Published in final edited form as:

Biol Psychiatry. 2018 July 15; 84(2): e9–e11. doi:10.1016/j.biopsych.2018.05.018.

Missed Connections: A Network Approach to Understanding Psychiatric Illness

Aaron F. Alexander-Bloch,

Department of Psychiatry, Yale University School of Medicine, New Haven, Connecticut

Danielle S. Bassett,

Departments of Bioengineering and Electrical and Systems Engineering, School of Engineering and Applied Sciences, University of Pennsylvania, Philadelphia, Pennsylvania

Department of Neurology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania

Department of Physics and Astronomy, College of Arts and Sciences, University of Pennsylvania, Philadelphia, Pennsylvania

David A. Ross

Department of Psychiatry, Yale University School of Medicine, New Haven, Connecticut

[T]he organ of our psychic life must also contain mechanisms that mediate a general connection of all parts of the psychic workshop among each other. Just the destruction of the psychic personality, of this inner harmony of all the parts of the psychic mechanism...[is] the real fundamental disorder in dementia praecox.

— Emil Kraepelin, *Dementia Praecox and Paraphrenia*

A century ago, Kraepelin described a critical aspect in the experience of people suffering from dementia praecox (what we now call schizophrenia): the sense of a disruption of “inner harmony.” Countless other writers have described this same sense of coming apart internally—from psychiatrists like Eugen Bleuler to the law professor Elyn Saks, who poignantly recounts her own experience with schizophrenia in *The Center Cannot Hold*. But Kraepelin’s intuition went further, connecting this qualitative experience to “the organ of our psychic life” and to the idea of early neuroanatomists (including Carl Wernicke and Theodor Meynert) that psychiatric illness resulted from the disruption of the anatomical fibers that connect different regions of the brain (1).

For many of the intervening years, through the middle of the 20th century, research into schizophrenia focused predominantly on psychological and social models. The treatment of choice was psychoanalysis. But in the past 20 to 30 years, research has shifted back to where it arguably began. There is no longer a question that schizophrenia has deep biological correlates (in addition to legitimate psychological and social ones). An early and widely

Address correspondence to Aaron F. Alexander-Bloch, M.D., Ph.D., M.Phil., Department of Psychiatry, Yale University School of Medicine, 300 George Street, Suite 901, New Haven, CT 06511; aaron.alexander-bloch@yale.edu.

The authors report no biomedical financial interests or potential conflicts of interest.

replicated finding was the increased size of brain ventricles in people with schizophrenia (2), possibly stemming from decreased gray matter volume. Postmortem pathology has shown decreased dendritic spine density, in particular cortical neurons (perhaps accounting for the decreased volume) (3). More than 100 genes have now been shown to confer risk (4).

More recently, a range of imaging studies have illustrated anatomical and functional alterations in virtually every region of the brain, from the cerebellum to the basal ganglia to specific locations within the prefrontal cortex. Many such findings have been paired with theoretical proposals for how a region of interest may play a causative role in disease pathology. But attempts to isolate pathology to a particular brain area may have overlooked a critical possibility: what if the problem is not in any particular region at all, but rather reflects alterations in the connections between regions?

The human brain includes an estimated 100,000,000,000 neurons. These cells connect and communicate with each other using electrical and chemical signals across approximately 1,000,000,000,000,000 synapses. For anyone berating the slow rate of progress of psychiatric neuroscience, it is worth reminding skeptics of the staggering complexity we face. If we counted one synapse an hour, our sun's thermonuclear expansion would destroy the earth before we finished counting the synapses of a single human brain.

Historically, it has not been possible to test hypotheses about brain-wide connectivity. With that many connections, where would one even begin? A key invention, in the wake of the first computed tomography scan (1967), was the advent in the late 1970s of magnetic resonance imaging (MRI). This enabled higher resolution (and safer) 3-dimensional visualization of the brain. Another breakthrough came in the early 1990s with the introduction of functional MRI (fMRI). By taking advantage of differences in the magnetic properties of blood based on its degree of oxygenation and taking advantage of the idea that more oxygenated blood flows to a region when it has higher metabolic demands, fMRI allowed researchers to track localized brain activity overtime. Whereas structural MRI scans were like high-resolution photographs, fMRI now offered the equivalent of a low-resolution movie.

In its early years, most fMRI research focused on task-specific activity in regions of interest, typically as compared with a "resting" condition (in which subjects were sometimes instructed to "just lie quietly with your eyes closed"). Media coverage of these early findings would often display colorful pictures of the brain and describe which areas would "light up" during performance of a particular task. But another critical step forward remained.

In 1995, Biswal *et al.* (5) published a landmark paper whose implications were not fully appreciated at the time. The authors showed that even when subjects were not engaged in a motor task, the fMRI signal still demonstrated correlations over time between different regions within the somatomotor system (5). Later, Raichle *et al.* (6) demonstrated what might seem obvious to people outside the neuroimaging community: the brain remains active even during "resting" conditions. Moreover, certain patterns of activation predominate, including between brain areas now well known as the default mode network

(6)—a system that is integral to autobiographical memory, planning the future, and a range of other functions.

These studies set the stage for a new type of analysis: rather than focusing on particular regions, one could focus on patterns of activity across every region, over time. From this, researchers could infer brain-wide patterns of connectivity. For example, if region A always fires in synchrony with region B, we can infer a relationship between them. The formal term for this type of interaction is a functional connection. We might call a few functionally connected brain regions a circuit and we might call a number of integrated circuits a module. The complete set of functional connections comprises the functional brain network, sometimes referred to as the functional connectome.

The complexity of the functional connectome defies simple visualization and analysis. Luckily for the neuroscience community, mathematicians and physicists had already begun to develop tools to study other complex networks—from the organization of computer circuits and the World Wide Web to global transportation systems to the social networks of humans and other animals. Critically, it may be that basic principles that govern these other systems may, similarly, have evolved in the brain (7) (Figure 1). Just as hub airports optimize the speed and efficiency of travel routes, analogous hubs in the brain may relay messages between localized systems to integrate information across diverse sensory, motor, and cognitive processes. Just as the central processing units of a supercomputer tend to be localized close together in physical space to enhance efficiency of communication in terms of time and energy, modules of the brain with interrelated functions may be anatomically located close to one another. Tellingly, despite the desirability of maximizing the computational potential of limited resources, companies still invest some of these precious resources on backups and redundancies to minimize the potential damage from a localized failure. The brain may be organized with similar safeguards.

Thinking about the brain at this level of analysis allows us to approach psychiatric neuroscience from an entirely new perspective. Historically, by virtue of the tools (and models) available at the time, much of our research focused on specific regions of interest. But what if the early insights by Kraepelin and others were correct? To what extent might network-level models better account for the causes of various psychiatric illness? A review of recent research offers considerable support for this model, including with respect to schizophrenia (8). One notable finding in the patient population (as shown in fMRI studies) is decreased “modularity,” wherein the healthy segregation between network modules is decreased. Put differently, there is a blurring of normal modular boundaries.

The article by Reinwald *et al.* (9) in this issue lends further support to this approach. The authors use an animal model to explore the causal impact of network disruption in a way that could never be done with humans. They reared rats in social isolation and showed that the animals have a reconfiguration of the functional connectome, including a loss of modularity. Intriguingly the rats also manifest a behavioral “isolation syndrome,” which has previously been demonstrated to be reversible with antipsychotics. Notwithstanding the limitations of rodent models of psychiatric disease, epidemiological evidence suggests social isolation and other early life stressors increase the risk of schizophrenia and other neurodevelopmental

psychiatric disorders, likely acting as “second hits” on top of genetic and other risk factors. These data illustrate how network phenotypes could serve as markers of disease vulnerability and perhaps, in humans, the feeling of internal disorder.

A century later, modern psychiatric research seems to have arrived back at Kraepelin’s prescient observation: perhaps schizophrenia reflects the failure of mechanisms that ordinarily integrate the component parts of the “psychic workshop.” Network-based approaches continue to be fueled by increases in the quality and quantity of available information—including from a range of multimodal imaging techniques—and from enhanced analytic models from diverse scientific disciplines (8,10). This work must also be linked to advances in genetics, as network disruption may mediate known genetic risk and provide novel phenotypes for future gene discovery. Especially when using complex methods and models that can be difficult to interpret, scientists must work in concert to ensure reliability and reproducibility of results. Though many challenges remain for this nascent field, viewing schizophrenia from the perspective of network connectivity may allow for new approaches to diagnosis and, one might hope, to new interventions that may help restore our patients’ “inner harmony.”

Acknowledgments and Disclosures

Clinical Commentaries are produced in collaboration with the National Neuroscience Curriculum Initiative (NNCI). David Ross, in his dual roles as co-chair of the NNCI and Education Editor of *Biological Psychiatry*, manages the development of these commentaries but plays no role in the decision to publish each commentary. The NNCI is supported by the National Institutes of Health Grant Nos. R25 MH10107602S1 and R25 MH08646607S1.

This work was supported by National Institutes of Health Grant No. 4T32MH019961-20 (principal investigator, Robert Malison) and the Detre Award from the Yale Department of Psychiatry (to AFA-B) and by the John D. and Catherine T. MacArthur Foundation, the Alfred P. Sloan Foundation, the Army Research Laboratory and the Army Research Office through Contracts W911NF-10-2-0022 and W911NF-14-1-0679, National Institute on Deafness and Other Communication Disorders Grant No. 2R01-DC009209-11, Eunice Kennedy Shriver National Institute of Child Health & Human Development Grant No. 1R01-HD-086888-01, National Institute of Mental Health Grant Nos. R01-MH-107235, R01-MH-107703, R01-MH-109520, and R21-MH-106799, National Institute of Neurological Disorders and Stroke Grant No. 1R01-NS-099348, the Office of Naval Research, and National Science Foundation Grant Nos. BCS-1441502, CAREER PHY-1554488, BCS-1631550, and CNS-1626008 (to DSB).

We thank Amanda Wang for creating the network illustrations.

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Figure 1.

Illustration of basic concepts in network science, also called graph theory, using a simplified air transportation (left) and brain network (right). A network (also called a graph) is a mathematical model of elements that interact or connect. The individual elements are called nodes and are illustrated by circles; these represent airports in the transportation network and areas of the cortex in the brain network (for simplicity, subcortical structures were excluded). The interactions or connections are called edges, and they are illustrated by lines; these represent flight patterns in the transportation network and functional connections between brain regions in the brain network. Some commonly described network properties are illustrated: a node's number of edges is its degree. Particularly high-degree nodes are "hubs"—colored yellow in the figure. The shortest "path length" between two nodes is the smallest number of edges that must be traversed to go from one node to another. Nodes with longer path lengths between them are further apart in network space—an example of a longer path is the green dashed line in each network. Nodes with shorter path lengths between them are closer together in network space—an example of a shorter path is the dark blue dashed line in each network. If a network tends to have short path lengths between all of its nodes, the network has low characteristic path length and high global efficiency. "Modularity" is present in a network when the network can be divided into modules, where nodes within a module tend to have more edges with one another and fewer edges with nodes outside of their module. Although networks can have many modules, the illustrated networks each have two (colored blue and green), which are organized geographically in the airline network and anatomically in the brain network. Many other commonly described network properties are not illustrated. If a node's neighbors (nodes to which it is directly connected by an edge) tend in turn to be neighbors of each other, then the node has a high "clustering" coefficient. A "small world" network has significantly high clustering as well as significantly low characteristic path length. A network with a "rich club" has significant core-periphery structure, where hub nodes preferentially connect with one another, and paths between peripheral nodes tend to pass through this core. These and other network concepts are described in more detail in many recent reviews (7–8,10).