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Enhancing Psychosis Risk Prediction Through Computational Cognitive Neuroscience

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Research suggests that early identification and intervention with individuals at clinical high risk (CHR) for psychosis may be able to improve the course of illness. The first generation of studies suggested that the identification of CHR through the use of specialized interviews evaluating attenuated psychosis symptoms is a promising strategy for exploring mechanisms associated with illness progression, etiology, and identifying new treatment targets. The next generation of research on psychosis risk must address two major limitations: (1) interview methods have limited specificity, as recent estimates indicate that only 15%–30% of individuals identified as CHR convert to psychosis and (2) the expertise needed to make CHR diagnosis is only accessible in a handful of academic centers. Here, we introduce a new approach to CHR assessment that has the potential to increase accessibility and positive predictive value. Recent advances in clinical and computational cognitive neuroscience have generated new behavioral measures that assay the cognitive mechanisms and neural systems that underlie the positive, negative, and disorganization symptoms that are characteristic of psychotic disorders. We hypothesize that measures tied to symptom generation will lead to enhanced sensitivity and specificity relative to interview methods and the cognitive intermediate phenotype measures that have been studied to date that are typically indicators of trait vulnerability and, therefore, have a high false positive rate for conversion to psychosis. These new behavioral measures have the potential to be implemented on the internet and at minimal expense, thereby increasing accessibility of assessments.

Key words: clinical high risk/schizophrenia prodrome/conversion

The large majority of people with schizophrenia demonstrate significant disability and premature mortality despite largely successful management of their positive symptoms.[1,2] Efforts to address morbidity and mortality have shifted to the earliest phases of the illness, with the idea that early intervention may improve long-term symptomatic and functional outcomes. Motivated by the results of the Recovery After an Initial Schizophrenia Episode (RAISE[3]) study, intensive intervention in first-episode psychosis (FEP) is now being brought to scale through the combined efforts of the National Institute of Mental Health (NIMH) and the Substance Abuse and Mental Health Services Administration (SAMHSA) to develop a nation-wide network of sites delivering evidence-based specialty care.

Building on the success of early intervention at the first episode, international efforts have sought to determine if it is possible to reliably identify people who appear to be at clinical high risk (CHR) for the onset of psychosis, with the goal of developing interventions to prevent or delay the emergence of a psychotic disorder, thereby altering

the clinical course. This first generation of CHR research focused on the development of reliable clinical interview methods to identify people who appeared to be at highest risk for conversion to psychosis so that they could receive careful monitoring and treatment as appropriate.[4–12] This approach has substantially improved our understanding of the prodromal stage of the disorder and highlighted biomarkers associated with CHR status and conversion (such as changes in electrophysiology, brain structure, and cognitive performance).[13–25]

While substantial progress has been made, several limitations of prevailing approaches suggest the need to develop innovative methods:

(1) ***Low Specificity.*** Current approaches using structured interviews to identify people at CHR have limited specificity: only 15%–30% of individuals who meet CHR criteria actually convert to a psychotic disorder over extended follow-up.[26–33] The low conversion rates associated with current assessment methods greatly confound attempts to power primary prevention trials, as seen in the recent NEURAPRO fish oil study.[34,35] We acknowledge that conversion to psychosis is not the only relevant clinical outcome and that many people who do not convert experience substantial symptom burden and functional impairment requiring clinical attention. However, we remain convinced that the prevention of conversion to psychosis should remain a public health priority, given the morbidity and mortality associated with these disorders. There is a clear need to increase the specificity and sensitivity of assessment of *imminent* risk, in order to enrich samples for future preventative intervention trials.[36–38]

(2) ***Limited Availability and Detection Power.*** The interview methods that are used for CHR identification require extensive training, in addition to the establishment of referral networks or public health awareness campaigns that involve significant resources and support. As a result, only a minority of people who develop FEP access specialty care for CHR syndromes. Even in the United Kingdom, where specialty CHR care is available via the National Health Service,[32,36,39–45] detection power of the CHR approach is limited in that only 5% of people who ultimately present with FEP have ever had any prior contact with CHR services.[4,31] In the United States, the availability situation is worse: until recently, CHR services have existed only in a few academic institutions,[5,46–48] and this has limited the public health impact of the first-generation studies. While the new NIMH Clinical High Risk for Psychosis initiative (U01 and U24 pair) will ultimately support a large treatment development network, different approaches are needed in order to increase the specificity and availability of CHR screening.

One potential solution is the use of biomarkers as stand-alone measures or to complement interviews. The first generation of CHR studies focused on neuropsychological and electrophysiological measures that were identified as markers of risk in family and "high-risk" studies over the last 30 years.[49–52] These were sensible measures to study at the time the original CHR studies were undertaken, as these measures were reliably abnormal in ill patients and some proportion of first-degree relatives, suggesting that they were assessing fundamental aspects of illness risk. That approach also inevitably led to poor specificity. That is, risk or trait vulnerability markers are often abnormal in people who never develop diagnosable psychotic disorders.[49] Such measures may be highly useful for the study of genetic risk; however, by definition, they will have unacceptable false positive rates in the prediction of conversion to psychosis. There are a number of neuroimaging biomarkers that may have enhanced specificity (eg, positron emission tomography imaging of dopamine synthesis capacity).[20] However, it is unlikely that such costly measures will become widely available considering the expense involved and the expertise required.

In our view, the major challenge facing the field is to increase assessment sensitivity and specificity for conversion to psychosis and to do so at scale. We believe that there is a path forward to meet these challenges. The strongest predictor of conversion in the existing CHR literature is symptom severity at baseline—the worse the positive, negative, and disorganization symptoms at initial presentation, the higher the probability of conversion across time.[14,53,54] Quantitative measures that assay the latent processes that underline symptom formation may offer a more sensitive assessment of evolving risk.

Recent advances in clinical cognitive neuroscience and computational psychiatry offer a mechanistic understanding of the genesis and maintenance of the defining symptoms of schizophrenia. As such, we might now predict conversion to psychosis, building upon the pioneering CHR work, but exploiting contemporary discoveries made long after those seminal projects were initiated. Taking a translational approach from the basic neuroscience of perception and cognition provides a conceptual framework and a set of behavioral paradigms that elicit symptom-relevant latent constructs.[55] These constructs, in turn, have the potential to offer objective measures that are more precise and free from the drawbacks of subjective clinical interview measures: interviewers differ in their skill in eliciting precise information and patients display varying levels of insight and willingness to disclose potentially stigmatizing information. Furthermore, there may be different pathways to the same observed behavior with different implications for conversion. For example, it is now clear that mood and psychotic disorders are both associated with motivational deficits and reward processing abnormalities. However, the nature of these

abnormalities differs. Mood disorders appear to be characterized by a true hedonic deficit, whereas people with schizophrenia exhibit motivational deficits consequent to impairment in explicit reinforcement learning (RL) and effort-cost decision-making, in the presence of intact reward sensitivity.[56,57] It is possible that hedonic deficits may not prove to be predictive of conversion to psychosis among those at CHR, whereas abnormalities in RL and effort allocation may. We hypothesize that measures derived from specific mechanistic models of symptoms may serve as better predictors of conversion to full psychotic disorder than subjective, interview-based measures and provide a better signal-to-noise ratio in the face of the substantial clinical heterogeneity that is characteristic of CHR samples.

New Directions in the Understanding of Symptom Mechanisms

Here, we briefly describe the cognitive computational mechanisms that underly the positive, negative, and disorganization symptoms that are the major diagnostic features of psychotic disorders and schizophrenia. A burgeoning literature—seeded by Stephan, Friston, Frith and colleagues[58]—has begun to define the neural and behavioral mechanisms of perception and belief and their interactions,[59–61] yielding a new understanding of hallucinations and delusions.[62–66]The idea that perception involves the combination of beliefs (or predictions) with incoming sensory data goes back at least to Helmholtz.[67]More recently, this fundamental notion has been cast in Bayesian terms where perception is considered as a form of probabilistic inference; incoming sensory information (likelihood) is compared against predictions (priors), and prediction errors (resulting when there is a mismatch between priors and incoming evidence) are computed between them, with the most likely cause of sensory data (posterior) becoming the percept.[59–61] Priors are represented with a certain precision (the inverse variance of the distribution of possible values the data could take). If priors are more precise than sensory inputs, they will dominate inference, we will perceive what we expect, and prediction errors will be ignored. Alternatively, precise sensory evidence will dominate less precise priors and drive belief updating (changing one's priors for subsequent inference). This scheme may be implemented via the hierarchical structure of cortex (priors are passed top-down, prediction errors bottom-up, through N-methyl-D-aspartate and a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, respectively).[59–61]Neuromodulators such as dopamine, acetylcholine, and serotonin (all implicated in schizophrenia[68–71]) are thought to underwrite the precision weighting of belief, perception, and their interactions.[72] By denying a strict distinction between perception and belief,[64] predictive coding provides a framework in which to understand hallucinations, delusions, and their co-occurrence.[65]

When prior beliefs are imprecise (or absent), many inputs will generate prediction errors and spur rapid learning and updating of the model of the world—humans and other animals are intolerant of uncertainty, even an erroneous belief is better than no explanation at all.[72–74] This spurious learning may result from experiences (stimuli, thoughts, and percepts) that have been rendered aberrantly salient[75] by virtue of contextually inappropriate dopaminergic signaling.[76–78] There are a variety of behavioral methods that are able to capture this kind of spurious prediction-error-driven-learning, and these methods have a track record of being associated with the severity of delusions.[76–78]

Once formed, prior beliefs can become so overweighted that no amount of contradictory evidence can generate a prediction error and drive new learning.[77] This is a way of understanding tenaciously held delusional beliefs that are strongly resistant to contrary evidence under typical conditions.[77] This same mechanism may be relevant for understanding hallucinations.[66] Several recent experiments suggest that hallucinations may result from strong priors that result in the perception of sound or of speech in the absence of clear sensory evidence.[79–81] The critical insight here is that perceptual systems are never truly quiescent—there is always a tonic activity that can be shaped and amplified by strong priors as seen, for example, in the commonplace experience of mistakenly believing that one's name is being called.[82] There are now a set of behavioral methods that are sensitive to individual differences in the proclivity to hear sounds in the absence of sounds and to perceive comprehensible speech when presented with highly degraded speech samples.[80,81,83] We hypothesize that measures from both of these "pathways" toward idiosyncratic percepts and beliefs are relevant for the prediction of conversion to psychosis.

A different mechanistic framework offers a new understanding of the motivational impairments that are critical for functional outcomes. For many years, it was assumed that decreases in goal-directed behavior were caused by anhedonia: there is little reason to pursue goals if attaining them brings little pleasure. However, experimental evidence clearly demonstrates that people with schizophrenia appear to have largely normal "in the moment" experiences of pleasure and neural responses to the experience of rewarding outcomes. However, these experiences do not have the expected motivational impact in terms of driving subsequent behavior.[84,85] A large body of experimental work provides two complementary perspectives on this impairment. First, a series of studies using a variety of RL paradigms suggest that people with schizophrenia have difficulty with explicit RL, whereas implicit RL may be intact.[86,87] Some studies suggest that this is a

consequence of impaired working memory processes that are required for explicit RL, which are critical for updating mental representations of value.[88,89] Other studies suggest that learning from rewarding outcomes may be differentially impaired relative to learning from loss avoidance and punishment.[90,91] Both lines of evidence suggest that deficits in RL underlie the failure to use value representations to drive decision-making and motivated behavior. There are a number of behavioral and computational modeling approaches that provide the ability to formally quantify the processes involved in generating this impairment.[90,92] Formal modeling that is able to quantify the contribution of several different discrete processes to the overall performance offers much finer resolution on origins of motivational impairment than interview-based negative symptom ratings.

There is a closely related body of work looking at how people with schizophrenia weigh potential rewards (benefits) vs the costs of the actions needed to obtain those benefits. Well-replicated evidence indicates that people with schizophrenia tend to avoid making high effort choices associated with higher levels of reward, with this bias being most evident in patients with more severe negative symptoms.[93,94] This is a rapidly developing literature, and there are new experimental and computational approaches that have promise in distinguishing the impact of reward devaluation from enhanced effort aversion.[95] As with the RL literature discussed above, these behavioral paradigms and computational analytic approaches offer a much more nuanced and specific understanding of the processes implicated in clinically manifest negative symptoms. The frontal-striatal circuits implicated in RL and effort-based decision-making are systems long-implicated in schizophrenia.[96–100]

Clinically manifest disorganization symptoms such as formal thought disorder and inappropriate affect are generally mild in CHR populations and have not emerged as potent predictors of conversion to psychosis in the various risk calculators that have been developed.[14,15,53,54,101] We suspect that the use of more sophisticated performance-based measures may be useful in detecting a wider range of individual differences, potentially enhancing predictive utility. In broad terms, symptoms of disorganization are thought to reflect alterations in the long-range connectivity and integration of distributed neural processing. Such dysconnectivity results in fragmentation in the coherence, or context-based linking, of mental representations, and in the sequencing of thought and motor behavior.[102] Tasks assessing the aspects of visual context processing and perceptual organization have been studied in people with schizophrenia, and relationships with the severity of disorganization symptoms have been observed in multiple studies.[103] As with positive and negative symptom mechanisms above, this approach to disorganization symptoms implicates a central neural abnormality observed in schizophrenia and conceptualizes laboratory-based examples of reduced representational organization as subtler forms of what is observed clinically as behavioral disorganization.

The utility of this proposed approach remains to be demonstrated. With recent support from NIMH for a five-site longitudinal study of 500 CHR, 500 psychiatric help-seeking controls, and 500 controls (Computerized Assessment of Psychosis Risk, or CAPR), we plan to administer a battery of computerized tasks that are tied to the symptom generation mechanisms described above. By including a help-seeking control group, we will be able to directly address issues of sensitivity as well as specificity and clinical heterogeneity. We hope to demonstrate that our approach enhances the precision of prediction of conversion as a prelude to making this type of screening available at scale on the Internet.

Summary

The translational approach—from the basic neuroscience of perception and cognition to the prediction of conversion to psychosis—involves two critical departures from the prevailing paradigm: (1) a shift from trait markers to cognitive and perceptual state markers related to symptom mechanisms and (2) a shift away from imaging biomarkers toward behavioral paradigms and computational analytic approaches that offer refined measurement of latent constructs implicated in symptom formation. Increased precision in the measurement of the mechanisms underlying symptom formation has the potential to enhance sensitivity and specificity over clinical interview measures. Behavioral measures also have the potential to be administered on the internet, increasing the availability of CHR screening.

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