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Commentary

Multiscale Analysis to Explore Neural Bases of Clinically Relevant Cognitive Processes

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Individuals present for care because of symptoms, not diagnoses. This is especially true for psychiatric disorders, which demonstrate significant symptom heterogeneity within and shared features across diagnostic groups. That is, patients who ultimately come to carry a wide range of diagnoses may initially present with concerns related to fundamental cognitive processes, such as working memory, inhibitory control, or social cognition. This has, in turn, motivated a recent focus on these dimensions of function, each with putatively distinct neurobiological underpinnings, and on the manifestations of anomalies in corresponding neural circuitry (1). Understanding the neural bases of these processes holds the promise of alleviating symptoms and minimizing functional impairment.

In the current issue of *Biological Psychiatry: Global Open Science*, Patel *et al.* (2) explore one such domain in schizophrenia: social cognition. In particular, Patel *et al.* seek to characterize neural correlates of visual social perception in healthy control subjects and patients with schizophrenia. Anomalies in early visual processing (e.g., motion perception) have been demonstrated in schizophrenia, contributing to deficits in social cognition (e.g., face emotion recognition) (3). Patel *et al.* build on a body of work from their group and others that 1) proposed the temporoparietal junction/posterior superior temporal sulcus (TPJ-pSTS) as a hub in a pathway crucial for social perception (4); 2) demonstrated altered activation, functional connectivity, and behavioral correlates of activity in this pathway in schizophrenia (5); and 3) found that visual search task performance tracks engagement of the attentional control system in individuals with schizophrenia but not in healthy control subjects (6). From these results, they propose a model of social cognition in schizophrenia: visual processing anomalies alter patterns of activity in the TPJ-pSTS pathway, resulting in increased compensatory reliance on prefrontal systems.

To pursue this model, Patel *et al.* (2) first identified brain regions activated by 3 tasks, each of which represents a system involved in visual social perception: face emotion recognition, visual processing and attention, and theory of mind. From average activation gradient maps, they derived 98 regions of interest and assigned them to 28 systems.

These were used in subsequent functional connectivity analyses. The authors first conducted a groupwise comparison of functional connectivity, finding decreased functional connectivity within face processing and pSTS systems in individuals with schizophrenia relative to healthy control subjects. They then leveraged a graph theory metric—weighted shortest path length (wSPL)—as a proxy for the efficiency of communication within these systems, focusing on paths connecting visual to theory-of-mind components. This revealed two pathways, one that passes through the TPJ-pSTS and one that passes through the prefrontal cortex. In healthy control subjects, the shortest path between these components more frequently passed through the TPJ-pSTS than the PFC, while the opposite was true in individuals with schizophrenia. With these paths in hand, the authors then explored which steps in each path—that is, component–component edges—are most related to the wSPL of the corresponding path. In the TPJ-pSTS pathway, they found pSTS–middle TPJ functional connectivity to track wSPL in healthy control subjects but not in individuals with schizophrenia. Conversely, in the PFC pathway, they found visual-to-dorsal attention network and dorsal attention network–to-prefrontal cortex functional connectivity to track wSPL in individuals with schizophrenia but not in healthy control subjects. Together, these results suggest specific differences in functional connectivity that may explain a shift in the balance of TPJ-pSTS versus PFC pathway use in schizophrenia.

Finally, to test for functional implications of these differences, the authors applied intersubject correlation (ISC) analysis (7) to data collected while a subset of the sample watched a movie, quantifying the similarity of individuals' posterior TPJ (TPJp) activity to healthy control subjects' movie-evoked TPJp activity. ISC values were then related, via correlation and stepwise regression, to pathway functional connectivity; TPJ-pSTS pathway functional connectivity was correlated with movie-evoked TPJp activity in both groups, while PFC pathway functional connectivity was correlated with movie-evoked TPJp activity only in individuals with schizophrenia. That is, for individuals with schizophrenia, greater PFC pathway functional connectivity tracked increased similarity of movie-evoked TPJp activity to healthy control subjects' TPJp activity. Together, these results suggest that the passage of information along the TPJ-pSTS pathway is related to TPJp activity during visual social inference, and that in schizophrenia, the balance between this pathway and an alternative, possibly compensatory PFC-based pathway shifts, with relatively more use of the latter.

This work makes contributions in several domains. First, it demonstrates an important methodological point: leveraging multiscale analysis approaches in creative combination advances the insights that can be gained from each (Figure 1A). Here, the authors used activation during localizer tasks to draw boundaries around functionally relevant brain regions, functional connectivity of these regions to characterize their organization into paths, and ISC to test the functional importance of these paths. Standard parcellations may blur task-induced

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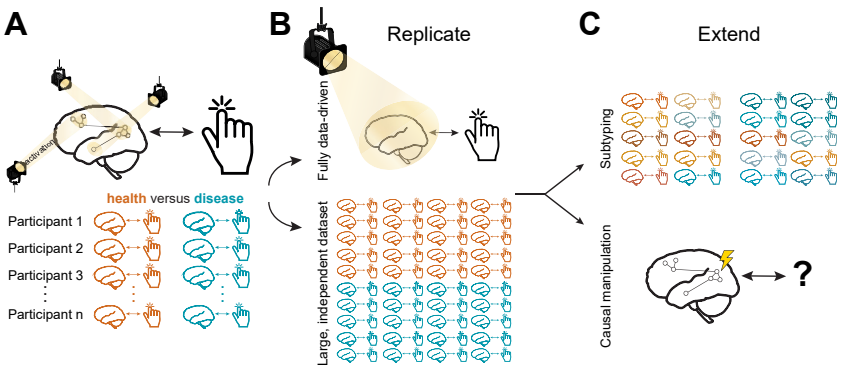

Figure 1. A framework to characterize and apply clinically relevant brain–behavior relationships (BBRs). **(A)** Analyses at multiple spatial scales (e.g., task activation, symbolized by spotlights, to identify regions of interest, paired with functional connectivity within and between these regions) can identify relationships between brain activity (left) and behavior (right), as well as differences in these relationships between participants with and without a given diagnosis. Note that regions and connections are for illustration and do not represent the specific results of Patel *et al.* (2). **(B)** Replication of these relationships in fully data-driven analyses (e.g., whole brain) (top) and large, independent samples (bottom) demonstrates their robustness and generalizability. **(C)** To maximize their clinical utility, BBRs' disease and subtype specificity should be explored. For example (top), a BBR characterized in a given group (e.g., without [orange] or with [teal] the diagnosis of interest) may not apply equally to all individuals in that group (degree of expression represented by shade), with some individuals' data more closely resembling that of the other group or reflecting a distinct BBR altogether. These analyses will make it possible to ask such questions as: to what extent is a given macroscale brain circuit associated with a given behavior in this individual? In addition, manipulations that perturb the identified circuit and measure resulting changes in brain activity and behavior (symbolized by the question mark) will confirm causality and inform clinical intervention (bottom).

changes in boundaries of functionally specialized brain regions (8); by using activation-based regions of interest, Patel *et al.* (2) were able to more precisely identify and subdivide regions by function (e.g., divide the TPJ into the TPJ anterior, middle, and posterior), with individual differences in such boundaries representing an opportunity for future work. Their parcellation, in turn, renders subsequent analyses more informative, e.g., by ensuring that time courses for functional connectivity and ISC analyses are derived from functionally homogeneous and interpretable regions. Similarly, the focal and distributed functional connectivity, as well as activation, analyses enhance the interpretability of each: decreased pSTS functional connectivity is associated with relatively decreased reliance on the TPJ-pSTS pathway in schizophrenia. This offers network context for a focal difference, with functional implications explored via ISC.

A related, albeit more general, methodological strength of the work is the use of constrained data-driven analyses. For example, while a more exploratory analysis, as is often used in functional connectivity–based studies, might identify all significant differences in whole-brain functional connectivity patterns between individuals with schizophrenia and healthy control subjects, Patel *et al.* (2) used previous work in schizophrenia to confine their search to brain regions involved in visual social perception. Similarly, they performed a theory-driven network analysis tracing pathways from visual to theory-of-mind brain regions, rather than using network metrics such as whole-brain modularity or density to characterize global connectivity patterns. While both fully hypothesis-driven and exploratory analyses have demonstrated utility, theory-driven constraints on their exploratory analyses allowed Patel *et al.* to boost analysis power and explore a specific theory while minimizing assumptions—at the expense, of course, of discovering unexpected group differences. This trade-off reflects the complementary nature of theory-driven and exploratory analyses, consistent with a call for hybrid approaches in computational psychiatry [e.g., (9)]. Further, replication of the findings of Patel *et al.* in fully data-driven follow-up work (e.g., testing the relationship between TPJp ISC and whole-brain functional connectivity in each group; Figure 1B, top) would strengthen their conclusions that the TPJ-pSTS pathway is critical for visual social inference, less accessible in schizophrenia, and supplemented by the PFC pathway.

Finally, Patel *et al.* (2) characterize differences in functional brain organization in schizophrenia and link these differences to observed functional impairment (Figure 1A). By advancing our understanding of the macroscale neural circuitry associated with a core, disease-relevant cognitive process, such work moves us closer to targeting this circuitry for therapeutic intervention. But to bring such clinical applications within reach will require future work, the steps of which comprise a general framework for translational cognitive neuroscience. First, as the authors point out, results must replicate in independent and larger samples to ensure their generalizability (Figure 1B, bottom). Second, and relatedly, case-control studies assume homogeneity of each group, but psychiatric diagnostic groups are notoriously heterogeneous and likely reflect many distinct pathophysiological processes. Conversely, impairments in social cognition may transcend diagnostic groups. Together, this suggests the promise of follow-up work to investigate the existence of disease subtypes and the disease specificity of alterations in TPJ-pSTS and PFC pathway balance (Figure 1C, top). Ultimately, these are also questions of generalizability that will prove crucial to moving human neuroscience from the bench to the bedside. A third step toward clinical utility is demonstration of causality, via either invasive (e.g., deep brain stimulation) or noninvasive (e.g., real-time neurofeedback, transcranial magnetic stimulation, vagus nerve stimulation, or focused ultrasound) intervention (Figure 1C, bottom). While a shift to reliance on the PFC over the TPJ-pSTS pathway is plausibly compensatory, this cannot be unequivocally demonstrated without causal manipulation, a point again noted by Patel *et al.* in their discussion of future directions. For example, repetitive transcranial magnetic stimulation directed at the TPJ-pSTS and PFC pathways, paired with behavioral data (e.g., performance on The Awareness of Social Inference Test) and existing ISC results, would permit exploration of the necessity and interaction of these circuits for normative brain activity patterns during visual social inference, and of the behavioral implications of changing functional connectivity in each pathway. Such an approach has already proved fruitful in the study of and intervention on the negative symptoms of schizophrenia (10).

Overall, Patel *et al.* (2) highlight the utility of leveraging multiple analytic approaches to characterize the neural circuitry associated with a cognitive process known to be altered in disease. With increasingly comprehensive and mechanistic circuit mapping, we move ever closer to an understanding of psychiatric disease that will permit targeted and personalized intervention.

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