Cognitive deficits in clinical high risk, genetically at high-risk for psychosis and patients with first-episode schizophrenia

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Abstract

Background: Cognitive deficits are core characteristics of schizophrenia, which precedes the emergence of psychotic symptoms. Clinical high risk for psychosis (CHR) individuals and genetically high-risk of psychosis (GHR) individuals also exhibit cognitive impairments, but it is not clear which domains of cognitive impairments in these two groups were more similar to those of schizophrenia patients. Moreover, it is not clear whether quality factors contribute to this impairment or the disease state causes it. This study aims to explore the cognitive impairments profiles in CHR, GHR and patients with first episode schizophrenia (FES).

Method: We compared the cognitive functions of three groups and a healthy control group (HCs) using the MATRICS Consensus Cognitive Battery (MCCB). Our sample consisted of 56 patients with FES, 42 individuals at CHR, 26 individuals at GHR, and 62 HCs.

Results: Individuals with FES, GHR, and CHR showed significant impairment in most MCCB domains, with the exception of visual learning, when compared to the HCs. None of the MCCB domains were able to accurately distinguish between CHR and GHR individuals. GHR and CHR individuals had intermediate scores between FES and HCs on the domain of processing speed and attention. However, the impairment levels in working memory and verbal learning were similar across all three groups. The CHR performance in social cognition was comparable to that of the HCs, whereas there was no significant difference in problem-solving scores between the GHR and HC groups.

Conclusion: Our findings suggest that significant cognitive deficits exist in CHR, GHR, and FES individuals, and these deficits vary across domains. Cognitive impairment may be a key feature of individuals with schizophrenia, with processing speed and attention potentially serving as reliable markers for identifying those at risk for psychosis. The damage of reasoning/problem solving may be qualitative trait, while as social recgnition may be state characteristic of schizophrenia.

BACKGROUND

Cognitive deficits are core characteristics of schizophrenia[1], affecting all aspects of neuropsychological functioning. Specifically, executive function, memory, and sustained attention seem to be especially impacted[2]. Evidence suggests that cognitive decline precedes the emergence of psychotic symptoms[3], after which cognitive function generally stabilizes until later in life[4].

Before the onset of schizophrenia, many individuals experience non-specific symptoms such as perceptual disturbances, unusual beliefs or magical thinking, attentional disruptions, and symptoms of anxiety and depression. These signs are collectively referred to as clinical high risk for psychosis (CHR)[5]. Approximately one-third of CHR individuals progress to schizophrenia within the subsequent 2–3 years[6]. Compared to healthy controls, CHR individuals display significant cognitive impairments, suggesting that neurocognitive dysfunction could serve as a potential marker for early detection and prognosis in this population[7].

Individuals who are genetically at high risk for psychosis (GHR) exhibit moderate cognitive deficits when compared with healthy controls, and their cognitive profiles resemble those of patients[8, 9]. Moreover, those who are GHR for schizophrenia typically demonstrate poorer cognitive functioning than those at risk for affective psychosis. This suggests that the genetic predisposition for schizophrenia, as indicated by a positive GHR, carries a particularly substantial impact on cognitive abilities[8].

Evidence indicates that any pronounced cognitive impairment among CHR individuals is largely attributable to their transition to psychosis (CHR-T); thus, neurocognitive deficits in CHR cohorts should be interpreted with caution when considering psychosis or even CHR status as the specific clinical syndrome of interest, as these impairments likely signify a transdiagnostic or psychosis-specific vulnerability[10]. It's important to note that the majority of CHR individuals do not develop psychosis[6]. Consequently, diminished cognitive functioning could either be due to a subgroup at a true risk for psychosis that is more severely impaired, or it could reflect generalized distress, psychopathology, or other psychiatric problems within CHR subjects[11], rather than cognitive impairment exclusively associated with emerging psychosis[12]. Some domains of cognitive impairment may represent qualitative traits, rather than states, of schizophrenia, and in these domains, the impairment in GHR individuals may be more akin to that of the patient population than that of CHR individuals. Conversely, in domains where cognitive impairment represents a state characteristic, the impairment may be more comparable to the patient population in CHR individuals than in GHR individuals.

While there is general consensus in the literature that both CHR and GHR individuals experience cognitive impairments, studies directly comparing cognitive function across CHR, GHR, First-Episode Schizophrenia (FES), and Healthy Controls (HCs) are scarce[13, 14]. Furthermore, previous research has not consistently utilized standardized cognitive assessment tools like the MATRICS Consensus Cognitive Battery (MCCB)[13], or has only employed four of the seven cognitive domains assessed by the MCCB[14]. Additionally, prior studies have not accounted for the potential impact of psychotropic medication use in the FES group[14]. Antipsychotic medication may potentially account for approximately half of the cognitive impairment observed in patients[15].

In this study, we leveraged the MATRICS Consensus Cognitive Battery (MCCB) to compare the cognitive functions of individuals with First-Episode Schizophrenia (FES) who are not on antipsychotics, those at Clinical High Risk (CHR), those Genetically at High Risk (GHR), and Healthy Controls (HCs). Our objective was to explore differences in cognitive profiles across these four groups. We aimed to identify which domains of impairment are common across all three at-risk groups and which domains of impairment are more pronounced in a specific group.

METHODS

This cross-sectional study was carried out at the Beijing Anding Hospital of Capital Medical University from January 2015 to January 2018. The study was reviewed and approved by the institution's ethics committee. All participants, or their guardians in applicable cases, provided their voluntary consent by signing written informed consent forms.

Participants

The study included individuals aged between 17 and 40 years, all of whom had completed at least elementary education. First-episode schizophrenia (FES) patients were sourced from either outpatient services or inpatient wards, while those at Clinical High Risk (CHR) were identified among the hospital's help-seeking population. Individuals at Genetic High Risk (GHR) and Healthy Controls (HCs) were recruited through advertisements.

FES patients met the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for schizophrenia, with a first episode of disease and duration less than three years. These patients had no history of medication or had used antipsychotics for no more than one continuous month since the onset of the disorder[16].

CHR individuals were screened using the Structured Interview for Psychosis-risk Syndromes (SIPS), qualifying if they met one or more of three conditions: Brief Intermittent Psychotic Symptoms Syndrome (BIPS), Attenuated Psychotic Symptoms Syndrome (APSS), or Genetic Risk and Deterioration Syndrome (GRD)[17].

GHR individuals were defined as first-degree relatives (siblings or children) of individuals diagnosed with schizophrenia. Any psychiatric disorders in GHR individuals and HCs were ruled out using the Structured Clinical Interview for DSM-IV Axis I Disorders-Patient Edition (SCID-I/P) and SIPS.

Participants were excluded if they had a severe physical illness or had undergone modified electroconvulsive therapy within the past six months.

Measures

Clinical assessment

The severity of symptoms in patients with FES was evaluated using the Positive and Negative Syndrome Scale (PANSS). This scale consists of 30 items, each with a defined criterion and a specific 7-level operational scoring standard (ranging from 1 to 7)[18].

To assess symptom scores for CHR, GHR, and HC individuals, we used the Scale of Prodromal Symptoms (SOPS) included in the Structured Interview for Psychosis-risk Syndromes (SIPS). The SOPS comprises 19 fundamental items, each rated on a 7-point scale (ranging from 0 to 6)[17].

Cognitive function assessment

The MATRICS Consensus Cognitive Battery (MCCB) was utilized to evaluate the neurocognitive levels of the individuals[19]. It encompasses 10 subtests which measure seven cognitive domains: information processing speed; attention/alertness; working memory; verbal learning; visual learning; reasoning and problem-solving; and social cognition. This study employed the Chinese version of the MCCB[20]. The assessors conducting the evaluations underwent training from staff at the Institute of Mental Health of Peking University, who participated in the development of the Chinese version of the MCCB. Raw scores were then converted into T-scores based on Chinese cognitive norms, with higher T-scores indicating superior cognitive function.

Statistical analysis

Data was processed using IBM SPSS Statistics 23.0 for Windows (SPSS, Inc., Chicago, IL, USA). General demographic data across the four groups were evaluated using one-way Analysis of Variance (ANOVA). Nonparametric tests were utilized to compare clinical data among CHR, GHR, and HC individuals. Categorical data were analyzed using a chi-squared test.

Differences in cognitive domains among the four groups were analyzed with a Multivariate Analysis of Covariance (MANCOVA), with gender, age, years of education, and unemployment status as covariates. An Analysis of Covariance (ANCOVA) was used to compare the overall composite scores among the four groups. Post-hoc comparisons were conducted using the Bonferroni correction. Effect sizes (Cohen's d) were calculated to identify differences in levels of cognitive performance. A p-value of less than 0.05 was deemed to represent statistical significance.

RESULTS

Demographics and clinical characteristics

During the initial screening, 5 individuals of FES and 2 individuals at CHR were excluded due to non-cooperation with cognitive testing. Ultimately, a total of 186 Chinese participants were recruited, comprising 56 FES patients, 42 CHR individuals, 26 GHR individuals, and 62 HCs (Refer to Table 1). No significant differences were observed among the

four groups in terms of age, education level, gender ratio, marital status, smoking status, or family history ratio. However, the FES group had a significantly higher rate of unemployment compared to the other three groups (χ^2 = 28.51, P < 0.001). Additionally, all scores on SOPS in the CHR group were significantly higher than those in the GHR and HC groups (P < 0.001).

Table 1
Demographics and clinical features of the participants *

	FES	CHR	GHR	HCs	Total	*F*	*P*
Subjects, n	56	42	26	62	186	—	—
Age, y	25.7 ± 6.5	23.8 ± 4.8	26.7 ± 4.8	25.1 ± 3.6	25.2 ± 5.1	2.07	0.11
Education, y	12.9 ± 3.2	14.3 ± 2.9	13.2 ± 3.2	14.2 ± 3.3	13.7 ± 3.2	2.60	0.05
Duration of illness, mo	27.4 ± 26.2	26.3 ± 27.8	—	—	27.0 ± 26.7	0.04	0.84
SIPS							
Positive	—	9.4 ± 4.1	0.3 ± 0.5	0.3 ± 1.2	3.1 ± 4.8	96.55	< 0.001
Negative	—	9.0 ± 5.2	0.7 ± 1.6	0.2 ± 0.8	3.0 ± 5.0	95.49	< 0.001
Disorganization	—	4.7 ± 3.4	0.5 ± 0.8	0.1 ± 0.5	1.6 ± 2.8	84.72	< 0.001
General	—	4.9 ± 3.5	0.8 ± 1.5	0.1 ± 0.5	1.7 ± 3.0	83.59	< 0.001
Total score	—	28.0 ± 12.4	2.2 ± 3.7	0.8 ± 2.6	9.4 ± 14.3	94.06	< 0.001
PANSS							
Positive	22.8 ± 6.1	—	—	—	—	—	—
Negative	21.0 ± 8.3	—	—	—	—	—	—
general psychopathology	41.9 ± 6.7	—	—	—	—	—	—
Total score	84.3 ± 15.0	—	—	—	—	—	—
						χ^2	*P*
Men	30 (53.6)	26 (61.9)	15 (57.7)	35 (56.5)	106 (57.0)	0.69	0.88
Married	11 (19.6)	5 (11.9)	8 (30.8)	10 (16.1)	34 (18.3)	4.12	0.25
Family history	9 (16.1)	12 (28.6)	—	—	47 (25.3)	1.83	0.18
Smoking	8 (14.3)	6 (14.3)	3 (11.5)	9 (14.5)	26 (14.0)	0.16	0.98
Unemployed	24 (42.9)	6 (14.3)	4 (15.4)	3 (4.8)	37 (19.9)	28.51	< 0.001
Medication	48 (85.7)	24 (57.1)	—	—	72	—	—
Unmedicated	8 (14.3)	18 (42.9)	—	—	26	—	—
AP	44 (78.6)	13 (31.0)	—	—	57	—	—
AD	0	5 (11.9)	—	—	5	—	—
AD + AP	1 (1.8)	4 (9.5)	—	—	5	—	—
Unspecified	3 (5.3)	2 (4.7)	—	—	5	—	—

* Data are reported as n (%), unless indicated otherwise. AD, antidepressant; AP, antipsychotic.

Comparison of cognitive performance among study groups

FES, CHR and GHR groups v. healthy controls

No significant differences were observed in MANCOVA analysis of the visual learning domain ($F = 1.96$, $P = 0.12$). However, significant differences among the groups were noted in the remaining cognitive domains and overall composite score (Refer to Table 2).

Table 2
Cognitive functions of the FES, CHR, GHR and HCs

Domains	FES	CHR	GHR	HCs	Total	Statistic [a]		Pairwise comparison [b]		
						F	*P*		*P*	*Effect size* [c]
Processing speed	33.0 ± 8.9	39.0 ± 7.6	40.6 ± 5.1	45.2 ± 6.9	39.5 ± 8.9	15.72	< 0.001	FES < CHR	0.008	0.73
								FES < GHR	0.04	1.09
								FES < HC	< 0.001	1.54
								CHR < HC	< 0.001	0.86
								GHR < HC	0.006	0.77
Attention/Vigilance	30.1 ± 10.1	40.8 ± 11.3	39.4 ± 8.1	46.0 ± 8.5	39.3 ± 11.5	18.69	< 0.001	FES < CHR	< 0.001	1.00
								FES < GHR	0.001	1.02
								FES < HC	< 0.001	1.71
								CHR < HC	0.03	0.53
								GHR < HC	0.004	0.80
Working memory	38.5 ± 9.7	39.1 ± 3.4	42.3 ± 17.0	46.6 ± 6.9	41.9 ± 11.6	5.88	0.001	FES < HC	0.001	0.98
								CHR < HC	0.001	1.46
								GHR < HC	0.016	0.36
Verbal learning	38.7 ± 9.0	42.2 ± 9.6	40.8 ± 6.2	46.9 ± 10.6	42.5 ± 9.9	5.15	0.002	FES < HC	0.001	0.84
								CHR < HC	0.007	0.47
								GHR < HC	0.005	0.73

[a] Multivariate analysis of covariance. [b] Bonferroni correction applied to post-hoc pairwise comparisons analyses. [c] After significant pairwise comparisons, effect sizes were calculated using Cohen's d.

Domains	FES	CHR	GHR	HCs	Total	Statistic [a]		Pairwise comparison [b]		
						F	*P*		*P*	*Effect size* [c]
Visual learning	39.3 ± 14.1	42.8 ± 11.8	44.9 ± 9.9	47.1 ± 10.3	43.5 ± 12.2	1.96	0.12	—	—	—
Reasoning/problem solving	34.4 ± 11.0	40.7 ± 11.3	37.6 ± 8.4	43.4 ± 10.5	39.3 ± 11.2	3.87	0.01	FES < CHR	0.018	0.57
								FES < HC	0.002	0.84
Social recognition	31.4 ± 12.3	36.6 ± 8.1	39.7 ± 10.4	39.3 ± 9.8	36.4 ± 10.8	3.92	0.01	FES < GHR	0.004	0.73
								FES < HC	0.003	0.71

[a] Multivariate analysis of covariance. [b] Bonferroni correction applied to post-hoc pairwise comparisons analyses. [c] After significant pairwise comparisons, effect sizes were calculated using Cohen's d.

Post-hoc comparisons revealed that the performance of FES was significantly poorer than that of the HCs in the six other cognitive domains excluding visual learning ($d = 0.71–1.71$). Compared to the HCs, both CHR ($d = 0.47–1.46$) and GHR (d = 0.36–1.80) groups exhibited significantly worse performance in the domains of information processing speed, attention/vigilance, working memory, verbal learning, and the overall composite score. The cognitive profiles of the FES, CHR, and GHR groups compared to the HC group are depicted in Fig. 1.

Comparison between FES Group and CHR Group

The FES patients scored lower than CHR individuals in the domains of information processing speed ($P = 0.008$, $d = 0.73$), attention/vigilance ($P < 0.001$, $d = 1.00$), and reasoning/problem solving ($P = 0.018$, $d = 0.57$).

Comparison between FES Group and GHR Group

FES patients performed worse than GHR individuals in the domains of information processing speed ($P = 0.04$, $d = 1.09$), attention/vigilance ($P = 0.001$, $d = 1.02$), and social cognition ($P = 0.004$, $d = 0.73$).

Comparison between CHR group and GHR group

No significant differences were observed in performance across all cognitive domains between the CHR and GHR groups.

DISCUSSION

In this study, cognitive performance among FES, GHR, CHR and HC groups were investigated. We discovered that individuals in the FES, GHR, and CHR groups performed significantly poorer in most domains of the MATRICS Consensus Cognitive Battery (MCCB) compared to the HCs group. While cognitive impairment was evident in both GHR and CHR individuals, it was not as severe as in FES patients.

In our study, cognitive functioning in CHR individuals occupied an intermediate position between that of HCs and FES, which aligns with previous findings[14, 21]. CHR individuals underperformed compared to HCs across all MCCB domains except for visual learning, especially in areas of processing speed and attention/vigilance. Past meta-analyses have similarly observed CHR subjects lagging behind HCs in all MCCB cognitive domains, particularly in processing speed, attention/vigilance, and working memory[22]. The domains of cognitive deficits identified in the CHR group in our study echo those found in previous studies.

Several studies have compared cognitive impairment among the FES, CHR, and GHR groups[13, 14, 23]. In a previous study[13], a significant difference was found between CHR and FES groups in terms of the composite global score; GHR and FES groups showed similar levels of impairment, with GHR performing better than FES specifically in the domain of sustained attention. However, another study arrived at a different conclusion, suggesting that cognitive performance gradually decreased from HCs to first-degree relatives (FDR) and ultra-high-risk (UHR) individuals, ultimately reaching the FES group. This implies that cognitive functioning in the UHR group was intermediate between the FES and FDR groups. The disparity in conclusions between that study and ours may be attributed to differences in the cognitive assessment tools used, with our study employing the MCCB that measures a broader range of cognitive domains.

In our study, we identified impaired processing speed, attention/vigilance, working memory, and verbal learning in the GHR group, with the most significant impairment observed in the attention/vigilance domain. This finding aligns with previous studies that have suggested GHR individuals exhibit cognitive impairments similar to their affected siblings and demonstrate deficits of moderate severity compared to healthy controls[8, 15, 24, 25]. Previous research has reported larger effect sizes for measures of full-scale IQ, vocabulary, and single word reading tests, while measures of declarative memory, sustained attention, and working memory showed more modest effect sizes[8]. The differences observed in cognitive impairment domains between our study and previous studies may be attributed to variations in assessment tools used.

Among the three groups (FES, CHR, and GHR), processing speed and attention/vigilance were consistently impaired, with CHR and GHR individuals exhibiting milder impairments compared to FES. This finding is in line with some previous research studies[23, 26]. These results suggest that processing speed and attention/vigilance may hold promise as biomarkers for the early detection and severity assessment of schizophrenia. We hypothesize that genetic factors, current symptoms, or other unknown factors may influence these cognitive domains, and their impact on the indicators may accumulate over time. Hence, the heaviest impairment in these domains was observed in the FES group.

Interestingly, the severity of impairment in the reasoning/problem-solving domain was comparable between GHR and FES (with no statistically significant difference), while GHR exhibited milder impairment compared to FES (with a statistically significant difference). On the other hand, the severity of impairment in social recognition was similar between CHR and FES (with no statistically significant difference), while GHR displayed less impairment compared to FES (with no statistically significant difference). Previous studies have consistently reported impaired social cognition in CHR individuals[27]. Research on social cognition in GHR individuals is limited and inconsistent, but previous findings have indicated that social cognitive impairments are significantly associated with psychopathology in young relatives of individuals with schizophrenia[28]. Based on these findings, we speculate that social recognition may be more closely related to the current state of individuals, while reasoning/problem-solving may be more indicative of qualitative differences.

The utilization of the MCCB in this study helped standardize cognitive testing and domains, and the inclusion of unmedicated FES individuals helped minimize potential confounders. However, it is important to interpret the results with caution due to several limitations. Firstly, the sample size was relatively small, which may limit the generalizability of the findings. Secondly, the cross-sectional design of the study prevents the determination of a predictive neuropsychological marker for the transition to psychosis in at-risk individuals. Thirdly, the family history of 12 CHR individuals may serve as a confounding factor. Future analyses could benefit from including a larger sample size and incorporating clinical and genetically high-risk psychosis groups to enhance the robustness of the findings.

CONCLUSIONS

Our study provides evidence for the presence of cognitive deficits in individuals at high risk for schizophrenia, both clinically (CHR) and genetically (GHR), prior to the onset of the first episode. Processing speed and attention/vigilance emerged as common and progressively impaired domains across the three groups, making them potential biomarkers for schizophrenia. The impairment in reasoning/problem-solving may represent a qualitative trait, while social recognition may reflect the current state of individuals. However, further rigorous research is needed to validate and confirm these findings.

Declarations

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Availability of data and materials

Data are available from the first and the corresponding authors.

Authors' contributions

Z.M and F.D managed the literature searches. Z.M and L.W undertook the statistical analysis. F.D wrote the complete first draft. Final review and editing by C.W. All authors have read and approved the manuscript.

Competing interests

All authors report no biomedical financial interests or potential conflict of interest.

Consent for publication

Not applicable.

Ethics approval and consent to participate

All procedures of the present study were performed in accordance with the Declaration of Helsinki. The study protocols were approved by the clinical research ethics committees of Beijing Anding Hospital, Capital Medical

University. All the subjects were aware of the purpose of the study and signed an informed consent form.

Author's information

All researchers in the study were trained regarding the protocol and Good Clinical Practice guidelines.

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Figures

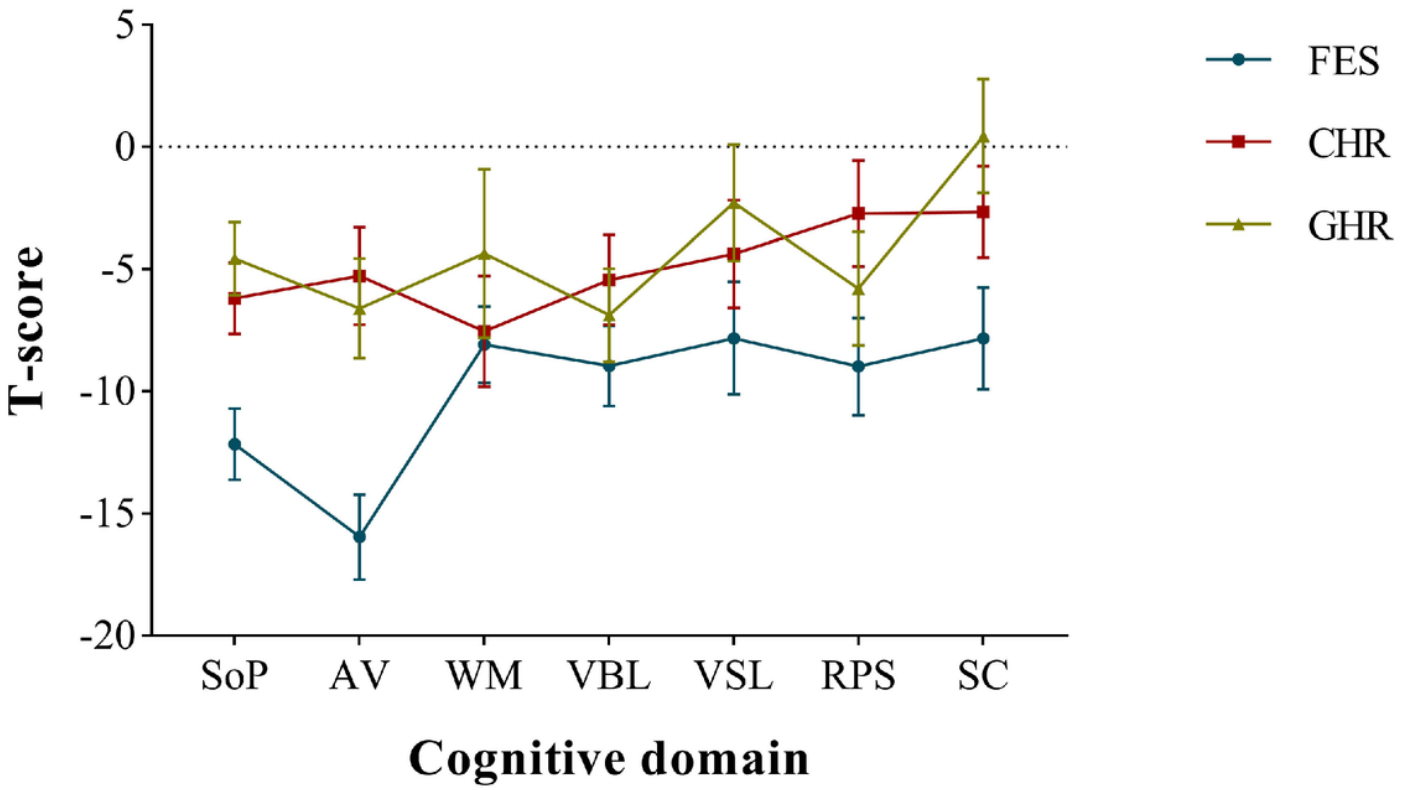

Figure 1

Cognitive profiles of the FES, CHR and GHR groups against HC group

Abbreviations: SoP: Speed of Processing, AV: Attention/Vigilance, WM: Working Memory, VBL: Verbal Learning, VSL: Visual Learning, RPS: Reasoning and Problem Solving, SC: Social Cognition. The Y-axis presents the mean and standard error of the difference between the study group and HC group.