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Neurocognitive resilience as a predictor of psychosis onset and functional outcomes in individuals at high risk

TianHong Zhang[1*†], XiaoChen Tang[1†], YanYan Wei[1†], LiHua Xu[1], HuiRu Cui[1], HaiChun Liu[2], ZiXuan Wang[3], Tao Chen[4,5], LingYun Zeng[6], YingYing Tang[1], ZhengHui Yi[1], ChunBo Li[1] and JiJun Wang[1,7*]

Abstract

Background Neurocognitive resilience (NCR) refers to the ability of individuals to maintain cognitive function despite the presence of risk factors for psychosis. Investigating NCR is important as it may help predict the onset of psychosis and functional outcomes in individuals at clinical high risk (CHR) for psychosis.

Methods This study employed a multi-group prospective design with a 3-year follow-up as part of the Shang-Hai At Risk for Psychosis-Extended project. Neurocognitive performance was assessed using the Chinese version of the Measurement and Treatment Research to Improve Cognition in Schizophrenia Consensus Cognitive Battery. The study focused on two primary outcomes: conversion/non-conversion to psychosis (CHR-C/CHR-NC) and non-remission/remission (CHR-NR/CHR-R). NCR was defined based on the adjusted cognitive variable relative to the healthy control(HC) group's mean, with three categories: NCR (NCR = 0) for scores within one standard deviation, NCR + (NCR = 1) for scores more than one standard deviation above, and NCR − (NCR = − 1) for scores more than one standard deviation below.

Results The study included 771 individuals at CHR (346 males, mean age 18.8 years) and 764 HCs (359 males, mean age 22.5 years). Among the CHR participants, 540 (70.0%) completed the 3-year follow-up, with 106 (19.6%) converting to psychosis (CHR-C) and 277 (51.3%) classified as non-remission (CHR-NR). Significant negative correlations were found between the total NCR score and various clinical symptoms. Comparing CHR-C and non-converters (CHR-NC), there were notable differences in NCR distributions across four cognitive measures, with a higher proportion of CHR-C individuals categorized as NCR − . For CHR-NR versus remission (CHR-R), CHR-NR individuals were more likely to be classified as NCR − across nearly all cognitive domains. The receiver operating characteristic (ROC) curve for predicting conversion to psychosis yielded an area under the curve (AUC) of 0.621 (95% CI (0.561–0.681), $p = 0.0001$), while the ROC for predicting non-remission demonstrated a higher AUC of 0.826 (95% CI (0.790–0.861), $p < 0.0001$).

Conclusions NCR was associated with both conversion to psychosis and non-remission outcomes in CHR individuals, showing notable predictive accuracy, particularly for non-remission.

†TianHong Zhang, XiaoChen Tang and YanYan Wei contributed equally to this work.

*Correspondence:
TianHong Zhang
zhang_tianhong@126.com
JiJun Wang
jijunwang27@163.com
Full list of author information is available at the end of the article

Keywords Cognition, Ultra high risk, Prodromal psychosis, Transition, Remission, Functional outcome

Background

Clinical high risk (CHR) for psychosis is a pre-onset state marked by a heightened vulnerability to developing a full-blown psychotic disorder [1]. Individuals in the CHR phase typically experience attenuated positive symptoms, which are milder versions of psychotic symptoms like hallucinations or delusions, along with some may show short-lived but more intense symptoms or significant functional decline in the context of genetic risk factors [2]. These symptoms may include perceptual abnormalities or thought content disturbances. Though not fully psychotic, these symptoms signal an elevated risk for progressing to psychosis [3, 4]. Extensive research has demonstrated that CHR individuals already exhibit cognitive impairments [5, 6]. Their cognitive deficits are more pronounced than the unimpaired cognitive state of healthy controls, while being less severe than those of first-episode psychosis patients [7, 8]. Importantly, the severity of cognitive impairment in CHR individuals has been strongly correlated with the likelihood of later developing psychosis [9, 10].

Resilience is commonly understood as the ability to adapt and recover in the face of adversity, stress, or trauma. In psychology, resilience refers to an individual's capacity to withstand challenging life events and maintain or regain mental health and well-being [11]. People with higher resilience are typically better able to manage difficult circumstances, such as trauma, loss, or prolonged stress, and emerge from them without long-term negative effects on their psychological or emotional functioning [12]. This concept has gained significant attention across various fields of mental health research, particularly in understanding how certain individuals resist developing psychiatric disorders despite being exposed to risk factors. In the context of mental health, resilience can also be applied to more specific domains, such as cognitive functioning. This is where the concept of cognitive resilience comes into play. Neurocognitive resilience (NCR) refers to the brain's capacity to maintain cognitive performance when exposed to risk factors or stressors that could potentially impair neurocognitive functioning. For individuals at CHR state, NCR could be crucial in determining whether they progress to a psychotic disorder or remain stable without significant functional decline.

Leveraging the large cohort with a 3-year follow-up of CHR individuals, our study aims to explore the role of NCR as a potential protective factor against the progression to psychosis and poor functional outcomes. Specifically, we seek to determine whether NCR can predict the likelihood of conversion to psychosis or non-remission over time. Our hypothesis is that higher NCR will be associated with a reduced risk of both psychosis and poor functional outcomes, while lower NCR will indicate a greater vulnerability to these adverse trajectories.

Methods

Participants and design

This study is part of the ongoing Shanghai At Risk for Psychosis-extended (SHARP-extended) program [13–15], involving a cohort of 771 individuals identified as being at CHR. These participants underwent comprehensive cognitive assessments after seeking help for the first time at the Shanghai Mental Health Center (SMHC) between January 1, 2016, and June 31, 2024. The research specifically focuses on individuals enrolled in an early psychosis identification program at SMHC, China. All participants provided written informed consent. For those under 18 years of age, written consent was obtained from both the participants and their parents. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2013. All procedures involving human subjects/patients were approved by the SMHC research ethics committee (IRB2016-009).

CHR status was determined through face-to-face interviews using the Structured Interview for Prodromal Syndromes (SIPS) [16, 17]. The participants, aged between 14 and 35 years, had a minimum of 6 years of primary education. Exclusion criteria included severe somatic illnesses (e.g., cancer), intellectual disabilities, developmental disorders, and substance abuse. At baseline, participants were screened with the Mini International Neuropsychiatric Interview (MINI 5.0) [18] to rule out other Axis-I psychiatric disorders. A key feature of the sample is that all participants were medication-naive at the time of enrollment and had never received treatment for any psychiatric condition. Moreover, the sample excluded individuals with a history of substance abuse or dependence that could lead to psychotic symptoms, such as methamphetamine, cocaine, lysergic acid diethylamide, phenylcyclohexyl piperidine, hallucinogenic drugs, and cannabis use. Healthy controls (HC), apart from not meeting the CHR criteria, were excluded if they had a personal history of mental disorders or a family history

of psychotic disorders, and other inclusion and exclusion criteria were the same as those for the CHR group.

Participants were followed for at least 3 years after their initial assessment, provided they consented to follow-up and completed the initial evaluation. Those at CHR were re-assessed annually, either by telephone or through face-to-face interviews, using the SIPS, unless they opted out of further contact. Among the 771 individuals at CHR, 540 (70.0%) completed the 3-year SIPS reassessments, 165 did not reach the end of the follow-up period, and 66 were lost to follow-up. Further details on the study's procedures, settings, measurements, and assessments can be found in previous publications [3, 19–21].

Clinical assessments and outcome definition

The SIPS [16] was utilized to identify individuals at CHR for psychosis, consists of 19 items that evaluate symptoms across four domains: positive symptoms (P1–P5: unusual thought content, suspiciousness, grandiosity, perceptual abnormalities, and disorganized communication), negative symptoms (N1–N6: social anhedonia, avolition, emotional expression, emotional experience and self-perception, ideational richness, and occupational functioning), disorganized symptoms (D1–D4: odd behavior or appearance, bizarre thinking, trouble with focus and attention, and impairment in personal hygiene), and general symptoms (G1–G4: sleep disturbance, dysphoric mood, motor disturbances, and impaired stress tolerance). The SIPS assessments conducted at the SMHC demonstrated high inter-rater reliability, with a correlation coefficient (r) of 0.96 ($p < 0.01$) for the SIPS scores, and a kappa value for agreement among the four interviewers ranging from 0.81 to 0.95. The inter-rater reliability (intraclass correlation coefficient, ICC) for SIPS-positive symptoms varied between 0.86 (P5) and 0.98 (P4) across the four raters.

This follow-up study primarily focused on two outcomes: conversion to psychosis and non-remission. Conversion was determined based on the Presence of Psychotic Symptoms in SIPS (POPS) criteria, which required participants to develop at least one psychotic-level symptom rated as a "6" on the SIPS positive symptom scale, with adequate frequency or duration. CHR individuals who completed the follow-up were categorized into those who converted to psychosis (CHR-C) and those who did not (CHR-NC).

Non-remission (CHR-NR) [22] included two subgroups: (1) individuals who converted to psychosis and (2) CHR individuals who either had persistent positive symptoms (that did not fully progress to psychosis) or exhibited poor global functioning at follow-up. The operational definition of CHR-NR included three criteria: (1) conversion to psychosis; (2) persistent symptoms, defined as scores of 3–5 on the SIPS positive symptoms at follow-up; and (3) poor global functioning, indicated by a Global Assessment of Functioning (GAF) score below 60 at follow-up [23, 24]. This subgroup represents an atypical form of conversion where CHR individuals do not fully convert to psychosis but still experience poor outcomes. The remaining CHR individuals were classified as being in remission (CHR-R). This comprehensive definition of non-remission is crucial as it captures the diverse range of sub-optimal outcomes in CHR individuals. By including both those who progress to full-blown psychosis and those with persistent sub-psychotic symptoms or poor functioning, our study can more accurately assess the overall impact of risk factors. It also aligns with the complex nature of psychosis-related disorders in real-world clinical settings, where patients often present with a spectrum of symptoms and functional impairments that may not neatly fit into a binary classification of remission or full-scale psychosis conversion.

It is important to note that there is an overlap between the "Converted to Psychosis" and "Non-Remission" groups. The "Converted to Psychosis" group is strictly defined by the appearance of a psychotic-level symptom, which represents a key milestone in the progression of psychosis. This categorization primarily focuses on the presence and severity of positive symptoms reaching a psychotic threshold. In contrast, the "Non-Remission" group has a broader scope. It encompasses not only those who have converted to psychosis but also individuals with persistent sub-psychotic positive symptoms and those with poor global functioning (CHR-S). This comprehensive approach is crucial as it reflects the diverse ways in which CHR individuals may experience less-than-optimal outcomes [25]. A Venn diagram (Fig. 1) is presented to illustrate these concepts.

Neuro-cognitive assessments and NCR criteria

Neurocognitive functioning was evaluated using the Chinese version of the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB) [26]. The assessments were administered in accordance with the standardized procedures outlined in the MCCB test manual. Similar to the original MCCB, this study incorporated eight subtests: (1) Trail Making Test, Part A (Trail Making A); (2) Symbol Coding from the Brief Assessment of Cognition in Schizophrenia (BACS); (3) Category Fluency Test (Category Fluency); (4) Continuous Performance Test, Identical Pairs version (CPT-IP); (5) Spatial Span from the Wechsler Memory Scale-III (WMS-3 Spatial Span); (6) Hopkins Verbal Learning Test-Revised (HVLT-R); (7) Brief Visuospatial Memory

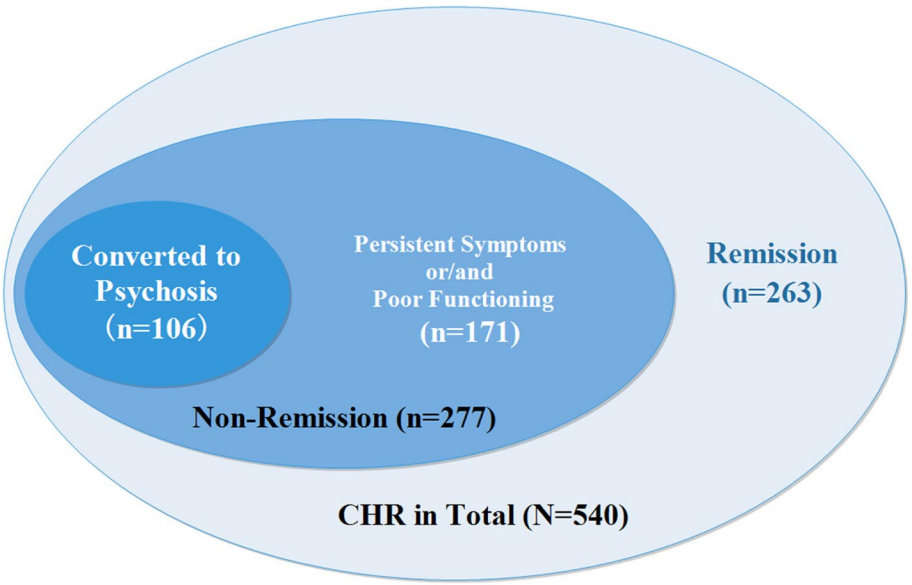


Fig. 1 Venn diagram illustrating outcome categories among CHR individuals. This Venn diagram depicts the distribution of 540 CHR (clinical high risk) individuals across three outcome categories: remission, non-remission, and conversion to psychosis. The non-remission group ($n = 277$) includes 106 individuals who converted to psychosis, as well as 171 individuals with persistent symptoms or poor functioning. The remission group consists of 263 individuals who have neither persistent symptoms nor poor global functioning. The overlapping and non-overlapping areas clearly show the relationships and categorization of CHR individuals based on their outcomes

Test-Revised (BVMT-R); and (8) Mazes from the Neuropsychological Assessment Battery (NAB Mazes). The inter-rater reliability of the MCCB, determined by the ratings of four trained evaluators, ranged from 0.82 to 0.95.

NCR is defined based on the adjusted cognitive variable in relation to the mean of the HC group. Specifically, NCR is categorized as follows: NCR (NCR = 0) indicates that the adjusted cognitive variable is within one standard deviation of the HC group's mean. NCR + (NCR = 1) denotes that the adjusted cognitive variable is more than one standard deviation above the HC group mean, while NCR − (NCR = −1) signifies that the adjusted cognitive variable is more than one standard deviation below the HC group mean. This operationalization assumes that cognitive performance relative to HC reflects resilience, as it captures the ability to maintain functioning despite prodromal symptoms (a known stressor). The MCCB subtests chosen (e.g., processing speed, working memory) were selected for their sensitivity to stress-induced impairments and relevance to real-world adaptive functioning.

In cognitive and clinical research, standard deviation-based cutoffs are a widely accepted method for categorizing cognitive variables relative to a reference group. Using the healthy control group as a reference, this approach allows for a direct comparison of an individual's cognitive performance. NCR = 0 represents normal cognitive resilience, NCR + indicates better-than-average resilience potentially protecting against psychosis, and NCR − suggests lower resilience. This categorization of NCR provides a straightforward and clinically relevant framework. It enables clinicians to quickly classify individuals at CHR into distinct groups based on their cognitive resilience, which can inform treatment decisions and intervention strategies. Additionally, this classification system allows for easier communication among researchers and clinicians, as it provides a standardized way to discuss and compare cognitive resilience levels across different studies and patient populations.

Data analysis

Quantitative variables were summarized as means ± standard deviations (SDs), while qualitative variables were expressed as frequencies and percentages. Cognitive variables were adjusted for age and sex using linear regression models to ensure that the comparisons were not confounded by these factors. The distribution of NCR categories was analyzed across various cognitive domains within the CHR group. To assess the relationship between total NCR scores and baseline clinical symptoms in the CHR group, Spearman correlation analysis was conducted. The distribution of NCR categories (NCR +, NCR, NCR −) was further examined in relation to clinical outcomes, specifically conversion to psychosis and non-remission, allowing for a detailed understanding of how cognitive

resilience impacts these outcomes. Receiver operating characteristic (ROC) curves were constructed to evaluate the predictive value of total NCR scores for both conversion and non-remission. The area under the curve (AUC) was calculated to quantify the overall accuracy of NCR scores in predicting these outcomes. Sensitivity and specificity were also computed at various NCR cut-off points to identify the optimal thresholds for distinguishing between CHR individuals who converted to psychosis or experienced non-remission, versus those who did not.

Results

The CHR group had a significantly younger mean age (18.79 years) compared to the HC group (22.45 years). There were no significant differences in gender distribution between the groups ($p=0.406$). The CHR group had fewer years of education (mean 10.82 years) than the HC group (mean 14.36 years) ($t=22.330$, $p<0.001$). Parental education levels did not differ significantly between the groups. In terms of cognitive functioning, the CHR group performed worse than the HC group across all cognitive tests, with all differences being statistically significant ($p<0.001$) (Table 1). Additional file 1: Table S1 compares the demographic, clinical, and cognitive characteristics among CHR-C, CHR-S, and CHR-R groups.

Linear regression models were employed to adjust cognitive variables for age and sex, yielding significant findings for several cognitive measures (Table 2). The regression coefficients (β) indicate how age and sex contribute to the original cognitive scores. For example, in the Trail Making A test, age had a significant negative effect ($\beta_{age}=-0.188$, $p=0.002$), while sex (being female) had a significant positive effect ($\beta_{sex}=1.631$, $p=0.011$). The adjusted cognitive score for each participant was calculated using the formula: Original Cognitive Score $-$ (Age $\times \beta_{age}$ + Sex $\times \beta_{sex}$ + Constant).

The distribution of the NCR, NCR+, and NCR− categories across various cognitive domains in the CHR

Table 1 Demographic, clinical, and cognitive characteristics and comparisons between CHR and HC

Variables (mean, SD)	HC		CHR		Comparisons	
					t/χ^2	*p*
Cases (*n*, %)	764		771		-	-
Age (years)	22.45	4.851	18.79	5.127	**14.344**	**< 0.001**
Male (*n*, %)	359	47.0%	346	44.9%	0.690	0.406
Female (*n*, %)	405	53.0%	425	55.1%		
Education (years)	14.36	3.066	10.82	3.144	**22.330**	**< 0.001**
Father education (years)	11.02	3.381	10.97	3.634	0.263	0.793
Mother education (years)	10.27	3.715	10.37	3.916	−0.514	0.607
Family history (none) (*n*, %)	-	-	577	74.8%	-	-
Family history (low-risk) (*n*, %)	-	-	151	19.6%		
Family history (high-risk) (*n*, %)	-	-	43	5.6%		
GAF score	-	-	57.21	8.047	-	-
Positive symptoms	-	-	9.09	3.716	-	-
Negative symptoms	-	-	11.53	5.799	-	-
Disorganization symptoms	-	-	5.32	3.166	-	-
General symptoms	-	-	8.25	3.514	-	-
SIPS total score	-	-	34.21	11.848	-	-
Trail Making A	28.85	10.479	33.79	13.936	**−7.836**	**< 0.001**
BACS symbol coding	64.93	10.095	56.97	10.439	**15.182**	**< 0.001**
HVLT-R	26.59	4.176	24.28	5.151	**9.675**	**< 0.001**
WMS-3 spatial span	16.69	2.951	15.37	3.190	**8.423**	**< 0.001**
NAB mazes	19.38	4.885	17.34	6.018	**7.306**	**< 0.001**
BVMT-R	28.35	5.342	26.27	6.399	**6.909**	**< 0.001**
Category fluency	23.65	5.671	20.26	5.726	**11.642**	**< 0.001**
CPT-IP	2.91	0.655	2.45	0.797	**12.460**	**< 0.001**

GAF Global Assessment of Functioning score, low-risk family history, having any family members with mental disorders or a first-degree relative with non-psychotic disorders; high-risk family history, having at least one first-degree relative with psychosis; *SIPS* Structured Interview for Prodromal Syndromes, *SD* Standard deviation, *BACS* Brief Assessment of Cognition in Schizophrenia symbol coding, *BVMT-R* Brief Visuospatial Memory Test–Revised, *CPT-IP* Continuous Performance Test–Identical Pairs, *HVLT-R* Hopkins Verbal Learning Test–Revised, *NAB* Neuropsychological Assessment Battery mazes, *WMS-3* Wechsler Memory Scale–Third Edition spatial span, t/χ^2 *t* for independent *t* test, χ^2 for kappa test. Significant statistical results are presented in bold

Table 2 Linear regression models for adjusting cognitive variables by age and sex

	Age (years)		Sex (1 = man; 2 = woman)		Constant	
	β (S.E.)	*t (p)*	*β (S.E.)*	*t (p)*	*β (S.E.)*	*t (p)*
Trail Making A	−0.188 (0.060)	**−3.125 (0.002)**	1.631 (0.641)	**2.543 (0.011)**	32.692 (1.634)	**20.010 (<0.001)**
BACS symbol coding	0.161 (0.053)	**3.052 (0.002)**	0.756 (0.562)	1.344 (0.179)	56.448 (1.433)	**39.385 (<0.001)**
HVLT-R	−0.021 (0.023)	−0.921 (0.357)	0.831 (0.247)	**3.368 (0.001)**	24.590 (0.628)	**39.137 (<0.001)**
WMS-3 spatial span	−0.004 (0.015)	−0.287 (0.774)	−0.945 (0.159)	**−5.930 (<0.001)**	17.571 (0.406)	**43.300 (<0.001)**
NAB mazes	−0.069 (0.026)	**−2.637 (0.008)**	−2.083 (0.280)	**−7.430 (<0.001)**	22.994 (0.714)	**32.202 (<0.001)**
BVMT-R	−0.078 (0.029)	**−2.709 (0.007)**	1.013 (0.305)	**3.322 (0.001)**	27.339 (0.777)	**35.188 (<0.001)**
Category Fluency	0.159 (0.028)	**5.609 (<0.001)**	−0.129 (0.302)	−0.428 (0.668)	18.876 (0.769)	**24.547 (<0.001)**
CPT-IP	0.034 (0.004)	**9.563 (<0.001)**	−0.025 (0.038)	−0.659 (0.510)	2.012 (0.097)	**20.721 (<0.001)**

Adjusted Cognitive Score = Original Cognitive Score − (Age × (β) + Sex × (β) + Constant)

β Denotes the regression coefficient, *SE* is the standard error. Significant statistical results are presented in bold

Abbreviations: BACS Brief Assessment of Cognition in Schizophrenia symbol coding , *BVMT-R*Brief Visuospatial Memory Test–Revised , *CPT-IP*Continuous Performance Test–Identical Pairs , *HVLT-R*Hopkins Verbal Learning Test–Revised, *NAB*Neuropsychological Assessment Battery mazes , *WMS-3*Wechsler Memory Scale–Third Edition spatial span

Table 3 Distribution of neurocognitive resilience (NCR) categories in CHR group across cognitive domains

CHR (*N* = 771)	NCR +		NCR		NCR −	
	N	*%*	*N*	*%*	*N*	*%*
Trail Making A	$TMT_{NCR+} > 8.41$		$-12.64 < TMT_{NCR} < 8.41$		$TMT_{NCR-} < -12.64$	
	62	8.0%	535	69.4%	174	22.6%
BACS symbol coding	$BACS_{NCR+} > 13.88$		$-6.46 < BACS_{NCR} < 13.88$		$BACS_{NCR-} < -6.46$	
	35	4.5%	440	57.1%	296	38.4%
HVLT-R	$HVLT_{NCR+} > 5.35$		$-2.93 < HVLT_{NCR} < 5.35$		$HVLT_{NCR-} < -2.93$	
	61	7.9%	439	56.9%	271	35.1%
WMS-3 spatial span	$WMS_{NCR+} > 3.59$		$-2.27 < WMS_{NCR} < 3.59$		$WMS_{NCR-} < -2.27$	
	37	4.8%	492	63.8%	242	31.4%
NAB mazes	$NAB_{NCR+} > 5.95$		$-3.68 < NAB_{NCR} < 5.95$		$NAB_{NCR-} < -3.68$	
	89	11.5%	435	56.4%	247	32.0%
BVMT-R	$BVMT_{NCR+} > 6.46$		$-4.07 < BVMT_{NCR} < 6.46$		$BVMT_{NCR-} < -4.07$	
	44	5.7%	491	63.7%	236	30.6%
Category Fluency	$CF_{NCR+} > 7.04$		$-4.23 < CF_{NCR} < 7.04$		$CF_{NCR-} < -4.23$	
	66	8.6%	460	59.7%	245	31.8%
CPT-IP	$CPT_{NCR+} > 0.82$		$-0.48 < CPT_{NCR} < 0.82$		$CPT_{NCR-} < -0.48$	
	66	8.6%	449	58.2%	256	33.2%

NCR (neurocognitive resilience) is defined as follows: NCR (NCR = 0): the adjusted cognitive variable is within one standard deviation of the mean of the HC group. NCR + (NCR = 1): the adjusted cognitive variable is greater than one standard deviation above the mean of the HC group. NCR − (NCR = − 1): the adjusted cognitive variable is less than one standard deviation below the mean of the HC group.

Abbreviations: BACS Brief Assessment of Cognition in Schizophrenia symbol coding, *BVMT-R* Brief Visuospatial Memory Test–Revised, *CPT-IP* Continuous Performance Test–Identical Pairs, *HVLT-R* Hopkins Verbal Learning Test–Revised, *NAB* Neuropsychological Assessment Battery mazes, *WMS-3* Wechsler Memory Scale–Third Edition spatial span

group is detailed in Table 3. For instance, in the Trail Making A test, 8.0% of the CHR group fell into the NCR + category, 69.4% were in the NCR category, and 22.6% were in the NCR − category. Similar patterns were observed across other cognitive measures, with varying percentages of the CHR group classified into each NCR category.

The Spearman correlation analysis was conducted to examine the relationship between the total NCR score and various baseline clinical symptoms in the CHR group. As illustrated in Fig. 2, significant negative correlations were observed between the total NCR score and several clinical symptoms, including positive symptoms ($r = -0.140$, $p < 0.001$), negative symptoms ($r = -0.222$,

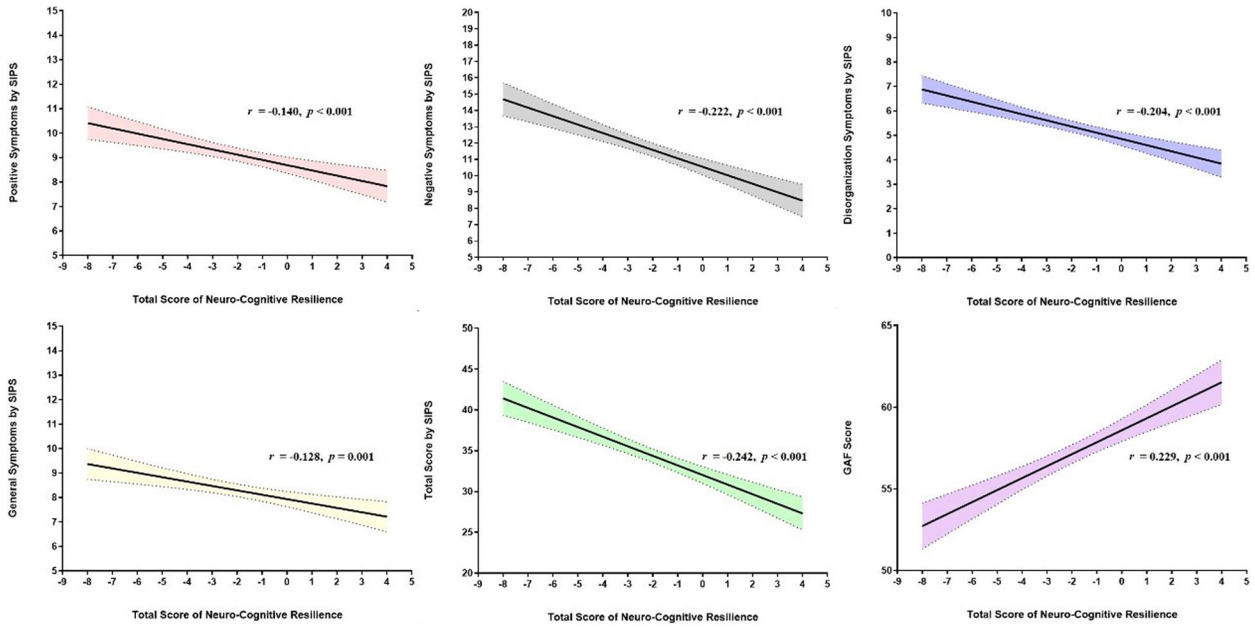


Fig. 2 Spearman correlations between total neurocognitive resilience (NCR) score and baseline clinical symptoms in the clinical high risk group. This figure displays six scatter-plot graphs, each illustrating the Spearman correlation between the total NCR score and a different type of baseline clinical symptom in the clinical high risk (CHR) group. The total score of NCR is calculated as the sum of the NCR values from 8 cognitive tests, where each test has NCR values of − 1, 0, or 1, resulting in a score range from − 8 to 8. Top–left graph: It shows the relationship between the total NCR score and positive symptoms as measured by the SIPS. The Spearman correlation coefficient (*r*) is − 0.140, with a *p*-value < 0.001. The negative correlation indicates that as the total NCR score increases, the level of positive symptoms tends to decrease. The shaded area around the regression line represents the confidence interval, providing an estimate of the uncertainty around the correlation. Top–middle graph: This graph depicts the correlation between the total NCR score and negative symptoms by SIPS. The *r* value is − 0.222, with a *p*-value < 0.001. Similar to the previous graph, a negative correlation is observed, suggesting that higher total NCR scores are associated with lower levels of negative symptoms. Top–right graph: It illustrates the relationship between the total NCR score and disorganization symptoms as measured by SIPS. The correlation coefficient *r* is − 0.204, with a *p*-value < 0.001, indicating an inverse relationship between the total NCR score and disorganization symptoms. Bottom–left graph: Here, the correlation between the total NCR score and general symptoms by SIPS is shown. The *r* value is 0.128, with a *p*-value < 0.001. This positive correlation implies that as the total NCR score increases, the level of general symptoms also tends to increase, though the correlation is relatively weaker compared to the negative correlations seen above. Bottom–middle graph: This graph represents the correlation between the total NCR score and the total score of SIPS. The *r* value is − 0.242, with a *p*-value < 0.001, showing a negative relationship where higher total NCR scores are associated with lower total SIPS scores. Bottom–right graph: It shows the correlation between the total NCR score and the Global Assessment of Functioning (GAF) score. The *r* value is 0.229, with a *p*-value < 0.001. A positive correlation is observed, meaning that higher total NCR scores are related to higher GAF scores, indicating better overall functioning. Note: GAF, Global Assessment of Functioning score; SIPS, Structured Interview for Prodromal Syndromes. The *r* refers to Spearman correlation coefficient

$p < 0.001$), disorganization symptoms ($r = -0.204$, $p < 0.001$) general symptoms ($r = -0.128$, $p < 0.001$), and SIPS total score ($r = -0.242$, $p < 0.001$). In contrast, a positive correlation was found between the GAF score and the total NCR score ($r = 0.229$, $p < 0.001$).

Among 540 CHR completed the 3-year follow-up, with 106 (19.6%) converting to psychosis and 277 (51.3%) classified as non-remission. The distribution of NCR categories (NCR+, NCR, NCR−) was analyzed among CHR individuals based on their conversion and remission outcomes. In Fig. 3A, comparing CHR-C to CHR-NC, significant differences in NCR distributions were observed across several cognitive measures, a higher proportion of CHR-C individuals fell into the NCR − category for BACS symbol coding ($\chi^2 = 11.236$, $p = 0.004$), HVLT-R ($\chi^2 = 6.107$, $p = 0.047$), NAB mazes ($\chi^2 = 10.107$, $p = 0.007$), and BVMT-R ($\chi^2 = 10.302$, $p = 0.006$). Figure 3B compares CHR-NR to CHR-R. The analysis revealed that CHR-NR individuals were more likely to be categorized as NCR − across almost all cognitive domains, including BACS symbol coding ($\chi^2 = 59.140$, $p < 0.001$), HVLT-R ($\chi^2 = 59.576$, $p < 0.001$), WMS-3 spatial span ($\chi^2 = 42.110$, $p < 0.001$), NAB mazes ($\chi^2 = 76.710$, $p < 0.001$), BVMT-R ($\chi^2 = 64.210$, $p < 0.001$), and CPT-IP ($\chi^2 = 67.254$, $p < 0.001$). Conversely, CHR-R were more likely to be categorized as NCR or NCR+.

In Fig. 4A, the ROC curve for predicting conversion shows an AUC of 0.621 (95% CI: (0.561–0.681), $p = 0.0001$). The table on the right indicates that a cutoff of NCR < − 2.5 provides a sensitivity of 60.38% and specificity of 61.75%, demonstrating a moderate ability of the

total NCR score to predict conversion. Figure 4B displays the ROC curve for predicting non-remission, with a higher AUC of 0.826 (95% CI: (0.790–0.861), $p < 0.0001$), indicating strong predictive accuracy. The corresponding table shows that a cutoff of total NCR score < −1.5 offers a sensitivity of 81.81% and specificity of 70.72%, highlighting the total NCR score's robust ability to distinguish between non-remission and remission. Additional files 2–3 (Tables S2–S3) and Additional files 4–5 (Figs. S1–S2) present the logistic regression models and ROC curves for predicting CHR-C or CHR-NR when treating cognitive characteristics as continuous variables.

Discussion

This study has several strengths, most notably the introduction and application of the NCR concept in a large sample of individuals at CHR for psychosis, compared with HC. This is the first study to calculate NCR while controlling for potential cognitive performance influences such as age and sex. The key findings reveal that NCR was associated with reduced risk of progression to psychosis and non-remission outcomes in CHR individuals. Specifically, the study demonstrates that lower NCR scores are associated with a higher risk of adverse outcomes, particularly non-remission. Furthermore, the study establishes that NCR is significantly correlated with baseline clinical symptoms and functional characteristics, where lower NCR scores correspond to greater symptom severity and poorer overall functioning. These findings underscore the potential of NCR as a predictive and protective factor in the management of CHR populations.

This study highlights a significant relationship between NCR and the outcome of conversion to psychosis, with specific cognitive domains showing stronger associations with conversion risk. Notably, individuals categorized in the NCR − group for the BACS symbol coding, HVLT-R, NAB mazes, and BVMT-R tests demonstrated a higher likelihood of conversion to psychosis. These four tests assess key neurocognitive abilities, such as processing speed (BACS symbol coding), verbal memory (HVLT-R), visuospatial memory (BVMT-R), and executive function (NAB mazes). The deficits observed in these areas [27] may reflect underlying vulnerabilities in cognitive processes that are crucial for managing daily life and coping with attenuated psychotic symptoms, which may exacerbate the progression toward psychosis [28–31]. These findings are in line with Cannon et al.'s development of the Individualized Risk Calculator for Psychosis [32], which also incorporated these two cognitive assessments into its predictive model. Our study further reinforces the importance of these cognitive domains in understanding psychosis progression, as individuals with lower NCR scores in these areas were more likely to convert to psychosis. The total NCR score demonstrates moderate predictive value for conversion to psychosis, underscoring the role of NCR in distinguishing individuals at higher risk. This suggests that higher levels of NCR may serve as a protective factor against the onset of psychosis, while lower resilience may increase vulnerability, offering critical insights for early intervention strategies aimed at enhancing resilience in at-risk populations.

Although our study has established notable links between NCR and outcomes in CHR individuals, exploring the underlying biological and neurodevelopmental mechanisms is crucial. One potential mechanism lies in neurotransmitter systems. Dopamine, for example,

(See figure on next page.)

Fig. 3 Distribution of neurocognitive resilience (NCR) categories across conversion and remission outcomes in the CHR group. **A** Depicts the distribution of NCR categories (NCR −, NCR, and NCR +) among CHR individuals who converted to psychosis (CHR-C) and those who did not convert (CHR-NC). The bars are color-coded, where the blue-background segments indicate the NCR categories for which the group-to-group comparisons (between CHR-C and CHR-NC) were statistically significant. The percentages within each bar show the proportion of individuals in each NCR category for the respective conversion outcome. For example, in the Trail Making A test, 22.64% of CHR-C individuals were in the NCR-category, 73.58% in the NCR category, and 3.77% in the NCR + category. Chi-square (χ^2) and *p*-values are presented above each set of bars to quantify the significance of the differences in NCR category distributions between the two conversion outcome groups for each cognitive test. A significant *p*-value ($p < 0.05$) implies that there is a notable difference in the distribution of NCR categories between CHR-C and CHR-NC for that specific test. **B** Shows the distribution of NCR categories among CHR individuals who did not achieve remission (CHR-NR) and those who achieved remission (CHR-R). Similar to **A**, the blue-background segments highlight the NCR categories with significant group-to-group differences (between CHR-NR and CHR-R). The percentages within each bar represent the proportion of individuals in each NCR category for the respective remission outcome. For instance, in the BACS symbol coding test, 54.15% of CHR-NR individuals were in the NCR-category, 44.40% in the NCR category, and 1.45% in the NCR + category. The χ^2 and *p*-values above each set of bars help assess whether there are significant differences in the NCR category distributions between CHR-NR and CHR-R for each cognitive test. Note: NCR (neurocognitive resilience) is defined as follows: NCR (NCR = 0): the adjusted cognitive variable is within one standard deviation of the mean of the HC group. NCR + (NCR = 1): the adjusted cognitive variable is greater than one standard deviation above the mean of the HC group. NCR − (NCR = − 1): the adjusted cognitive variable is less than one standard deviation below the mean of the HC group. Abbreviations: BACS, Brief Assessment of Cognition in Schizophrenia symbol coding; BVMT-R, Brief Visuospatial Memory Test–Revised; CPT-IP, Continuous Performance Test–Identical Pairs; HVLT-R, Hopkins Verbal Learning Test–Revised; NAB, Neuropsychological Assessment Battery mazes; WMS-3, Wechsler Memory Scale–Third Edition spatial span

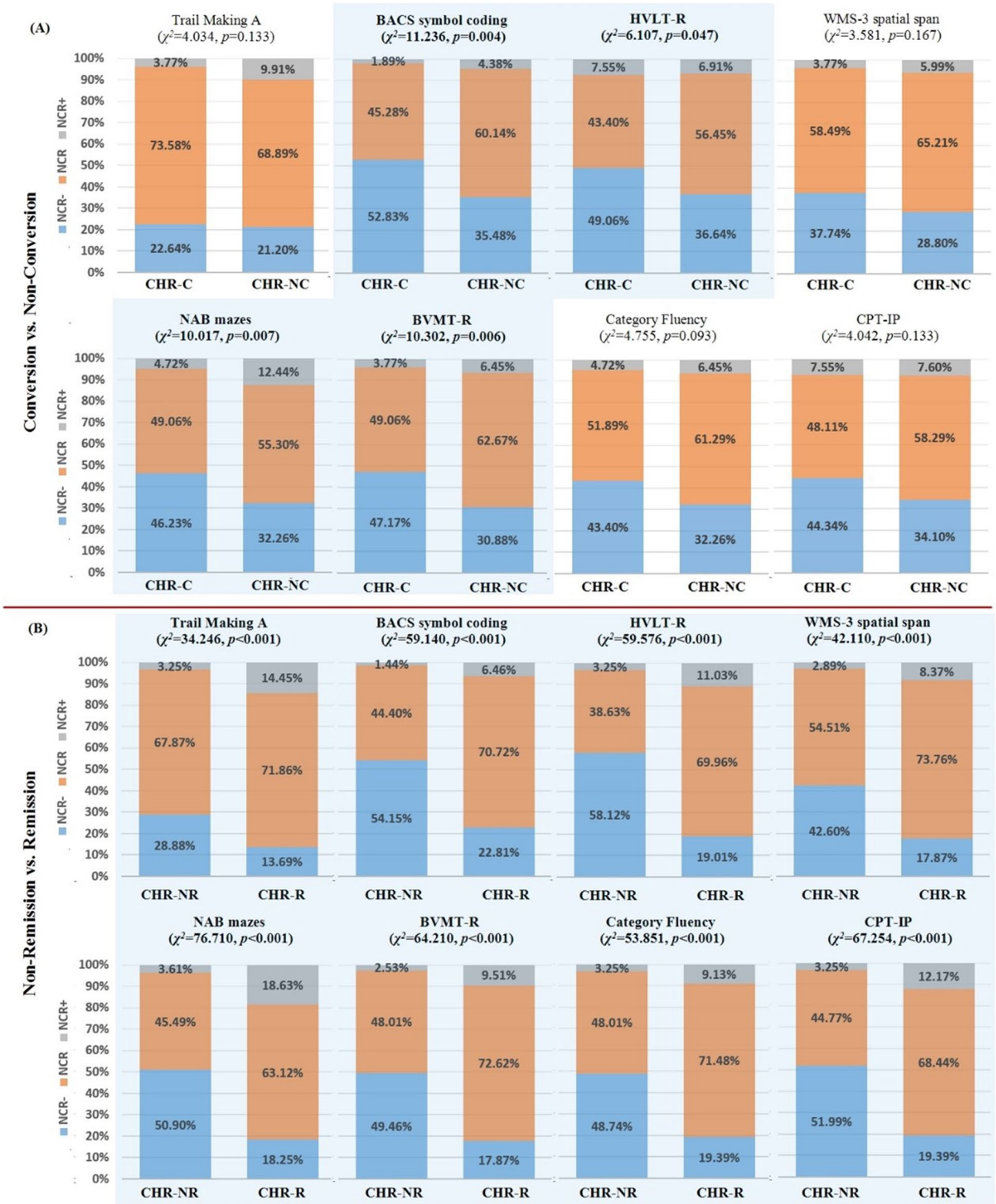


Fig. 3 (See legend on previous page.)

is integral to cognitive function; its dysregulation may disrupt neural communication in key brain regions like the prefrontal cortex [33, 34], which is vital for executive functions. This could lead to reduced cognitive resilience and increased risk of adverse outcomes in CHR individuals. Neural connectivity also plays a significant role.

Altered connections between the hippocampus and prefrontal cortex, involved in memory and decision-making [35], may be associated with lower NCR. These connectivity changes could stem from genetic factors or early-life experiences [36]. Future research could use genetic analysis to identify genes related to NCR-associated neurotransmitter and connectivity changes, and longitudinal neuroimaging to monitor these changes over time in CHR individuals. This would enhance our understanding of NCR's role in psychosis development and potentially inform more effective early-intervention strategies.

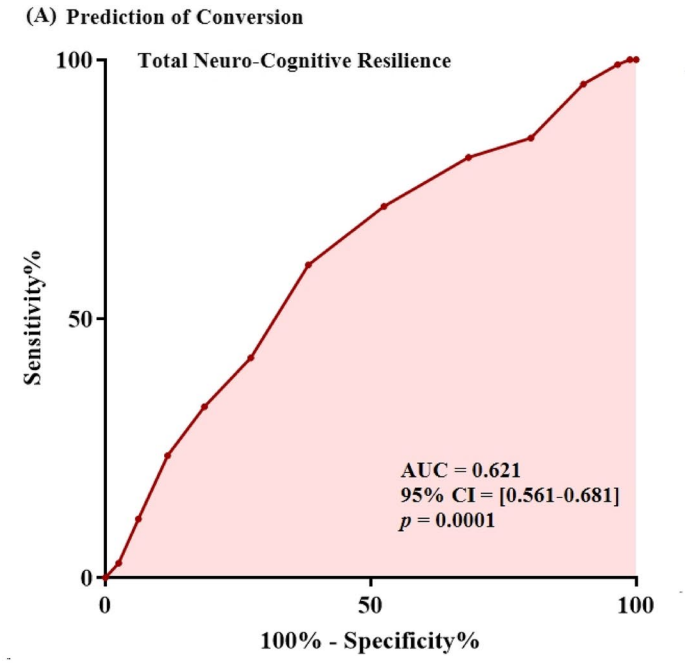
One of the key findings in this study is that NCR demonstrates even greater predictive accuracy for poor functional outcomes, with an accuracy rate reaching 82%, surpassing its ability to predict conversion to psychosis. This suggests that NCR is more directly related to functional outcomes than to the progression of psychosis itself [37]. One possible explanation is that cognitive resilience, as captured by NCR, reflects an individual's capacity to maintain cognitive performance in the face of attenuated positive symptoms, which in turn directly influences functional status [38]. In contrast, while cognitive deficits are linked to psychosis conversion, the relationship might be less direct, as conversion could involve mainly about the progression of positive symptoms [39]. This finding aligns with previous research that emphasizes the role of cognition in long-term functional outcomes [38, 40]. This deeper relationship between NCR and functional impairment could also explain why traditional models of psychosis risk, which emphasize conversion, might overlook those CHR individuals who do not transition but still experience long-term disability due to cognitive deficits. The divergence between predicting conversion and poor function could also be due to the inherent differences in how cognitive resilience operates. For functional outcomes, maintaining resilience may play a more continuous and protective role, while psychosis conversion might involve more acute and severe in positive symptoms, where resilience plays a secondary role.

The potential of NCR as a tool for identifying individuals at CHR for psychosis warrants more in-depth consideration. NCR, which measures cognitive resilience relative to HC, can act as a crucial biomarker in clinical practice. For personalized interventions, those with low NCR scores, who are at higher risk of psychosis conversion or non-remission, could benefit from tailored cognitive training [41]. This could involve exercises to enhance attention, working memory, and executive functions, aiming to boost cognitive resilience. Additionally, resilience-building programs focusing on stress management, emotion regulation, and social support could be customized based on NCR assessment, helping individuals better cope with psychosis-related stressors [42]. Moreover, NCR can serve as a metric for evaluating intervention effectiveness; regular NCR assessments during treatment can inform clinicians on whether adjustments are needed. Overall, exploring NCR-guided personalized interventions offers significant potential for reducing psychosis risk and improving outcomes in CHR individuals, and merits increased research in the future.

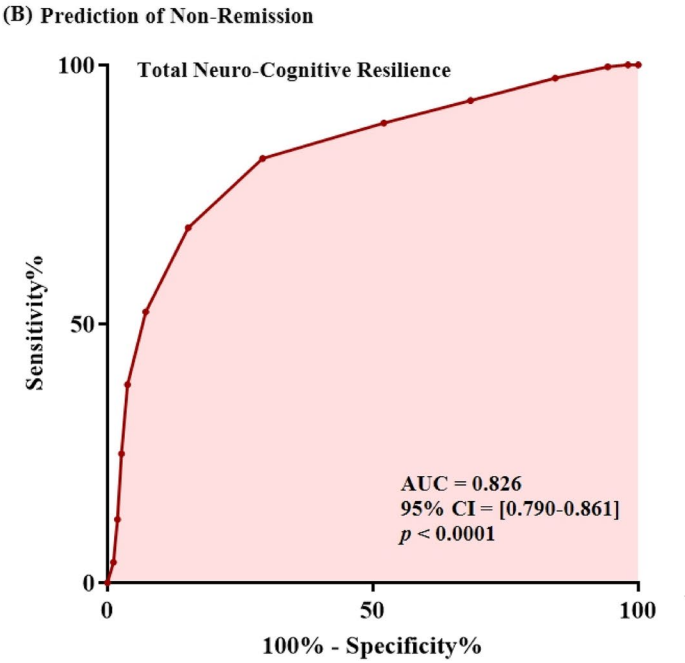
There are several limitations in this study that should be acknowledged. First, the single-center design, along with the exclusion of individuals with comorbid non-psychotic disorders and substance abuse, while allowing for a more focused examination of primary psychosis risk, limits the generalizability of the findings. The restricted

(See figure on next page.)

Fig. 4 ROC curves for predicting conversion and non-remission using total neurocognitive resilience (NCR) scores. **A** Prediction of conversion. This panel presents a receiver operating characteristic (ROC) curve that evaluates the ability of total NCR scores to predict conversion to psychosis among CHR individuals. The curve plots the true-positive rate (sensitivity) on the *y*-axis against the false-positive rate (100% − Specificity) on the *x*-axis. The area under the curve (AUC) is 0.621, with a 95% confidence interval (CI) of (0.561–0.681) and a *p*-value of 0.0001, indicating that the total NCR scores have a statistically significant but modest ability to predict conversion. Adjacent to the curve is a table that lists various cutoff values for total NCR scores, along with their corresponding sensitivity and specificity percentages. For example, a cutoff value of < − 2.500 has a sensitivity of 60.38% and a specificity of 61.75% (highlighted in the table), meaning that when the total NCR score is below this value, the test correctly identifies 60.38% of the individuals who will convert to psychosis and correctly classifies 61.75% of those who will not convert. **B** Prediction of non-remission. The ROC curve assesses the predictive power of total NCR scores for non-remission in CHR individuals. The AUC for this curve is 0.826, with a 95% CI of (0.790–0.861) and a *p*-value < 0.0001, suggesting a relatively strong and statistically significant ability of total NCR scores to predict non-remission. The accompanying table provides different cutoff values for total NCR scores and their associated sensitivity and specificity values. For instance, a cutoff of < − 1.500 has a sensitivity of 81.95% and a specificity of 70.72% (highlighted), indicating that a total NCR score below this value correctly identifies 81.95% of the individuals who will not achieve remission and correctly classifies 70.72% of those who will achieve remission. Note: NCR (neurocognitive resilience) is defined as follows: NCR (NCR = 0): the adjusted cognitive variable is within one standard deviation of the mean of the HC group. NCR + (NCR = 1): the adjusted cognitive variable is greater than one standard deviation above the mean of the HC group. NCR − (NCR = − 1): the adjusted cognitive variable is less than one standard deviation below the mean of the HC group. Abbreviations: BACS, Brief Assessment of Cognition in Schizophrenia symbol coding; BVMT-R, Brief Visuospatial Memory Test–Revised; CPT-IP, Continuous Performance Test–Identical Pairs; HVLT-R, Hopkins Verbal Learning Test–Revised; NAB, Neuropsychological Assessment Battery mazes; WMS-3, Wechsler Memory Scale–Third Edition spatial span



Cutoff	Sensitivity%	Specificity%
< -7.500	2.83	97.47
< -6.500	11.32	93.78
< -5.500	23.58	88.25
< -4.500	33.02	81.34
< -3.500	42.45	72.58
< -2.500	60.38	61.75
< -1.500	71.7	47.47
< -0.5000	81.13	31.57
< 0.5000	84.91	19.82
< 1.500	95.28	9.908
< 2.500	99.06	3.456
< 3.500	100	1.152



Cutoff	Sensitivity%	Specificity%
< -7.500	3.971	98.86
< -6.500	12.27	98.1
< -5.500	24.91	97.34
< -4.500	38.27	96.2
< -3.500	52.35	92.78
< -2.500	68.59	84.79
< -1.500	81.95	70.72
< -0.5000	88.81	47.91
< 0.5000	93.14	31.56
< 1.500	97.47	15.59
< 2.500	99.64	5.703
< 3.500	100	1.901

Fig. 4 (See legend on previous page.)

sample may not fully represent the broader CHR population, particularly those with co-occurring mental health conditions or substance use, which are common in real-world settings. Second, the SHARP cohort reflects a naturalistic, real-world clinical environment where routine treatments were not standardized or strictly controlled. This means that some participants may have been prescribed medications during the follow-up period, and the specifics of medication use, including dosage and adherence, were not systematically monitored. This introduces medication as a potential confounding factor, which could have influenced both cognitive outcomes and clinical trajectories, thereby complicating the interpretation of the results [43–45]. Third, IQ was not assessed in this study, limiting our ability to account for its possible effects on NCR evaluation. Since cognitive resilience

might vary across different IQ levels, the absence of IQ data makes it difficult to determine how intellectual capacity could have influenced the findings, especially in relation to NCR and its association with clinical outcomes. To address these limitations, future research should conduct multi-center studies with a more inclusive sample that incorporates individuals with comorbid non-psychotic disorders and substance use. Additionally, strict monitoring of medication use, including dosage and adherence, and assessment of IQ should be integrated into the research design to better understand their impacts on NCR and psychosis-related outcomes.

Conclusions

This study introduces the novel concept of NCR and its operational definition in a large CHR cohort, providing a valuable tool for assessing cognitive resilience in individuals at risk for psychosis. While NCR is operationalized here as relative cognitive performance compared to HC, it aligns with resilience theory by reflecting the capacity to maintain cognitive functioning despite prodromal symptoms (a risk factor). The MCCB battery was selected for its established sensitivity to stress-related cognitive decline and its clinical relevance to functional outcomes. However, we acknowledge that NCR, as defined, may not fully capture dynamic resilience processes (e.g., recovery from acute stressors), and future research should integrate longitudinal stress reactivity measures to validate this construct further. The findings demonstrate that lower NCR was significantly associated with poor outcomes, particularly non-remission. NCR showed stronger associations with functional outcomes, suggesting its potential as a marker for identifying individuals at higher risk of poor functional prognosis. This research offers important insights into early intervention strategies and the potential role of NCR in mitigating the progression of psychosis.

Abbreviations

AUC	Area under the curve
BACS	Symbol Coding from the Brief Assessment of Cognition in Schizophrenia
BVMT-R	Brief Visuospatial Memory Test-Revised
CHR	Clinical high risk
CHR-C	CHR individuals who converted to psychosis
CHR-NC	CHR individuals who did not convert to psychosis
CHR-NR	CHR individuals were classified as being in non-remission
CHR-R	CHR individuals were classified as being in remission
CPT-IP	Continuous Performance Test, Identical Pairs version
HVLT-R	Hopkins Verbal Learning Test-Revised
ICC	Intraclass correlation coefficient
GAF	Global Assessment of Functioning
MCCB	Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery
MINI	Mini International Neuropsychiatric Interview
NAB Mazes	Mazes from the Neuropsychological Assessment Battery
NCR	Neurocognitive resilience
SHARP-extended	Shanghai At Risk for Psychosis-extended
SIPS	Structured Interview for Prodromal Syndromes
SMHC	Shanghai Mental Health Center
WMS- 3	Wechsler Memory Scale-III

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-025-04059-1.

Additional file 1: Table S1. Demographic, clinical, and cognitive characteristics among CHR-C, CHR-S, and CHR-R groups.

Additional file 2: Table S2. Logistic regression models for predicting conversion to psychosis (CHR-C vs. CHR-NC).

Additional file 3: Table S3. Logistic regression models for predicting non-remission (CHR-NR vs. CHR-R).

Additional file 4: Figure S1. ROC curves for predicting conversion to psychosis using continuous cognitive variables.

Additional file 5: Figure S2. ROC curves for predicting non-remission using continuous cognitive variables.

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None.

Authors' contributions

Dr. TH.Z. and JJ.W. conceptualized the study, wrote the first draft of manuscript and conducted the statistical analyses. LH.X., XC.T., HR.C., and YY.W. collected and organized the primary data. YY.T., LY.Z., HC.L., T.C., and HR.C. managed the literature searches, statistical analyses and edited the manuscript. TH.Z., JJ.W., ZH.Y., and CB.L. designed the study and provided supervision in the implementation of the study. All authors have approved the final manuscript.

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Data availability

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Ethical approval for the research (including the consent procedure) was granted by the Institutional Review Board of the Shanghai Mental Health Center (IRB2016-009). All participants provided written consent to be involved in the study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details

[1]Shanghai Engineering Research Center of Intelligent Psychological Evaluation and Intervention, Shanghai Key Laboratory of Psychotic Disorders, Shanghai Mental Health Center, Shanghai Jiaotong University School of Medicine, Shanghai 200030, China. [2]Department of Automation, Shanghai Jiao Tong University, Shanghai 200240, China. [3]Shanghai Xinlianxin Psychological Counseling Center, Shanghai, China. [4]Big Data Research Lab, University of Waterloo, Waterloo, ON,

Canada. [5]Labor and Worklife Program, Harvard University, Cambridge, MA, USA. [6]Department of Psychiatric Rehabilitation, Shenzhen Kangning Hospital, Shen-Zhen, GuangDong, China. [7]Department of Psychiatry, Nantong Fourth People's Hospital & Nantong Brain Hospital, Suzhou 226000, China.

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