Original article

Neurocognitive assessment of ultra high risk of psychosis states using the MATRICS battery (Measurement and Treatment Research to Improve Cognition in Schizophrenia)

Avaliação neurocognitiva dos estados de risco ultra-alto de psicose usando a bateria MATRICS (Medição e Pesquisa de Tratamento para Melhorar Cognição na Esquizofrenia)

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Abstract

Background: Several neuropsychological deficits have been detected in subjects at ultra high risk of developing psychosis, but the best neuropsychological instruments to detect these deficits are yet to be determined. **Objectives:** Assess neuropsychological profile of subjects at ultra high risk of psychosis (UHRP) using MATRICS battery (Measurement and Treatment Research to Improve Cognition in Schizophrenia) compared with age, gender and Intelligence Quotient matched controls. **Method:** Neuropsychological functioning was measured in 27 UHRP patients and 38 controls using MATRICS battery. UHRP was diagnosed using the Cognitive Assessment of at Risk Mental States (CAARMS) scale, and both social and global functioning was assessed as well. Comparisons between groups were established using ANOVA, ANCOVA and Pearson correlation. **Results:** UHRP subjects scored 0.5 to 1.7 SD below controls in working memory, verbal and visual learning and social cognition. **Discussion:** UHRP subjects exhibit selective deficits in neuro-cognitive functioning when compared with controls, which can be detected with MATRICS. This instrument seems to be helpful for early detection of UHRP states.

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Keywords: Neuro-cognition, UHRP, MATRICS.

Resumo

Introdução: Diversos déficits neuropsicológicos têm sido detectados em indivíduos com risco ultra-alto de desenvolver psicose, mas o melhor instrumento neuropsicológico para detectar esses déficits está ainda para ser determinado. **Objetivos:** Avaliar o perfil neuropsicológico de indivíduos em risco ultra-alto de psicose (UHRP) usando a bateria MATRICS, em comparação com controles combinados por idade, gênero e quociente de inteligência. **Método:** O funcionamento neuropsicológico foi medido em 27 pacientes em UHRP e 38 controles usando a bateria MATRICS. UHRP foi diagnosticado usando a escala para Avaliação Cognitiva de Estados Mentais em Risco (CAARMS), e tanto o funcionamento social como o global também foram avaliados. As comparações entre grupos foram estabelecidas usando ANOVA, ANCOVA e correlação de Pearson. **Resultados:** Os sujeitos em UHRP marcaram 0.5 a 1.7 desvios-padrão abaixo dos controles na memória de trabalho, aprendizagem verbal e visual e cognição social. **Conclusão:** Indivíduos em UHRP apresentam déficits seletivos no funcionamento neurocognitivo quando comparados com controles, que podem ser detectados com MATRICS. Esse instrumento parece ser útil para a detecção temporã de estados de UHRP.

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Palavras-chave: Neurocognição, UHRP, MATRICS.

Introduction

Cognitive impairment is a frequent issue in UHRP patients and stands up as a core feature of this pre-clinical condition[1]. Neuropsychological state is a better predictor of functional outcomes and a putative focus for intervention. Several studies assessing cognitive functioning in UHRP patients had inconsistent or partial results[2,3]. In addition, UHRP patients show distinct neuro-cognitive profiles from other diagnostic categories such as depression or bipolar disorder. Some of the studies that investigate cognitive profile in ultra high risk of psychosis subjects have found worse performance at selective and continuous attention[4-6]. Other studies have found cognitive handicap in every category explored[7-10], but due to the diversity of batteries used, it remains a difficult task to set a characteristic pattern of impairment. UHRP criteria are intended to avoid difficulties resulting from the unspecific nature of prodromal symptoms of psychosis which cannot predict which subjects will develop frank psychosis or schizophrenia. Using this approach a certain number of measurements are registered in order to focus risk level on the selected sample. In other words, a subject is expected to meet a number of criteria to be included in Ultra high risk of psychosis group. To detect those subjects who are prone to developing psychosis in a future time, symptoms and signs are checked along with other risk factors, such as age, being adolescence a hallmark for higher incidence of psychosis[11,12]. Other risk factors are functional impairment and prodromal symptoms, appearing immediately before frank psychosis development. Subjects fulfilling these criteria are classified as ultra high risk of psychosis, to distinguish them from those who exhibit genetic risk factors only. This approach had made possible to detect those subjects at high risk of psychosis within a relatively short lapse (1-2 years) with a conversion rate of approximately 40%. The following are additional criteria: age between 14 to 29 years, attending an outpatient health service to get psychological or psychiatric assessment, and meet one of three group criteria: (a) positive attenuated psychotic symptoms during last year, (b) brief limited intermittent psychotic symptoms (BLIPS); with bouts of frank psychotic symptoms, lasting less than a week and

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vanishing spontaneously, (c) trait and state risk factors; schizotypal personality disorder[13], or first degree relatives with psychotic disorder, and a meaningful reduction of 30% in social functioning during last year[14,15]. Ultra high risk criteria have been replicated in other studies with conversion rates between 10% and 50%[16]. As UHRP patients has a lower frequency than those with full blown schizophrenia the use of a standard battery such as the MATRICS would allow for comparison between small samples. It has to be taken into account, however, that the scientific foundation of the MATRICS battery is based on patients, and it hasn't yet been extensively used in UHRP patients[17-19]. The aims of the current study are, thus, to examine whether the MATRICS battery will differentiate between subjects with UHRP and a control group in terms of affected areas, and assess technical difficulties that may arise on using the MATRICS battery.

Methods

Subjects

Subjects at UHRP were recruited among students assisting at three public schools who were referred for evaluation to a community mental health service due to behavior disorders exhibited in classes or low academic results. Inclusion criteria were age below 21 years and fulfill the Comprehensive Assessment of at Risk Mental State (CAARMS) battery[20] for UHRP condition.

Participants had to meet criteria for one of three prodromal syndromes assessed with the CAARMS scale, based in the presence of (1) attenuated psychotic symptoms; (2) brief limited intermittent psychotic symptoms (BLIPS); or (3) 30% or greater fall in social functioning added to schizotypal personality or the presence of psychotic disease in first degree relatives (trait and state risk factors). Patients who meet anyone of DSM-IV axis I criteria for schizophrenia-spectrum disorder were excluded, such as schizophrenia, schizoaffective disorder, schizophreniform disorder or psychosis not otherwise specified (NOS). Also were excluded patients with central nervous system diseases or trauma with loss of consciousness longer than 30 minutes, with or without any neurological sequelae or an estimated IQ below 70. A total of 27 subjects at UHRP naive to antipsychotics were included.

Control subjects were recruited through healthy volunteers with sports minor injuries assisting to a physical rehabilitation facility. The M.I.N.I. 5.0 was administered to control subjects to detect any psychiatric disorder[21-23], and was excluded in case of a positive answer to any of the screening questions. Patients and controls were matched on age, sex, and instruction years. After giving a complete description of the study to the subjects, written informed consent was obtained from patients and controls, as well as their parents, if the adolescents were below legal age. The study was submitted and approved by Committee of Ethics for research in human subjects.

Methods

Patients were interviewed by researchers, clinical psychologists and psychiatrists, who had access to clinical relevant data and information files of patient's family provided by treating doctors. All subjects completed the Structured Clinical Interview for axis I DSM-IV disorders (SCID-I)[24], to exclude diagnosis of psychosis. Interviewers joined regular meetings to establish consensus for clinical diagnosis and were leaded by a psychiatrist trained in clinical research. The mean *kappa* value for diagnosis of psychosis during consensus meetings was 0.81. Those patients diagnosed with psychosis were excluded from the research. Also patients and controls completed the Wechsler Adult Intelligence Scale III[25], the SIPS scale (Structured Interview for Prodromal Syndromes)[26] to assess the risk of transition to psychosis, Social coping and fit was assessed using the GAF (Global Assessment of Functioning)[27], and the Social Functioning Scale[28]. This is a widely used, self-completed measure with established reliability and validity designed to evaluate critical areas of social functioning which may be needed to keep community adjustment. The scale contains 79 items covering basic social behaviors and skills whose presence and frequency of occurrence are informed. This scale includes sub-scales with continuously distributed scores for: a) social withdrawal, b) performance and competence in activities of daily living, and c) occupational function. Higher scores indicate better level of social functioning. Neurocognitive assessment was carried out by clinical psychologists with training in standardized NP testing. Cognitive battery MATRICS (CBM) is intended to assess key deficits isolated from schizophrenic-spectrum using purpose specific selected tests, with high test-retest value, good correlation with functional outcomes and well tolerated by patients. The battery is usually completed within an hour and a half session and covers the following seven domains: 1) Speed of processing: 1-a) category fluency[29], 1-b) symbol coding[30] and 1-c) Trail Making A[31]; 2) Attention/vigilance: Continuous Performance Test, Identical Pairs (CPT--IP)[32]; 3) Working memory[33] using 3-a) the letter-number span and 3-b) spatial span (Wechsler Memory Scale III)[34]; 4) Verbal learning using the Hopkins Verbal Learning Test, Revised[35]; 5) Visual learning: Brief Visuospatial Memory Test, Revised[36]; 6) Reasoning and problem solving: mazes [Neuropsychological Assessment Battery (NAB)][37]; 7) Social cognition: Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT) – sub-test managing emotions[38]. MATRICS is available in a South American Spanish translation but no validation has yet been performed for argentine population[39]. An IQ evaluation was also administered using a short form of the WAIS III[40-42]. The WAIS abbreviated form can be administered in 30 minutes and meets the demand for a quick and reliable measure of intelligence in Psychosis research setting. The WAIS abbreviated form has been standardized, offers the three traditional scores: verbal, performance and IQ total scale. The WAIS abbreviated form used in this study and which best predicts the full scale IQ is integrated by the following tests: similarities (verbal comprehension), picture completion (perceptual organization), digit-span (working memory) and digit-symbol coding (speed of processing). The IQ full scale can be obtained by dividing the addition of the four tests by 4 and multiplying the result by 11. This is equivalent to multiply the addition of scalar products by 2.75. The score obtained is transferred to the corresponding scale to obtain the total IQ. Data were analyzed using the SPSS statistical package (version 16.0). Two tailed Student *t* test was used for group comparisons of continual data, chi square for group comparisons of categorical data, and Pearson *r* for correlations. The standard deviation was calculated transforming the tests raw scores into *z* scores on the basis of the media and standard deviation of the control group to allow for comparisons between different measures in both groups. The mean *z* value in the control group was taken as the zero line, and SD = 1 for all measured tests. The level of significance was set at $p > .001$. In working memory and speed of processing domains, where higher scores pointed to greater impairment, the values were reverted so the higher scores always indicated better cognitive performance. Cutoff score to consider minimal neuro-cognitive impairment was set at 1.5 SD below mean value in the control group, and a cutoff score of 2 SD below mean value in the control group was associated with full blown impairment. According to those cutoff scores, subjects at UHRP were classified as having minimal cognitive impairment with scores below 1 SD and affecting up to 3 domains, and severe cognitive impairment with scores below 2 SD and affecting up to 7 domains, compared with healthy controls. Analysis of variance (ANOVA) followed by Newman-Keuls group comparisons was used to disclose differences between the three groups at high risk of psychosis (a- attenuated psychotic symptoms, b- brief limited intermittent psychotic symptoms (BLIPS) and c- trait and state risk factors). To evaluate generalized *versus* specific cognitive impairment an analysis of covariance (ANCOVA) was performed to adjust MATRICS tests scores for IQ.

The sample size of subjects at risk was estimated using the following formula:

x*xs = sd; n = sample size; error = 1.96*s/sqrt(n)

Using an anticipated standard deviation of 1.0, and an acceptable error (+/- distance from mean) of 0.4 with a 95% confidence limit, a minimum of 24 subjects had to be included in the study. To minimize possible errors, 3 more subjects were included in the study, to complete the final number of 27 subjects.

Results

Table 1 shows data and clinical profile of UHRP subjects and controls.

Table 2 shows raw scores in UHRP and controls on individual MATRICS tests. UHRP had more impairments than controls in most measures. Differences were greater in categorical fluency, Continuous Performance Test, visuospatial memory and mazes, reflecting impairment in verbal and visual learning and working memory domains. In general, UHRP performances were between 0.5 and 1.7 SD below controls. Almost 67% of UHRP had an impairment in up to 3 domains with a cutoff of 1 SD, and in up to 7 domains with a cutoff of 2 SD (48% with modest impairment and 19% with severe impairment), compared with 14% of controls (with modest impairment in up to 3 domains and none with severe impairment).

Figure 1 shows MATRICS tests *z* scores. A clear cut difference appears between both groups in performance profile. Analyses were

Table 1. Characteristics of patients and control subjects

Characteristics	UHRP (n = 27)	Control (n = 38)	Test statistics
Age (y), media (SD) [rank]	17.4 (4.32) [12-20]	18.2 (3.52) [13-21]	*t* = -0.42 ns
Education (y), media (SD) [rank]	6.21 (2.21) [4-10]	7.73 (2.81) [4-11]	*t* = -1.73 ns
Gender n (%)			
Male	22 (81)	31 (81)	X^2 = .00 ns
Female	5 (19)	7 (19)	X^2 = .00 ns
Hands dominance n (%)			
– Left	4 (15)	6 (16)	X^2 = .00 ns
– Right	23 (85)	32 (84)	X^2 = .00 ns
Schizotipal personality n (%)	3 (11)	0	
Psychosis in first degree relative n (%)	4 (14)	0	
GAF media (SD) [rank]	44.23 (8.39) [18-80]	87.4 (4.57) [81-92]	^{t} = 0.11 <-001
SFS media (SD)			
– social withdrawal	8.22 (2.10)	9.12 (1.02)	
– relationships	5.10 (1.37)	6.33 (1.98)	
– social activities	19.7 (4.21)	22.4 (2.75)	
– recreational activities	9.63 (2.34)	10.2 (2.31)	
– independence/competence	2.16 (.24)	3.25 (.45)	
– employment	4.51 (1.84)	4.99 (1.29)	
– competency	29.2 (5.17)	32.2 (4,98)	
– global	96.36 (21.79) [78-106]	99.98 (14.52) [89-116]	^{t} = 034 <-001
WAIS media (SD) [rank]	102.7 (17.83) [72-135]	107.31 (13.1) [81-138]	^{t} = -1.71 ns
CAARMS n (%)			
Attenuated psychotic symptoms	17 (63)	0	
Brief limited intermittent Psychotic symptoms	3 (11)	0	
State and trait risk factors	7 (26)	0	

GAF: Global Assessment of Functioning; SFS: Social Functioning Scale; WAIS: full-scale Wechsler Adult Intelligence Scale (abbreviated version); CAARMS: Cognitive Assessment of at risk Mental States.

Table 2. Differences in neuropsychological scores between UHRP and controls

	UHRP	Controls	*t*	*P*
	Media SD	Media SD		
WAIS short version	42.4 (7.6)	65.2 (8.2)	-3-21	.003
Vocabulary	35.3 (4.9)	45.9 (9.6)	-3.41	.002
Similarities	41.9 (6.1)	57.2 (6.22)	-3.91	<.001
Cubes	40.6 (7.9)	49.6 (5.2)	-2.18	.005
Shapes	23.1 (4.2)	39.7 (3.7)	-4.60	<.001
Categorical fluency	15.2 (4.7)	26.2 (5.2)	-5.15	<-001
Symbol codification	41.5 (8.8)	65.3 (7.2)	-5.29	<.001
Trail Making Test A	61.4 (12.8)	31.1 (7.9)	1.97	.005
CPT-IP	0.8 (0.2)	3.2 (0.9)	-3.19	<.001
Letter-number span	9.7 (2.4)	16.6 (3.2)	-5.21	<.001
Spatial s pan total	12.6 (3.1)	19.5 (3.7)	-7.28	<.001
HVLT-R total	20.6 (4.2)	29.4 (5.17)	-5.19	<.001
BVMT-R	21.7 (5.1)	28.7 (4.83)	-6.28	<.001
Mazes (NAB) total	14.2 (7.1)	19.8 (5.21)	-3.82	.007
EIT(MSC)	68.2 (12.6)	97.3 (14.83)	-7.27	.004

WAIS: Wechsler Adult Intelligence Scale short version; HVLT-R: Hopkins Verbal Learning test-revised; BVMT-R: Brief Visuospatial Memory Test – Revised; Mazes (NAB): Neuropsychological Assessment Battery; EITMSC: Emotional Intelligence Test Mayer-Salovey-Caruso, Continuous Performance Test, Identical Pairs.

repeated to account for differences that may be due to IQ influence, using ANCOVA to detect IQ influence size on test results. After those analyses, differences in results for both groups remained identical, being independent for IQ in each one of neuro-cognitive measures, (F from 1.3 to 32.2, P from .000 to .031), with the only exception of speed of processing (verbal categorical fluency [F = 2.7, P = .08] and trail making test A [F = 0.9, P = .39]). No meaningful differences were found in neuropsychological scores between the three groups (attenuated psychotic symptoms, brief intermittent symptoms and trait and state risk factors) measured with ANOVA test (F from 1.8 to 36.9, P from 0.11 to 0.72). A meaningful correlation was found between neuropsychological domains a Social Functioning Scale measured with Pearson test (r from .45 to .74, P from .007 a .001), with the exception of Trail Making Test A (r = 0.15, P = .92).

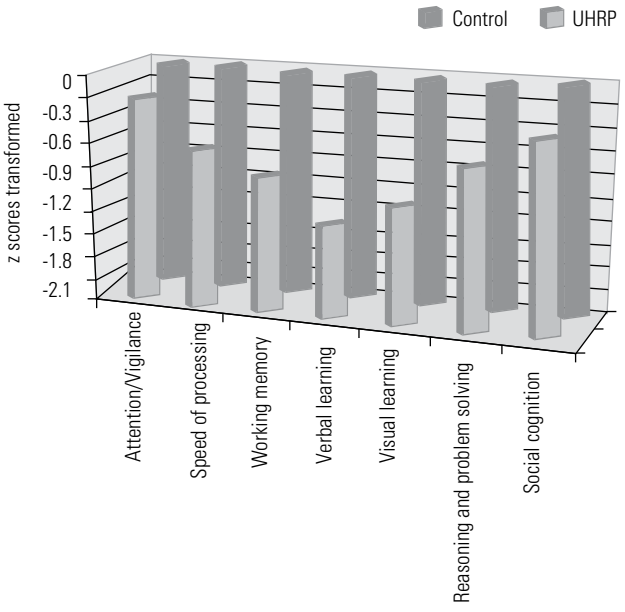

Figure 1. Differences in performance profile between UHRP and controls.

Discussion

Data show that MATRICS is useful for distinguishing between UHRP and healthy controls in cognitive domains with the exception of executive function. It seems to exist a continuity in neuropsychological functioning, evidenced with the finding of 19% of UHRP with severe impairment, 48% with minimal impairment and 37% with no impairment at all, suggesting that risk of developing psychosis in UHRP subjects as those presented in this study, can coexist with some level of functionally preserved cognition, albeit with some degree of emotional and social impairment. Small correlation between Emotional Intelligence and trail making test A can be accounted by the fact that processes of set maintenance and shifting explored in executive functions are far from social and emotional domain, more related with decision making in real contexts[43]. On the other side, no statistically meaningful difference exists between neuropsychological impairment in the three UHRP measured with the CAARMS. Impairment in 4 main domains explored in UHRP (executive function, working memory, verbal and visual learning) points to a damage in left frontal and temporal/hippocampal areas in the pre-clinical state of those subjects at high risk of developing psychosis, in accordance with previous studies but which didn't used MATRICS to assess neuropsychological deficits[44]. Speed of processing and problem solving are less impaired, which may be explained by the fact that these domains are usually preserved in young people. Additionally, the trail making test used to measure executive functioning doesn't take into account verbal abilities, being less sensitive to changes in this area. Differences between control and UHRP in social cognition as measured with Emotional Intelligence Test (EIT-MSC) had a smaller size than in other domains, which may be due to the fact that UHRP subjects develop strategies to manage social situations, but tend to be less effective in real environments due to impulsive behaviors that are hard to stop. Other studies[5-7] have found that results were influenced by general intellectual abilities and demographic characteristics, but this was not replicated in the present study as IQ and demographical data couldn't account for differences between UHRL and control. Opposed to some studies[8] we didn't found an early executive dysfunction, which was less affected than verbal memory and working memory. Emotional intelligence was preserved, although other studies[9] found a compromised interpersonal functioning. MATRICS was originally designed to assess schizophrenia spectrum disorders, some of the instructions and vignettes used to illustrate emotional intelligence tasks could be relatively simple for UHRP subjects, limiting the number of options in response choices and posing a ceiling effect. A limit to this investigation is the small sample of subjects, besides the difficulty imposed by using IQ as a group comparison factor. As UHRP don't have frank psychosis, it may be possible that their IQ could be more preserved than in later stages of the illness. Other limits to this study were lack of standardized application norms for MATRICS in other clinical populations besides schizophrenics, and absence of validation studies in argentine population.

Conclusion

MATRICS is a sensitive and reliable instrument to detect neurocognitive impairments in UHRP, allowing prediction of more affected areas in subjects at high risk of developing psychosis. Using it in the earlier stages of the disease, even when no typical symptoms of psychosis are yet present, would made it possible to begin a neuro--rehabilitation program, increasing cognitive abilities and delaying the first psychotic episode. Provided that there are no differences in MATRICS results between the three groups of at risk mental states, symptoms doesn't seem to play a role as worsening factors in cognitive status, pointing to the existence of a common base for cognitive impairments as an endophenotypical trait in ultra high risk of psychosis subjects.

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