Connectome-wide association of resting fMRI and 18-FDOPA PET in healthy adults

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Background: Dopamine is a neurotransmitter with widespread actions throughout the brain, including modulatory effects on executive, motor control, and reward circuits. It is also implicated in a number of human pathologies, such as psychosis, addiction, Parkinson’s disease, and ADHD. Despite the widespread effects of dopamine and its importance in human disorders, few studies have examined the relationship between dopamine functioning and intrinsic brain connectivity. Here, using resting state fMRI and [18F]-fluorodopa (FDOPA) positron emission tomography (PET), a method for directly measuring regional dopamine synthesis and storage capacity in vivo, we performed a connectome-wide association analysis (CWAS) to identify brain regions where functional connectivity was associated with FDOPA uptake (Ki).

Methods: Seventy-six healthy adults (mean age 39.6±13.4 years, 36 males) underwent 12 minutes of 3T resting fMRI (TR/TE=2000/24ms, 184 images) and FDOPA PET (16 mCi, 27 dynamic scans over 90 minutes). fMRI preprocessing steps included motion correction, normalization to MNI space, censoring of corrupted volumes, anatomic CompCor, and bandpass filtering (0.008<f<0.1 Hz). For PET scanning, FDOPA tracer uptake (Ki) was measured using the Patlak-Gjedde method and a cerebellar reference region. A CWAS analysis was performed to determine voxels where connectivity was associated with FDOPA Ki values, extracted from bilateral ROIs in dopaminergic brain centers (midbrain, ventral striatum, pre- and post-commisural caudate, and pre- and post-commisural putamen). Data were corrected for multiple comparisons (p<0.05) based on 10,000 Monte Carlo simulations and a p<0.005 uncorrected voxel-wise threshold.

Results: Midbrain FDOPA Ki was significantly associated with resting state connectivity of bilateral caudate extending to the ventral striatum. Post-commisural caudate Ki was associated with posterior cingulate connectivity. FDOPA Ki values extracted from pre-commisural caudate and post-commisural putamen were both associated with resting connectivity of a nearly identical region in the left DLPFC. FDOPA Ki values from ventral striatum and pre-commisural putamen showed no significant associations with resting connectivity in any regions. Post-hoc seed-based analyses using ROIs from the CWAS results to examine resting state connectivity patterns revealed that the findings with midbrain and post-commisural caudate Ki were driven by connectivity of the identified striatal and posterior cingulate regions with motor and dorsal attention networks, whereas pre-commisural caudate and post-commisural putamen results were driven by connectivity of DLPFC with fronto-parietal and default networks.

Conclusions: Here, we show that regional dopamine tone is associated with the intrinsic functional connectivity of the human brain. The regions in which whole brain resting state connectivity correlated with dopamine tone are known from preclinical studies to be important hubs of dopamine innervation. Further characterization of this relationship, in both health and disease, may help to characterize neuropathologic mechanisms and provide biomarkers for diagnosis and treatment.