The fiber pathways of the brain organized as a highly curved woven grid

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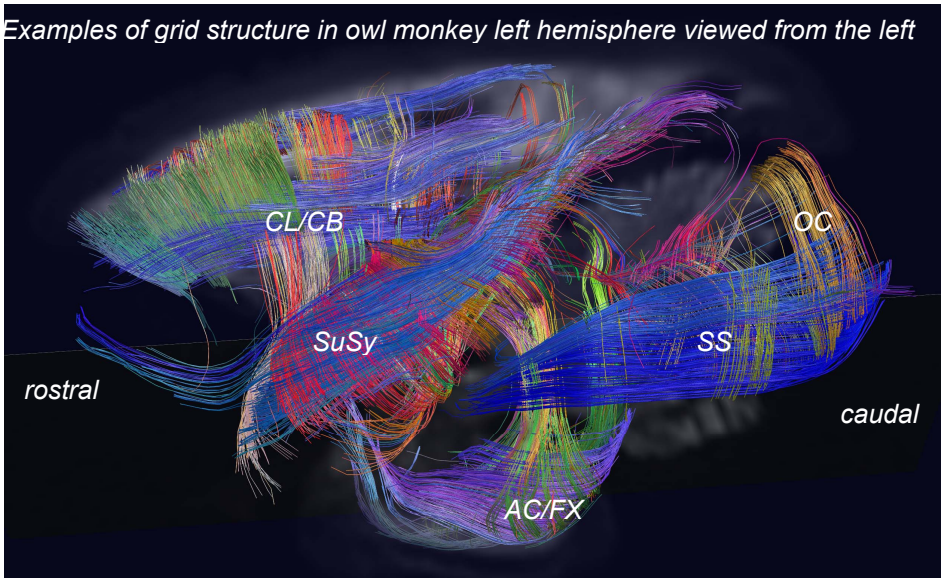
Introduction: Our understanding of the large-scale structure and organization of the fiber pathways of the brain, or connectome, derives from two principal approaches - microscopy which reveals 3D structure, and tract tracing which reveals long-range connectivity. While complementary, a synthesis of their perspectives is challenging and incomplete. To better understand the 3D organization of the fiber pathways of the brain, we performed ex-vivo diffusion spectrum MRI (DSI) of fixed whole brain specimens of 11 mammalian species of several orders, including primates. With interactive software, we performed a novel analysis of the relations of 3D spatial adjacency between reconstructed fiber pathways, displaying for any pathway the set of all other pathways that approach it to within 1 voxel in the spatial image. This is termed its "path neighborhood" as is equivalent to a topology on the space of paths.

We find such neighborhoods to be astonishingly well organized as 2D sheets of parallel pathways in two orthogonal directions that together form a 3D grid. Moreover, this motif extends coherently over the totality of cerebral fiber pathways of the entire CNS. Validation is provided by internal consistency, specifically that path rectangles form closed loops rather than open spirals in three-dimensions, whose *a priori* probability is vanishingly small (by the Frobenius theorem of differential geometry). Accordingly, we conclude that the connectome approximates a highly curved 3D woven grid of parallel pathways that cross orthogonally in 3 axes continuously aligned with the developmental axes – longitudinal, transverse and dorso-ventral - of the bilaterian body plan.

Method: DSI was obtained at 4.7T in perfusion-fixed whole-brain specimen, including 4 non-human primates, 2 carnivores, and 2 euarchontoglires. Human tissue specimens were also scanned. The DSI used an SE sequence, TR/TE 1000/70 ms, hybrid 3DFT/EPI spatial encoding, isotropic spatial resolution 350-450μm, diffusion encoding time Δ/δ 22/14 ms, and DSI encoding in a cubic lattice of 515 gradient values out to a limiting sphere of radius b_{max} = 38,000 s/mm^2, and total scan times of 14-21 hrs. Following reconstruction, path tracking was performed for each data set with first-order streamline tractography, and analyzed using TrackVis software augmented by functionality to compute the path neighborhood of any chosen pathways.



Owl monkey cerebral path neighborhoods as parallel grids: supra-sylvian(Su/Sy); corpus callosum/cingulum bundle (CC/CB); anterior commissure/fimbria-fornix (AC/FX); sagittal stratum (SS); occipital (OC).

Results: Figure 1 shows local grid structure of fiber pathways in four regions of the cerebral white matter of the owl monkey - frontal, occiptal, callosal, and mesial temporal. Colored paths have been given white stripes to highlight structure. Paths in each region form a sheet of orthogonal pathways which subsume most or all intra-cerebral pathways. These paths belong to two orthogonal families of longitudinal and transverse paths that almost everywhere cross at near right angles. In addition, projection pathways from cortex to thalamus and midbrain form a 3rd orthogonal axis. Infrequent turns between cardinal axes are also noted. This motif is found in all species studied, throughout the entire CNS, including basal ganglia, cerebellum, and brainstem.

Conclusions: Analysis of path neighborhoods in MRI forms a bridge to 3D structure, and to global geometric order of cerebral connectivity. This analysis would be difficult or impossible with previous methods. We find to an excellent approximation, the pathways of the cerebral connectome are organized as a highly curved orthogonal 3D grid derived from the body axes. Thus, the complexity of the connectome as a network emerges from a simple geometric order - biological Cartesian coordinates - observed at all scales, expressing its local order as well as its global relation to the bilaterian body plan. This order sheds light on the evolution, development, and adaptation of the brain, the topography of cortical specialization, and the spatial-temporal coherence of neural coding, and should facilitate the quantitative comparative analysis of the brain across species and human subjects.