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Cognition in Tunisian Adolescents at Ultra High Risk of Psychosis

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Abstract: ***Background: Impaired cognition is at the core of schizophrenia and those cognitive deficits could precede the onset of the clinical symptoms of psychosis. Several studies have suggested that individuals at Ultra-High Risk (UHR) of psychosis show similar cognitive impairments. However, previous findings in this fieldare heterogeneous regarding which cognitive changes are specific to the development of schizophrenia. Our aim was to investigate the neurocognitive performance of adolescents at UHR of psychosis as compared to Help-Seeking Controls. Methods: We studied 33adolescents consisting of 17 at UHR of psychosis and 16 help-seeking adolescents, meeting the inclusion criteria of a National Research protocol for Early Detection of Psychosis. Six neurocognitive domains were measured with validated instruments: executive functions, processing speed, cognitive flexibility, attention, visual memory, and verbal fluency. Analyses compared cognitive performance between the two groups. Results: The UHR subjects had significantly lower performance than the control group in visual memory (p=0.010) and verbal fluency (p=0.040; p= 0.032; p=0.029). Conclusions: Our findings suggest that visual memory and verbal fluency could serve as specific markers in UHR adolescents. However, experimental tasks challenging these cognitive functions are needed to interpret the predictive value of these findings.***

Keywords: early detection, neurocognition, psychosis, schizophrenia

1. Introduction

Schizophrenia is often a chronic and debilitating disorder, characterized by an acute phase, and an episodic or continuous course. The acute phase can be preceded by a prodromal period, with non-specific symptoms of lower severity [1]. Previous studies have revealed that a prolonged duration of untreated psychosis (DUP) was associated with more severe cognitive impairments in patients with schizophrenia [2, 3]. Predicting the onset of psychosis remains difficult despite the existence of several studies and is still a field of critical research. Over the last twenty years, interest has been growing exponentially in the early detection and prediction of psychosis [4]. In Australia, The Personal Assessment and Crisis Evaluation clinic (PACE), was the first program specifically focused on the study and thetreatment of individuals at risk for psychosis [5]. Research from this group of investigators has led to the definition of clinical criteria of 'Ultra High Risk' (UHR) individuals and to the construction of The Comprehensive Assessment of At-Risk Mental States (CAARMS). The CAARMS was the first instrument designed specifically for the identification of help-seeking individuals, through a detailed exploration of subclinical psychopathology, indicating the imminent development of at first-episode psychosis. The CAARMS includes positive symptoms used to define UHR and additional ways of documenting psychopathology [6]. Inter-rater reliability, and discriminant, concurrent and predictive validity of the CAARMS have already been examined [6, 7]. Results indicate that the CAARMS is a useful instrument for detecting and monitoring sub-threshold psychotic symptoms and to identify individualswhomight develop a full-threshold psychotic and other disorders, such as mood disorders [8]. However, the identification of these subthreshold symptoms can be difficult and improving the detection strategy with complementary approaches is still needed.

Impaired cognition is now fully recognized as being at the core of schizophrenia and could precede the onset of clinically significant psychotic symptoms [9]. Some specific cognitive impairments are already detectable before the onset of the disease, and could help to improve early detection of individuals at risk of psychosis[10]. For that purpose, it is crucial to determine when specific impairments are perceptible and whether some deficits could be more specific of UHR individuals and more predictive of conversion to psychosis.

2. Literature Survey

Multiple studies describing patients with prodromal symptoms have tried to identify a specific cognitive dysfunctionprofile using established batteries. General cognitive aptitude remains relatively intact on UHR individuals and represents a poor predictor of transition to psychosis. Therefore, more specific cognitive domains could represent a better discriminative factor in UHR individuals[11].Thereby, cross-sectional and long-term follow-up studies on neurocognitive indicators of an increased risk of developing psychosis have been published, and were from Europe, North America, Asia and Australia. Different cognitive functions were assessed, such as attention, executive functions, verbal fluency, and visual and verbal memory. Results show that significant and widespread impairments in neurocognitive functioning were found to be constant in UHR groups. However, impaired specific cognitive functions were variable and differed between studies [10, 12, 13].

Problem Definition

The aim of our study is to investigate the neurocognitive performance of adolescents at UHR of psychosis, and to compare them to cognitive functions of adolescent controls referred to the department of child and adolescent psychiatry, who did not meet the criteria of UHR for psychosis.

3. Methods

Setting

Our study was initiated as part of a National Research protocol for Early Detection of Psychosis, as part of developing and fostering multicenter research. Our researchobjectives were to determine the socio-demographic and clinical characteristics of UHR patients, and to study the value of neuropsychological markers as predictors of psychotic transition. This protocol was developed by the department of psychiatry inFarhatHachad hospital (Sousse, Tunisia).

Our study was performed by the 12SP20 Research Unit 'Cognitive processes in psychiatric disorders'- Faculty of School of Medicine of Tunis. This research was approved by Razi Hospital Ethical Committee, and conformed to the provisions of the Declaration of Helsinki. After explaining the procedure and the aim of the study, written informed consent was obtained from all adolescents and their parents. The protocol was conducted by the research team and neurocognitive assessments were administered by an experienced consultant research child psychiatrist. Inter-rater reliability was achieved by extensive pre-training by one of the study authors and by repeated training sessions.

Subjects

The target population consisted of Tunisian adolescents referred for the department of child and adolescent psychiatry in Razi Hospital (aged between fourteen and eighteen years), between February 2015 and July 2016.

The first stage of recruitment was based on the identification of subjects with non-specific symptomsusing the Basel checklist for risk. That checklist contains the most specific prodromal symptoms of psychosis and allows early detection of potential signs of early psychosis. The checklist explores changes in reality perception, behavioral changes, personality changes, changing feelings and interests, modification of relational capacity, disorganized speech, bizarre behavior, substance use and family history of psychosis[14]. Then, adolescents who reached a threshold of non-specific symptoms were referred to our research team who selected participants for the study, based on inclusion and exclusion criteria.

Inclusion criteria were adolescents aged between fourteen and eighteen years, meeting the criteria of the Basal checklist, the absence of danger for the interviewer and the patient and effective communication in Arabic. All the participants were of Tunisian origin.

Exclusion criteria were subjects aged under fourteen and over eighteen, patients in acute decompensation, serious or ongoing medical or neurological disorders or significant head injury, cannabis or alcohol consumption in the last 72 hours, current treatment by benzodiazepines or antipsychotics, and severe intellectual dysfunction altering communication (IQ below 70).

Exclusion criteria were a lifetime diagnosis of a psychotic episode, a current or previous diagnosis of a schizophrenia spectrum disorder (meeting DSM-5 criteria of schizophrenia, schizoaffective disorder, brief psychotic disorder, or schizophreniform disorder), a current or previous diagnosis of bipolar disorder or obsessive-compulsive disorder, substance dependence or abuse (DSM-5 criteria) during the previous year or for more than five years. In total, 33 adolescents were enrolled in the study.

Clinical ratings

The Comprehensive Assessment of At-Risk Mental State, CAARMS-Arabic Version was used by a child psychiatrist qualified and trained in the administration of the instrument. Analysis of the results of construct validity, concurrent validity and reliability of the CAARMS had indicated that the Arabic version is valid and reliable[6, 15].The CAARMS is a semi-structured interview and consists of 27 items which are grouped in seven scales: positive symptoms; cognitive change; emotional disturbance; negative symptoms, behavioral change; motor/physical changes; and general psychopathology. For each item, severity and frequency is mentioned [6].

Two groups of help-seeking adolescents were formed following the criteria of the CAARMS: Ultra High Risk (UHR) and Help-Seeker Controls (HSCo). The UHR group were classified into three sub-groups: 'Vulnerability' group including a combination of trait risk factor and a significant deterioration in mental state and/or functioning; 'Attenuated psychosis' group including young people presenting with a limited psychotic syndrome; a 'Brief Limited Intermittent Psychotic Symptoms (BLIPS)' group comprising young individuals presenting with a recent history of clear psychotic syndrome with severity and frequency above the threshold but that disappeared, without any psychotic drug, in less than a week. HSCo group corresponds to young help-

seekers with psychiatric disorder or psychological distress, but who do not respond to the CAARMS criteria of at-risk mental state.

Cognitive measures

Neuropsychological functions were assessed for each adolescent. The comprehensive neuropsychological battery which includes the Stroop Test [16, 17], the Trail making Test part A and B[18-20], the Rey Complex Figure Test (RCFT)[16], the verbal fluency test Arabic version[21, 22], the Grober-Buschke test [23]. According to the literature, all tests were categorized into six neurocognitive domains: executive function; processing speed and cognitive flexibility; attention; visual memory; and verbal fluency [16, 20, 24].The tests are outlined in Table 1.

Statistical analysis

Data analysis was performed using the software Statistical Package for the Social Sciences (SPSS), IBM, version 18 for Windows. Characteristics of the two groups (UHR subjects and the Help-Seeker Controls group) were compared using the chi-squared test for categorical variables. As for continuous variables, normality was checked by the Shapiro Wilk test. When the distribution was approximately normal, the t test was used to compare groups. Otherwise, the non-parametrical Mann-Whitney test was used. The significance level was set to 0.05.

4. Results

Subjects

Among the 33 adolescents included, 17 met criteria of UHR and 16 were considered as Help-Seeking Controls. Among UHR participants, only three reached exclusively criteria for vulnerability and two exclusively criteria for BLIPS (see Figure 1). The small size of these two subgroups compared to 'attenuated psychosis' precluded a comparative analysis between subgroups and we only considered the whole sample of UHR in our analysis. Table 2 summarizes the baseline characteristics of the study participants. There were no group differences (table 2) on gender, age, parental socioeconomic status and educational level between the UHR group and the HSCo group.

Neurocognitive assessments:

The table 3 illustrates the mean performances across the six neurocognitive domains for the clinical high-risk group in comparison to the Help-Seeker Controls group. The table 4 summarizes the significant differences between groups. The UHR group showed the largest deficit in spatial memory and verbal fluency. However, performance in executive function, processing speed, cognitive flexibility, attention and verbal memory didn't differ between groups. In the Stroop Test, the UHR group had lower score in corrected read answers during the three stages of the test with no significant statistical difference.

In the TMT-A, and the TMT-B, the mean duration of the test and the average number of errors was higher in the UHR group. However, comparaisons revealed no significant differences between groups.

Concerning performances in the RCFT, the mean standardized scores in immediate and delayed recall were higher in the HSCo group, but the difference was significant only in memory (p=0,010). The elapsed time for immediate and delayed recall did not vary significantly between the two groups.

In the Grober-Buschke Test, the average of total correct words during the three short delay free recalls and the long delay free recall were higher in the HSCo group. Total number of repetitions and intrusions during the three short delay free recalls were higher in the UHR group. No difference in scores was significant throughout the test. In the verbal fluency task, phonemic fluency (letter B and K) was impaired in the UHR group (p=0,040; p=0,032) . Semantic fluency was also impaired in the UHR group (fruits category p=0,040).

5. Discussion

The present study examined and compared the neurocognitive performance between Tunisian adolescents at UHR of psychosis and Help-Seeking Controls. To the best of our knowledge, this is the first study which focus specifically on the cognitive profile of adolescents at ultra high risk of psychosis.The comparaison with help seeking adolescent patients is a strength of our study as this population is representative of the clinical reality of our specialized outpatient psychiatry service. We preferred this approach over a comparaison with healthy controls, as the latter are per se not help-seeking and are not seen in outpatient services. The results shows that very specific neurocognitive impairments were already evident in individuals at ultra high risk of psychosis. Spatial memory and verbal fluency were significantly impaired compared to the Help-Seeking Controls, which is consistent with other studies showing that specific domains of neurocognition, spatial memory and verbal fluency, could caracterise individuals at risk of psychosis.

Although visual memory has been assessed less often than verbal memory, some studies have shown that visual memory was altered in UHR subjects. Recent longitudinal studies have attempted to determine predictive markers for schizophrenia by examining performance between converters and non-converters, and reported that visual memory predicted the transition to overt psyhosis [16, 25-27]. De Hert, in his meta-analysis, has shown that the performance on visual memory of the UHR group who convert is worse than who did not convert to psychosis[28].

In contrast, previous studies have considered verbal fluency in UHR groups and concluded that it was also impaired in UHR individuals[29-31]. However, attention, verbal memory, executive functions, processing speed and cognitive flexibility didn't differ between the two groups in our study.Our data are broadly consistent with those from previous findings examining cognitive deficits in prepsychotic individuals, although the exact domains of impaired functioning differ across research centers.The previous findings are heterogenous and there is a lack of consensus on which changes are specific to the development of schizophrenia. Some neurocognitive dysfuntions are

emerging or aggraved in certain stages during the developmental period and seem to vary with disease progression.[32].

There are several possiblities for the inconsistancies in studies on neurocognitive performance in UHR and for explaining our inability to replecate the finding of previous studies in domains such as verbal memory. Recently, functional and structural brain imaging studies have highlighted some of the brain changes occuring in early childhood and adolescence. One of these studies showed accelerated gray matter loss with a dynamic pattern (from parietal to frontal) in childhood-onset schizophrenia patients during adolescents[33]. This pattern is probably an exaggeration of the healthy developmental process[34], and may account for the transitional UHR state, which shows different levels of performance in various neurocognitive domains[16].

Others reasons for inconsistent findings might be due to a lack of consensus regarding which mesures are specific for the early detection of the 'true' prodromal phase, different assessment used to definy high-risk sample (the CAARMS, the Scale of Prodromal Symptoms (SOPS) contained within the sturctured interview of Prodromal symptoms(SIPS)[20, 24, 35], demographic differences, reliability and sample sizes, levels of instruction of subjects included, and conceptual imprecision in communicating results as well as inhomogeneity of age groups. In our study, only adolescents were included as compared with other studies that included UHR patients over the age of 18. Moreover,some studies did not exclude patients on neuroleptics during recruitment.Antipsychotics could affect their cognitive performance as well as their clinical evolution towards psychosis or remission.[16, 20, 29, 35-37]. None of our patients was on psychotropic drugs.

Finally, the literature shows that identical neuropsychological tests were used to assess different domains[10]. In our study, performances in the Verbal Fluency Test and the Rey Complex Figure Test were altered in the UHR group. Yet, these tests were used in other studies to evaluate executive functions [38-40]. This observation could lead us to consider that in our study, executive functions are altered in the UHR group.

Cognition appears to be impaired prior to the emergence of psychotic symptoms and cognitive deficits may therefore serve as possible predictors of schizophrenia prior to the onset of full illness.

Spatial memory and expressive language may predict global functional outcome of early psychosis in adolescents. These neurocognitive tests are easy to incorporate in clinical settings and may be included in routine clinical assessments for prediction of functionnal outcome in early psychosis

6. Conclusion

In summary, the present study shows that neurocognitive impairments were evident in UHR adolescents. Furthermore, spatial memory and verbal fluency were significantly altered and could predict the onset of psychotic illness in adolescents. Our finding suggests that a psychosocial intervention consisting of cognitive remediation therapy might be indicated to prevent psychotic transition in UHR individuals and to preserve abilities that have not yet been impacted by the illness.

7. Future Scope

Although this current study is limited by the small simple. In fact, recruitment of adolescents with non-specific symptoms were difficult and obtaining parents and adolescents approval for the assessment was sometimes difficult, probably because of their apprehension about a possible predisposition to psychosis or denial or a possible prodromal psychotic disorder. Moreover, we didn't examine effects of specific variables such as family history of psychosis and we did not attempt to match the study groups on gender, socioeconomic status and age. However, the groups did not differ in terms of age, school education, gender, and socioeconomic status.

To our knowledge, this is the first study of cognitive functioning in adolescents at UHR for psychosis in the Middle-East North-African region.

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Table 1: Cognitive measures

	Test	Variable employed
Executive function	Stroop Color and Word Test	Board 1-3: Corrects read answers Corrected errors Non corrected errors
Processing speed and cognitive flexibility	TMT-B	Time to competition (sec) and errors
Attention	TMT-A	Time to competition (sec) and errors
Visual memory	RCFT	Immediate recall: standardized score Time Delayed recall: standardized score Time
Verbal memory	Grober-Buschke test	Short delay free recall (trial 1-3): total corrects words Total number of repetitions Total number of intrusions Long delay free recall: total corrects words Recognition trial: correct words
Verbal fluency	Verbal fluency test: Phonological fluency (letter k, b) Semantic fluency (category animals, fruits)	Total correct words generated Total repetitions Total intrusions

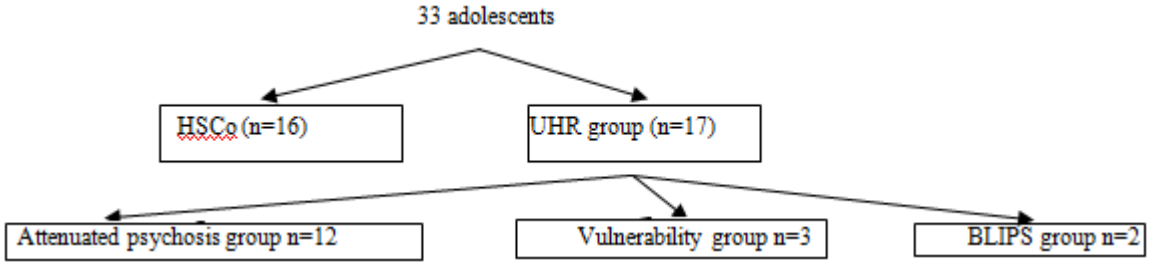

Figure 1: Study Population Flow Chart and Classification according to the CAARMS-criteria
UHR: Ultra High Risk of Psychosis; HSCo: Help-Seeker Controls; BLIPS: Brief Limited Intermittent Psychotic Symptoms

Table 2: Demographic and clinical sample characteristics

	UHR group (n=17)	HSCo group (n=16)	p
Age	14,92 ± 0.88	15,12 ± 1.06	0.855
Gender: % female	64.7	62.25	0.951
Parental socioeconomic status			
% low	29,41	31,25	0.072
% middle	52,94	50	0.068
Years of education	9 ± 0.45	9± 1.25	ns

UHR: Ultra High Risk of Psychosis; HSCo: Help-Seeker Controls.

Table 3: Comparaison of neurocognitive performance between patients at UHR of psychosis and Help-Seeker Controls group

Test	UHR (n=17)	HSCo(n=16)	p
Stroop Test			
Board 1:			
Corrects read answers	56,9 ±3,7	60,3±5,2	ns
Corrected errors	1±0,93	1±0,7	ns
Non corrected errors	0,23±0,4	0,25±0,5	ns
Board 2:			
Corrects read answers	71,2±8,3	76,1±6,81	ns
Corrected errors	0,71±0,41	0,56±0,38	ns
Non corrected errors	0.12±0,24	0,89±0,33	ns
Board 3:			
Corrects read answers	35,88±8,5	36,75±6,7	ns
Corrected errors	1,94±1,1	2,56±1,36	ns
Non corrected errors	2,06±1,4	1,88±1,16	ns
TMT-A			
Time to competition in sec	76,9 ± 34,2	56,6 ± 29,56	ns
Errors	0,64 ± 1.05	0,62 ± 1	ns
TMT-B			

Time to competition	202,4 seconds ± 101,5	184,5 seconds ± 87,6	ns
Errors	2,5± 3,7	2,4 ± 3,1	ns
RCFT			
Immediate recall:			
standardized score	53,3±6,1	55,6±8,8	ns
Time to competition in sec	358,2±140,9	341,9±77,53	ns
Delayed recall:			
standardized score	27,2±10,8	36,6±9,4	0.01
Time to competition in sec	261,4±103,2	272,6±94,5	ns
Grober-Buschke Test			
Short delay free recall total corrects words	31,47±7,7	33,81±5,72	ns
Short delay free recall Total number of repetitions	1,18±1,33	0,75±1,18	ns
Short delay free recall Total number of intrusions	0,88±1,5	0,56±0,89	ns
Long delay free recall: total corrects words	10,94±2,7	11,44±2,31	ns
Recognition trial: correct words	16	16	ns
Verbal fluency:			
Phonological fluency letter b			
Total correct words generated	5,23 ±3,38	7,43±2,4	0.04
Total repetitions	0	0,12±0,5	ns
Total intrusions	0,23±0,75	0,25±0,44	ns
Phonological fluency letter k			
Total correct words generated	6,64±2,7	8,81±2,7	0.032
Total repetitions	0,11±0,48	0	ns
Total intrusions	0,04±0,24	0,03±0,25	ns
Semantic fluency category animals			
Total correct words generated	18,3±4,8	17,5±5,3	ns
Total repetitions	0,47±1	0,43±0,8	ns
Total intrusions	0,11±0,33	0,06±0,72	0.029
Semantic fluency category fruits			
Total correct words generated	10,8±3	13±2,9	0.04
Total repetitions	0,1±0,33	0,1±0,34	ns
Total intrusions	0,17±0,72	0,25±0,57	ns

TMT-B: Trail Making Test - B; TMT-A: Trail making Test- A; RCFT: Rey complex figure test; UHR: Ultra High Risk of Psychosis; HSCo: Help-Seeker Controls.

Table 4: Significant differences of neurocognitive performance between patients at UHR of psychosis and Help-Seeker Controls group

Test	UHR (n=17)	HSCo(n=16)	p
RCFT			
Delayed recall: standardized score	27,2±10,8	36,6±9,4	0.01
Verbal fluency:			
Phonological fluency letter b: Total correct words generated	5,23 ±3,38	7,43±2,4	0.04
Phonological fluency letter k: Total correct words generated	6,64±2,7	8,81±2,7	0.032
Semantic fluency category animals: Total intrusions	0,11±0,33	0,06±0,72	0.029
Semantic fluency category fruits: Total correct words generated	10,8±3	13±2,9	0.04

RCFT: Rey complex figure test; UHR: Ultra High Risk of Psychosis; HSCo: Help-Seeker Controls.

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