NEUROCOGNITION AND FUNCTIONING IN ADOLESCENTS AT CLINICAL HIGH RISK FOR PSYCHOSIS

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Abstract

Background

Once psychosis has set in, it is difficult for patients to achieve full the recovery. Prevention of psychosis and early intervention are promising for improving the outcomes of this disorder. In the last two decades, neurocognition has been studied as a biomarker for clinical-high risk for psychosis (CHR-P). However, neurocognitive functioning has been under-investigated in adolescents.

Methods

We enrolled 116 adolescents from 12 to 17 years old (*mean* = 15.27, *SD* = 1.56; 76 females). This 3-year cohort study aimed to identify differences in neurocognitive and overall functioning in three groups of adolescent patients divided according to the semi-structured interview Comprehensive Assessment of At-Risk Mental States (CAARMS): adolescents with established psychosis, adolescents with CHR-P, and adolescent not meeting either criteria (non-CHR-P). To differentiate the profiles, clinicians administered cognitive evaluation and neuropsychological tasks. Moreover, they filled in scales to assess their global, social, and role functioning and a questionnaire to assess the severity of the disease.

Results

We made a between-group comparison on neurocognitive measures and found that the CHR-P and the psychosis groups differed in processing speed (TMT-A; $p = .002$ in BVN categorial fluency ($p = .018$), and Rey–Osterrieth complex figure drawing from memory task ($p = .014$), with psychosis group showing worse performance. No differences emerged between non-CHR-P and CHR-P ($p = .014$) individuals. CHR-P had better functioning than the psychosis group but worse than the non-CHR-P one.

Conclusions

These results confirm that neurocognition can be a helpful biomarker in identifying specific subgroups of adolescents with emerging psychopathology and help clinicians develop stratified preventive approaches.

Keywords: Adolescence, clinical high risk for psychosis, functioning, neurocognition, psychosis

Introduction

Psychotic disorders typically have their onset in adolescence and early adulthood, with the peak of the risk occurring between the ages of 12 and 25 years [1]. After the onset of the disorder , it is challenging to improve its course and lead the patient to complete recovery [2,3]. Therefore, prevention of psychosis and early intervention are promising paths for improving outcomes [4]. In light of the above, in the last twenty years, attention to prevention has focused on the clinical-high risk for psychosis (CHR-P) population. CHR-P population includes three subgroups: Attenuated psychotic Syndrome (APS), Brief intermittent psychotic symptoms (BLIPS), and Genetic risk and Deterioration Syndrome (GRD) [5]. Several studies have highlighted the importance of detection, prognosis, and interventions for CHR-P individuals and the formulation of updated recommendations, mainly because detection of CHR-P individuals is based on patients' referral, and symptoms may remain undetected for a long time [6]. So, childhood and adolescence represent a critical developmental window where opportunities to gain social and adaptive abilities depend on the individuals' neurocognitive performance [1]. Therefore, early intervention and particularly preventive approaches in young people with subtle signs and symptoms of the psychotic disorder (termed 'primary indicated prevention' [4,7]) have the potential to benefit the lives of many young people.

Although the CHR-P prevention paradigm is particularly promising, especially in young people, empirical challenges arise [8]. Researchers stated that neurocognition could be a biomarker that may help professionals distinguish CHR-P from health controls (HC) and could help determine the risk of transition to psychosis. In this connection, a recent meta-analysis [9] comparing a total of 78 independent studies with 5162 CHR-P individuals and 2865 HC described that the first group showed medium to significant deficits in the studied neurocognitive domains. Moreover, CHR-P people were less impaired than individuals with a first episode of psychosis. Knowing the global functioning and performance trends of CHR-P patients on neuropsychological tests can also help clinicians intervene

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early to reduce the risk of transition to psychosis, which is currently relevant in the adolescent population [10,11].

Despite this recent work, there is not much evidence that synthesizes current knowledge about neurocognitive functioning in adolescent individuals [12–17], specifically about longitudinal changes across time in this population [13,17]. Moreover, as shown in the metanalysis [9], studies in adolescence show different results because of different tasks used, non-homogeneous samples, or severe comorbid disorders [8,17]. Indeed, it is crucial to find biological and psychological markers of transition to psychosis to help clinicians detect psychotic symptoms, preventing psychotic disorders, and formulating a prognosis to offer the most appropriate interventions. Overall, the empirical literature on the neurocognitive performance of children and adolescents is poorer in comparison with the one on young adults, so there is a gap in the literature.

In light of that, this study aimed to identify differences in neurocognitive functioning and overall functioning in three groups of adolescent patients divided according to their emerging psychopathology ascertained through the semi-structured interview Comprehensive Assessment of At-Risk Mental States (CAARMS) criteria [18]: i) Psychosis, ii) CHR-P, and iii) non-CHR-P.

We expected to find worse performance in neurocognitive tasks and lower functioning in the psychosis group, moderate deficits in the CHR-P group, and average performances and adequate global functioning in the non-CHR-P group.

Methods

Study Design

We planned a 3-year cohort study, previously described in the literature [19], conducted according to the Reporting of studies Conducted using the Observational Routinely collected health Data (RECORD) statement (see supplementary). The study received the approval of the Ethics Committee of Policlinico San Matteo in Pavia, Italy (P-20170028892). The authors assert that all

procedures contributing to this work comply with the Helsinki Declaration of 1964 and its later amendments and with the ethical standards of the relevant national and institutional committees on human experimentation. The dataset is available upon request in Zenodo [20].

Sample

We enrolled 116 participants who have been referred to the Child Neurology and Psychiatry Unit of the third-level Scientific Hospitalization and Treatment Institution (IRCCS) Mondino Foundation in Pavia from 2017 to 2020. Mondino Foundation is a clinical and research institute; where many workers also have a role within the University. cCinical practice is almost always carried out together with research, so the opportunity to participate in research protocols is well received by patients and families. Specifically, the Child Neurology and Psychiatry Unit is a department with several teams of physicians and psychologists. Our group focuses on the psychiatry branch and is specialized in the diagnosis and care of patients with serious psychopathological diseases.

As stated in the original protocol [19], we included in the study help-seeking male and female inpatients adolescents between 12 - 17 years of age from all over Italy and taken care of for psychiatric disorders at Child Neurology and Psychiatry Unit and who had provided, together with their parents or guardians, their written informed consent.

We excluded participants who had a history of psychosis according to DSM-5 criteria before assessment, who had head injuries or any other underlying medical/neurological condition that could explain psychiatric symptoms, who had a current DSM-5 illicit substance addiction or induced mental disorders, who presented intellectual disability ($IQ \leq 70$) assessed through WISC-IV [21] or WAIS-IV [22], or whose parents declined participation or did not provide written informed consent.

To homogenize the CHR-P group, we excluded adolescents who met the CAARMS [18] criteria for the vulnerability group, i.e., with a combination of a trait risk factor and significant

functioning impairment, and those who met Brief Limited Intermittent Psychotic Symptoms (BLIPS) group criteria given the phenotypic overlap of this subgroups with the psychosis one.

We divided eligible patients into three groups according to the semi-structured interview CAARMS, a valuable tool to be integrated into diagnostic assessment in Child Neuropsychiatry services [23–26]. The three groups were i) Psychosis, including adolescents who received over-threshold scores for the CAARMS psychosis group; ii) CHR-P, including adolescents who both met the criteria for Attenuated psychotic Syndrome (APS) according to the DSM-5 [27] and received suprathreshold scores for the CAARMS CHR-P groups (i.e., intensity or frequency) (in our sample the CHR-P group overlapped the definition of APS); iii) non-CHR-P, including patients who did not meet the CAARMS criteria for psychosis group nor CHR-P groups. *Although* the third group not including healthy controls, we referred to previous studies that used a sample of subjects with different diseases of milder severity than the patient group (e.g., headache, learning disabilities, internalizing problems) [28,29]. An appropriately trained psychologist or neuropsychiatrist on the CAARMS administered the interview. For cases in which there were doubts, the assessor compared with an expert colleague and the score was given following their discussion. Figure 1 shows the study population flowchart, and Table 2 shows the patients' diagnoses for each group in detail.

Figure 1. Flowchart of the study sample.

[Figure 1 about here]

Instruments

A trained psychologist thoroughly explained the study to families. A clinician collected sociodemographic information, previous medical and psychiatric history, socio-economic status (SES) [30], and family history of any DSM-5 psychiatric disorders. A child neuropsychiatrist or a psychologist administered the Wechsler scale to exclude intellectual disability and then conducted the standardized clinical interview Kiddie Schedule for Affective Disorders and Schizophrenia -

Present and Lifetime Version (K-SADS-PL) for DSM-5 [31,32] with the participants and their parents or guardians separately, to confirm the diagnosis. All diagnoses were made according to DSM-5 criteria [27] and confirmed using K-SADS-PL. To assess symptoms attributable to personality disorders and structuring personality disorders, we administered the Structured Clinical Interview for DSM-5 Personality Disorders (SCID-5 PD) [33] to patients aged 14 and over.

A trained psychologist administered an in-depth neuropsychological assessment focusing on several neurocognitive domains to assess the neurocognitive profile. To assess the intelligence quotient (IQ), we administered the Wechsler intelligence scale (WISC-IV or WAISIV) [21,22,34]. To assess visuospatial planning and attention, we administered Rey–Osterrieth complex figure test (ROCF) [35–37], and to evaluate processing speed and executive functioning, we administered the Trail Making Test Part A (TMT-A) and B (TMT-B), both measuring processing speed [38,39] and TMT-B executive functioning. Moreover, we used many of the subtests contained in the BVN 12-18 (Batteria per la Valutazione Neuropsicologica dell'Adolescenza - Adolescent Neuropsychological Assessment Battery) [40] to assess lexical denomination, verbal working memory (forward and backward digit span), nonverbal working memory (Corsi Block-tapping test), selective auditory and visual attention, phonemic and categorial fluency, and reasoning and problem-solving (Elithorn Perceptual Maze).

To evaluate the level of functioning, clinicians compiled the Children's Global Assessment Scale (CGAS) [41] and the Social and Occupational Functioning Assessment Scale (SOFAS) [42]. We also compiled the Global Functioning: Role scale (GF:R) (Niendam et al., 2006) and Global Functioning: Social scale (GF:S) [44]. Clinicians assessed the overall severity of illness using the Clinical Global Impression-Severity (CGI-S) scale [45,46].

Statistical methods

Descriptive analyses were performed for demographic and clinical characteristics, for the total sample, and separately for each of the three groups (Psychosis vs. non-CHR-P vs. CHR-P). These

analyses included mean value and standard deviation (SD), as appropriate for continuous variables, and absolute and relative frequencies for categorical variables. Statistical comparisons between the three groups completed descriptive analyses. Given the small sample size, Kruskal-Wallis was used for numerical variables (i.e., age), complemented by post hoc analyses (Dunn test), and the Fisher's exact test for categorical variables (i.e., gender, ethnicity, and SES). To reduce the chance of type I error due to multiple testing, Bonferroni correction was applied to all post hoc analyses. We then performed a between-group comparison on neurocognitive measures (i.e., WISC-IV/WAIS-IV, TMT-A, TMT-B, BVN subtests, and ROCF). Since our groups were non-equal in size, we used the Kruskal-Wallis test, complemented by post-hoc Dunn's test with a Bonferroni correction. Statistical analyses were performed with IBM SPSS version 27.0 [47].

Results

Participants

The sample comprised 116 adolescents aged between 12 and 17 years old. Figure 1 shows the study population flowchart.

Considering the whole sample, 26 adolescents (22.4%) came from low socio-economic status (SES) families, 26 (22.4%) came from low-to-medium-low SES families, 36 adolescents (31.0%) from medium SES families, 18 (15.5%) from medium-to-high SES families, and 6 (5.2%) from high SES families.

At baseline, 19 out of 116 (16.4%) met the CAARMS criteria for psychosis, 47 (40.5%) met the criteria for CHR-P, and 50 (43.1%) met neither criterion. Table 1 shows sociodemographic information and family history of psychiatric disorders in the total sample and the three subgroups.

[Table 1 about here]

Table 2 shows patients' history of psychiatric disorders, psychopathology, global functioning, and baseline exposure to psychiatric treatments in the sample and the subgroups. Supplementary Table 1 shows post-hoc analyses.

[Table 2 about here]

The three groups (i.e., psychosis, CHR-P, non-CHR-P) did not differ in terms of age $H(2) = 1.398$, $p = .49$; gender, $H(2) = 1.670$, $p = .43$; SES, $H(2) = 4.796$, $p = .78$; or ethnicity, $H(2) = 2.822$, $p = .24$.

Neurocognition

Tables 3 and 4 show between-groups comparisons of IQ dimensions, neurocognitive tasks, and post-hoc analyses. Results revealed significant differences in the working memory performance and processing speed subtests of the Wechsler scale between adolescents from psychosis and non-CHR-P groups, showing psychotic adolescents perform worse than the non-CHR-P ones. Focusing on neuropsychological domains, adolescents from the psychosis group significantly differed from the CHR-P and non-CHR-P group in TMT-A, indicating a lower performance, BVN categorical fluency, revealing more inadequate flexibility skills. Psychotic adolescents also had a lower performance in BVN forward and backward verbal digit span and visual attention than Non-CHR-P adolescents and worse performance in Rey–Osterrieth complex figure test than CHR-P adolescents.

[Table 3 about here]

Functioning

Results showed the CHR-P group to have a more adaptive functioning (e.g., SOFAS, GF:R, GF:S, and CGAS) than the psychosis group but worse functioning than the non-CHR-P group on all the

scales. We also found that the CHR-P group presented a lower CGI-S level than the psychosis group but higher than the non-CHR-P one, as shown in Table 2.

Discussion

This work highlighted significant differences between the three groups of patients in neurocognition and functioning. However, they did not differ in age, gender, socio-economic status, ethnicity, adoption, separated/divorced parents, or history of family psychiatric disorders. Regarding neurocognitive functioning, the CHR-P group performed better than the psychosis group on the working memory and backward verbal digit span tasks, as previous research suggested [14,16]. Results in the adult population showed that the CHR-P group could be distinguished from the psychosis group using verbal learning tasks, since the latter group seem to perform worse [9]. This could be explained because language development is still evolving in adolescents; at this stage of life, they learn to think abstractly and develop the use of pragmatics and semantics. Therefore, language-related difficulties may be more evident in an adult population sample. Moreover, the difference between our data and adults and adolescent-adult samples may be explained by possible biases due to the greater presence of females in our sample that may have created a bias given the higher prevalence of psychotic onset in the male population. Literature states that psychosis typically onsets in adolescence and early adulthood [1] and much research has highlighted the importance of detection, prognosis, and interventions for improving the outcomes of CHRP people because it is challenging to lead the patient to complete recovery from psychosis [2,3]. Despite childhood and adolescence representing a complex developmental phase studies in this population are few [12–17,48] as it is challenging to investigate neurocognition in young patients. This is one of the few works that explored this domain.

Furthermore, our data did not show substantial differences in neurocognition between CHR-P and non-CHR-P patients' performances, maybe because our non-CHR-P sample was composed of

patients who presented other psychiatric symptoms without psychotic symptoms and were not healthy controls. Likewise, our results did not match those found among adults between CHR-P patients and healthy controls, which see the CHR-P group performing worse in every neurocognitive task, maybe because the adolescent brain goes through a critical developmental period of increased neural plasticity, unlike adults, and this may also reflect the greater number of comorbidities in our patient sample [9,49]. Moreover, as previous literature stated [50], we should consider adolescents as a more heterogeneous group than adults, and we have to think in terms of a developmental psychopathology perspective, not only to deepen the knowledge of adolescent psychopathology but also to understand developmental processes more generally [1].

In line with previous literature [14–16], patients in the psychosis group compared to the non-CHR-P group, exhibited significant deficits in working memory, processing speed, forward verbal digit span, backward verbal digit span, visual attention, categorical fluency, executive functions, psychomotor speed, and visuospatial attention and planning tasks.

As for the overall functioning, the CHR-P group exhibited better global functioning, better role and social functioning than the psychosis group, but still worse functioning than the non-CHR-P group [51]. Moreover, the CHR-P group showed a more significant presence of diagnoses of structuring personality disorder and bipolar symptoms. This group has many diagnoses of eating disorders [52,53]. In line with the literature [16], we found that the psychosis group had a massive presence of severe positive and negative symptoms compared to the other groups and was also the group with the lowest global functioning, the most compromised role and social functioning, and the most severe level of disorder severity based on clinical evaluation.

The study has some limitations. Future studies could consider a larger sample of adolescent patients or even younger participants to study the possibility of increasingly early prevention of developing psychotic symptoms. Furthermore, researchers could select different neuropsychological tests to identify better areas that do not show a significant difference in our population sample (e.g.,

problem-solving, comprehension tasks, Theory of Mind). Finally, our results could be implemented by including a longitudinal study phase that could document transition rates.

These results examining a population understudied contribute to making the assessment more rigorous, and specific functional and neurocognitive impairments can be a prognostic biomarker in identifying particular groups of patients, even in a developmentally complex period such as adolescence, and recommending the most appropriate course of treatment and preparing, where necessary, prevention pathways, as many studies over the years have pointed out [9,17,54–58]. Moreover, given the not consistently overlapping results [9], this research opens up new studies to standardize the assessment and to better detect the risk of transition to psychosis.

Declarations

Ethics approval and consent to participate

The study received the approval of the Ethics Committee of Policlinico San Matteo in Pavia, Italy (P-20170028892). Every participant gave his/her written informed consent and was free to withdraw their participation in the study at any time.

Consent for publication

Not applicable

Availability of data and materials

The dataset generated and analysed during the current study is available upon request in the Zenodo repository [20] at 10.5281zenodo.6325531.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

MMM, PFP and RB contributed to the conception and design of the study. MO and MMM contributed to data acquisition. MMM, MO, AC, and PFP contributed to literature searches. EC, MMM, MO, AC, PFP, and RB participated in data analysis. MO drafted the manuscript. Each author participated sufficiently in the work to take public responsibility for appropriate portions of the content. All authors critically revised the manuscript and approved the final version submitted. MO agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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