Magnetic Resonance Microscopy Provides Multiple Biomarkers in Animal Models of Neurological Diseases

Alexandra Badea, PhD

Department of Radiology, Department of Neurology, Center for In Vivo Microscopy, Brain Imaging and Analysis Center; Duke University Medical Center, Durham, NC 27710

Network approaches provide sensitive biomarkers for neurological conditions such as Alzheimer's disease (AD). Mouse models provide tools to dissect vulnerable circuits, and to assess the effects of interventions. We hypothesized that magnetic resonance microscopy applied in mouse models is a suitable approach for understanding multifactorial diseases such as AD. This is because it provides sensitive contrast in brain tissue, high resolution, and multivariate biomarkers. We show that MRM based approaches using multiple biomarkers help identify vulnerable circuits in normal aging, and in mouse models of AD.

We used *in vivo* manganese enhanced MRI at 7.1T, at 100 μm isotropic resolution, followed by traditional voxel based analyses to reveal regional differences in volume (morphometry), signal intensity (activity), and magnetic susceptibility (iron deposition, demyelination). These regions included the hippocampus, olfactory areas, entorhinal cortex and cerebellum, as well as the frontal association area. The properties of these regions, extracted from each of the imaging markers, were used to predict spatial memory. We used eigenanatomy, which reduces dimensionality to identify sets of regions that explain the variance in the data. For each imaging marker, eigenanatomy revealed networks underpinning a range of cognitive functions including memory, motor function, and associative learning. The integration of multivariate markers in a supervised sparse canonical correlation approach outperformed single predictor models and had significant correlates to spatial memory (1).

Diffusion tensor imaging is particularly well suited for examining brain networks, and how their properties change with aging, or in AD. But connectomic studies in mouse models require long times for *in vivo* acquisitions. We have thus used DTI in *ex vivo* specimens at 9.4T to examine in detail vulnerable brain networks, with reduced time constraints. Based on a data set (2) acquired over 10 days using 120 diffusion directions, and 43 um resolution we have produced simulated connectomes, aiming to balance angular, spatial resolution and scan time. We evaluated protocols with 6, 12, 15, 20, 30, 45, 60 and 120 angles; and voxel sizes of 43, 86 and 172 μm. Our results indicate that a scheme using 46-60 directions, and 86 μm resolution retrieve similar connectomes to a high spatial, high angular resolution sampling scheme, while increasing efficiency. Using compressed sensing has allowed us to accelerate imaging protocols, allowing us to efficiently acquire 51 directions (46 diffusion weighted, interspersed with 5 non diffusion weighted scans), and reconstruct these at and 55 μm resolution in a high performance computing cluster environment (3). The tracts connecting pairs of atlas regions (4) were used to build connectomes based on a constant solid angle implemented in DIPY (5). Tracts were visualized using MI brain (imeka.ca), and statistically analyzed to reveal network changes. We analyzed network changes based on a recently proposed method for dimensionality reduction (6), called tensor network factorization, which relies on a generalization of principal component analysis (6). Our results indicated that even though qualitatively differences were subtle between representative animals of the two age groups/and genotypes, we could separate the groups based on a tensor network decomposition. We identified the top ranked pairs of regions (out of 54780 connections) in terms of changes in connectivity with age. Our top 30 ranked results pointed to a role for the hippocampus, entorhinal and piriform cortex, and the cerebellum, as well as for the cerebellar white matter and corpus callosum. Extending the list to the top 100 ranked regions helped identify an extended network comprised of 13 gray matter regions, and 4 white matter regions which contributed to distinguishing between the old and young groups. The gray matter regions included: accumbens, amygdala, caudomedial entorhinal cortex, cerebellar cortex, globus pallidus, hippocampus, hypothalamus, piriform cortex, preoptic telencephalon, septum, striatum, superior colliculus, and rest of thalamus. The white matter regions included the fimbrian, corpus callosum, but also the cerebellar white matter, the inferior cerebellar peduncle. We found an overlap between these regions and those distinguishing mouse models of AD from their age matched controls, in particular for the piriform cortex, hippocampus and cerebellum. Advanced bundle analytics improved the sensitivity and resolution to changes in specific connections. Our results suggest that regions commonly involved in age related neurodegeneration, as well as the cerebellum may play a role in age related vulnerability.

References

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