantify changes in vascular permeability in normal and inflamed guinea-pig cochlea.

2. Investigate the translation of these DCE-MRI techniques to study the vascular permeability of the human inner ear.

METHODS

- **Animal model of cochlear inflammation:** Guinea-pigs (GP n=8) were sensitised with bacterial lipopolysaccharide (LPS, 0.8mg/kg, ip) followed by (24 hrs) bilateral intra-tympanic injection (LPS, 30µl). Controls (n=5) were either not treated with LPS (3) or injected with saline (0.8mg/kg, ip), followed by intra-tympanic saline (30µl).
- **Human participants:** Volunteers (30 years old, n=2) with normal hearing and no otological disease. All received a single dose of contrast agent (Dotarem, Guerbet, 0.1mmol/kg, bolus injection 2.5mL/s).
- **MRI protocol for animals (Fig 1):** LPS-treated GP were scanned at 4 (n=7), 7 (n=4) and 10 days (n=3) after injection. Control GP were scanned once (untreated, day 0) or at 4, 7 and 14 days (saline-treated) after injection. To estimate early changes in vascular permeability and GBCA plasma concentration LPS (n=2) and control (n=1) GP were scanned once at 4 days.
  All scans were based on a slab-selective 3D Gradient Recalled echo sequence: T1-w coronal, acquisition matrix=512*256*16 and FOV=80mm*50mm*12mm, TR=20ms, TE=4.5ms, FA=50°, single average, total acquisition time=81s using a Varian 4.7T MRI.
- **MRI protocol for human (Fig 2)**: All subject had DCE-MRI (VIBE sequence, TR/TE=20/3.7ms, spacing=[0.3,0.3,0.5] mm, matrix=512*512*44, FOV=1329mm*759mm*759mm acquisition time: approx. 9 min) before DGBCA injection, 2 minutes and 3h30 to 4h30 post-injection using a 3T MRI (Skyra Magnetom, Siemens). The spatial resolution shows different turns of the cochlea, but is not sufficient to differentiate fluid compartments.

RESULTS

Normal MRI: Animal Studies

- Representative proton density-weighted MR image demonstrates cochlear position and structure (**Fig.1**).

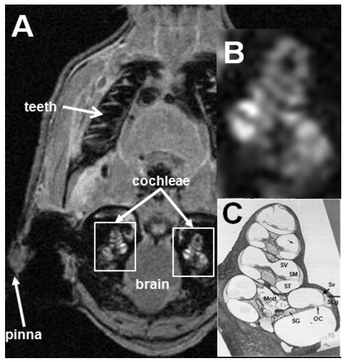

Fig.1 A: Proton density MRI 75 min post GBCA injection. **B:** Higher magnification (white rectangle) shows cochlear structures identified **(C)** in a mid-modiolar cochlear section. **C:** Fluid compartments, scala tympani (ST), media (SM), vestibuli (SV); organ of Corti (OC), modiolus (Mod), spiral ganglion (SG), stria vascularis (Sv) and spiral ligament (SLg).

Normal MRI: Human Studies

- MRI image with a T1-w VIBE sequence before injection of the contrast agent **(Fig 2)**.

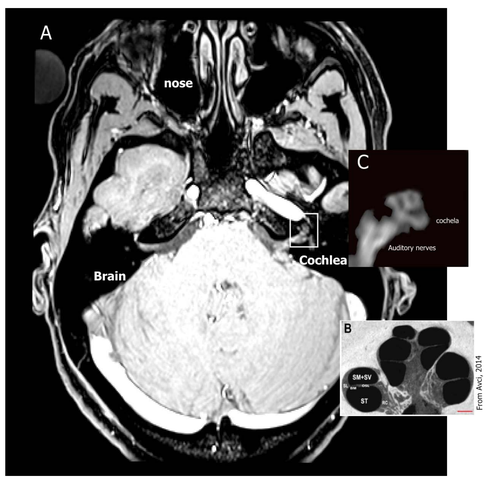

Fig.2A: Transversal plane of the VIBE MRI acquisition. **B:** air-filled human cochlea illustrating the three fluid compartments: Scala Tympani (ST), Scala Vestibuli (SV) and Scala Media (SM), illustration from [4]. Scale bar is 1mm, **C:** Higher magnification (white rectangle) shows the cochlea with the auditory nerve.

4D Gadolinium contrast distribution: Animal Studies

Fig.3 A: DCE-MRI 55 min after GBCA in same LPS-treated animal 4, 7, 10 days after LPS. (Insets, magnified cochlea ROI).

Fig.3 B: DCE-MRI 55 min after GBCA in same LPS-treated animal 4, 7, 10 days after LPS. (Insets, magnified cochlear ROI).

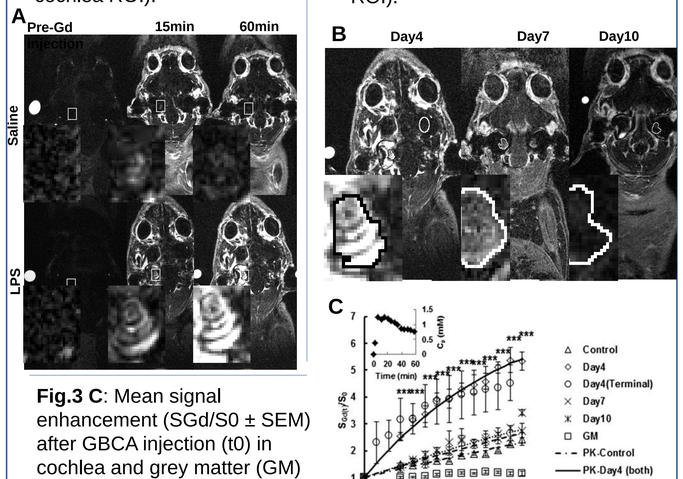

Fig.3 C: Mean signal enhancement (SGd/S0 ± SEM) after GBCA injection (t0) in cochlea and grey matter (GM) of control and LPS-treated GP (4, 7, 10 days.

4D Gadolinium contrast distribution: Human Studies

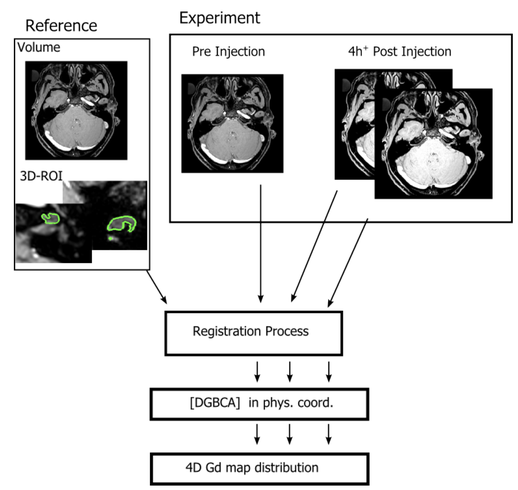

Fig 4: 3D registration pipeline concept: the Regions of Interest (ROIs) are defined based on a Reference volume. A registration based algorithm sets all the volumes in a coherent physical space and export the ROIs to total volume. This process allows to define bijections between images and then to estimate the uptake of DGBCA over time for each physical coordinate.

4D Gadolinium cochlear distribution

- **Guinea Pig:** Uptake is measured as mean of manually defined ROIs. These show slight increase in signal intensity in control GP cochlea over 60mins (**Fig.3A**). In contrast, LPS-treated animals (4 days after LPS) had stronger signal enhancement over 60 min, indicating increased GBCA extravasation and increased vascular permeability (**Fig.3A,3B**). By day 7 and 10 signal enhancement in the same animals matched control, indicating normalisation of permeability. These data (**Fig. 3C**) show that GBCA with DCE-MRI can be used to demonstrate inflammation in the animal cochlea which can be quantified.
- **Human:** The methodology to define the permeability changes in humans is feasible [5]. Pixel enhancements are observed inside the inner compartments using VIBE sequence but GBCA uptake can take up to 4hrs suggesting a very tight BLB.
- **The registration** pipeline is defined as a combination of affine and non rigid registrations between the Reference Volume (RV) and a given set of DCE-MRI captions (pre and post injection). This process enables us to measure spatial and temporal DGBCA distribution. It can be apply to any DCE-MRI human or GP data.
  - **ROIs exportation**: Once the data are registered, the ROIs defined inside the RV space can be exported to any MRI to retrieve organs of the inner ear.
  - **4D map definition**: Pixel intensities provide an estimation of DGBCA concentration The different scans registered allow the estimation of the uptake of DGBCA along the time at each physical locations inside the inner ear.

CONCLUSIONS

- DCE-MRI can quantitatively monitor reversible changes in cochlear vascular permeability (Blood-Labyrinth Barrier) in a guinea pig model of inner ear inflammation.
- DCE-MRI can quantitatively assess BLB in humans and establish DCE-MRI as a promising diagnostic tool for assessing BLB in inner ear disease.
- The VIBE sequence enables good spatial resolution and a rapid acquisition time. The registration pipeline sets together all the measurements, allowing us to estimate temporal changes of the contrast agent inside the inner ear.

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