Functional brain imaging tools have proven valuable in the study of the cognitive impairment in PD. Recent advances in imaging methodology and analysis have provided novel insights into the pathophysiology of cognitive decline in these patients. To identify metabolic brain networks associated with PD, we have applied a voxel-based spatial covariance approach to the analysis of functional imaging data. This approach allows for the identification of abnormal disease-related metabolic patterns (i.e., brain networks) and the quantification of the expression of known patterns (i.e., network activity) in individual subjects. Specific metabolic networks have been found to mediate the motor and cognitive aspects of PD. These networks have been demonstrated to be robust descriptors of the parkinsonian disease processes.

The motor manifestations of PD are associated with a highly reproducible disease-related spatial covariance pattern (PDRP) characterized by relative metabolic increases in pallidal, ventral thalamic, and pontine areas, associated with reductions in premotor and posterior cortical association regions. PDRP has been shown to be consistently correlated with standardized ratings of motor disability, and has been extensively validated as a treatment biomarker. A separate cognition-related spatial covariance pattern (PDCP) has also been identified and validated in non-demented PD patients. This pattern is characterized by metabolic reductions in frontal and parietal association areas, associated with relative metabolic increases in the cerebellum. Both the PDRP and PDCP have excellent test-retest reproducibility. The PDCP has been demonstrated to correlate with neuropsychological measures specifically associated the subcortical dementia syndrome. Network expression is most strongly associated with performance on tests of memory and executive functioning. A relationship with visuospatial and perceptual-motor speed has also been found. The PDCP does have some overlap with the PDRP, with approximately 15% of region weight variability shared across the two patterns. That said, the activity of these metabolic networks in individual subjects has proven to be dissociable at multiple levels. In longitudinal studies, we documented that PDRP expression is elevated in early disease, whereas a significant degree of PDCP network expression cannot be discerned until approximately six years after symptom onset. In other words, net-
work expression parallels symptom onset with the motor manifestations preceding cognitive dysfunction. In addition, PDRP expression is sensitive to pharmacologic and surgical therapies directed at the motor manifestations of the disease. On the other hand, PDCP expression remains stable with these interventions, consistent with the lack of a treatment effect on cognitive functioning based on repeated psychometric testing.

Subsequent studies have suggested that the PDCP is sensitive to early cognitive decline. PDCP activity was found to increase in a stepwise fashion with worsening cognitive performance. Healthy control subjects had lower PDCP expression than PD patients without MCI, who in turn had lower values than those with cognitive impairment. Moreover, patients with single domain mild cognitive impairment (MCI) maintained an intermediate position between those with involvement of multiple cognitive domains and those without cognitive impairment. PDD patients exhibited greater PDCP elevations than those with multiple-domain MCI.

The anatomic regions that contribute most to the PDCP network are the medial aspects of the lateral frontal and parietal association areas, and therefore somewhat reminiscent of the “default mode network.” Therefore, it is possible that abnormal elevations in PDCP activity denote reduced capacity to allocate neural resources, as well as a diminution in cognitive reserve. Given the lack of a significant effect of levodopa on mean PDCP expression, this network is unlikely to be a simple reflection of mesocortical dopaminergic dysfunction. Current research is addressing non-linear, baseline-dependent effects of PDCP expression on determining the cognitive treatment response to dopaminergic medication. Potential modifying factors such as the val/met COMT haplotype and disease-related alterations in caudate vs. putamen dopaminergic inputs are also under investigation.