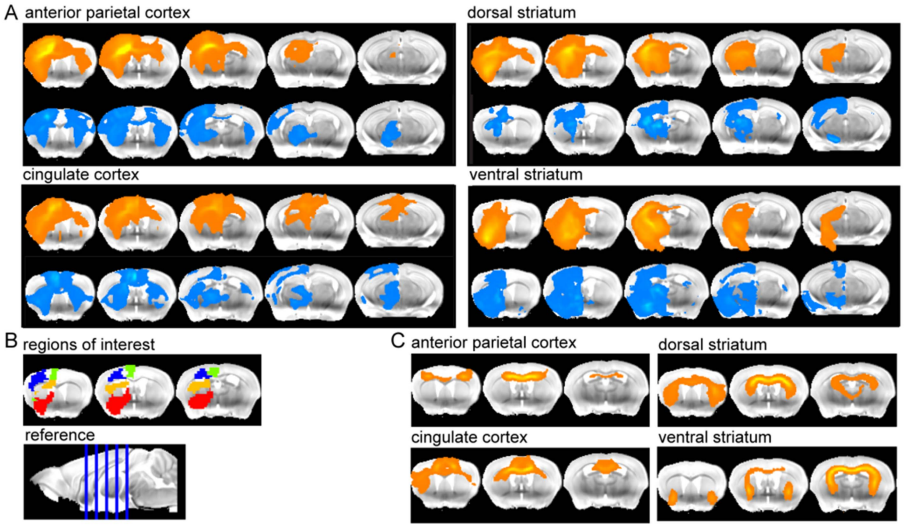
# The structural connectivity basis for supporting functional connectivity in mice

Joanes Grandjean[1], Zsófia Pröhle[2], and Markus Rudin[1,3]

*[1]Institute for Biomedical Engineering, ETH and University Zurich, Zurich, Switzerland, [2]Department of Physics, ETH Zurich, Zurich, Zurich, Switzerland, [3]Institute of Pharmacology and Toxicology, University Zurich, Zurich, Switzerland*

Resting-state fMRI (rs-fMRI) offers insights into the functional connectome, although the nature of the elucidated networks remains elusive. An important finding is that regions that are functionally connected do not necessarily also present direct structural connections as shown e.g. for bilateral extra-striate cortexes as part of the visual network in humans[1]. Similarly, the caudate-putamen, which is part of the dorsal striatum network in mice, appears as bilateral structure with rs-fMRI[2], despite the absence of direct synaptic connections between the two hemispheres. While an intermediately region could relay the functional information between the two regions, such a putative region is not apparent on the functional network maps of these networks. Such observations raise the questions of the nature of the substrate supporting the functional networks commonly observed in humans and in rodents, and highlight the importance of structural-functional correlations.

Independent component analysis (ICA) was performed on rs-fMRI data of isoflurane+medetomdine anesthetized C57/B6 mice[2], components were extracted, from which unilateral regions-of-interest (ROIs) were defined. Diffusion tensor imaging (DTI) data was acquired in 14 C57/b6 mice using a 9.4T scanner (Bruker BioSpec 94/30) equipped with a 2x2 phased-array cryogenic receiver coil and a BGA12S gradient system capable of a maximum gradient strength of 400 mT/m with a 80 ms rise time. A DTI echo planar imaging (DTI-EPI) sequence was used with repetition time 3000 ms, echo time 25 ms, pulse angle 90°, matrix dimension 128x128, pixel dimensions 160 x130 $\mu m^2$, slice thickness 500 µm, interslice distance 200 µm, number of slices 14, *b0* value of 1000 s/mm2, 36 diffusion encoding directions, 1 average. DTI images were processed with FSL (FMRIB, Oxford, England), linear and non-linear transformations to a reference image were computed using the intensity images. Probabilistic tracking was applied using BEDPOSTX and PROBTRACKX for FSL. Connectivity data from the Allen Brain Institute derived from viral injection experiments[3] were compared to the probabilistic tracking maps derived from DTI. Injections sites identified within the ROIs were used to download the corresponding structural connectivity maps using the application programming interface. The maps were transformed to a common space and averaged.




We observed a good correspondence between the probabilistic tracking and viral injection-based connectivity maps (**A**, DTI-based connectivity = orange, injection-based connectivity = blue) for the ROIs considered (**B**, anterior parietal cortex = blue, cingulate cortex = green, dorsal striatum = orange, ventral striatum = red). In particular, injection-based connectivity maps indicate no contralateral projections from the injection sites in the dorsal and ventral striatum regions. Discrepancies between DTI-based and injection-based connectivity may relate to the bias of the different approaches, such as low fractional anisotropy values in some tracks, poor spatial resolution, poor identification of crossing fibers and distance-bias to the ROIs for DTI-based connectivity, and monosynaptic labeling for injection-based connectivity. Tractography analysis was then performed between the pairwise bilateral components of the functional networks to identify tracks involved (**C**). The corpus callosum was identified in all 4 ROIs. For the ROIs located in dorsal striatum network there was also evidence for structural connection via the thalamus.

In all networks assessed, DTI-based tractography identified connectivity across the two hemispheres, despite the absence of direct contralateral monosynaptic connections in the regions part of the dorsal and ventral striatum network. Relay regions are critical for supporting the bilateral functional organization of these networks, either via cortical or thalamic connections; however, such relay regions have not been identified as part of functional networks as derived from rs-fMRI. A comparison with acallosal mice, or following targeted lesions induced in the murine brain may help to identify the necessary elements supporting the organization of specific functional networks. Such studies may play an important role in our fundamental understanding of the functional networks with implications in the study of the connectome in rodents and in humans.

1) van den Heuvel et al. Hum Brain Mapp. 2009 Oct;30(10):3127-41 2) Grandjean, Schroeter et al. Neuroimage. 2014 Aug 28;102P2:838-847. 3) Oh et al. Nature. 2014 Apr 10;508(7495):207-14