Wanted Dead or Alive? The tradeoff between in-vivo versus ex-vivo MR brain imaging in the mouse.

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Introduction

Brain morphology in the mouse is a sensitive indicator of disease, treatment, and environmental effects on the brain. It is unclear, however, when to select an in-vivo longitudinal or an ex-vivo cross-sectional study design. Ex-vivo imaging allows for longer imaging times, gadolinium-based contrast agents, and does not suffer from motion artefacts. At the field-strengths commonly employed for mouse imaging this results in beautifully detailed anatomical images with voxel sizes between 20-30 micron isotropic [1,2]. For obvious reasons ex-vivo necessitates different samples at each time point. In-vivo imaging, on the other hand, allows for longitudinal studies, but is limited by scan time due to anaesthesia tolerance, physiological motion, and difficulties in adding extraneous contrast agents. Commonly obtained resolutions thus range from 100-200 micron isotropic [3,4]. The question we sought to address was: at what point does the addition of scanning at multiple timepoints per subject make up for the reduced resolution/SNR of in-vivo imaging?

Methods

To address the relative power of longitudinal in-vivo versus cross-section ex-vivo imaging we set up a simulation framework based on the following assumptions:

1. There will be two groups of subjects that do not differ at baseline but will differ at the end of the study.
2. The increase in the volume of a brain structure of interest from baseline to the end of the study will be linear.
3. Volumes at baseline are normally distributed, i.e. $Baseline \sim normal(\mu_{population}, \sigma_{population})$
4. Volumes at each subsequent timepoint increase towards a total change of μ_β and have an additional normally distributed error, i.e.

$$Timepoint_i \sim Baseline + normal\left(\mu_\beta\left(\frac{timepoint_i - 1}{N_{timepoints} - 1}\right), \sigma_{subject}\right)$$

For the simulation we restrict our attention to hippocampal volumes and assumed an estimated change of 3.5% over the course of the simulated experiment, which is within the range of what we recently detected in a short-term study of the effect of learning on the brain [5]. The effects of increasing timepoints per subject, changing within-subject variances, etc., where then simulated.

Results

Ex-vivo data from our experiments suggests that the mean volume of the hippocampus is 18.1mm^3 and its standard deviation is 0.57mm^3 [5]. Two representative in-vivo datasets produces a similar mean but a population standard deviation of 1.14mm^3 or 0.96mm^3 and within-subject standard deviation of 0.69mm^3 or 0.58mm^3 while imaging at (1) 9.4T with 156µm isotropic voxels using a 3D inversion recovery spin echo sequence with 2 month timepoint intervals or (2) 7T with 100µm isotropic voxels gradient echo sequence and 1 day timepoint intervals. Given these numbers and assuming ten subjects per group, our simulation of ex-vivo experiments suggests that the power (1 – false negative rate) of these repeated experiments is 0.68 when allowing a false positive rate of 0.05; alternately, the false positive rate is 0.11 when the power is set at 0.8. In-vivo studies with their larger standard deviations match this statistical power at 3-5 scans per subject. The power of in-vivo imaging increases considerably if the within-subject variance can be reduced.

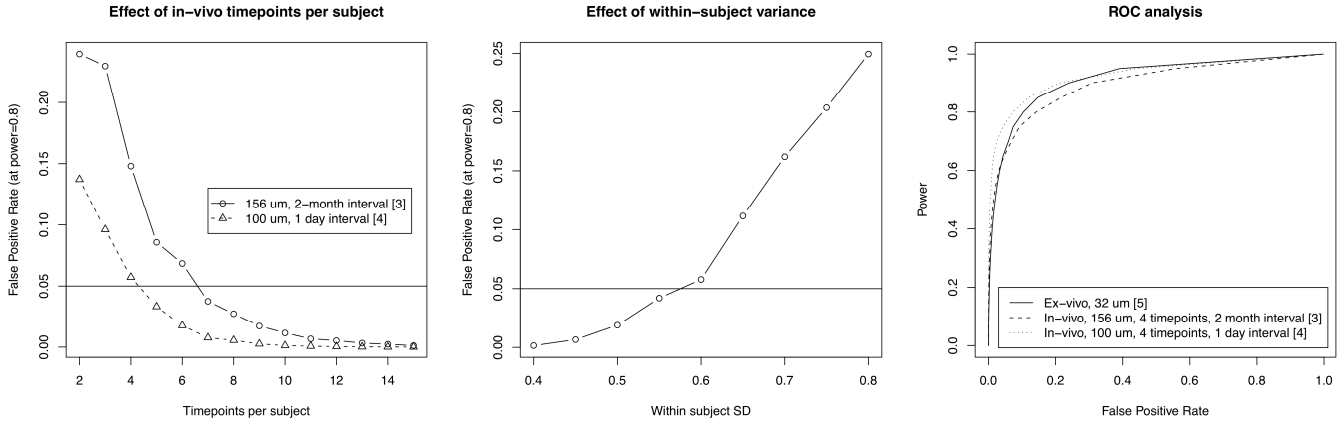

Figure 1: The left-most panel shows that, given the variances described in previously published data, 3-5 in-vivo scans per subject result in similar statistical power as the fixed brain experiment. The middle panel illustrates that the key is to keep within-subject variance at less than 0.7mm^3 of hippocampal volume (assuming 4 timepoints per subject). The rightmost panel shows the tradeoff between power and false positive rate in the three experimental setups.

Discussion

Our simulations suggest that longitudinal in-vivo scanning needs 3-5 scans per subject to obtain similar statistical power as fixed brain imaging. These results are, of course, dependent on multiple assumptions (linearity of change, knowing when these volume differences start and end, etc.), yet they provide important insights into the nature of the trade-off between high-resolution ex-vivo imaging and lower resolution longitudinal scanning for experiments attempting to map a growth curve in neuroanatomy.

References: [1] Henkelman et al., ISMRM 2006. [2] Badea et al., NeuroImage (37), 2007. [3] Lau et al., NeuroImage (42), 2008. [4] Nieman et al., NeuroImage (50), 2010. [5] Lerch et al., NeuroImage (in Press), 2010.