With new access to unprecedented amounts of data over intervals that can range up to years per individual, the methods used to analyze data need to evolve alongside the technology that has enabled this new potential data resource. Digital phenotyping creates the potential for a new generation of relapse prediction models that do not fall victim to the ergodic fallacy, and can make personal and more preventive psychiatry a reality.

This reality is approaching faster now, as the COVID-19 pandemic has accelerated the field’s use of telehealth and acceptance of smartphone data to supplement care. As patients can no longer fill out paper-and-pencil surveys and hand them to clinicians, use of patient-reported outcomes captured via computers and smartphones has become necessary for everyday care. As barriers to using smartphone data continue to fall, and the evidence for benefit continues to expand, the real question is not when but how relapse prediction data will be used.

While it is easy to imagine ideal uses for smartphone relapse prediction, as outlined in the A-CHESS study, the broader realities must also be considered. In Fall 2019, the concept of using smartphone prediction not towards relapse, but rather violence prediction among people with serious mental illness, was floated. This idea was met with concerns around ethics, feasibility and stigma, but highlights how easily a seeming boon to the field can turn into a potential liability.

Another pressing challenge is how health systems can respond to smartphone relapse prediction data. Relapse may happen at 2am on Sunday morning, and the clinical team can be alerted at the same time. The real solution is designing new clinical services that are able to respond to digital data. Designing these new services along with new technologies in an inclusive, collaborative, iterative manner across disciplines will result in solutions that will bridge the research to practice (or code to clinic) gap and help prevent relapse.

The digital clinic of tomorrow may not look like the traditional clinic of today. Our teams in Boston, New York and Philadelphia are piloting digital clinic models where we have learned first-hand the rewards and challenges of this approach. In relapse prediction, the new technology can offer a first line of response with just-in-time adaptive interventions in a stepped care manner – in some cases removing the need for an immediate personal response from the clinical team. But there is always the need for a personal connection with every patient. For example, a patient recently appeared at risk for a manic relapse given elevated levels of phone activity but, upon reaching out, he informed us that he had started letting his roommate use his smartphone when working the night shift. This explained the lack of sleep and increased activity captured by the smartphone, which had been interpreted incorrectly as elevated risk. Fully automated interventions could be problematic with respect to false positives and should instead be seen as complementary to the human element of care.

The potential of personalized preventive mental health care is within reach with smartphone-based relapse prediction. As the next generation of studies explore prospective validity, the clinical need for these models will drive further innovation. The convergence of these approaches is not a decade away, but will likely be as swift as it is transformative.

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Brain networks and cognitive impairment in psychiatric disorders

Cognitive impairments are a prominent feature of all psychiatric disorders. The goal of mapping each disorder to individual brain areas has now been largely abandoned, and supplanted by systems neuroscience approaches which focus on distributed circuits and large-scale brain organization1.

Although the nature of cognitive impairments varies across disorders, a common underlying feature is the inability to adaptively regulate or control behavior in relation to changing goals and saliency of external stimuli and internal mental events. Dysregulation of the brain’s cognitive control systems thus lies at the crux of most behavioral impairments. Cognitive control is a dynamic process, which relies on flexible goal-relevant modulation of brain networks, and investigations of dynamic network inter-

actions are advancing fundamental knowledge of the neurobiological basis of psychiatric disorders2.

The human brain is intrinsically organized into networks, each consisting of a distinct set of cortical and subcortical areas linked by temporally synchronous neural activity1. The intrinsic connectivity of brain networks displays close correspondence with task-related co-activation of brain regions, and this correspondence has allowed intrinsic and task-related connectivity to be demarcated and studied under a common systems neuroscience framework3.

Brain networks not only provide a unifying framework for characterizing functional organization of the neurotypical brain, but also for probing the neurobiological basis of psychiatric disor-
ders. In particular, aberrations in large-scale brain networks that implement cognitive control have now been shown to transdiagnostically underpin virtually all psychiatric disorders.

Cognitive control processes are implemented by distinct large-scale brain networks, each with unique spatial and temporal properties. Three brain networks have received considerable attention in the context of impairments of cognitive control in psychiatric disorders: the salience network (SN), anchored in the anterior insula and dorsal anterior cingulate cortex, with prominent subcortical nodes in affect and reward processing regions; the fronto-parietal (FPN) “central-executive” network, anchored in dorsolateral prefrontal cortex and posterior parietal cortex; and the default mode network (DMN), anchored in the medial posterior cingulate cortex, ventromedial prefrontal cortex, medial temporal lobe, and angular gyrus.

The SN network is crucial for “salience mapping”, i.e., detecting salient external stimuli and internal mental events and facilitating engagement or disengagement of brain systems relevant for goal-relevant behaviors. The FPN is involved in active maintenance and manipulation of information in working memory. The DMN is typically suppressed during focused attention to external stimuli, and is involved in self-referential and autobiographical processes. These networks are fundamental to human cognition and are critical for regulating adaptive goal-directed behaviors.

A synthesis of findings over the past decade has led us to propose a triple network model of psychopathology, which posits that aberrant functional organization of the SN, FPN and DMN and their dynamic interactions underlie a wide range of psychiatric disorders. Dysfunction in one or more of these networks has been reported in many psychiatric disorders, including autism, anxiety and mood disorders, schizophrenia, bipolar disorder and substance abuse.

The model specifically hypothesizes a central role for the SN in aberrant salience assignment and mapping of external and internal events, leading to altered dynamic temporal interactions with the FPN and DMN. Misattribution of salience and the resulting dysregulation in engagement of appropriate task-relevant brain networks is thus predicted to be a proximal factor underlying cognitive impairments, and evidence in support of this model has been accumulating over the past decade in multiple psychiatric disorders.

Critically, integrative between-network communication is crucial for efficient cognitive control and adaptive behaviors. Models incorporating cross-network dynamics have identified robust neurobiological features capturing cognitive phenotypic characteristics in psychiatric disorders. These models better reflect aberrations in the waxing and waning of network-wide co-activation patterns arising from externally and internally driven mental events. The temporal evolution of the ensuing dynamical states captures clinical symptomatology and cognitive impairments better than static network features.

In a recent study, we examined whether aberrant functional organization of the SN, FPN and DMN contributes to psychosis in schizophrenia. We found that dynamic SN-centered cross-network interactions were significantly reduced, less persistent, and more variable in patients with schizophrenia compared to neurotypical controls. Moreover, dynamic time-varying measures of cross-network interactions were correlated with cognitive dysfunction and positive, but not negative, symptoms. Thus, aberrations in time-varying engagement of SN with FPN and DMN are a clinically relevant neurobiological signature of psychosis in schizophrenia. The discovery of dysregulated brain dynamics in the triple-network salience model further highlights the value of theory-driven systems neuroscience approaches for characterizing core cognitive impairments and clinical symptoms associated with schizophrenia.

Delineation of the brain network basis of cognitive control impairments in the developing brain holds particular promise for early intervention. The earliest manifestations of major psychiatric disorders typically occur in childhood and adolescence, and cognitive, affective and behavioral deviations are often seen years before illness onset and clinical diagnosis. The neural signatures of these deviations have been reported in multiple brain networks, and evidence that aberrations in dynamic interactions of cognitive control networks contribute both to general cognitive impairments and specific phenotypic features is accumulating in studies of autism, attention-deficit/hyperactivity disorder and many other neurodevelopmental disorders. Characterization of the developmental trajectories of cognitive control networks, and in particular early identification of network dysfunction, has the potential to improve early diagnosis, treatment and outcomes.

A primary goal of psychiatry is identifying psychological and biological factors underlying cognitive impairment that cut across diagnoses and explain fundamental aspects of mental illness. Impairments in cognitive control systems that regulate the ability to adaptively engage with and respond to changing goals and contexts have emerged as a hallmark of psychopathology. A convergence of empirical findings and theoretical frameworks for examining aberrations in brain networks that underlie cognitive impairments have provided foundational information about transdiagnostic circuits and promising targets for intervention. Brain network models also provide critical insights into sources of variability in the expression of clinical symptoms, behavioral phenotypes, and their neurodevelopmental bases.

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