Bayesian Dysconnections

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It is a pleasure to comment on the Greenman et al. (1) study of parieto-prefrontal disconnection in schizophrenia. The authors' work brings together advanced data analytics and theoretical neurobiology to paint a compelling, mechanistic picture of the disintegration of the psyche in schizophrenia. In fact, some of the analyses and constructs are so cutting edge, even the most academic of us might be forgiven for feeling out of our depth. I will therefore use a conversational style to unpack the simplicity and importance of this work and how it cuts across emerging themes in schizophrenia research.

In brief, the authors furnish clear evidence for aberrant belief updating in the kind of higher cognitive processing that people with schizophrenia find particularly difficult. Crucially, the mechanisms that underwrite this difficulty are tied down to specific—and directed—connections from posterior (parietal) parts of the brain, involved in processing numbers, to anterior (prefrontal) parts of the brain responsible for deep (hierarchical) processing and implicit working memory. The authors then validate this selective and pernicious disconnection in terms of its predictive validity, using polygenetic risk for schizophrenia (in control subjects) and a propensity for delusional thinking (in people with schizophrenia). This remarkable finding did not come out of the blue: it inherits from decades—if not centuries—of careful thinking about the psychopathology and pathophysiology of schizophrenia. In what follows, I will briefly rehearse the back story that underwrites this study and then focus on its particular contributions that rest on an eclectic approach to the deficit at hand.

The Back Story: Disconnection and the Bayesian Brain

Greenman et al. (1) have discovered, at its simplest, a particular disconnection between parietal and prefrontal regions that is evinced in a context-sensitive way. In other words, they characterize a failure of functional integration during working memory manipulation, relative to simply maintaining items (i.e., numbers) in mind. In itself, this is important because it is a statement about connectivity, or, more precisely, a functional dysconnection. This notion was articulated formally about three decades ago, notably by the coauthors of the present study (2, 3). The notion of schizophrenia as a d*isconnection* syndrome comes, historically, in two flavors. It can be traced back to the sejunction hypothesis of Wernicke that entails a disruption of the (white matter) "organs of connection" (4). The alternative sort of *dysconnection* can plausibly be attributed to Bleuler (5), who conceived of a more nuanced, context-sensitive functional disintegration that we would currently see in terms of a synaptopathy or, more precisely, a loss of ability to contextualize or modulate synaptic efficacy (6). On this view, macroscopic changes seen in brain imaging and neuropathological studies stem from a primary synaptopathy that, almost inevitably, implicates neuromodulatory systems such as the ascending neuromodulatory transmitters (e.g., dopamine, and its interaction with NMDA receptors, particularly on fast-spiking inhibitory GABAergic interneurons).

Perhaps it is of no surprise that people started taking the dysconnection view more seriously with the advent of whole brain functional imaging, where, for the first time, it became possible to measure effective connectivity in vivo. Interestingly, the dynamic causal modeling procedures used in the Greenman et al. study were originally developed—like statistical parametric mapping—for schizophrenia research. Over the subsequent decades, brain imaging shifted its focus from neophrenology and functional segregation toward the directed (effective) connectivity that underwrites functional integration and the disintegration of the psyche proposed by Bleuler. This is all well and good, but it says nothing about psychopathology and even less about delusions. So where does the story go from here?

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Precision Psychiatry

With the new millennium, the cognitive sciences started to embrace predictive processing as a way of understanding functional brain architectures—and neuronal message passing within that distributed (and usually hierarchical) anatomy (7–9). Predictive processing usually appeals to the notion of the Bayesian brain to emphasize the assimilation of sensory evidence under uncertainty—or its complement, *precision* (9). In brief, this account treats the brain like a little scientist, making inferences about the causes of (sensory) data. These inferences follow naturally from Bayes's rule, which says that the probability of a cause, given some data, is proportional to the probability of the data, given the cause,

multiplied by the (prior) probability of the cause. This offers a crisp and formal way to describe belief updating, where a prior belief is combined with sensory evidence to produce a posterior or Bayesian belief.

Before the advent of predictive processing—e.g., hierarchal predictive coding models of message passing in the brain (10)—functionalist versions of disintegration used notions like aberrant salience, with a nod to the role of dopamine in the reward learning literature (11). Over the past decade, a more precise formalism became available, in which salience could be understood in terms of the reliability or newsworthiness of certain messages or efferents passed along neuronal connections (12). Perhaps the easiest way to understand this is in terms of predictive coding (a.k.a. Bayesian filtering). Put simply, this regards neuronal message passing as exchanges of signals in the service of updating Bayesian beliefs about the causes of sensory input. This usually involves the forward passing of prediction errors to update Bayesian beliefs at higher levels in a cortical hierarchy. These updated beliefs or expectations then generate predictions that descend to lower hierarchical levels, in order to evaluate a prediction error. The key move in this scheme is to note that not all prediction errors are equal. In other words, there are certain situations in which prediction errors convey precise information and others in which they are unreliable (e.g., visually palpating a dark room). This means that the brain has to estimate the precision of prediction errors. This estimation can be regarded as the basis of sensory attention and attenuation (13).

This is interesting. From the purely theoretical perspective of predictive processing, one might imagine that aberrant belief updating and formation—in the setting of a Bayesian brain—will be particularly sensitive to the neuromodulatory mechanisms that set the attentional gain or precision of ascending prediction errors conveyed by forward connections (14). However, this is exactly the endpoint of the functional dysconnection story: namely, an aberrant modulation of synaptic efficacy. This convergent evolution of theoretical and empirical arguments also fits comfortably with treatments of schizophrenia in terms of excitation-inhibition balance in the cortex and the attending synaptic mechanisms (15–19).

A Slight Problem

In the past decade, a whole host of psychiatric and neurological conditions have been explained in terms of a failure to modulate the precision of prediction errors (i.e., neuronal messages). Perhaps the best example here is autism, which is generally ascribed to a failure to attenuate the precision of sensory prediction errors: i.e., a failure of sensory attenuation (14). Without going into detail, this presents an interesting challenge for the notion of delusions (16). If sensory information is afforded too much precision in schizophrenia, then one would imagine that delusional beliefs—that play the role of prior beliefs—would be more susceptible to revision, as they are updated by unattenuated prediction errors. However, much of the phenomenology of delusion formation—and things like jumping to conclusions (20)—suggests an overreliance on higher-level prior beliefs. This suggests that delusional beliefs are more *resistant* to ascending prediction errors, rendering them recalcitrant and immutable. This is currently a focus of many debates and papers. Perhaps one could regard delusion formation as a paradoxical lesion (21). In other words, a failure of sensory attenuation calls for a complementary rebalancing of hierarchical message passing by increasing the precision of prior beliefs. This compensatory pathophysiology means that high-level beliefs would become desensitized to unattenuated prediction errors from below. If this is the right explanation for delusions, what would one expect to see empirically?

Disconnections of a Certain Kind

We would expect to see a context-sensitive reduction in the influence of a lower (e.g., parietal) part of the brain on a higher (e.g., prefrontal) part—in short, a selective and context-sensitive reduction in the effective connectivity of forward connections. This is exactly what Greenman et al. report in this issue. Furthermore, not only were the authors able to demonstrate this context-sensitive (manipulation-dependent) failure to respond to ascending prediction errors, they were also able to show that alternative explanations for this dysconnectivity can be discounted. To do this, they used their experimental design to look for variations in (dynamic causal modeling estimates of) effective connectivity to show that in non-schizophrenia control subjects, they predict polygenetic risk scores for schizophrenia. Crucially, this predictive validity cannot be explained away by confounding factors in people with schizophrenia.

In a complementary analysis, the authors addressed between-subject variability within the schizophrenia group using a rather clever analysis. Instead of just testing for group-by-(cognitive) condition interactions, they used predictions of the condition-specific connectivity during the manipulation condition, based on the connectivity established during the maintenance. Crucially, they used the control subjects to map from the pattern of connectivity during maintenance to the pattern instantiated during manipulation. This enabled them to establish a neurotypical, condition-specific functional connectome for people with schizophrenia. Finally, deviations from this pattern were then shown to predict the propensity for delusional beliefs in this group. This disclosed a remarkable correlation, such that as delusion severity increases, people with schizophrenia failed to sensitize themselves to parietal (feedforward) afferents in the way that somebody without schizophrenia would.

In summary, Greenman et al. leverage a series of high-end analytics to ask a simple question that emerges from the theoretical neurobiology of schizophrenia, namely, can we explain delusions in terms of a failure of (Bayesian) belief updating, in which higher-level beliefs become resistant to

revision by ascending hierarchical connections in the brain? I think that they can congratulate themselves on providing us with an affirmative answer.

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