Biological Psychiatry: Celebrating 50 Years

Commentary

Connections With Connections: Dopaminergic Correlates of Neural Network Properties

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In major neuropsychiatric illnesses, such as schizophrenia, substance use disorders, and Parkinson's disease, cognitive and behavioral correlates of clinical deterioration are complex. Insufficient knowledge of pathophysiological mechanisms in these conditions is a key impediment to directing the development of disease-modifying treatments, and derives, in part, from an incomplete understanding of normative neural systems operations. Illness-associated alterations in neuroimaging measures of multifaceted neurotransmitter systems, such as that of dopamine, and of composite interactional functional imaging metrics, such as magnetic resonance imaging (MRI)–based interregional correlations in blood oxygen level–dependent signal, have increasingly been investigated as potential discovery-leading phenotypes. However, these important findings rely on systems-level signals that are often challenging to interpret in isolation, and integrative work leveraging complementary imaging modalities and experimental tools in concert is critical to meaningfully advance the comprehension of these neural signals in both health states and disease states.

For instance, the examination of low frequency, spontaneous interregional covariation in blood oxygen level–dependent signal during resting states with functional MRI (fMRI) has established reliable, large-scale neuroanatomically described network components (1). Preclinical data have indicated that such "resting-state connectivity" corresponds to ongoing fluctuations in local field potential and that these fluctuations reflect topographical components of neuronal activity coherence (2); however, specific drivers of systems-level variation in each of these components remain inadequately elucidated. Thus, despite intriguing findings in patient groups (3), the biological significance of most variability in resting-state fMRI network components across individuals is unclear. Neuroanatomical literature in nonhuman primates has documented the broad extent of dopaminergic projections across mesolimbic, mesocortical, and nigrostriatal pathways as well as the prominence of organized corticostriatal recurrent circuitry (4), suggesting that striatal dopamine system properties may be related to the activity of considerable swaths of cortex. If so, it is possible—though not necessarily the case—that such properties are linked to the type of cortical activity indexed by interindividual differences in fMRI-assayed resting-state networks.

In work bridging resting-state fMRI and positron emission tomography measurements, McCutcheon *et al.* (5) provide a valuable step toward characterizing striatal dopamine-related variability in resting-state network connectivity. By examining, in two separate experiments, the resting-state fMRI correlates of both limbic striatal dopamine synthesis capacity (DOPA decarboxylase activity) and dopamine release (D_2 receptor ligand displacement), this study offers strong evidence that basal ganglia neurochemical traits do align with wider network function in the healthy, living human brain at rest. Specifically, a metric of salience network coherence showed positive and negative correlations with limbic striatal dopamine synthesis capacity and dexamphetamine-induced dopamine release capacity, respectively. These findings obtained in two sets of over 20 volunteers and showing substantial effect sizes (Pearson's r^2 values of .26 and .18 for synthesis and release capacity, respectively) help validate the notion that salience network measurements contain (but are not synonymous with) important dopamine systems information. The opposing direction of the release relative to synthesis findings was unexpected by McCutcheon *et al.* (5) and is difficult to predict from existing pharmacological fMRI literature, though in at least one previous study, amphetamine-induced dopamine release corresponded to connectivity decrements in salience executive networks (6), potentially consistent with the direction if not scope of the release findings here. Furthermore, previous experimentation has identified independence of these two measurements when performed in the same individuals (7), indicating that a unidimensional model of basal ganglia function is not sufficient and suggesting that concurrent study of different dopaminergic metrics may be needed to more fully explain variance in large-scale, resting-state network functions.

Given the broad span of meso-cortico-striatal loops and regional importance of dopamine systems to executive, motor, limbic, and other circuitry throughout the cortex, appreciating differential contributions of dopamine systems function to the basal physiology of diverse canonical neural networks and how each of these relationships shapes behavior is a daunting task. By isolating four such networks from resting-state fMRI data and testing for correlations with limbic striatal dopamine positron emission tomography parameters, McCutcheon *et al.* (5) found that associations with limbic striatal dopamine synthesis and release occurred more consistently with the strength of the salience network than with strength of the default mode, sensorimotor, or visual networks. If this specificity is confirmed to be statistically robust, it may present novel insight into the overall signal properties of these large networks and potential biological biases in their regulation.

McCutcheon *et al.* (5) used a graph theory approach to elaborate on comparative dopaminergic correlates of resting-state networks. When parcellated brain regions were classified as to whether they were network hubs (regions showing strong signal correlations with many other regions, participating in a large number of shortest paths between other regions, and showing more connections outside of its local

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cluster), McCutcheon *et al.* (5) found that salience network regions showing associations with limbic striatal dopamine synthesis were more likely to be network hubs than would be expected by chance. This intriguing finding raises questions about the organization of dopamine-linked networks, which could ultimately guide computational models of disease or biomarker development in some way but currently require further study. Whether hubs as defined in this work are more densely innervated by dopaminergic inputs or are more likely to send efferent projections to the basal ganglia is unknown and constitutes an important anatomical hypothesis to test. As this and other reductive complex network analytic techniques are increasingly used in highly dimensional functional data, it will be imperative to engage in experimentation that tethers observations to known biological processes (e.g., dopaminergic mechanisms) and contexts to promote consequential and actionable advancement of neuroscientific knowledge, particularly as related to disease.

Importantly, what can these integrated neurochemical–neurofunctional findings tell us about approaching the pathophysiology of neuropsychiatric disorders? Certainly, as McCutcheon *et al.* (5) and others have pointed out, these systems—i.e., dopaminergic basal ganglia and salience networks—show alterations in several different patient groups and have been particularly well-implicated in some illnesses, such as schizophrenia (8,9). Understanding the normative structure of these key neuroimaging variables is an important foundation upon which to build models of illness and develop biomarkers. Ultimately, these must be tested with comprehensive and carefully integrated multimodal experimentation in patients, as illness-related neural dynamics are anticipated to be complex. For example, previous work has demonstrated that relationships between limbic striatal $D_{2/3}$ dopamine receptor function and meso-cortico-striatal resting-state network connectivity may be markedly different in certain patient populations (10), which suggests that the same could be true for dopamine synthesis and release capacities.

In sum, the results reported by McCutcheon *et al.* (5) integrate neurochemical and neurofunctional experimentation in humans. Such multimodal data, along with advanced computational approaches, are increasingly needed to address unanswered mechanistic questions about systems-level functioning in health and disease.

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References

1. Fox MD, Snyder AZ, Vincent JL, Corbetta M, Van Essen DC, Raichle ME (2005): The human brain is intrinsically organized into dynamic, anticorrelated functional networks. Proc Natl Acad Sci U S A 102:9673–9678.
2. Shmuel A, Leopold DA (2008): Neuronal correlates of spontaneous fluctuations in fMRI signals in monkey visual cortex: Implications for functional connectivity at rest. Hum Brain Mapp 29:751–761.
3. Viviano JD, Buchanan RW, Calarco N, Gold JM, Foussias G, Bhagwat N, *et al.* (2018): Resting-state connectivity biomarkers of cognitive performance and social function in individuals with schizophrenia spectrum disorder and healthy control subjects. Biol Psychiatry 84:665–674.
4. Haber SN (2014): The place of dopamine in the cortico-basal ganglia circuit. Neuroscience 282:248–257.
5. McCutcheon RA, Nour MM, Dahoun T, Jauhar S, Pepper F, Expert P, *et al.* (2019): Mesolimbic dopamine function is related to salience network connectivity: An integrative positron emission tomography and magnetic resonance study. Biol Psychiatry 85:368–378.
6. Schrantee A, Ferguson B, Stoffers D, Booij J, Rombouts S, Reneman L (2016): Effects of dexamphetamine-induced dopamine release on resting-state network connectivity in recreational amphetamine users and healthy controls. Brain Imaging Behav 10: 548–558.
7. Berry AS, Shah VD, Furman DJ, White RL 3rd, Baker SL, O'Neil JP, *et al.* (2017): Dopamine synthesis capacity is associated with D2/3 receptor binding but not dopamine release. Neuropsychopharmacology 43:1201–1211.
8. Eisenberg DP, Yankowitz L, Ianni AM, Rubinstein DY, Kohn PD, Hegarty CE, *et al.* (2017): Presynaptic dopamine synthesis capacity in schizophrenia and striatal blood flow change during antipsychotic treatment and medication-free conditions. Neuropsychopharmacology 42:2232–2241.
9. Gohel S, Gallego JA, Robinson DG, DeRosse P, Biswal B, Szeszko PR (2018): Frequency specific resting state functional abnormalities in psychosis. Human Brain Mapp 39:4509–4518.
10. Kohno M, Okita K, Morales AM, Robertson CL, Dean AC, Ghahremani DG, *et al.* (2016): Midbrain functional connectivity and ventral striatal dopamine D2-type receptors: Link to impulsivity in methamphetamine users. Mol Psychiatry 21:1554–1560.