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Similarities in cognitive impairment between recent-onset and chronic schizophrenia patients: a consideration for the neurodevelopmental hypothesis

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ABSTRACT.

Impairment in attention, memory, processing speed and executive functions have been described in patients with schizophrenia. Such impairments can be observed in early stages of the disease and in chronic patients; discrepancy in findings regarding the cognitive deficits at different stages of the illness keeps the debate about schizophrenia as a neurodegenerative condition which courses with continuous deterioration, or if deficits remain stable, as the neurodevelopmental hypothesis suggests. The aim of the present study was to compare the cognitive performance of recent-onset (RO) and chronic (CH) schizophrenia patients to contrast the neurodevelopmental hypothesis against the neurodegenerative approach.

Methods. Twenty RO participants (< 5 years from first psychotic episode) and 30 CH patients (> 5 years from first psychotic episode) were included in the sample. The MATRICS Consensus Cognitive Battery (MCCB), Tower of London test (ToL), Wisconsin Card Sorting Test (WCST) and Stroop Test were used for cognitive evaluation. ANCOVA analysis was performed for group comparisons.

Results. No differences between RO and CH patients were identified on most cognitive tests. However, a significant difference was observed in the visual spatial span test from MCCB.

Conclusions. We conclude that cognitive deficits remain stable over the course of the disease. Our findings are consistent with the neurodevelopmental hypothesis of schizophrenia rather than the neurodegenerative approach.

Key Words. Schizophrenia; Neurocognition; Chronicity; Recent onset; Neurodevelopmental hypothesis

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SIMILITUDES EN EL DETERIORO COGNITIVO DE PACIENTES CON ESQUIZOFRENIA DE INICIO RECIENTE Y PACIENTES CRÓNICOS: UNA CONSIDERACIÓN SOBRE LA HIPÓTESIS DEL NEURODESARROLLO

Resumen. Se ha descrito la presencia de déficits cognitivos en pacientes con esquizofrenia, dichas alteraciones pueden observarse en fases tempranas y crónicas de la enfermedad. Sin embargo, los hallazgos respecto a los déficits en estas fases aún mantienen el debate sobre si la esquizofrenia es una condición neurodegenerativa que cursa con un deterioro continuo o si los déficits permanecen estables, como sugiere la hipótesis del neurodesarrollo. En el presente estudio se compara el rendimiento cognitivo de pacientes con esquizofrenia de inicio reciente (RO) y pacientes crónicos (CH) con la finalidad de contrastar la hipótesis del neurodesarrollo con la perspectiva neurodegenerativa.

Método. Se incluyeron 20 participantes de RO (< 5 años desde el primer episodio psicótico) y 30 pacientes de CH (> 5 años desde el primer episodio psicótico). Para la evaluación cognitiva se utilizó la Batería Cognitiva Consensuada MATRICS (MCCB), la Prueba Torre de

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Londres, la Prueba de Clasificación de Tarjetas de Wisconsin y la Prueba de Stroop. Se utilizó ANCOVA para las comparaciones de grupos.

Resultados. No hubo diferencias entre los grupos en la mayoría de las pruebas cognitivas. Se observó una diferencia significativa en la prueba de span espacial del MCCB.

Conclusiones. Los déficits cognitivos permanecen estables a lo largo del tiempo; nuestros hallazgos son consistentes con la hipótesis del neurodesarrollo de la esquizofrenia más que con el enfoque neurodegenerativo.

Palabras clave. Esquizofrenia, neurocognición, cronicidad, inicio reciente, hipótesis del neurodesarrollo

INTRODUCTION

Schizophrenia is a chronic psychiatric disorder characterized by the presence of positive symptoms which include delusions, hallucinations, and disorganized behavior; as well as negative symptoms, which are expressed by restricted affective responses, diminished verbal production and loss of interest and motivation[1]. Besides, cognitive symptoms are considered a core feature of schizophrenia, although they are not explicitly codified into international diagnostic guidelines like DSM-5 or CIE-11[2]. Moreover, cognitive impairment is closely related to patient's functionality[3].

Considering that schizophrenia is a chronic disorder that causes long-term disability and has shown a calculated total remission rate of 13.5%, which is considered as very low[4], two main hypotheses have been proposed regarding the course of the illness: The first one, proposes that schizophrenia is a neurodegenerative condition, which causes continuous deterioration, thus chronic patients (CH) would be significantly more impaired than recent-onset patients (RO). The other hypothesis considers that schizophrenia is a neurodevelopmental disorder, which is expressed in early adulthood, and the impairment associated to it remains stable throughout the course of illness[5]. Although several authors have reported significant differences between RO and CH regarding symptom severity, cognition, and functionality[6,7,8], others have failed to observe such differences[9]. For these reasons, the evidence supporting both approaches remain inconclusive[10].

In the cognition domain, patients with schizophrenia show deficits in attention, verbal learning, verbal/visual memory, working memory, processing speed, executive functioning, and social cognition[11]. The occurrence of such deficits and the severity of impairment may generate heterogeneous profiles, that can be observed in early stages of the disease[12,13,14,15,16] as well as in CH patients[10,13,17,18,19,20]. According to several authors, the profiles are divided into mild, moderate, and severe impairment. In the first profile, deficits can be observed mainly in attention and social cognition domains, while the remaining two profiles show generalized impairments across multiple cognitive domains[21,22,23].

Interesting findings have been reported in comparative studies between RO and CH. Albus *et al.*[13] showed that first-episode psychosis patients outperformed CH in cognitive flexibility tasks. Besides, a higher performance was observed in abstraction, visoconstruction, and visual memory by Addington *et al.*[12] in RO patients compared with CH. Also, Braw *et al.*[24] found that RO patients (i.e., 48 months from diagnosis) displayed a better performance in psychomotor processing, visual memory, verbal working memory, cognitive flexibility, and planning compared with CH patients (i.e., 64 months from diagnosis). Notwithstanding, Barder *et al.*[25] described patients in a 5-year follow-up period, who improved their baseline performance in psychomotor speed, working memory and impulsivity. In the same line, Rodriguez-Jimenez *et al.*[7] reported CH (i.e., 17.1 years from diagnosis) achieved significant higher scores than RO patients (i.e., 0.7 years from diagnosis) in a CPT task, which measures sustained attention and vigilance. Sponheim *et al.*[26] found that CH displayed poorer performance on time-based measures of problem solving and fine motor dexterity. However, they observed an overall comparable cognitive impairment across RO and CH patients. In the same line, McCleery *et al.*[9] used the MATRICS Consensus Cognitive Battery (MCCB) for cognitive assessment, and did not observe significant differences between first-episode psychosis and CH. Finally, in a recent review published in 2018[27], it has been identified that cognitive impairment increases in ultra-high risk for psychosis population over its development, but stabilizes by the first psychotic episode.

As mentioned before, discrepancy in findings regarding the cognitive deficits at different stages of the illness keeps the debate about schizophrenia as a neurodegenerative condition which courses with continuous deterioration, or if deficits remain stable, as the neurodevelopmental hypothesis suggests. Thus, the aim of the present study was to compare the cognitive performance of RO and CH to contrast the neurodevelopmental hypothesis against the neurodegenerative approach. Neurocognitive processes were assessed with the MCCB, which is considered the international gold standard for cognitive assessment in

schizophrenia. Moreover, cognitive flexibility, planning and inhibition tasks were included to extend the evaluation of the executive functioning domain.

METHODS

Participants

Fifty patients diagnosed with schizophrenia according to DMS-5 criteria were recruited at the National Institute of Psychiatry "Ramón de la Fuente Muñiz" (INPRFM) in Mexico City. All participants were over 18 years old, had achieved at least six years of formal education, and were under pharmacological treatment at the time of the assessment. Another inclusion criterion was fulfilling clinical stability, which was defined as, a) Having no increase on the antipsychotic medication dose over the last 3 months and, b) Achieving a total score between 60 and 90 of the Positive and Negative Syndrome Scale (PANSS) Spanish version[28,29].

The exclusion criteria included additional diagnosis of any neurological condition, comorbid substance abuse (excluding nicotine), clinical diagnosis of intellectual disability, and scores lower that 7 in the WAIS-III Vocabulary Test[30]), or perceptual impairment that could restrict the assessment. Two groups were formed depending on the years of chronicity, 20 patients were included in the RO group, defined as having less than 5 years passed from the first psychotic episode and 30 comprised the CH group with more than 5 years passed from the first episode of psychosis. The study was approved by the Research Ethics Committee of the INPRFM and the Ethics Committee of the Facultad de Estudios Superiores Iztacala (FESI).

Demographic data were obtained with a structured interview. The PANSS, which has been suggested as the gold standard tool for the assessment of psychotic symptoms[31], was used to obtain clinical data measurements. For the cognitive assessment, the MCCB Central and South American version was used[32], this battery includes a wide variety of cognitive domains: processing speed, attention/vigilance, verbal and visual learning, verbal and visual working memory, reasoning and problem solving, and social cognition. The tests comprising the MCCB are the following: Symbol Coding of the Brief Assessment of Cognition in Schizophrenia (BACS-SC), Trail Making Test part A (TMT-A), Continuous Performance Test: Identical Pairs (CPT-IP), Category Fluency: Animal Naming (CF), Wechsler Memory Scale: Spatial Span (WMS-SS), Letter-Number Span (LNS), Hopkins Verbal Memory Scale-Revised (HVLT-R), Brief Visuospatial Memory Test-Revised (BVMT-R), Mazes from the Neuropsychological Assessment Battery (NAB-M) and the Managing Emotions subtest of Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT-ME). Additionally, the executive functioning assessment was extended by including the Wisconsin Card Sorting Test (WSCT)[33], Stroop Test[34] and Tower of London Test (ToL)[35] to explore cognitive flexibility, inhibitory control and planning respectively.

Procedure

Clinical diagnosis of the patients was performed at the INPRFM by specialized psychiatrists. After verifying inclusion/exclusion criteria, participants signed an informed consent letter. Three research assistants with master's degrees in neuropsychology were trained in the administration of the tests. Under the supervision of the principal investigator, the assessment was performed in a single session, into a quiet, sound-controlled, and illuminated room. The neuropsychological assessment was conducted in the following order: MCCB, WCST, Stroop, and ToL. If requested by the participant, a break period after MCCB application was granted, but not during the execution of any test. The complete evaluation lasted about 90 minutes.

Statistical analysis

The data were analyzed with SPSS 20 version; chi square and *t* student tests were calculated for socio-demographic and clinical data. For normality analysis the Shapiro-Wilk test was used, and an ANCOVA was performed for group comparisons, whereas age was introduced as a covariable due to the expected differences between RO and CH. Effect sizes were calculated with partial eta squared (n^2_p).

RESULTS

The normality test showed that data were normally distributed, with $p > .05$ for both groups. Regarding sociodemographic variables, no difference was found between RO and CH groups for years of education, sex, age of the first psychotic episode, pharmacological treatment or PANSS scores; the expected differences were observed in age and chronicity (Table 1).

The comparison between groups regarding MCCB performance is shown in Table 2. No differences were found in most variables but WMS-SS, which measures visual spatial span. Such difference had a medium effect size. Although non-significant, small effects were observed in TMT-A, BACS-SC, LNS, HVLT-R, BVMT-R, NAB-M, MSCEIT-ME, and MCCB Total Score. Poor performances for both groups were observed in TMT-A, MSCEIT-ME and MCCB

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Table 1 Demographic and clinical data

	Recent onset	Chronic	p
n	20	30	
Male	14 (70%)	20 (66.7%)	0.8
Age	26.55 (4.19)**	42.4 (13.29)	**< 0.01**
Age of onset	23.8 (4.34)	26.93 (10.43)	0.15
Years of education	13.9 (2.97)	13.43 (3.27)	0.61
Chronicity (years)	2.72 (1.56)**	15.43 (9.06)	**< 0.01**
Positive symptoms	19.69 (6.52)	20.14 (6.16)	0.83
Negative symptoms	23.08 (7.49)	23.46 (7.92)	0.88
PANSS Total score	71.36 (13.56)	79.14 (16.71)	0.14
First gen antipsychotics	25%	23.3%	0.89

	Mg (mean)	Chlorpromazine 100mg oral equivalent	Mg (mean)	Chlorpromazine 100mg oral equivalent
Aripiprazole	21	7	16	5.3
Clozapine	287	95	325	108
Haloperidol	1.42	0.47	4.1	1.3
Olanzapine	7.5	2.47	12.8	4.22
Risperidone	2.75	0.91	3.1	1.03
Sulpiride	400	133	350	116.3
Trifluoperazine			7.5	2.5

** Differences between recent onset vs chronic, $p < 0.01$

Total Score, in which patients achieved scores below 2 standard deviations.

Executive functioning performance is shown in Table 3, raw scores were transformed into Z-scores. Both groups displayed a similar performance, with no significant differences in any variable. A marginal significant trend was observed in the Stroop Test`s interference ratio with a medium size effect (Table 3). Most remaining variables showed small effect sizes.

Table 2 Comparison of MCCB performance among groups

	RO		CH					
	Mean	SD	Mean	SD	*F*	*p*	n^2_p	Effect size
Processing speed								
TMT-A	21.9	16.7	28.5	13.0	0.6	0.42	0.01	Small
BACS-SC	31.9	13.2	31.9	13.0	0.7	0.39	0.01	Small
CF	39.7	9.7	41.6	11.3	0.1	0.71	0.00	No effect
Attention								
CPT-IP	30.3	10.8	32.6	14.2	0.9	0.75	0.00	No effect
Working memory								
WMS-SS	42.5	10.5	42.4	12.9	4.7	0.03	0.092	Medium
LNS	34.8	11.2	34.8	10.1	1.7	0.19	0.035	Small
Learning								
HVLT-R	34.5	6.5	35.8	8.4	1.4	0.24	0.029	Small
BVMT-R	35.3	15.8	37.1	16.8	1.4	0.25	0.029	Small
Planning								
NAB-M	36.2	10.6	39.6	10.8	0.9	0.33	0.020	Small
Social cognition								
MS-CEIT-ME	27	6.6	25.8	8.4	0.8	0.38	0.016	Small
MCCB Total Score	-1.6	0.7	-1.5	0.8	1.3	0.25	0.027	Small

RO = Recent Onset; CH = Chronic; SD = Standard Deviation; TMT-A = Trail Making Test – Part A; BACS-SC = Brief Assessment of Cognition in Schizophrenia – Symbol Coding, CF = Category fluency; CPT-IP = Continuous Performance Test – Identical Pairs; WMS-SS = Wechsler Memory Scale – Spatial Span; LNS = Letter–Number Span; HVLT-R = Hopkins Verbal Learning Test – Revised; BVMT-R = Brief Visuospatial Memory Test – Revised; NAB-M = Neuropsychological Assessment Battery – Mazes; MSCEIT-ME = Mayer-Salovey-Caruso Emotional Intelligence Test – Managing Emotions.

Table 3 Comparison of executive function performance among groups

	RO		CH					
	Mean	SD	Mean	SD	F	p	n^2_p	Effect size
WCST								
Total number of trials	-1.36	1.00	-1.64	0.87	0.72	0.40	0.020	Small
Perseverative responses	-3.09	3.72	-3.27	3.33	1.65	0.21	0.044	Small
% Conceptual responses	-1.99	1.72	-2.17	1.41	1.64	0.21	0.044	Small
ToL								
Total of movements	-1.18	1.44	-1.37	0.96	1.30	0.26	0.035	Small
Number of hits	-0.69	0.85	-0.67	0.71	1.81	0.19	0.048	Small
Total time	-0.92	1.39	-1.09	1.22	1.27	0.18	0.034	Small
Rule violations	-4.96	9.82	-4.38	5.76	0.72	0.40	0.019	Small
Stroop								
Word	-0.14	1.06	0.24	0.79	1.2	0.27	0.033	Small
Color	-0.31	0.76	-0.45	0.60	0.15	0.90	0.000	No effect
Word-Color	-0.10	0.52	-0.40	0.53	1.51	0.23	0.040	Small
Interference	0.15	0.85	-0.38	0.58	3.83	0.06	0.096	Medium

RO = Recent Onset; CH = Chronic; SD = Standard Deviation; WCST = Wisconsin Card Sorting Test; ToL = Tower of London

DISCUSSION

The objective of the present work was to compare cognitive performance between RO and CH schizophrenia patients to contrast the neurodevelopmental hypothesis against the neurodegenerative approach. The scores obtained in several cognitive domains evaluated by the MCCB and executive functioning tests indicate that RO and CH patients display a similar cognitive impairment. These findings are consistent with previous reports, which indicate that patients with schizophrenia can be found up to 1.6 standard deviations below the general population according to standardized cognitive evaluations[36].

The main finding of this study is the similar performance observed in the RO and CH groups, no significant differences were found in most MCCB variables, or in executive functioning scores. Our results are in agreement with those reported by McCleery *et al.*[9] and Solis-Vivanco *et al.*[37]. The latter compared the groups of ultra-high risk for psychosis, first psychotic episode, and chronic patients without antipsychotic treatment with the MCCB and the same homogeneity in cognitive performance was observed independently of the stage of the disease. These findings, together with our data, indicate that cognitive impairment can be observed in the early stages of the disease, and is not modified over time by the natural course of the disease. The differences observed with other studies can be partially explained by the clinical characteristics of samples and with the tests used for cognitive assessment.

Interestingly, the only difference found between RO and CH was in the WMS-SS, whereas RO barely outperformed CH. This finding is intriguing considering the homogeneity among the cognitive profiles; a possible explanation for this difference could be the effect of age on the performance decline in visual working memory tasks that have been reported in recent studies[38,39]. It has been described that in healthy aged subjects a decrease in the ability to maintain bound object features over short intervals exists; and two reasons for the decline in performance are postulated, the former involves a decrease in the ability to fixate an object in space and the latter includes a decrease in the ability to fixate the features of the object presented. Such assumptions are supported by the neurobiological modifications associated with the normal aging process itself, in which there is a decrease in hippocampal volume and in regions of the occipital and parietal cortex required for these tasks, without this implying a pathological process. It is possible that these modifications observed in our sample as a wider variance, without differences between the mean scores among CH compared to the RO group are a consequence of the aging process itself. However, there are also data reporting that in patients with schizophrenia, there are no differences

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in working memory measures between CH and younger patients[40]. New studies with a much larger sample will be necessary to study the modifications of aging in patients with schizophrenia.

Regarding the marginal trend observed in the Stroop interference effect, it is noteworthy to mention that previous analyses of our data had shown significant differences among groups in this variable, however, when controlling for age, such difference was no longer significant. This finding suggests that ageing, but not chronicity, may affect the interference effect assessed by the Stroop task. A recent meta-analysis in which Stroop performance was adjusted by processing speed, which clearly decreases as we age, confirmed that age negatively affects Stroop's execution[41].

Our results suggest that schizophrenia patients do not experience continuous cognitive deterioration along the course of the illness. These results are more congruent with the neurodevelopmental hypothesis as a possible explanation of schizophrenia etiopathology[26]. The neurodevelopmental approach suggests that schizophrenia is the result of multiple aberrations among different brain maturational processes during childhood and adolescence[42]. Such abnormalities are the result of complex interactions between genetic factors, obstetric complications, and environmental insults like substance abuse. Thus, during adolescence, normal maturational processes like apoptosis or synaptic pruning become more aggressive in the psychosis-vulnerable brain, surpassing a threshold that could lead to a psychotic breakdown[43]. Several studies have shown neurodevelopmental abnormalities in brains of ultra-high risk populations, as well as in schizophrenia diagnosed patients. Thus, as Solis-Vivanco *et al.*[37] point out, this implies that the observed cognitive deficits had been present since adolescence. On the other hand, the absence of gliosis as a fundamental characteristic of neurodegenerative processes, and the inconsistency in the reports about cortical degeneration associated with illness chronicity in schizophrenia[44], may support the neurocognitive stability observed in this study.

Although our results may imply that schizophrenia patients do not deteriorate over time, this is not necessarily applicable to all cases. In our study, the similar performance among groups was observed in patients with adequate pharmacological control and clinical stability. So, our findings are not generalizable to patients with a progressive functional decrease, chronic patients with multiple psychotic episodes, or patients who are refractory to treatment[44]. In this regard, the hypothesis of schizophrenia as a progressive developmental disease, which affects brain plasticity, aging, and increases vulnerability at different stages of life, proposed by de Hann and Bakker[42], and Gupta and Kulhara[44] is a promising approach.

The limitations of the present study include the small sample size and the lack of a control comparison group, which would have provided more precise observations about the patients´ cognitive performance. A methodological limitation also includes the lack of an inter-rater consistency index. Although, the raters were trained and instructed, subtle modifications between applications could also had an impact on the measurements. Additionally, no evaluation for substance use in the participants was carried out, the information was collected only by clinical interview.

As mentioned above, a more exhaustive study including subgroups of patients with multiple episodes, with resistance to pharmacological treatment or with the presence of other adjuvant treatments, other comorbidities and substance abuse should be conducted, to support our results or to accurately establish variations in cognitive performance in association with such variables.

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