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Early Detection of Psychosis: Recent Updates from Clinical High-Risk Research

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Abstract

The debilitating nature of schizophrenia necessitates early detection of individuals at clinical high-risk (CHR) in order to facilitate early intervention. In particular, comparisons between those who develop fully psychotic features (CHR+) and those who do not (CHR−) offer the opportunity to reveal distinct risk factors for psychosis, as well as possible intervention target points. Recent studies have investigated baseline clinical, neurocognitive, neuroanatomic, neurohormonal, and psychophysiological predictors of outcome; premorbid social dysfunction, deficits in neurocognitive performance, neuroanatomic changes, and hypothalamic-pituitary-adrenal (HPA) axis dysfunction have been implicated in psychosis emergence. However, several challenges within CHR research remain: heterogeneity in long-term diagnostic outcome, the variability of research tools and definitions utilized, and limited longitudinal follow-up. Future work in the field should focus on replication via extended longitudinal designs, aim to explore the trajectories and inter-relationships of hypothesized biomarkers, and continue to investigate interventions that seek to prevent psychosis emergence through symptom reduction.

Keywords

Clinical high-risk; Psychosis; Early detection; Clinical functioning; Neurocognition; Neuroimaging

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Conflict of Interest

Carrie Bearden and Ariel Schvarcz have no conflicts of interest.

Compliance with Ethics Guidelines

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by the author.

Introduction

Schizophrenia is a debilitating disorder associated with poor long-term outcomes and large societal costs. Within the United States alone, the economic burden has been estimated around 60 billion dollars annually and is a direct consequence of reduced productivity, high direct medical costs (e.g., outpatient, inpatient, long-term care, and medication), and high non-health care costs (e.g., living cost offsets) [1]. Recent work has highlighted the exacerbation of such costs by longer duration of untreated psychosis (DUP), which has been linked to more severe symptomatology, poorer global outcomes, decreased social functioning, and lower likelihood of remission [2, 3]. The additional correlation between longer DUP and increased delays in accessing mental health services [3] emphasizes the need for early intervention and detection to minimize such morbidity.

Over the last two decades, a multitude of research has emerged focusing early detection efforts on the “clinical high-risk (CHR)” state (also known as “ultra high-risk” or putatively prodromal phase of illness), which refers to individuals identified as having pre-psychotic clinical symptoms and functioning. In particular, the comparison between CHR individuals who ultimately develop fully psychotic features (CHR+, or converters) and those who do not (CHR− or nonconverters) suggests a potentially fruitful way of ascertaining distinct risk factors for the emergence of overt psychotic-spectrum disorders, as well as possible intervention targets. With new literature on this population emerging daily, it seems prudent to draw attention to the most current work, and how it is shaping our understanding of psychosis prediction and the underlying mechanisms leading to illness onset. To that effect, this article aims to provide a comprehensive review of recent progress in the early detection and prediction of psychosis.

Identifying the Clinical High-Risk State

As referenced above, the CHR construct is broadly defined in terms of operationally defined thresholds of pre-psychotic or subthreshold symptoms. Although the diagnostic tool varies slightly across sites (e.g., Structured Interview for Prodromal Syndromes [SIPS] [4], Comprehensive Assessment of At-Risk Mental State [CAARMS] [5], etc.), the criteria are typically defined as the presence of one or more of the following: attenuated positive symptoms (APS), brief intermittent psychotic symptoms (BIPS), and familial genetic risk or schizotypal personality disorder combined with prominent deterioration in functioning (GRD). Positive, negative, general, and disorganized symptoms are typically rated on a scale addressing typical/healthy ranges, prodromal ranges, and psychotic ranges. Other work has focused on basic symptoms, or cognitive abnormalities in domains such as language, perception, motivation, and/or thought processing that may reflect earlier stages of risk [6••–8•]. The criteria for conversion to psychosis typically converge on the presence of at least one fully psychotic symptom occurring several times a week for at least one week to one month, depending on the interview. For recent, comprehensive reviews of CHR criteria and diagnostic instruments, readers are directed elsewhere [6••–8•].

Studies of the validity of the CHR state and research classification system have revealed some evidence of convergent, discriminant, and predictive power. Specifically, recent work

from the North American Prodromal Longitudinal Study (NAPLS) Consortium found that individuals who continue to meet CHR criteria over time as compared to symptomatic remitters (i.e., those no longer having symptoms in the prodromal range in any positive symptom domain, sustained for at least six months) were reported to have worse long-term functioning [9]. CHR status appeared distinct from symptoms meeting criteria for Major Depressive Disorder; and those that met criteria for CHR status progression (i.e., an increase by at least one point in one positive symptom domain within a year) were more likely to convert to overt psychosis than those with stable CHR classification or those who remit.

CHR Features and Factors Contributing to the Emergence of Psychosis

Clinical Symptoms and Functioning

As compared to healthy controls (HC), CHR individuals were found to have significantly greater impaired stress tolerance, despite similar rates of self-reported life events; in the CHR cohort, impaired stress tolerance was linked to poorer long-term global functioning and increases in depression, anxiety, conceptual disorganization and total negative symptoms over a four-year follow-up period, independent of the number of stressful life events [10]. Social and role functioning in CHR youth has also been separately predicted by negative symptoms and a composite neurocognitive factor within the multisite NAPLS cohort, with negative symptoms mediating the effects of neurocognition [11]. CHR individuals, those diagnosed with schizophrenia (SZ), and those with a first-degree family member with schizophrenia (genetic high risk; GHR) all perform similarly on tasks of emotion perception, and more poorly than HC [12]. However, patients with SZ performed more poorly than CHR individuals on tasks of emotion differentiation (i.e., distinguishing happy versus sad facial expressions), suggesting some emotion-based deficits may develop later in the course of illness. Yong et al. (2014) found that this decreased ability to recognize and label facial affect among CHRs, as well as deficits in theory of mind ability, were correlated with neurocognitive deficits in attention and working memory [13]. However, no control group was included in this study, limiting interpretability of the results.

Research on retrospective risk factors leading to the emergence and progression of psychosis has converged on premorbid social dysfunction. Poor adolescent social functioning has been shown to predict psychosis emergence over a 2.5-year follow-up, with high specificity and positive predictive power when combined with baseline-rated suspiciousness [14]. This relationship was observed irrespective of both early childhood social functioning and severity of most positive and negative symptoms at baseline. However, baseline disorganized communication, suspiciousness, social anhedonia, and reduced ideational richness mediated this relationship. Interestingly, observed decreases in role and global functioning over time did not predict conversion. Additionally, in this cohort poor adolescent social functioning was more likely to predict onset of schizophrenia as opposed to other psychotic disorders, suggesting some diagnostic specificity [15]. Further supporting this possibility, premorbid social functioning seems to differentiate future schizophrenia-spectrum disorders from other psychiatric conditions even when rated by school teachers of 10 to 13-year-old children at genetic high risk (GHR) for psychosis [16].

Other research using predictive models of observed long-term social and role deficits have confirmed the above findings. Both clinical and neuropsychological measures appear relevant; Carrion et al. found that baseline-evaluated social functioning, global disorganized symptomatology, and decreased processing speed predicted impaired social functioning at three to five year follow-up [17]. Similarly, poor role functioning, motor disturbances (e.g., clumsiness), and verbal memory deficits at baseline predicted later role outcome. However, only impaired social outcome significantly correlated with conversion to psychosis, while predictors of role outcome were independent of conversion. Therefore, while poor functioning in both domains persists among CHR patients, early social deficits again seem to confer specific vulnerability for psychosis. Gender differences may also be relevant to these findings, as Walder and colleagues (2013) found that baseline social functioning and overall positive symptom severity predicted conversion in male CHR patients only [18]. However, given that females were rated to have higher overall functioning at baseline in this study, and the fact that males demonstrated an association between greater deficits in childhood social adjustment and severity of later symptoms, these findings will need to be confirmed in an independent study.

In addition to the significance of early social dysfunction, the above work highlights the focus on baseline-rated features in the prediction of subsequent psychosis outcome. To investigate this further, one European study used latent class analysis to determine if certain baseline factors distinguished future CHR converters from nonconverters [19]. While latent class membership failed to separate anything other than overall CHR participants and healthy controls, the baseline SIPS factor score was significantly higher in subsequent converters than nonconverters. Specifically, higher total positive symptom scores (as well as higher cognitive disturbances scores on another semi-structured interview measure) indicated later conversion in an independent sample [20]. In a related investigation, baseline and three- to six-year follow-up ratings of global functioning (i.e., Global Assessment of Functioning (GAF); Quality of Life Scale) were split at the median, resulting in ‘good’ and ‘poor’ functioning groups [21]. Individuals were additionally characterized as ‘deterioriating’ or ‘improving’ based on functioning changes from baseline to a three- to six-year follow-up. Those meeting criteria for poor functioning at baseline and deteriorating function over time demonstrated the highest likelihood of converting to psychosis, with the deteriorating factor proving to be the most predictive (i.e., the ‘poor baseline functioning and improving function’ group had lower conversion risk than the ‘high baseline functioning and deteriorating’ group). This suggests that investigation of progressive changes in social and role functioning over time may be a better predictor of psychosis risk than is functioning at a single time point.

Substance use has also been investigated as a risk factor for conversion; in the Enhancing the Prospective Prediction of Psychosis (PREDICT) study, reduced use of alcohol (and not cannabis or tobacco) was a predictor of later psychosis [22]. However, this may be a proxy for increased social withdrawal as indicated by reduced social drinking, rather than a distinct predictor. A more comprehensive review of ten studies found that while CHR participants commonly reported use of cannabis, alcohol, and nicotine/tobacco, only two of the ten studies found a positive association between substance use and subsequent conversion to psychosis [23]. One found that nicotine and cannabis abuse were predictive (cannabis

dependence was exclusionary) [24], and the other found that general substance abuse was associated with conversion when included in a multivariate prediction model [25]. However, as the authors highlight, most of the included studies analyzed only baseline or lifetime levels of substance use, rather than changes in usage over time throughout the study. Neuroimaging work has additionally proposed a schizophrenia-specific vulnerability to the effects of cannabis due to the correlation between structural brain changes and substance use observed in CHRs only [23, 26].

Additionally, some researchers have found that the presence of sexual abuse during childhood or adolescence, rather than broad presence of abuse or neglect, was associated with conversion [27]. Specifically, high sexual abuse scores on a self-report questionnaire led to a two- to four-fold increase in the rate of conversion as compared to those with low scores. This suggests that trauma-related stress may confer additional vulnerability for psychosis emergence, though additional work on abuse severity and frequency/duration is warranted.

Neuropsychological Factors

Neuropsychological studies have revealed differences in the overall cognitive functioning of CHR youth as compared to HCs. For example, in comparison to individuals who recently experienced their first psychotic episode (FE) and non-CHR help-seeking patients (HS), Magaud and colleagues (2014) found that CHRs do not show significant differences in overall IQ, nor on specific subscales, based on conventional statistical approaches (e.g., analysis of variance) [28]. However, analyses examining differences within subtests of an index revealed a higher proportion of diverse verbal comprehension profiles among CHR versus both FE and HS individuals. CHR individuals therefore appear to demonstrate specific patterns of subtle, early changes in their verbal cognition that may be best detected by investigating subscales rather than global index scores using classic analytic techniques.

Global intelligence has also been evaluated for its ability to predict psychosis emergence in conjunction with SIPS positive symptoms, with the combination producing slightly more accurate prediction of conversion than SIPS positive symptoms alone [20]. In this study, both high severity of symptoms and low IQ were deemed the only factors to independently forecast psychosis from among a wide range of clinical and neurocognitive variables, over a six-year follow-up period. Although both clinical and neurocognitive measures were assessed in conjunction with global functioning (GAF), only increased disorganization symptoms at baseline significantly correlated with poorer functioning at follow-up, suggesting a greater ability of clinical measures over neuropsychological ones to predict transition and long-term outcome. This has been affirmed through other work in which a best fit prediction model assessing several variables was created based on CHR APS criteria, basic symptoms of cognitive disturbances (COGDIS) and delayed processing speed [29]. Although the combination of clinical and neuropsychological features conferred the highest risk for conversion, individually, APS + COGDIS alone predicted conversion above and beyond the presence of processing speed deficits alone.

Studies examining neurocognitive predictors independent of positive or other symptoms have similarly been conducted with mixed findings. In a recent meta-analytic review, broad

cognitive deficits (i.e., current and premorbid IQ, processing speed, visual and verbal memory, verbal and visuospatial working memory, attention, and fluency) were observed in CHR and GHR individuals as compared to healthy controls, with more severe cognitive deficits in all areas save sustained attention predicting conversion [30•]. However, modest effect sizes for baseline group differences between CHR+ and CHR− again suggest a limited generalizability of baseline cognitive factors as stand-alone predictors of psychosis.

In contrast, another study examining pattern of changes in CHR neurocognitive ability over one year revealed that, among a large number of neuropsychological variables assessed, a significantly larger effect size for verbal memory deficits alone (e.g., failure of CHR+ individuals to meet normative performance at the one year follow-up) was found for converters versus nonconverters [31]. No differences were found in overall neuropsychological impairment or effect sizes for executive functioning scores at follow-up between CHR+ and CHR− groups. However, overall CHR neurocognitive functioning was reduced at a one-year follow-up relative to baseline, with executive function and verbal memory ability significantly below healthy control performance. No evidence was found for progressive changes in IQ in the CHR group, nor were group differences found between CHRs and HC in the domains of sustained attention and motor functioning. This work suggested that only progressive verbal memory impairments may be related to psychosis emergence, though the sample size and conversion rate here were notably small, especially given the short follow-up time period.

Using a slightly different approach in a Korean sample, CHR converters were compared to nonconverters, full remitters, and HC to assess for baseline neurocognitive differences among the groups and prediction of symptom abatement over a 12- to 24-month follow-up [32]. At baseline, those whose prodromal symptoms subsequently remitted performed better on measures of verbal fluency and memory, immediate visual memory, and attention as compared to converters, and in fact performed equally to healthy controls in all cognitive domains. Over time, CHR remitters demonstrated improvement in semantic fluency while performance of non-remitting, non-converting CHR individuals declined despite the absence of significant baseline differences, implying that investigation of cognitive trajectories over time may clarify probability of transition.

Neuroimaging Factors

Neuroimaging studies investigating high-risk cohorts have found abnormalities in the white matter organization in the brains of CHR individuals as compared to HCs using diffusion tensor imaging (DTI), particularly in brain regions known to undergo significant changes from adolescence to adulthood such as the superior longitudinal fasciculus [33]. However, to date no baseline differences between subsequent CHR converters and nonconverters have been reported utilizing either DTI or volumetric techniques, though to date very few studies have reported on this comparison [34••].

Research using positron emission tomography (PET) to estimate dopamine synthesis capacity in the striatum found elevated dopamine synthesis capacity in the whole, associative and sensorimotor (but not limbic) striatum, suggesting the presence of

dopaminergic abnormalities that precede psychosis onset [35]. These intriguing findings have potential implications for early initiation of antipsychotic medications in these patients.

Findings related to the predictive utility of neuroanatomic findings have been inconsistent, in part due to methodological differences. Multivariate pattern classification has been used to classify converters and nonconverters based on baseline group differences in gray matter volume in cerebellar, prefrontal, cingulate, and striatal structures, with classification algorithms attaining 80% accuracy in test cases [36]. When an independent sample of CHR participants were then classified into low, intermediate, and high risk groups by the multivariate pattern analysis, low versus high risk group transition rates were 8 and 88% respectively, demonstrating fairly accurate conversion predictions from such neuroanatomic algorithms. However, while a recent review of the high-risk literature [34••] supports the notion of anatomic changes over time that distinguish CHR+ from CHR− individuals, reports of baseline and follow-up group differences are inconsistent. For example, various studies have found that CHR+ individuals demonstrate baseline volumetric abnormalities in several regions such as the interior frontal gyrus [37], prefrontal cortex [38], cerebellum [38], and cingulate cortex [38] as compared to nonconverters, with particularly converging evidence for the insula [38, 39] and superior temporal gyrus [37, 38]. Converters also have been reported to evidence greater volumetric reductions over time in the insular cortex [39], superior temporal gyrus [40], and inferior frontal gyrus [37] as compared to nonconverters over a 1- to 4-year follow-up period.

Cortical thickness abnormalities have also been investigated, with no significant whole-brain or region of interest differences found between converters and nonconverters despite overall decreased cortical thickness in the right parahippocampal gyrus observed in CHRs as compared to controls [41]. Importantly, findings from the NAPLS consortium in a sample of 135 controls and 274 CHR youth, 35 of whom converted, indicated no cortical thickness or volumetric group differences at baseline, but significantly greater rates of *change* in cortical thickness in superior frontal, middle frontal, and medial orbitofrontal regions within the right hemisphere in CHR+ versus CHR− and HC groups [42] (see Fig. 1). CHR+ individuals also evidenced greater expansion of the third ventricle over time as compared to CHR− and controls. These changes were not due to antipsychotic medication exposure as both medicated and nonmedicated converters showed similar rates of gray matter loss. Additionally, converters demonstrated stronger correlations between rates of right hemisphere cortical thickness reduction and levels of pro-inflammatory markers measured in blood plasma, although this association was present among the entire sample. This work highlights the need for more research on the role of neuroinflammatory factors in psychosis onset, and their temporal relationship to neurochemical and neuroanatomic changes.

Psychophysiological Factors

Various quantitative electroencephalogram (qEEG) parameters, such as resting EEG frequencies, have also been assessed for their utility in psychosis prediction [43]. These include alpha (awake, relaxed, closed-eye state), beta (active thinking state), theta (drowsy/meditative state; REM sleep), and delta (slow-wave sleep) activity. In the European Prediction of Psychosis Study (EPOS) study, variables of occipital-parietal alpha peak

frequency (point of greatest power estimate within the alpha, frequency band), frontal delta, and frontal theta power were included in a final model and analyzed for prognostic power. Three classes of participants emerged (e.g., healthy controls, low psychosis-risk CHRs, and high psychosis-risk CHRs), with low and high-risk CHRs demonstrating statistically significant different rates of conversions. Additionally, CHR+ individuals were found to have higher frontal/central delta and theta and lower occipital-parietal alpha peak frequency, suggesting baseline resting EEG differences that can be used to predict later psychosis and potentially function as a point of individualized intervention. Resting state-EEG microstates, or transient patterns occurring during spontaneous mental operations, have also differentiated CHR patients from other symptomatic groups and HC [44]. Schizophrenic and CHR patients significantly differed in their temporal microstates as compared to controls, as well as from each other. In particular, microstate class A, one of the four typical microstates that may be active during phonological processing, seemed to most prominently predict transition to psychosis in light of its correlation with positive symptom severity, though it may also simply be a proxy for anxiety and impaired stress tolerance.

EEG-based event-related potential (ERP) work has additionally revealed a promising biomarker via auditory mismatch negativity (MMN), an ERP component resulting from hearing a discordant sound among repeated standard sounds. In a comparison of CHR, FE, and HC individuals, HCs had significantly higher MMN amplitudes compared to FE and CHR groups, while CHR and FE groups did not differ [45]. Within the CHR group, converters showed distinct profiles of lower MMN amplitudes at baseline compared to nonconverters, a finding that was not accounted for by antipsychotic medication. Further analysis suggested only one of two types of deviant MMN (double-deviant) predicted psychosis when factoring in the time delay between ERP evaluation and conversion, highlighting more specific potential predictors for further evaluation.

Neurohormonal Factors

Previous research has implicated stress and underlying neurohormonal factors in the etiology of schizophrenia, such that indicators of hypothalamic-pituitary-adrenal (HPA) axis activity are elevated in individuals with psychotic-spectrum disorders and appear to be affected by both antipsychotic medications that reduce psychotic symptoms and recreational substances that exacerbate such symptoms [46, 47]. The association between elevated cortisol and dopamine activity in high-risk populations further suggests a role of neurohormonal factors in the emergence of psychosis [46]. Recently, two measures of HPA activity (salivary cortisol response to awakening and daytime salivary cortisol release) within a CHR cohort were examined [48]. CHR individuals, particularly those who were unmedicated, demonstrated a smaller cortisol awakening response compared to healthy controls. No group differences were observed within daytime cortisol levels, nor were clinical symptoms significantly correlated with cortisol levels. However, the small sample size and confounds of medication plus psychosocial treatment throughout the study suggest notable limitations.

To better assess the predictive power of neurohormonal factors, the NAPLS consortium investigated salivary cortisol levels and found significant correlations to baseline symptoms

across positive, negative, general, and disorganized domains, with particular significance for dysphoric mood and impaired stress tolerance [49]. Baseline cortisol levels among CHR+ patients were also found to be higher than that of CHR− or healthy control groups. Here too, effects were independent of antipsychotic or other medication use. Therefore, the role of HPA axis dysfunction as a potential risk biomarker warrants additional attention, particularly given recent reviews highlighting the role of stress and impaired immune functioning in the etiology of psychosis [50].

Challenges Associated with CHR Research

Despite the wealth of information we have accumulated from the CHR literature, several issues associated with the reliability and utility of the construct remain. One of the most prominent is the lack of specificity for determining later psychosis as opposed to other psychiatric disorders, broadly defined poor functioning, or brief psychotic symptoms that ultimately remit [51–55]. As some suggest, this may be partially due to limited long-term follow-up, research definitions of conversion that typically are based on psychotic-level symptomatology at a single time point, and the diversity of research tools and analytic strategies used among research sites [56, 57]. Variability in long-term outcome, specifically the high number of CHR individuals who do not convert to psychotic disorder, may also reflect access to effective intervention, sampling from heterogeneous help-seeking populations, and conversions occurring outside of study follow-up points [58]. Much of the CHR research to date has focused on relatively short follow-up periods, thereby potentially missing some cases of conversion (‘false negatives’) and confounding predictive algorithms. Some suggestions for increasing specificity have been proposed, such as including the COGDIS criterion into CHR criteria to increase the positive predictive power of conversion [59]. For example, the incorporation of basic symptoms at baseline has indeed been shown to increase the likelihood of predicting schizophrenia over affective psychosis [60], although this meta-analysis has been criticized for the use of limited, potentially underpowered studies [61]. Regardless, the inclusion of basic symptoms does not address the full spectrum of outlined concerns.

Psychosis Risk Syndrome in DSM-V

Many of the above arguments and challenges observed in CHR research put forth above became a part of the recent discussion and controversy regarding the inclusion of an Attenuated Psychosis Syndrome into the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) [62]. Although the full debate is beyond the scope of the current article, we highlight several themes and point the reader in the direction of more comprehensive reviews of the topic [7, 63]. As put forth by the DSM psychotic disorders task force, the defined Attenuated Psychotic Symptoms (APS) syndrome significantly increases the likelihood of predicting future psychosis [64]. However, as highlighted above, limitations to the current evidence base exist: the overwhelming presence of comorbid diagnoses, the range of non-psychotic psychiatric outcomes, and the decreased diagnostic reliability among community clinical settings outside of the research or academic domains. Therefore, continued investigation of the syndrome and its connection to other related

disorders like Schizotypal Personality Disorder is necessary before inclusion into the DSM as a formal disorder.

Summary and Conclusions

Recent research has continued to clarify the CHR state and long-term outcomes, finding that negative symptoms in CHR individuals predict deficits in functioning at baseline and follow-up, and that decreased functioning correlates with neurocognitive factors across all time points [11]. In particular, premorbid social dysfunction appears to have some diagnostic specificity for predicting emergence of schizophrenia over other psychiatric outcomes, including other psychotic disorders. Additionally, the combination of clinical and neuropsychological variables such as IQ, verbal memory, or processing speed increases predictive power [20, 29]. Baseline differences in neuroanatomic structures have also been reported in CHR versus HC groups, with structural differences in the superior temporal gyrus and insula appearing in multiple studies. Progressive gray matter changes within several anatomic regions may be particularly relevant as predictors of psychosis outcome, although the implicated regions vary across studies. HPA axis dysfunction is also hypothesized to be relevant to psychosis risk; this possibility is supported by the finding of elevated baseline cortisol levels among CHR+ individuals. Lastly, most of the recent work conducted has focused on baseline predictors of psychosis, though it has also been suggested that the field should shift to assessing overall deterioration throughout study duration. Table 1 provides a summary of the clinical and neurocognitive prediction findings, while Table 2 summarizes neuroimaging, psychophysiological, and neurohormonal predictors of transition to psychosis.

Despite this progress, findings across studies do not yet fully converge on common factors, highlighting the complex nature of schizophrenia and its etiology [65•]. Therefore, there are still many areas requiring clarification within the psychosis risk prediction literature. As with all budding research, many findings need to be replicated using larger sample sizes and extended longitudinal designs to confirm their validity and reliability; multisite studies such as the NAPLS consortium (e.g., [23]) may prove to be particularly useful here. It will also be imperative to pin down the timing and trajectories of suggested biomarkers in order to facilitate intervention. Although recent publications have highlighted promising interventions that seek to prevent psychosis emergence via symptom reduction, such as medications including Omega-3 fatty acids [66–68] and glycine [69], psychosocial therapies [70–74], cognitive remediation training [75], and combined treatment approaches [76•, 77], this field is still in its infancy.

Among other factors, potential regional/cultural variability in help-seeking behavior and health care programs [78, 79] has not yet been sufficiently addressed. Additionally, there continues to be a paucity of current research on the ethnic and cultural differences in CHR classification and outcomes, as well as whether distinct conversion predictors exist within ethnic groups as some have suggested [80]. From a clinical standpoint, delays in obtaining access to care also present a substantial obstacle to receiving accurate early diagnosis and treatment. Future work must also continue focusing on improving functioning and symptom reduction via more comprehensive and multimodal wrap-around services [1, 66, 81], and

including empirically supported treatments for schizophrenia such as psychosocial therapy and mindfulness interventions [82–85]. Given observed progressive declines in global cognitive function in patient with schizophrenia over time [86], increased participation in cognitive remediation training programs [87–89] and/or cognitive control programs [90] may be additionally useful. Lastly, researchers and clinicians alike should aim to reduce the gap between their respective fields in order to facilitate widespread utility of CHR classification and intervention. This likely begins with addressing classification discrepancies and refining clinical/research tools as needed; specifically, whether it is more efficacious to define psychosis from a dichotomous or continuous perspective. The adoption of low-cost screening methods may also prove fruitful here [91, 92].

In conclusion, many important findings in CHR research have emerged over the past year, particularly in the domain of clinical functioning. This field continues to progress in its attempts to clarify both clinical and biological markers of psychosis risk, and has begun to offer important insight into interventions for reducing the likelihood of psychosis emergence. Although more work is necessary to elucidate and expand the current literature, we have started gaining traction on utilizing research findings to reach a point of meaningful intervention and prevention of psychosis.

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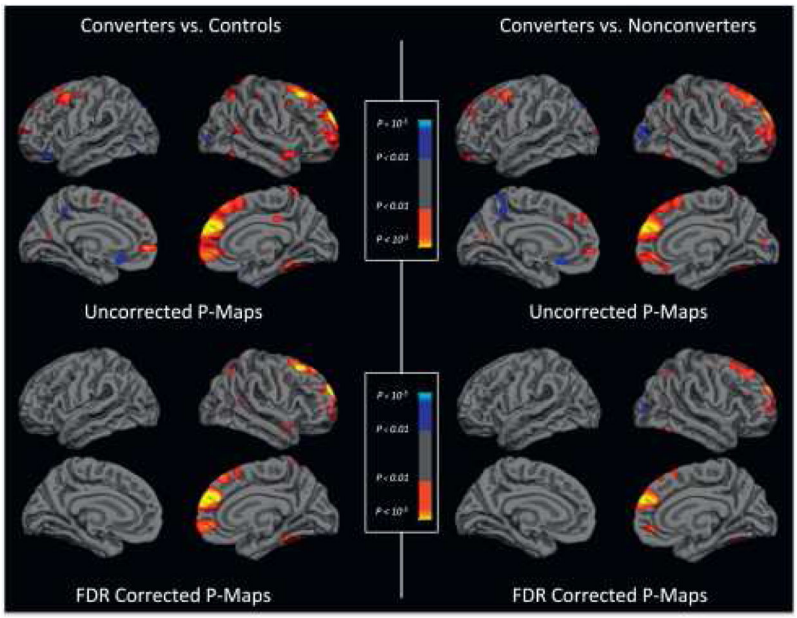

Figure 1.

Statistical brain atlases from the NAPLS Consortium neuroimaging study [42] reveal significantly greater cortical thinning (warmer colors) over time in several, predominantly frontal brain regions (e.g., right superior frontal, middle frontal, and medial orbitofrontal regions) among CHR converters (n = 35) as compared to both nonconverters (n = 239) and healthy controls (n = 135) (lower panel: FDR corrected, $p \leq .01$).

Table 1

Recent Clinical and Neurocognitive Predictors of Transition to Psychosis (Individual Studies)

Source	HR Group	Sample Size[a]	CHR Diagnostic Tools	CR (%)	Follow-up (yrs)	Predictors	
Tarbox et al., 2013 [20]	CHR	270	SIPS	28.9	2.5	**1**	Impaired early adolescent social functioning
Tarbox et al., 2014 [21]	CHR+	54	SIPS	N/A[b]	2.5	**1**	Impaired late adolescent social functioning
Tsuji et al., 2013 [22]	GHR	244	Psychiatric records[c]	13.5	20	**1**	Teacher-rated impaired childhood social functioning
Carrión et al., 2013 [23]	CHR	92	SIPS	16.3	5.0	**1**	Impaired social long-term functioning
Walder et al., 2013 [24]	CHR	276	SIPS	25.4	2.5	**(1–2)**	BL social functioning and SIPS positive symptoms among male CHRs only
Velthorst et al., 2013 [25]	CHR	147	SIPS; PANSS	19.0	2.0	**1**	Higher BL SIPS factor score
Ziermans et al., 2014 [26]	CHR	43	SIPS; BSABS	23.3	6.0	**1**	BL SIPS positive symptom severity
						2	BL BSABS cognitive disturbances severity
						3	BL impaired full-scale IQ
Velthorst et al., 2013 [27]	CHR	157	CAARMS; SANS	21.0	6.0	**1**	Low + deteriorating functioning
Buchy et al., 2014 [28]	CHR	170	SIPS	17.1	4.0	**1**	Reduced BL alcohol consumption
Thompson et al., 2013 [29]	CHR	233	CAARMS; BPRS; CASH	23.6	7.0[d]	**1**	Self-reported childhood sexual abuse
Michel et al., 2014 [30]	CHR	97	SIPS; SPI	45.4	2.0	**1**	APS + COGDIS at-risk criteria
						2	Processing speed
Woodberry et al., 2013 [32]	CHR	53	SIPS	18.9	1.0	**1**	Large effect size for verbal memory deficits

Abbreviations: HR=high-risk; CR=conversion rate; SIPS=Structured Interview for Prodromal Syndromes; N/A=not applicable; BL=baseline; PANSS=Positive and Negative Syndrome Scale; BSABS=Bonn Scale for the Assessment of Basic Symptoms; CAARMS=Comprehensive Assessment of At-Risk Mental State; SANS=Scale for the Assessment of Negative Symptoms; BPRS=Brief Psychiatric Rating Scale; CASH=Comprehensive Assessment of Symptoms and History; SPI=Schizophrenia Proneness Instrument

[a] Of HR group only

[b] All participants in study had converted

[c] GHR status established through psychiatric hospital diagnosis of schizophrenia

[d] Average follow-up time

Table 2

Recent Neuroimaging, Psychophysiological, and Neurohormonal Predictors of Transition to Psychosis (Individual Studies)

Source	HR Group	Sample Size[a]	CHR Diagnostic Tools	CR (%)	Follow-up (yrs)	Predictors	
Van Tricht et al., 2013 [34]	CHR	113	SIPS; SPI	19.5	1.5	**1** **2** **3**	Occipital-parietal APF frontal delta power frontal theta power
Andreou et al., 2014 [35]	CHR[b]	18	SIPS; SPI; PANSS	NR	NR	**1**	Temporal microstate A
Perez et al., 2013 [36]	CHR[b]	38	SIPS; PANSS	39.5	2.5	**1**	Smaller MMN amplitudes (2) greater MMN deficits (3) Double-deviant MMN[c]
Kautsouleris et al., 2013 [37]	CHR	73	BSIP; BPRS, SANS, PANSS	45.2	4.0	**1** **2**	Reduced GM in bilateral prefrontal and lateral subcortical structures (basal ganglia, cerebellar lobules, vermal lobules) Increased GM in lateral perisylvian/ temporal and subcortical structures (pallidum, verbal lobules, cerebellar lobules)
Tognin et al., 2013 [39]	CHR	167	CAARMS; BSIP; BSABS	29.9	2.0	•	None reported (trend for cortical thinning in inferior frontal gyrus)
Cannon et al., 2014 [40]	CHR	274	SIPS	12.8	12	**1** **2** **3**	Steeper rates of cortical thinning in superior frontal, middle frontal, and medial orbitofrontal gyri Greater third ventricle expansion Greater correlation between prefrontal cortical thinning and high levels of proinflammatory markers
Walker et al., 2013 [41]	CHR	256[d]	SIPS	23.5[d]	24	**1**	Higher BL cortisol levels

Color-coding: Blue=psychophysiological studies; pink=neuroimaging studies; yellow=neurohormonal studies

Abbreviations: HR=high-risk; CR=conversion rate; SIPS=Structured Interview for Prodromal Syndromes; SPI=Schizophrenia Proneness Instrument; PANSS=Positive and Negative Syndrome Scale; NR=not reported; BSIP=Basel Screening Instrument for Psychosis; BPRS=Brief Psychiatric Rating Scale; SANS=Scale for the Assessment of Negative Symptoms; GM=Gray matter; CAARMS=Comprehensive Assessment of At-Risk Mental State; BSABS=Bonn Scale for the Assessment of Basic Symptoms; BL=baseline

[a] Of HR group only

[b] As compared to FE/SZ & HC

[c] Predicts time to conversion

[d] Prediction analyses were conducted on subset of 136 individuals