

The Quest for a Selective Mapping Between Striatal Dopamine Subcircuits and Psychosis Symptoms

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Dopamine has been thought to play a key role in psychosis since the 1960s (1). Confirming this hypothesis, experiments demonstrated the dopamine receptor binding of antipsychotics and the psychotogenic effects of dopamine agonists. Models of psychosis were then further refined by in vivo imaging studies of dopaminergic function that localized dopaminergic dysfunction to the striatum using techniques such as positron emission tomography (PET) (2). Converging evidence across studies indeed points to a consistent increase in dopaminergic function (particularly dopamine release and synthesis capacity) in the striatum of patients with schizophrenia compared with control subjects, with a meta-analytic effect size (Cohen's d) of 0.68 (2).

Critically, these increases in striatal dopaminergic function are not homogeneous across the whole striatum but tend to predominate in the associative striatum (AST) and sensorimotor striatum (SMST) subregions, compared with the limbic striatum (LST) subregion, consistent with a selective role of specific striatal subcircuits in the pathophysiology of schizophrenia and psychosis. Furthermore, the domain of positive symptoms (hallucinations and delusions) has been most consistently linked to increased dopaminergic function through pharmacological studies, and specifically to increased dopaminergic function in the striatum through PET studies (1), with some studies suggesting a transdiagnostic relationship to symptom severity across various psychotic disorders (3).

While the link between psychosis and striatal dopaminergic hyperfunction is well established, the roles of distinct functional subcircuits within the striatum have been relatively understudied. Evidence for functionally distinct cortico-striato-thalamo-cortical circuits that are modulated via separate dopamine pathways (1) motivated the intuition that dopaminergic dysfunction in specific subregions maps onto distinct behavioral or symptom domains (which we will refer to as “subregion-symptom mappings”)—e.g., dysfunction in subregions of the striatum connected to the dorsolateral prefrontal cortex may cause working memory deficits, while dysfunction in the LST may cause amotivation. This influential notion drove important refinements in the definition of striatal subregions-of-interest afforded by higher-resolution PET studies that moved from dopamine measurements in the whole striatum to measurements in anatomically defined functional subdivisions: the LST, the AST, and the SMST (4). While the anatomically based subdivisions were critical in refining models of psychosis and were rooted in strong preclinical work, their reliance on coarse, fixed landmarks stands in contrast with the soft and interindividually variable boundaries that likely exist between subregions. More technically, measures of dopaminergic

function in the three anatomical subdivisions correlate highly with each other, hampering investigations into selective subregion-symptom mappings. Perhaps because of these limitations, previous studies have failed to identify consistent subregion-symptom mappings (with the possible exception of a relatively consistent link between AST dopaminergic function and positive symptoms) and have not established a role for striatal dopaminergic dysfunction in cognitive and negative symptoms.

The limitations in current methods call for more refined parcellations of the striatum to elucidate subregion-symptom mappings in schizophrenia. In this issue of *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, McCutcheon *et al.* (5) provide a first attempt at solving this important problem by integrating subject-specific functional parcellations of the striatum based on resting-state functional magnetic resonance imaging (rs-fMRI) with ^{18}F -DOPA PET imaging of dopamine synthesis capacity in patients with first-episode psychosis. In short, after assigning cortical nodes to one of six networks (the default mode, sensorimotor, cingulo-opercular, dorsal attention, auditory, and visual networks) based on group-level rs-fMRI functional connectivity profiles, striatal voxels for each individual are then assigned a weight denoting their mean rs-fMRI functional connectivity to each of the six networks (resulting in six scores per striatal voxel, each indicating how strongly a voxel loads on the corresponding network) (Figure 1). An estimate of network-specific dopamine synthesis capacity for each “striatal network” is then accomplished via a weighted sum of the dopamine synthesis capacity for each voxel multiplied by the corresponding network weight in that voxel.

McCutcheon *et al.* (5) go on to assess the test-retest reliability of their method, both for the striatal parcellation itself and for the resulting network-specific dopamine synthesis capacities. After establishing good test-retest reliability, they attempt to answer the first major question: do their network-specific measures of striatal dopaminergic function minimize intersubregion correlations compared with the conventional anatomical subdivisions (4)? Their new method indeed tends to produce lower correlations in dopamine synthesis capacity between subregions ($r = .23$ – $.67$ compared with $r = .71$ – $.91$), with this decrease reaching statistical significance in most cases. McCutcheon *et al.* (5) then attempt to answer the second major question: do their network-specific measures of striatal dopaminergic function improve subregion-symptom mappings? After grouping symptom scores from the Positive and Negative Syndrome Scale into the five Marder factors (6), they show that dopamine synthesis capacity in the striatal

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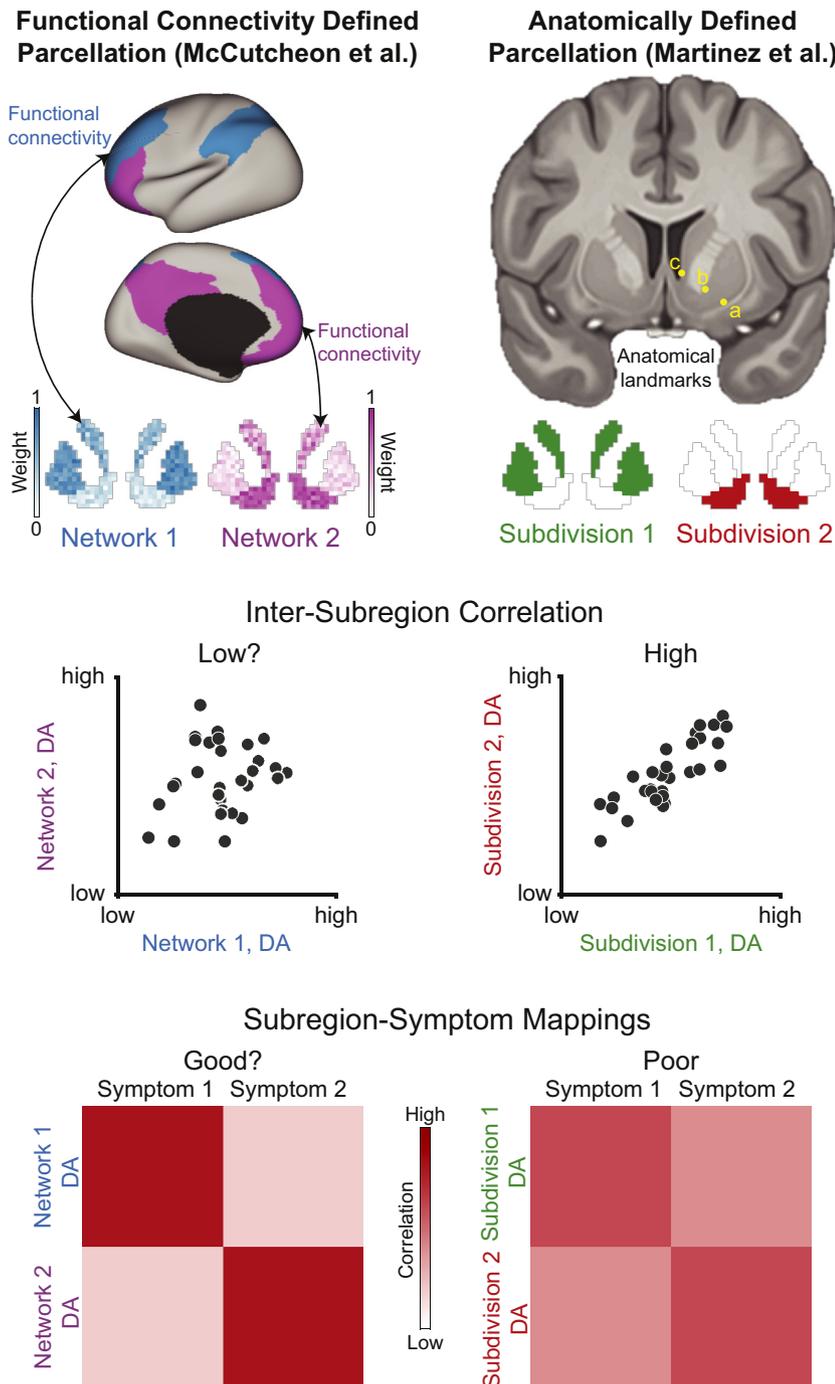


Figure 1. Graphic summary of the method proposed by McCutcheon *et al.* (5) (left) compared with the literature standard (right) and the main questions of their study. A single coronal slice of the striatum (7 mm anterior of the anterior commissure) shows two hypothetical cortical networks with their corresponding functional striatal networks (network 1 and network 2; left) and two anatomical subdivisions of the striatum (subdivision 1, corresponding to the associative striatum; and subdivision 2, corresponding to the limbic striatum; right). The networks, anatomical subdivisions, and two hypothetical symptoms (symptom 1 and symptom 2) are used for demonstrative purposes. In the proposed method (left), weights for each striatal voxel are determined by their functional connectivity—defined by resting-state functional magnetic resonance imaging—to each network. In the standard method in the literature (right), anatomical landmarks (points a, b, and c; identified using the putamen and anterior commissure–posterior commissure line) are instead used to determine hard boundaries between striatal subregions and to generate binary subdivisions. Correlations between dopaminergic (DA) function in each of the subregions (e.g., network 1 vs. network 2, or subdivision 1 vs. subdivision 2) can be investigated to determine their shared variance or orthogonality. DA function in the subregions can also be related to the severity of different symptoms (e.g., network 1 vs. symptom 1, or network 1 vs. symptom 2) to determine subregion-symptom mappings. The goals of the method proposed by McCutcheon *et al.* (5) are to reduce intersubregion correlation of DA function and to improve the specificity of subregion-symptom mappings.

default mode network significantly correlated with both the depression/anxiety and negative symptom factors. In contrast, using the conventional anatomical subdivisions (4), dopamine synthesis capacity in both the AST and the SMST significantly correlated with the depression/anxiety symptom factor, and dopamine synthesis capacity in the AST also correlated with the excitement symptom factor. Surprisingly, the authors failed to detect any relationships with positive symptoms unless

minimally treated participants were removed from the sample; even then, they did not detect a correlation with any network-specific measures and the positive symptom factor, although they did detect a correlation with dopamine synthesis capacity in the AST and the SMST, consistent with the literature. Another surprising finding was the failure to reproduce, in this sample, the well-established difference in dopaminergic function between patients with schizophrenia and control subjects.

Overall, the study by McCutcheon *et al.* (5) provides a novel approach with potential to improve investigations into subregion-symptom mappings. The use of rs-fMRI to define subject-specific probabilistic parcellations of the striatum accounts for interindividual variability in anatomical connections and for the likely overlap and soft regional boundaries in the underlying striatal neurons by allowing striatal voxels to be assigned to more than one network. The authors go a long way in characterizing their method by comparing it with the literature standard (4) and by assessing its reliability. Furthermore, they use sophisticated permutation tests and a robust factorization of symptoms to provide a thorough investigation of subregion-symptom mappings.

In our view, this study represents a cogent first step moving the field in the right direction, but there is always room for improvement. The network-specific dopamine synthesis capacities showed good reliability, but the striatal parcellation for some of the networks was suboptimal (e.g., intraclass correlation coefficient of 0.32 for the dorsal attention network). One possibility for improving this would be to circumvent the cortical node network assignment step by using predefined cortical networks such as those defined by Yeo *et al.* (7). Alternatively, precision mapping of cortical networks through high-density sampling (8) could afford more personalized, subject-specific striatal parcellations. On the other hand, striatal connectivity in schizophrenia exhibits alterations that could be mediated by dopamine, suggesting a potential confound in studying network-specific dopaminergic function that warrants further consideration. Another important consideration for future work will be deriving parcellations that account for specific striatal subregions characterized by their convergent input from several networks (9) and that are thought to integrate convergent information (10), particularly because these areas tend to abound in parts of the AST that are central to psychosis.

A crucial next step for the field is to enhance investigations into subregion-symptom mappings by collecting larger samples that enable the investigation of single-item scores as opposed to symptom factors, which would also benefit from more fine-grained symptom assessments. To overcome the invasive and costly nature of PET studies, larger samples could be achieved through data-sharing initiatives such as those that have become commonplace in MRI research. Lastly, although correlations in dopaminergic function between striatal subregions hinder statistical analyses, it is not clear what these correlations represent. While phasic dopamine signals are likely to be controlled independently in meso-striatal pathways innervating distinct striatal functional subregions, common molecular factors affecting dopaminergic function across these subcircuits (e.g., *DAT1* genetic variants) could account for some of the observed intersubregion correlations in PET dopamine measures. The true test of a method's ability to independently measure striatal subregion dopaminergic function will require specific modulation of dopaminergic function in independent subcircuits. Such preclinical experiments could inform human parcellation methods to disentangle subregion-symptom mappings in psychosis. Ultimately, the ideal method will be one that best captures the underlying, functionally homogeneous subregions of the striatum—

which may or may not correspond to parcels defined by rs-fMRI connectivity with brainwide networks—and not necessarily one that finds more selective subregion-symptom mappings with dopaminergic function; the existence of selective subregion-symptom mappings is precisely the hypothesis that an ideal, independently validated method should be able to falsify. To conclude, the approach by McCutcheon *et al.* (5) represents a solid attempt at solving this long-standing issue, but several relevant questions need to be addressed before it can be adopted as the new standard.

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