Many life scientists eagerly await new imaging techniques for the large-scale, high-resolution, three-dimensional (3D) reconstruction of intact brain. However, 3D imaging at high resolution requires laborious mechanical serial sectioning or optical sectioning which is limited by light scattering due to tissue opacity. Due to these constraints, current technologies simply cannot achieve 3D reconstruction of large brain structures. In contrast, optical and fluorescence tomographic technologies can image large areas of tissue, but lack the subcellular resolution afforded by serial or optical sectioning approaches. Thus, there is a great gap in the practical coordination of sufficient scale and resolution of 3D reconstruction between these two types of imaging technologies. We address this technological gap with a simple and powerful technique that is easy to use and, we believe, will be widely and rapidly adopted by the neuroscience community [1]. The Scale technique for clearance of biological tissue, which we report in this paper, enables us to perform high-resolution 3D reconstructions of millimeter scale brain structures. Remarkably, the maximum depth of imaging is now limited only by the working distance of the objectives used. For example, we perform 3D reconstructions of entire neural circuits in fixed, unsectioned mouse brain samples where specific cell types are labeled with fluorescent proteins. It is important to note that the Scale clearing solution completely preserves the signals of fluorescent proteins allowing sweeping views of axon projections and dendrite arbors over millimeter-scale distances throughout the brain. We feel this technical innovation could help to promote a new era of neural circuit genetics and “projectomics”, new approaches to behavioral anatomy, and alternate technical strategies for large-scale brain connectomic mapping. However, I should note that applications of the Scale technique will go well beyond neuroscience into the realm of systems biology as it is applicable in principle to any biological tissue or organism, indeed as we show with images of intact mouse embryo. [1] H. Hama et al., “Scale: a chemical approach for fluorescence imaging and reconstruction of transparent mouse brain,” Nat. Neurosci. 14, 1481-1488 (2011).