MR-based anatomical covariance predicts brain structural connectivity in mice

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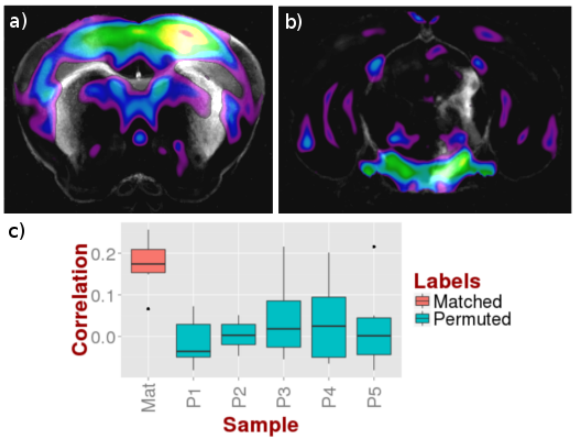
Target audience: neuroscientists using MR to characterize brain connectivity in health and disease.

Introduction: Brain function arises from the non-random arrangement of neurons into a complex information-processing network; many disorders of the nervous system are often described as disorders of connectivity within this network. Commonly, DTI is used to image the network's structural components. Here, we describe an alternate method to image connectivity across a sample using MR images of brain anatomy, termed anatomical covariance (AC). We construct AC networks in the mouse brain and show that the correlations between these AC networks and neuronal tracer data from the Allen Brain Institute (ABI)[1] are statistically highly significant.

Methods: AC networks are networks of covariances in brain region volume, computed pairwise between volumes of each region-pair[2]. Here, we extend AC to voxelwise covariances by producing AC maps of covariances between eight "seed" regions and the rest of the brain voxelwise. Covariances are computed at each voxel using voxel volume changes—obtained via deformation based morphometry—rather than the larger brain region volumes. T2-weighted whole brain images of 109 "wildtype" mice across several strains were obtained. All images were registered together, providing a common average created from resampled images with an image size of 172×340×225 voxels and isotropic resolution of 56 μm. Jacobian determinants for each image were computed at each voxel, these determinants indicate the change in voxel volume due to nonlinear transformations to the common average induced by the image registration. Correlations computed between the Jacobian determinants across the whole brain and the seed region were used to build AC maps for each of the eight seed regions. Seed regions (listed in the results) were chosen to match injection regions from the ABI tracer experiments that had sufficient data.

We compared these voxelwise AC maps to tracer data from the ABI. We used tracer data rather than DTI because of its ability to capture very fine fiber tracts. In the ABI tracer experiments, mice were injected in various brain regions with a retrograde rAAV tracer and imaged using serial two-photon microscopy. The tracers map out axonal projections from the injection site to connected regions of the brain. We registered and overlayed AC maps with seeds that roughly matched the tracer injection site on the ABI tracer images to address the extent to which AC maps determine structural connectivity. We quantified this by correlating the intensities of the AC maps to the tracer signal intensities, after masking out the seed region to reduce bias introduced by high covariances within the seed.



Results: AC maps were generated for seeds in the primary motor cortex, primary visual cortex, primary auditory cortex, mediodorsal entorhinal cortex, perirhinal cortex, superior colliculus, secondary motor cortex, and the bed nucleus of stria terminalis. AC maps showed high covariance in the seed regions and their bilateral counterparts (figure (a), coronal slice of a mouse brain at the primary motor cortex seed). In general, AC covariances are highly bilateral. Qualitatively, AC maps indicated covariance in regions at the ends of traced fibers, for example in the pontine nucleus for the primary motor cortex seed (figure (b), coronal slice of the mouse brain at the pontine nucleus). In figures (a) and (b), the magnitude of the AC covariances are represented as a colour spectrum with the highest covariance in red; these are overlayed on the ABI tracer signal shown in greyscale. Various regions not connected by tracer signal also had high covariance, suggesting that AC may show connectivity mediated by multi-neuronal connections. Quantitatively, the pearson correlation coefficient was computed between each AC image and its tracer counterpart (with seed region masked out). The mean correlation coefficient of these pairs was 0.176; the distribution of these eight correlation coefficients are shown in the figure (c) as the red box. Permuting the data labels provides an indication of the null distribution (blue boxes show example permutations), and suggests that the correlation between AC maps and tracer images are highly significant.

Discussion: Given that AC maps correlate significantly with fiber projections, AC may be an alternate method to determine brain connectivity in a sample of subjects through anatomical MR images of each subject's brain. AC maybe particularly advantageous when conventional methods of determining connectivity are constrained by resolution or are time consuming. AC only provides an idea of connectivity across a sample however, and does not provide any indications of connectivity variance within a sample. Open questions on the biological origins of AC remain: are these correlations in brain region volume/growth the result of common developmental cues, functionally-driven plasticity, or physical forces acting on parts of the brain? Here, we showed that AC correlates significantly with structural connectivity. Answers to these questions may also provide hints on the extent that AC is an indication of functional connectivity, and the link between structure and function. Additionally, more work must be done in addressing AC structural connectivity—the ABI tracer data is directional and does not cross synapses for example, whereas AC maps yield symmetric connections that may be mediated by multiple neurons. These differences may explain further variance in the data and address why the correlation coefficient, although highly significant, is low. Further issues that must be addressed in AC are 1) whether certain brain connections are more plastic and therefore more prone to covariance in volume, 2) the number of samples required for a sufficiently powered AC study, and in comparing connectivity methods, 3) accuracy of registration and seed region choice.

Conclusion: In summary, MR-based voxelwise anatomical covariance (AC) was used to determine brain connectivity to various seed regions in a sample of 109 wildtype mice. Comparing these connectivity maps to neuronal tracer injections at the seed regions, we found that AC connectivity very significantly correlated with structural fiber connectivity determined via tracers, thus providing an alternate method to image structural connectivity. AC is a relatively new technique however, and several questions, particularly biological ones, remain unanswered.

References:

1. Allen Institute for Brain Science. Allen Mouse Brain Connectivity Atlas [Internet]. http://connectivity.brain-map.org/. Accessed November 11, 2014.
2. Evans, A. Networks of anatomical covariance. Neuroimage 2013;80-489:504.