Retrospective R1 Atlas Mapping of Brain Infusions

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INTRODUCTION

New treatments of brain diseases like Parkinson's disease and brain tumors are focusing on direct and local delivery of therapeutics in the brain. Convection-enhanced delivery (CED) has been proposed to increase the distribution and dose of therapeutic agents in a target area beyond simple diffusion. Accurate targeting of the intended brain region using this method is critical for delivering effective treatment in the target tissue, minimizing the dose necessary for treatment and minimizing exposure to other tissues outside of the target area. It is thus important to obtain insight into factors for successful and unsuccessful infusions. For example, some factors that might influence outcomes include the cannula design and geometry, the position of the cannula and the infusion rate. In this project we developed an image analysis framework to retrospectively generate a normalized statistical atlas of infusion studies, which will facilitate the investigation of how different infusion factors influence the treatment outcome. For this study, we applied the framework to characterize the infusion patterns and consistency of experimental studies using a T1-enhancing agent (Prohance) into the putamen of macaque monkeys as a model for delivery of therapeutic agents to treat patients with Parkinson's disease. Time-resolved maps of the inverse of the T1 relaxation time, R1 (= 1/T1) were used to estimate the spatial/temporal concentrations of the delivered agent.

METHODS

Animals: This study is based upon six studies of image-guided CED delivery of Gadolinium tracer into the putamens of macaque monkeys. The experiments were performed according to the federal guidelines of animal use and care and with approval of the local IACUC. The targeting and delivery of the tracer were performed *in vivo* under MRI guidance using a 3T MRI scanner using a fused silica cannula and a Navigus MR-compatible catheter navigation system, which has been shown to enable targeting of drugs in the brain to within 1 mm of the target site [1]. The monkey was placed in an MR-compatible stereotaxic frame in the sphinx position. Cannulas were inserted through the the dorsal surface of the skull and targeted into the caudal portion of the putamen (post- anterior cingulate) roughly 8-10 mm in depth from the top of the putamen. A 100 µl solution of gadoteridol (ProHance, Bracco Diagnostics; 2mMol/L) in phosphate buffered saline was used for *in vivo* MRI visualization of the infusate, at an average flow rate of 1.0 µl/min.

MRI Acquisition: Scans were acquired on a 3.0 Tesla GE Signa MR750x (GE Healthcare; Waukesha, WI) using a 3-inch diameter surface coil placed on the top dorsal surface of the head. Structural 3D T1W scans were acquire as a anatomical reference using an MP-RAGE sequence with 450ms TI, 9.2ms TR, 4.1ms TE, 12° flip angle, 140x105mm in-plane FOV, matrix size of 256x224x128, and a 0.8mm slice thickness.

R1 Mapping: R1 mapping was performed using a spoiled gradient echo (SPGR) pulse sequence with two flip angles [2]. The SPGR sequence parameters were TR/TE=21/6ms, NEX=1, and alternating flip angles α = [6 34]º collected separately (roughly 4.5 minutes each). Scans were acquired at 256x256x64 matrix and 0.55x0.55x0.8 mm^3 voxel size. A sliding window estimation method was used to estimate R1 maps at roughly 4.5 minute intervals, which is sufficient for infusions this slow.

MRI Post-Processing: A schematic of the atlasing pipeline is shown in Fig 1. SPGR and 3D T1W anatomical brain volumes were skull stripped using the brain extraction tool from FSL [3], with some manual refinements. The SPGR images were co-registered using a rigid body registration (df=6) [3] prior to R1 estimation. Rigid body registration was also used to map the R1 images to the T1W anatomicals. A high quality, high resolution, population-averaged 3D T1W template was generated by applying a diffeomorphic spatial normalization tool, ANTS [4]. Finally the time-resolved R1 maps were then warped to the T1W template space using the transform defined by the diffeomorphic registration. For each time point (roughly every 4.5 minutes) statistical maps (mean, standard deviation, minimum and maximum) of the R1 for all six animals were computed.

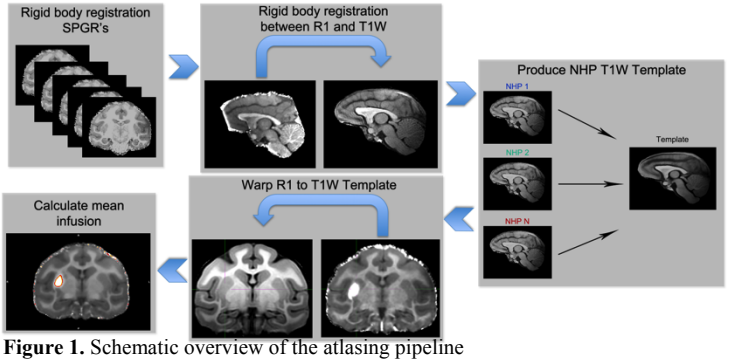

Figure 1. Schematic overview of the atlasing pipeline

RESULTS

The normalized statistical maps of the infusions studies are shown in Fig 2. The top part of this figure displays the mean R1 maps of the right infusion at five time intervals, approximately 13.5 minutes apart. The bottom part shows the standard deviation of the infusions. The mean infusions show clear overlap with the targeted putamen area.

DISCUSSION

This framework can be used to characterize the consistency of infusion studies. Future versions of this atlas will include borders of the target region (e.g., putamen outline), change in concentration maps (ΔR1), which is more directly related to the concentration, locations of the cannula and original target. While this study used a T1-enhancing tracer, the framework may also be applied to infusions with other T1 or T2 properties. Further, this pipeline would also be amenable to application in clinical CED studies in patient populations that are monitored with MRI.

REFERENCES

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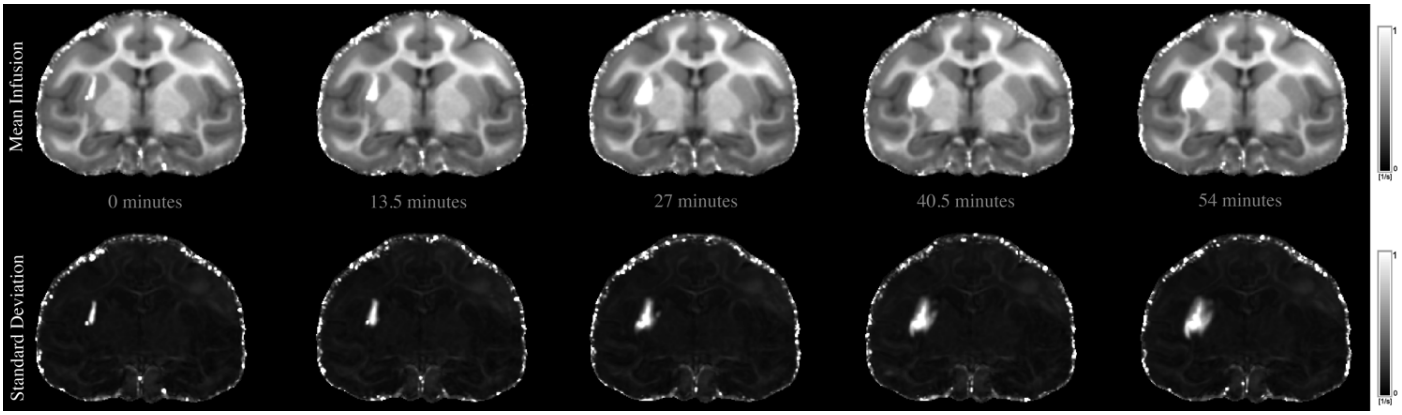

Figure 2. R1 mean and standard deviation at 13.5 minute time intervals