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Heritability of imaging phenotypes from combined magnetic resonance and light sheet microscopy

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Magnetic resonance histology (MRH) has a resolution 2–3 million-fold higher than clinical MRI. Here we have used MRH with diffusion tensor imaging (DTI) to systematically estimate heritabilities of brain structures and connectomes in sex-balanced cohorts of mice (PM:32818613). Brains are imaged in the skull to ensure high geometric accuracy. In initial work, eight each of C57BL/6J, DBA/2J, CAST/Ei, and BTBR were scanned at 45 µm using a high performance 9.4 T connectome MRI. We extracted volumes, scalar DTI metrics, and connectomes for 166 regions of interest bilaterally using a novel workflow. Volumes were highly heritable across almost all regions. Errors of h^2—estimated by resampling—are generally ±0.1–0.2. Sex differences were negligible. Fractional anisotropy was highly heritable in cerebellar white matter and neocortex. Roughly 280 of 332 connectome subnetworks had significant heritabilities and ~150 remain so even when excluding the acallosal BTBR. We are now reimaging cases using SHIELD light sheet microscopy (PM:30556815) with LifeCanvas Technology to get subcellular cytoarchitectural phenotypes for many isogenic BXD progeny strains (PM33472028). Brains are dissected, cleared, and stained for Syto-16,NeuN, MBP and other markers; and scanned at in-plane resolution of 1.8 µm. We use a custom *big-image data infrastructure* (BIDI) to register all 3D data (~ 1.5 TB/brain) into a common reference atlas adapted for diverse genometypes. Image-based phenotypes like those of the ENIGMA and UKBiobank can now be derived in systematically controlled genetically diverse FAIR models to study GXE, addiction, aging, and neurotoxicology.